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Novartis Research and Development

QGE031 / Ligelizumab

Clinical Trial Protocol CQGE031C1301 / NCT03907878

A multi-center, open-label study to investigate the safety/tolerability and efficacy of ligelizumab (QGE031) in the treatment of adult Japanese patients with Chronic Spontaneous Urticaria (CSU) inadequately controlled with H1 antihistamines

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List of abbreviations

[redacted]	[redacted]
[redacted]	[redacted]
AC	Adjudication Committee
ACR	Albumin-Creatinine Ratio
ADA	Anti-Drug Antibodies
AE	Adverse Event
AH	Anti-Histamine
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BP	Bullous pemphigoid
bpm	Beats per minute
CINDU	Chronic inducible urticaria
CIU	Chronic Idiopathic Urticaria
CMO & PS	Chief Medical Office and Patient Safety
CO	Country Organization
CRF	Case Report/Record Form (paper or electronic)
CRO	clinical research organization
CS	Corticosteroids
CSU	Chronic Spontaneous Urticaria
CT	Computerized Tomography
CTC	Common Toxicity Criteria
CTCAE	common terminology criteria for adverse events
CU	Chronic Urticaria
CV	coefficient of variation
DDE	Direct Data Entry
DLQI	Dermatology Life Quality Index
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic Data Capture
eDiary	Electronic Diary
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EoS	End of study
EoT	End of treatment
[redacted]	[redacted]
EU	european union
FcεRI	IgE receptor
FcεRII	IgE receptor

[redacted]

FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
β-hCG	Beta-Human Chorionic Gonadotropin
[redacted]	[redacted]
HRQoL	Health-Related Quality of Life
HSS	Hives Severity Score
HSS7	Weekly Hives Severity Score
IB	Investigator's Brochure
IC	Informed consent
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgE	Immunoglobulin E
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISS	Itch Severity Score
ISS7	Weekly Itch Severity Score
IUD	Intrauterine device
IUS	Intrauterine system
JDA	japanese dermatological association
LLOQ	lower limit of quantification
LTRA	Leukotriene Receptor Antagonist
MedDRA	Medical dictionary for regulatory activities
MMRM	Mixed effect Model Repeat Measurement
MoA	Mechanism of Action
MRI	Magnetic Resonance Imaging
NYHA	New York Heart Association
[redacted]	[redacted]
[redacted]	[redacted]
PMDA	Pharmaceuticals and Medical Devices Agency
PRO	Patient Reported Outcomes
PSD	Premature subject discontinuation
PT	prothrombin time
q4w	Every 4 weeks
QALYs	Quality-adjusted life-years
QMS	Quality Management System
QoL	Quality of life
QTcF	QT interval corrected by Fridericia's formula
SAE	Serious Adverse Event

[redacted]

sc	Subcutaneous
sCr	Serum creatinine
SD	standard deviation
SOC	System organ class
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBL	total bilirubin
TD	Study Treatment Discontinuation
UAS	Urticaria Activity Score
UAS7	Weekly Urticaria Activity Score
ULN	upper limit of normal
UPDD	Urticaria patient daily diary
VAS	Visual Analog Scale
[redacted]	[redacted]
WHO	World Health Organization
WoC	Withdrawal of consent
[redacted]	[redacted]

[redacted]

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Cohort	A specific group of subjects fulfilling certain criteria and generally treated at the same time
Control drug	A study drug (active or placebo) 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 subject in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
eCRF	Electronic case report form
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. 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
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
eSource	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. 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.
Investigational drug/treatment	The drug whose properties are being tested in the study
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
Part	A sub-division of a study used to evaluate specific objectives or contain different populations. For example, one study could contain a single dose part and a multiple dose part, or a part in subjects with established disease and in those with newly-diagnosed disease
Patient	An individual with the condition of interest for the study
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Premature subject withdrawal	Point/time when the subject exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued and no further assessments are planned
Personal Data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples
Screen Failure	A subject who did not meet one or more criteria that were required for participation in the study
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

[redacted]

Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first subject
Study treatment	Any single drug or combination of drugs or intervention administered to the subject as part of the required study procedures
Study treatment discontinuation	When the subject permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
Subject	A trial participant (can be a healthy volunteer or a patient)
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts
Variable	A measured value or assessed response that is determined from specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent (WoC)	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer and does not allow any further collection of personal data

[redacted]

Amendment 01(14-Feb-2020)

Amendment rationale:

CQGE031C1301 is currently recruiting. This amendment primarily aims to provide clarification on:

a. Clarifies that an urinalysis sample is to be collected Week 24
b. Clarifies that if a subject takes concomitant omalizumab (outside of study assigned treatment), the subject must discontinue from the study, in which case, [redacted]/ADA samples should not be collected at the End of Study (EoS) visit.
c. Clarifies that all subjects will be given three stool samples collection kits at screening Visit1 and Visit320.

It also includes other minor clarifications and editorial changes.

Changes to protocol and rationale:

- **Glossary of terms**: updated with the 'Personal data' definitions.
- **Protocol summary includes the following changes:**
  - "CSU diagnosis for ≥ 6 months" changed to "CSU diagnosis for ≥ 6 months (defined as onset of CSU with supporting documentation)". Section 5.1 updated accordingly
  - "Subjects must be on H1-AH at only approved doses for treatment of CSU starting at Visit 1 (Day -28 to Day -14)" changed to "Subjects must be on H1-AH at only local label approved doses for treatment of CSU starting at Visit 1 (Day -28 to Day -14)" similar change is reflected in Section 4.1.1 and Section 5.1
  - "Any H2 antihistamine, Leukotriene Receptor Antagonist (LTRA) (montelukast or zafirlukast) or H1 antihistamines use at greater than approved dose after Visit 1" changed to "Any H2 antihistamine use or LTRA (montelukast or zafirlukast) after Visit 1 and any H1 antihistamine used as background medication at greater than local label approved doses after Visit 1" similar changes is reflected in Section 5.2
- **Section 4.1.1**: Added, "If a subject must switch to another background H1-AH (at approved dose) as a result of an AE, the subject will be considered to have remained on stable treatment."
- **Section 5.1:** Included the word "local label" in Inclusion Criterion 4.
- **Section 5.2:** Added the term "background medication" and "local label" to Exclusion Criterion #10 in order to clarify that higher than approved doses of H1-AH as background medication are not allowed after Visit 1. This criterion does not apply to H1-AH taken as rescue medication which can be taken up to 4 times the approved dose.
- **Section 5.2:** Exclusion criterion 14 is amended to exclude hypersensitivity to all study drugs
- **Section 5.2:** Exclusion criterion 19, changed "History of" to "History of" and clarifies, that an INR > 1.5 (not INR > 1.5 ULN) is an exclusion criterion for this study.
- **Section 5.2:** Exclusion criterion 24, changed "basic contraception methods" to "Acceptable contraception methods" to be consistent with the CTFG guidelines for

[redacted]

contraception requirements in order to participate in the study. Section 4.5 and Section 7 updated accordingly.

- **Section 6.2.2: Table 6-2**
  - Clarifies the term Routine as "more than 3 doses over a 5 day period" use of oral corticosteroids. Included IV/IM/IA corticosteroids as prohibited systemic routes of corticosteroid administration, with minimum required period without medication mentioned as 30 days prior to Visit 1.
  - Included the phrase "Other immunosuppressive medication with or without known effect on CSU including but not limited to" to clarify that immunosuppressive medication is not limited to the medications mentioned in the table.
  - Revised the footnote to clarify the use of oral corticosteroids as rescue therapy is allowed only after Week 12.
  - Footnote clarifies that other preparations of corticosteroids (CS) with limited systemic exposure for non-CSU indications can be used (e.g. Intra nasal or any topical CS) as-needed basis
- **Section 6.2.2:** Section is updated to clarify that if subjects are administered omalizumab (outside of study assigned treatment) in the follow-up phase they should be discontinued from the study and collection of any efficacy or safety assessments should not be done at EoS visit. Table 8-1 footnotes updated accordingly. Section 9.1.1 updated accordingly
- **Section 6.2.3:** Provided clearer guidance and discontinuation criteria on the use of oral corticosteroids as rescue therapy and deleted the sentence indicating that instructions on use of corticosteroids will be provided to the investigators.
- **Section 8:** Following changes made to Table 8-1
  - Clarification added to "Family history of malignancy" indicating that CRF is to be completed retrospectively for any subject who develops malignancy during the study.
  - There is no need to dispense H1-AH or oral corticosteroids as rescue medications at Visit 1999 or Week 64, hence "s" deleted at that Visit
  - Clarifies that "At Visit 1 and Visit 320, dispense 3 stool collection kits. Patients should collect samples, within seven days of Visit1 and in the week prior to Visit 1999/EOS/PSD"
  - Added "INR at Visit 1, V110 and UPV" for determining exclusion criteria 19 and liver safety follow up. Table 8-10 updated accordingly.
  - Added Urine Dipstick to Visit 170/Week 24 for renal safety monitoring
  - Added a separate line for "serum β-hCG" to clarify that a serum β-hCG sample should be taken for all pre-menopausal women who are not surgically sterile at Visit 1, followed by urine pregnancy test starting at V110 to Visit 1999/EOS/PSD.
- **Section 8.4.1**: is updated with text 'In case of lab abnormalities, an additional re-draw for central laboratory assessment is allowed during the screening period to confirm eligibility criteria' and 'A serum β-hCG will be collected for all pre-menopausal women who are not surgically sterile at Visit 1'.
- **Section 8.4.3:** Clarification is provided on stool sample dispensation and collection of stool samples at not only Screening period Visit 1 and Visit 320 but also advised that if diarrhea, or any other symptoms suggestive of parasitic infection, develops at any time

[redacted]

before the end of study. The section also clarifies that pathogenicity of parasitic organisms will be defined as per the local laboratory.

- **Section 8.4.4**: Section update to provide clear guidance on pregnancy and assessments of fertility
- **Section 10.1.3**: Section updated to provide clarification on SAE reporting
- **Section 10.1.4**: Clarifies that pregnancy follow-up should be for up to 12 months following the birth of the baby.
- **Section 11.2**: the updated details pertaining to 'Stool samples will be processed by local labs and the results will be collected by Novartis via eCRFs' AND Patients will fill in their daily diary data on a smart phone device at home. PROs will be completed by patients on site on the day of applicable visits.
- **Section 16.2**: Table 16-1 and 16-2 clarifies the definition of liver events to be identified based on Guidance for detection, assessment, and management of drug-induced liver injury (DILI) in clinical development, Version 2 (15-Apr-2019)
- **Section 16.3**: Updated Table 16-3 and 16-4 based on the Clinical Development Safety Guideline for Drug Induced Nephrotoxicity Version 2.0 (DIN ClinDevSafetyGuide 2017)
- **Section 16.6**: Updated Appendix 6: World allergy organization grading system based on Cox L, Sanchez-Borges M, Lockey RF (2017) World Allergy Organization Systemic Allergic Reaction Grading System: Is a Modification Needed?. J Allergy Clin Immunol Pract; 5(1):58-62. Reference in section 9.1.1 updated accordingly.

[redacted]

Protocol summary

Protocol number	CQGE031C1301
Full Title	A multi-center, open-label study to investigate the safety/tolerability and efficacy of ligelizumab (QGE031) in the treatment of adult Japanese patients with Chronic Spontaneous Urticaria (CSU) inadequately controlled with H1 antihistamines
Brief title	A Phase III study of safety and efficacy of ligelizumab in the treatment of CSU in Japanese patients inadequately controlled with H1- antihistamines
Sponsor and Clinical Phase	Novartis Phase III
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to evaluate the safety and efficacy of ligelizumab in adult Japanese subjects with CSU, who remain symptomatic despite treatment with H1-antihistamines (AHs) at locally approved doses.
Primary Objective(s)	The primary objective of this study is to investigate the safety and tolerability of ligelizumab 120 mg subcutaneous (sc) every 4 weeks (q4w) for 12 months.
Secondary Objectives	The secondary objective is to evaluate the efficacy of ligelizumab 120 mg sc q4w by evaluation of: • Weekly Urticaria Activity Score (UAS7), Weekly Hives Severity Score (HSS7) and Weekly Itch Severity Score (ISS7) change from Baseline over time • Achievement of the complete UAS7 = 0, HSS7 = 0 and ISS7 = 0 response over time • Profile of change from baseline in the Dermatology Life Quality Index (DLQI) • Achievement of DLQI = 0/1 by visit up to end of study (EoS)
Study design	This is a Phase III multi-center, open-label, single arm study. There is screening period of up to 28 days, a 52 week treatment period, and a 12 week post-treatment follow-up period.
Population	The study population will consist of approximately 65 male and female subjects aged ≥ 18 years who have been diagnosed with CSU and who remain symptomatic despite the use of H1-AH.

Key Inclusion criteria	• Signed informed consent must be obtained prior to participation in the study
	• Male and female subjects ≥ 18 years of age at the time of screening
	• CSU diagnosis for ≥ 6 months (defined as onset of CSU with supporting documentation)
	• Diagnosis of CSU refractory to H1-AH at locally-approved doses at the time of Baseline (Visit 110, Day 1), as defined by all of the following:
	  • The presence of itch and hives for ≥ 6 consecutive weeks at any time prior to Visit 1 (Day -28 to Day -14) despite current use of non-sedating H1-AH (at locally approved doses) during this time period
	  • UAS7 score (range 0-42) ≥ 16 and HSS7 (range 0-21) ≥ 8 during the 7 days prior to baseline (Visit 110, Day 1)

	• Subjects must be on H1-AH at only local label approved doses for treatment of CSU for starting at Visit 1 (Day -28 to Day -14) • Willing and able to complete a daily symptom electronic Diary (eDiary) for the duration of the study and adhere to the study visit schedules • Subjects must not have had any missing eDiary entries in the 7 days prior to baseline (Day 1, Visit 110). i.e., 14 eDiary entries required. Rescreening may be considered only once
Key Exclusion criteria	• History of hypersensitivity to any of the study treatments or excipients or to drugs of similar chemical classes (i.e. to murine, chimeric, or human antibodies) • Subjects having a clearly defined, predominant trigger of their chronic urticaria (CU) (chronic inducible urticaria (CINDU)) including • urticaria factitia (symptomatic dermographism), cold-, heat-, solar-, pressure-, delayed pressure-, aquagenic-, cholinergic-, or contact-urticaria • Diseases, other than chronic urticaria, with urticarial or angioedema symptoms such as urticarial vasculitis, erythema multiforme, cutaneous mastocytosis (urticaria pigmentosa), and hereditary or acquired angioedema (e.g., due to C1 inhibitor deficiency) • Subjects with evidence of helminthic parasitic infection as evidenced by stools being positive for a pathogenic organism according to local guidelines. All subjects will be screened at Visit 1. If stool testing is positive for pathogenic organism, the subject will not enter treatment period and will not be allowed to rescreen • Any other skin disease associated with chronic itching that might influence in the investigator's opinion the study evaluations and results (e.g. atopic dermatitis, bullous pemphigoid (BP), dermatitis herpetiformis, senile pruritus, etc) • Prior exposure to ligelizumab • Any H2 antihistamine use or LTRA (montelukast or zafirlukast) after Visit 1 and any H1 antihistamine used as background medication at greater than local label approved doses after Visit 1
Study treatment	Ligelizumab 120 mg sc q4w
Efficacy assessments	• Weekly urticaria activity score (UAS7) • Weekly hives severity score (HSS7) • Weekly itch severity score (ISS7) • Dermatology Life Quality Index (DLQI)
Key safety assessments	Safety evaluations include adverse events (AEs), laboratory values, vital signs and electrocardiogram (ECG).
Other assessments	[132] [redacted] • [redacted] Anti-drug antibodies (ADA), [redacted] [132] [redacted]
Data analysis	As the study objective is to assess the safety with no specific safety hypothesis, treatment emergent adverse events during the study will be considered as a primary variable. All adverse events which start after the first dose of the study medication will be summarized as treatment emergent adverse event by system

[redacted]

	organ class (SOC) and preferred term. No formal statistical analysis will be provided.
Key words	Anti-Immunogloblin E (IgE), chronic spontaneous urticaria (CSU), safety, Japanese, hives severity score (HSS), itch severity score (ISS), urticaria activity score (UAS), long term, ligelizumab, QGE031, UAS7

1 Introduction

1.1 Background

Urticaria is classified into inducible and spontaneous. Spontaneous urticaria presents with hives spontaneously without a direct cause, and the Japanese Dermatological Association Guideline for the Treatment of Urticaria 2011 (hereafter referred to as the JDA Guideline 2011) defines chronic urticaria as "urticaria persistent for ≥ 1 month from onset" (Hide et al 2011). The Western EAACI/GA^{2}LEN/EDF/WAO Guideline 2017 (hereafter referred to as the EAACI Guideline 2017) defines chronic Spontaneous Urticaria (CSU), also known as Chronic Idiopathic Urticaria (CIU) as the spontaneous occurrence of itchy wheals (hives), angioedema or both lasting for at least 6 weeks (Zuberbier et al 2014, Kaplan et al 2016, Zuberbier et al 2018). These Japanese and foreign guidelines use the different terms and define the different duration of symptoms, but these differences do not interfere with diagnosis and thus, these are considered the same disorder (Hide et al 2012).

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, 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 overall burden of CSU is substantial; CSU has a negative impact on patients' lives and health-related quality of life (HRQoL) and work productivity (Maurer et al 2017).

Urticaria treatment aims at fully suppressing both symptoms of itch and hives and ultimately preventing the occurrence of symptoms altogether without need for medication, and all in all Japan and other countries share this treatment strategy (Hide et al 2012).

A majority of CSU patients can be treated with H1-antihistamine (H1-AH) monotherapy (Kozel and Sabroe 2004), which is frequently used at doses up to 4 fold the approved dose (Zuberbier et al 2014, Zuberbier et al 2018). The use of H2 antihistamines and Leukotriene Receptor Antagonists (LTRAs) has in the past been recommended in treatment guidelines for patients who remained symptomatic despite treatment with H1-antihistamines (Zuberbier et al 2009, Bernstein et al 2014), although their use has not been as well supported by clinical studies. In the latest version of the treatment guidelines (Zuberbier et al 2018), neither H2-antihistamines nor LTRAs are now perceived to have evidence to maintain them as recommendable in the algorithm. These drugs are not approved for treatment of CSU in Japan and other countries (Hide et al 2012). Systemic corticosteroids are sometimes added to the treatment regimens, however they are not recommended in treatment guidelines for long term treatment as patients are then at risk of adverse effects associated with chronic systemic corticosteroid exposure.

In patients not responding adequately or intolerant to these treatment options, use of cyclosporine or other immunosuppressants is considered an option as alternative treatment (Hide et al 2012). However, cyclosporine has not been approved in Japan and is associated with renal dysfunction, hypertension and other adverse reactions even at low doses. Thus, its use is limited to severe patients (Hide et al 2011).

[redacted]

More recently omalizumab, a less potent monoclonal antibody than ligelizumab that also targets immunoglobulin E (IgE), has been approved in several countries including those in the European Union, the United States, Japan and Switzerland as add-on therapy in patients with CSU with symptoms despite treatment with antihistamines. Omalizumab improved the signs and symptoms of urticaria (i.e. hives and itch) in patients who failed treatment with H1-antihistamines as well as in those who failed treatment with a combination of H1- and H2-antihistamines and a LTRA (Gober et al 2008, Kaplan et al 2008, Maurer et al 2013, Kaplan et al 2013, Hide et al 2017).

Ligelizumab (QGE031) is a humanized IgG-type monoclonal antibody that binds to human IgE with higher affinity than omalizumab. Upon binding to specific epitopes in the C3 region of IgE, ligelizumab is able to block the interaction of IgE with both the high and low affinity IgE receptors (FcεRI and FcεRII). Ligelizumab does not mediate IgE receptor cross-linking and consequent histamine release (i.e. is non-activating). This overall mechanism of action (MoA) is shared with omalizumab (Chang et al 2015).

When subjects are treated with ligelizumab, circulating IgE is rapidly bound by the anti-IgE antibody and becomes inaccessible to IgE receptors on mast cells and basophils (Arm et al 2014, Gauvreau et al 2016). Ligelizumab has demonstrated dose- and time-dependent suppression of free IgE, reduction in basophil FcεRI expression and thus basophil surface IgE, and inhibition of skin prick test responses to allergens, superior in extent and duration to those observed with omalizumab (Arm et al 2014, Gauvreau et al 2016). IgE is necessary for the enhanced expression of the FcεRI seen in atopic subjects (MacGlashan et al 1997, MacGlashan et al 1998), and thus a decrease in FcεRI expression on circulating basophils accompanies ligelizumab treatment. Other potentially beneficial effects from anti-IgE therapy include decreased IgE production (Lowe and Renard 2011), reduced IgE+ B cell numbers (Ota et al 2009) and reduced cytokine production by T cells (Coyle et al 1996).

1.2 Purpose

The effect of ligelizumab in patients with CSU inadequately controlled with H1-antihistamines was investigated in the Phase II dose-range finding study [CQGE031C2201] and demonstrated a dose-dependent response to ligelizumab and superior efficacy in multiple ligelizumab dose groups compared to the omalizumab treatment group. No safety concerns were identified in the ligelizumab groups. Two ongoing Phase III studies, [CQGE031C2302] and [CQGE031C2303], are intended to support the registration of ligelizumab for the treatment of patients with CSU in adolescents and adults inadequately controlled with H1-antihistamines.

There is relatively low number of Japanese subjects treated with the intended dose for registration or higher for 1 year in those Phase III studies above. Therefore, the purpose of this CQGE031C1301 study is to evaluate the safety and efficacy of ligelizumab in adult Japanese subjects with CSU, who remain symptomatic despite treatment with H1-antihistamines at locally-approved doses, over 12 months of treatment with ligelizumab and a post-treatment follow-up period of up to 12 weeks. It is a trial intended to support the registration of ligelizumab for the treatment of CSU in Japan.

[redacted]

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• The primary objective of this study is to investigate the safety and tolerability of ligelizumab 120 mg q4w for 12 months	• Overall safety data, assessed as treatment emergent adverse events during the study
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**

• To evaluate the efficacy of ligelizumab 120 mg q4w by evaluation of:
  • UAS7, HSS7 and ISS7 change from baseline over time
  • Achievement of the complete UAS7 = 0, HSS7 = 0 and ISS7 = 0 response over time
  • Profile of change from baseline in the Dermatology Life Quality Index (DLQI)
  • Achievement of DLQI = 0/1 by visit up to end of study
	• Absolute change from baseline of UAS7, HSS7 and ISS7 by visit up to end of study
	• Proportion of subjects with UAS7 = 0, HSS7 = 0, and ISS7 = 0 response by visit up to the end of study
	• Absolute change from baseline of DLQI by visit up to end of study
	• Proportion of subjects with DLQI = 0/1 by visit up to end of study

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

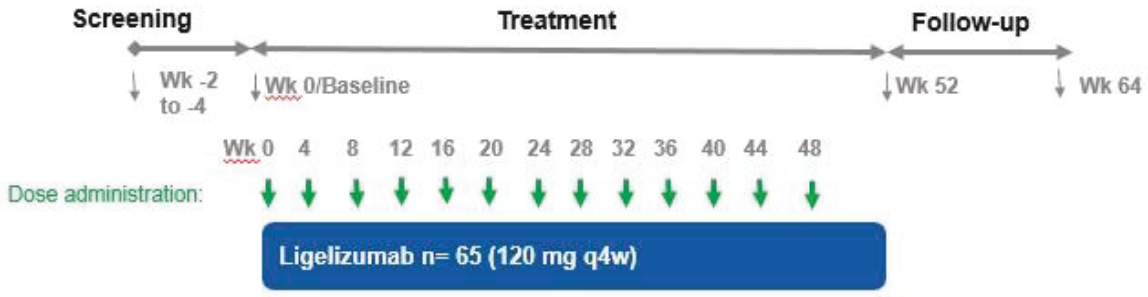
Objective(s)	Endpoint(s)
[redacted]	[redacted][32]

3 Study design

This is a Phase III multi-center, open-label, single arm study. The study consists of 3 distinct periods:

- Screening period (Day -28 to Day -14): Duration of up to 4 weeks in which subjects who have given informed consent are assessed for eligibility.
- Treatment period (52 weeks): The subjects will be seen in the clinic every 4 weeks.
- Post-treatment follow-up period (12 weeks): This period consists of a subject visit in the clinic every 4 weeks with the final visit (Visit 1999) occurring 16 weeks after the last treatment dose.

Figure 3-1 Study design



[redacted]

Screening period

Subjects will have a screening period to establish eligibility for the study. Subjects will be required to attend 1 visit during screening period: Visit 1 (Day -28 to Day -14). An extended screening period will be permitted only in exceptional circumstances when information concerning eligibility is outstanding (eg, pending laboratory data).

Rescreening may be allowed for subjects who failed initial screening. Only 1 rescreening will be allowed (see Section 5.1 and Section 5.2). If a subject is rescreened for the study, the subject must sign a new informed consent and will be issued a new subject number. Informed consent for a rescreened subject must be obtained prior to performing any study-related assessments or collecting any data for the Screening visit.

Treatment period

On Day 1, eligible subjects will enter an open-label treatment period to receive ligelizumab 120 mg sc q4w. The first dose of study drug will be administered on Day 1 (Visit 110). The last dose of ligelizumab 120 mg will be administered on Day 337 (Week 48, Visit 230) study visit.

Approximately 65 subjects will be allocated to the ligelizumab 120 mg q4w arm. Subjects are expected to attend all site visits based on the assessment schedule (Table 8-1).

Post-treatment follow-up period

The post-treatment follow-up period is 12 weeks with the last follow-up visit (Visit 1999) corresponding to 16 weeks after the last treatment dose. No investigational treatment will be given during the post-treatment follow-up period. Subjects will be allowed to take their rescue medication on an as needed basis, assessed on a daily basis by the subjects. Subjects will be required to visit the study center every 4 weeks during the post-treatment follow-up period.

Patients will be eligible for post-trial access after completion of the study.

4 Rationale

4.1 Rationale for study design

Data from the dose-range finding Study [CQGE031C2201] suggest that ligelizumab treatment improves itch and hives in adult subjects with CSU who have failed treatment with H1-antihistamines and those who failed treatment with a combination of H1 and H2 antihistamines and LTRA. The Phase III studies [CQGE031C2302] / [CQGE031C2303] are ongoing to further evaluate the efficacy and safety of ligelizumab in adults and adolescent CSU subject's refractory to antihistamines at ligelizumab doses 72 mg or 120 mg for 1 year, respectively. As the number of Japanese CSU patients exposed to ligelizumab of the intended dose or higher for registration is expected to be limited, the study, CQGE031C1301, is designed to obtain additional safety data of ligelizumab of 120 mg for one year in Japanese CSU patients to support the registration of ligelizumab in Japan.

An open-label design without comparator arm is considered adequate to evaluate long term safety for CSU in Japanese and accepted by Japanese Health Authority.

The target population for this study consists of CSU subjects who remain symptomatic despite treatment with H1-AHs at locally approved doses.

[redacted]

Subjects treated with omalizumab previously as well as subjects with chronic spontaneous urticaria as their predominant disease who also suffer from chronic inducible urticaria will be allowed to enroll into this study to collect the safety data in Japanese CSU patients.

After the completion of the treatment period, subjects will enter a post-treatment follow-up period to allow for further characterization of [redacted], collection of additional efficacy and safety data (eg, relapse), and evaluation of the presence of anti-drug antibodies (ADAs).

4.1.1 Rationale for choice of background therapy

All subjects will receive standard of care therapy (H1-antihistamines at (local) approved doses) as background medication. Subjects must remain on a stable treatment regimen (type and dose of H1-AH) throughout the study. If a subject must switch to another background H1-antihistamines (at approved dose) as a result of an AE, the subject will be considered to have remained on stable treatment.

4.2 Rationale for dose/regimen and duration of treatment

Rationale for dose/regimen

One ligelizumab dose of 120 mg will be tested in this Phase III study. On-going global Phase III studies [CQGE031C2302] / [CQGE031C2303] are evaluating two doses of ligelizumab, 72 mg and 120 mg in CSU patients including Japanese.

[redacted]

Rationale for route of administration

[redacted]

Ligelizumab was administered subcutaneously in the CQGE031C2201 study and is also administered subcutaneously in the on-going Phase III studies CQGE031C2302 and CQGE031C2303. The subcutaneous route of administration will continue to be used, due to the favorable bioavailability demonstrated with ligelizumab in previous studies and because of its ease of administration.

[redacted]

4.3 Rationale for choice of control drugs (comparator/placebo) or combination drugs

Not applicable.

4.4 Purpose and timing of interim analyses/design adaptations

No formal interim analysis is planned for this study.

4.5 Risks and benefits

In the overall ligelizumab clinical program, approximately 900 subjects have been exposed across 12 studies, covering the indications of CSU, asthma, atopic dermatitis, and bullous pemphigoid (BP). The longest individual continuous exposure to ligelizumab is 12 months ([CQGE031C2201E1] and [CQGE031B2201E1]). Cumulative (continuous and interrupted) human duration of exposure to ligelizumab is approximately 16 and 17 months (across the [CQGE031B2201]/CQGE031B2201E1 asthma studies and the [CQGE031C2201]/CQGE031C2201E1 CSU studies, respectively). The following doses have been tested in the clinical programs: 12 mg, 24 mg, 36 mg, 72 mg, 180 mg and 240 mg sc q4w, 280 mg q2w and 120 mg sc single dose. To date in the CSU program alone, 254 subjects have been exposed to ligelizumab at doses up to 240 mg sc q4w.

Overall, no apparent dose-dependent safety signals (except for a trend in injection site reactions, which can be easily managed clinically) have been observed to date, although the number of subjects studied is relatively small, in line with the development phase of the CSU program. In the clinical study CQGE031B2201 in the patients with asthma, there appeared to be a dose dependency of injection site reactions between ligelizumab high dose group (28.6% of 199 subjects) and ligelizumab low dose group (12.5% of 40 subjects), which was comparable to omalizumab (14.5% of 131 subjects). The incidence of injection site reactions was higher among all the active treatment groups compared to that of placebo (5.2% of 96 subjects). Similarly, in the CSU dose-finding study (CQGE031C2201), the overall safety profile was comparable between different doses of ligelizumab (24 mg, 72 mg and 240 mg q4w or 120 mg

[redacted]

single dose), omalizumab and placebo. In both studies (CQGE031B2201 and CQGE031C2201), the patients on the higher doses of 180 mg and 240 mg had 2 injections with active in contrast to the patients on lower doses of 12 mg, 36 mg, 72 mg and 120 mg who received one active and one placebo injection. The exceptions were AEs related to injection site reactions, where a possible trend of dose dependency for ligelizumab was observed. All cases of injection site reactions (except 1 case of medical significance) regardless of treatment group or doses were non-serious, mild to moderate in severity, reversible, and did not lead to discontinuation of study treatment.

With regards to Serious Adverse Events (SAEs), the incidence of SAEs was comparable between subjects treated with ligelizumab and those receiving placebo in both asthma and CSU indications. There has been no dose dependency in SAEs observed among subjects treated with different doses of ligelizumab ([CQGE031B2201] in asthma and [CQGE031C2201] in CSU).

IgE is an antibody that may have an adaptive role in immunity to parasitosis, particularly helminthic infections. Thus, blocking the interaction of IgE and its receptors with ligelizumab may alter immunologic responsiveness to parasites. Bearing this in mind, monitoring for the occurrence of infection and response to therapy is recommended for subjects at high risk of geohelminth infection who receive ligelizumab. Insufficient data are available to determine the length of monitoring required for geohelminth infections after stopping ligelizumab. However, it is expected that ligelizumab will not interfere with a polyclonal reaction triggered by exposure to parasites. .

Therefore, based on the cumulative data available across all clinical studies in different patient populations for ligelizumab, the current evidence demonstrates that ligelizumab demonstrates a favourable benefit-risk profile and is well-tolerated and thus appropriate for further development.

The data from CQGE031C2201 demonstrates that ligelizumab administration results in significant improvement of CSU symptoms including itch, hives, angioedema and quality of life (QoL) irrespective of CU index status. Hence the potential benefit to the subject from participation in the current study is that treatment with ligelizumab could improve their CSU symptoms, leading to a better QoL.

The inclusion and exclusion criteria are selected to enroll subjects with CSU likely to benefit from participating in the study. The overall risk will be minimized by compliance with the inclusion/exclusion criteria, close clinical monitoring, the use of an electronic diary at home to monitor symptoms [redacted].

Investigators will be instructed on acceptable treatments for managing worsening of disease with rescue medication during the course of this study (see Section 6.2.3), thereby allowing subjects to continue in the study as long as possible. The investigator will provide the subject with written instructions to contact them if symptoms of CSU worsen.

Women of child bearing potential and sexually active males 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 acceptable contraception measures as outlined in the exclusion criteria (Section 5.2). If there is any question that the subject will not reliably comply, they should not be entered or continue in the study.

[redacted]

5 Population

The study population will consist of approximately 65 male and female subjects aged ≥ 18 years who have been diagnosed with CSU and who remain symptomatic despite the use of H1-AH.

It is anticipated that approximately 81 subjects will need to be screened (an estimated screening failure rate of 20%) in order to enroll approximately 65 subjects into the 52 week treatment period (see Figure 3-1).

5.1 Inclusion criteria

Subjects eligible for inclusion in this study must meet **all** of the following criteria:

Main study

1. Signed informed consent must be obtained prior to participation in the study.
2. Male and female subjects ≥18 years of age at the time of screening
3. CSU diagnosis for ≥ 6 months (defined as onset of CSU with supporting documentation).
4. Diagnosis of CSU refractory to H1-AH at locally approved doses at the time of baseline (Visit 110, Day1), as defined by all of the following:

   a. The presence of itch and hives for ≥ 6 consecutive weeks at any time prior to Visit 1 (Day -28 to Day -14) despite current use of non-sedating H1-AH (at locally approved doses) during this time period

   b. UAS7 score (range 0-42) ≥ 16 and HSS7 (range 0-21) ≥ 8 during the 7 days prior to baseline (Visit 110, Day 1)

   c. Subjects must be on H1-AH at only local label approved doses for treatment of CSU for starting at Visit 1 (Day -28 to Day -14)
5. Willing and able to complete a daily symptom eDiary for the duration of the study and adhere to the study visit schedules.
6. Subjects must not have had any missing eDiary entries in the 7 days prior to baseline (Day 1, Visit 110). i.e., 14 eDiary entries required. Re-screening may be considered only once.

[redacted]

5.2 Exclusion criteria

Main study

1. Use of other investigational biological drugs within 5 half-lives, or within 30 days (for small molecules) prior to Visit 1, or until the expected PD effect has returned to baseline (for biologics), whichever is longer.
2. History of hypersensitivity to any of the study treatments or excipients or to drugs of similar chemical classes (i.e. to murine, chimeric, or human antibodies).

[redacted]

3. Subjects having a clearly defined, predominant trigger of their chronic urticaria (chronic inducible urticaria) including:
   - urticaria factitia (symptomatic dermographism), cold-, heat-, solar-, pressure-, delayed pressure-, aquagenic-, cholinergic-, or contact-urticaria.
4. Diseases, other than chronic urticaria, with urticarial or angioedema symptoms such as urticarial vasculitis, erythema multiforme, cutaneous mastocytosis (urticaria pigmentosa), and hereditary or acquired angioedema (e.g., due to C1 inhibitor deficiency).
5. Subjects with evidence of helminthic parasitic infection as evidenced by stools being positive for a pathogenic organism according to local guidelines. All subjects will be screened at Visit 1(see Section 8.4.3). If stool testing is positive for pathogenic organism, the subject will not enter treatment period and will not be allowed to rescreen.
6. Any other skin disease associated with chronic itching that might influence in the investigator's opinion the study evaluations and results (e.g. atopic dermatitis, bullous pemphigoid, dermatitis herpetiformis, senile pruritus, etc.).
7. Prior exposure to ligelizumab.
8. Any H2 antihistamine use after Visit 1.
9. Any LTRA (montelukast or zafirlukast) after Visit 1.
10. Any H1 antihistamine used as background medication at greater than local label approved doses after Visit 1.
11. History or evidence of ongoing alcohol or drug abuse, within the last 6 months prior to baseline (Visit 110, Day 1).
12. Inability to comply with study and follow-up procedures.
13. Use of prohibited treatment detailed in protocol (Table 6-2).
14. Contraindications to or hypersensitivity to suggested rescue medications including but not limited to fexofenadine, loratadine cetirizine, rupatadine, epinephrine, levocetirizine, desloratadine or any of their ingredients.
15. Documented history of anaphylaxis.
16. History of malignancy of any organ system within the past 5 years (except for basal cell carcinoma, 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).
17. Presence of clinically significant cardiovascular (such as but not limited to myocardial infarction, unstable ischemic heart disease, New York Heart Association (NYHA) Class III/IV left ventricular failure, arrhythmia and uncontrolled hypertension within 12 months prior to Visit 1), 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 subjects, interfere with evaluation or interpretation of the study results, or preclude completion of the study.
18. 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.

[redacted]

19. History of, or current treatment for, hepatic disease including but not limited to acute or chronic hepatitis, cirrhosis or hepatic failure or Aspartate aminotransferase (AST)/Alanine aminotransferase (ALT) levels of more than 1.5 x upper limit of normal (ULN) and International Normalized Ratio (INR) of more than 1.5 at Visit 1.(see Section 8.4.1)
20. History of renal disease or creatinine level above 1.5x ULN at Visit 1.
21. Platelets < 100,000/µL at Visit 1.
22. History of long QT syndrome or whose QT interval corrected by Fridericia's formula (QTcF) (Fridericia) measured at Visit 1 is prolonged (> 450 ms for males or > 460 ms for females) and confirmed by a central assessor (these subjects should not be re-screened).
23. Pregnant or nursing (lactating) women.
24. Women of child bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using basic (acceptable effective) methods of contraception for the duration of study (approx. 4 months, i.e. 5 half-lives, after last dose of ligelizumab). Acceptable contraception methods include:

    a. Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable effective methods of contraception

    b. Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment

    c. Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject

    d. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps)

    e. Use of oral (estrogen and progesterone), 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 or placement of an intrauterine device (IUD) or intrauterine system (IUS)

    In case of use of oral contraception women should be stable on the same pill for a minimum of 3 months before taking investigational drug.

    Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

[redacted]

[redacted]

6 Treatment

6.1 Study treatment

6.1.1 Investigational drugs

Table 6-1 Investigational drug

Investigational Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
Ligelizumab 120 mg per 1 mL	Liquid in vial	sc	Open label subject packs; vials	Sponsor local

6.1.2 Additional study treatments

No other additional treatment beyond investigational treatment is requested for this trial. Subjects will continue to use their background medication H1-antihistamines at (locally approved doses) with a stable regimen during the study. For rescue medication, see Section 6.2.3.

6.1.3 Treatment arms/group

All eligible subjects will be assigned at Visit 110 to ligelizumab group. Each subject will receive 1 injection of 1.0 mL ligelizumab every 4 weeks.

During the treatment period, study drug will be administered for 13 visits as per Table 8-1.

6.1.4 Treatment duration

The planned duration of treatment is 52 weeks. Subjects may be discontinued from treatment earlier due to safety concerns or disease progression and/or at the discretion of the investigator or the subject. For subjects who in the opinion of the investigator are still deriving clinical benefit from QGE031, every effort will be made to continue provision of study treatment.

[redacted]

6.2 Other treatment(s)

6.2.1 Concomitant therapy

This study requires concurrent use of one second generation H1-AH at locally approved doses as background medication. Subjects must remain on a stable treatment regimen (type and dose of H1-AH) throughout the study.

If a subject must switch to another background H1-AH (at approved dose) as a result of an AE, the subject will be considered to have remained on stable treatment.

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

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 entering a subject into treatment period or allowing a new medication to be started.

6.2.2 Prohibited medication

Use of the class of treatments displayed in Table 6-2 is NOT allowed after start of screening. The minimum required period without prohibited treatment before Visit 1 is also listed in Table 6-2. Each concomitant medication 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 medical monitor or delegate before entering a subject to treatment period or allowing a new medication to be started.

Table 6-2 Prohibited medication

Medication	Minimum required period without medications
Omalizumab	4 months prior to Visit 1
Ligelizumab	No prior use allowed
Routine (more than 3 doses over a 5 day period) oral corticosteroids*	30 days prior to Visit 1
IV/IM/IA corticosteroids	30 days prior to Visit 1
Beta-blocker therapy	7 days prior to Visit 1
Leukotriene antagonists	Stop at Visit 1
H2-antihistamines	Stop at Visit 1
First generation H1-antihistamines	Stop at Visit 1
Hydroxychloroquine or chloroquine	30 days prior to Visit 1
Other immunosuppressive medication with or without known effect on CSU including but not limited to Methotrexate, cyclosporine A, cyclophosphamide, tacrolimus and mycophenolate mofetil	30 days prior to Visit 1
Intravenous immunoglobulin G	30 days prior to Visit 1

[redacted]

Medication	Minimum required period without medications
Plasmapheresis	30 days prior to Visit 1
Regular (daily or every other day) doxepin (oral)	14 days prior to Visit 1
Vaccination with inactivated viruses	48 hours prior to each dosing visit (i.e. Visit 110 to Visit 230)
Live attenuated vaccine	30 days prior to Visit 1
[redacted]	[redacted]

* Allowed only as rescue therapy only after Week12, on an as-needed basis for unbearable symptoms as per Section 6.2.3. Other preparations of CS with limited systemic exposure for non-CSU indications can be used (e.g. Intra nasal or topical CS) as needed basis.

If the prohibited treatment was used during the study for any indication, the subject must discontinue use of the prohibited treatment if he/she wishes to continue in the study. If the subject received a live virus vaccination during the study, the subject must discontinue study treatment.

If a subject takes concomitant omalizumab (outside of study assigned tr[redacted] in the follow-up phase, the subject must discontinue from the study, in which case [redacted]ADA samples should not be collected at the End of Study (EoS) visit.

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

6.2.3 Rescue medication

In addition to being used as background medication (see Section 6.2.1), the non-sedating H1-AH fexofenadine, loratadine, cetirizine, rupatadine levocetirizine and desloratadine will also be allowed as rescue medication used on an as needed basis for subjects with flare-ups of unbearable symptoms of their disease during screening, treatment and post-treatment follow-up periods. The selection of a H1-AH rescue medication should be made only once for an individual subject. For each individual subject, the AH rescue medication used must differ from the AH used for background medication (see Section 6.2.1), in order to avoid AHs at non-approved doses. A switch of the H1-AH rescue medication for an individual subject is not permitted except due to an adverse event.

Prior to Week 12, any corticosteroid use for CSU is prohibited. After the Week 12, subjects will be permitted to use oral corticosteroids such as prednisone, or its equivalent, as rescue medication if needed. The selection of oral corticosteroid to be used as rescue medication after Week12, should be made only once for an individual subject. A switch of oral corticosteroids as rescue medication for an individual is not permitted except due to an adverse event. The CSU treatment guidelines suggest that systemic corticosteroids may be used for up to 10 consecutive days to manage flare-ups in clinical practice. However in this clinical study, corticosteroid use will be limited to 3 days in a 30 day period and a maximum of 9 doses in total (i.e. a maximum of 9 days of corticosteroids in total) after Week 12 to avoid any confounding suppression of signs and symptoms of CSU. If a subject uses more than 3 doses of corticosteroid in a 30 day period or more than 9 doses of corticosteroid in total during the study period (including the follow-up period), the subject will be discontinued from study treatment.

[redacted]

Rescue medication will be sourced locally. [redacted]

6.3 Subject numbering, treatment assignment, randomization

6.3.1 Subject numbering

Each subject is identified in the study by a Subject Number (Subject No.) that is assigned when the subject is first enrolled for screening and is retained as the primary identifier for the subject 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 subject is numbered uniquely across the entire database. Upon signing the informed consent form, the patient is assigned to the next sequential Subject No. available.

6.3.2 Treatment assignment, randomization

This is a single arm, non-randomized study.

Upon completion of all the required screening assessments, eligible subjects will start ligelizumab treatment at Visit 110.

6.4 Treatment blinding

Treatment will be open to subjects, investigator staff, persons performing the assessments.

6.5 Dose escalation and dose modification

Study drug dose adjustments are not permitted. Any interruption of study drug administration should be discussed with Novartis or delegate regarding the subject's eligibility to continue investigational treatment.

Any missed or altered study drug administration must be recorded on the appropriate eCRF in order to reconstruct an accurate dosing history for each subject.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

Subjects will receive 1 subcutaneous injection every 4 weeks at 13 visits during the treatment period. Compliance is assured as study drug must/ will be administered by investigator and/or study personnel via subcutaneous injection at the site. Administration of study drug must be recorded in the source documents and the corresponding eCRF for each administration.

6.6.2 Emergency breaking of assigned treatment code

Not applicable for this open-label study.

6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under Section 6.7.1.1. [redacted]

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels and in the Investigator's Brochure. 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 subject.

The investigator 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.

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

6.7.1.2 Handling of additional treatment

Not applicable.

6.7.2 Instruction for prescribing and taking study treatment

The injections can be administered in the deltoid region on the right and/or left arm, and/or in the right and/or left thigh, or the abdomen as preferred by subject and/or site. The injections are administered subcutaneously after aspiration of the plunger of the syringe. If blood appears at the needle hub or blood is drawn into the syringe upon aspiration, the needle must be withdrawn without administration of the dose and the injection site changed. Each injection must be administered at a different site (eg, right arm and left thigh).

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

Subjects will remain on-site for observation for a period of 2 h post-dose for the first 3 study drug administrations at Visits 110, 120 and 130, and 30 min post-dose for all other drug administrations. These observation periods follow the recommendation suggested by the National Heart, Lung, and Blood Institute and by the American Academy of Allergy, Asthma & Immunology and the American College of Allergy, Asthma and Immunology Executive Committees Joint Task Force (Cox et al 2007) for the anti-IgE therapy currently available (omalizumab). As described in the Investigator Brochure (IB), the site needs to ensure readiness to react to anaphylactic events (eg, have available injectable epinephrine, antihistamine, corticosteroids, intravenous supplies, oxygen, an oral airway, Ambu bag and the ability to transport a subject rapidly to an emergency department/hospital).

[redacted]

All study drug dosages prescribed and dispensed to the subject and all dosing errors or missed administrations during the study must be recorded on the appropriate eCRF.

The investigator must promote compliance by instructing the subject to ensure scheduled visits are made to the site in order to take the study treatment as prescribed and by stating that compliance is necessary for the subject's safety and the validity of the study.

7 Informed consent procedures

Eligible subjects may only be included in the study after providing (witnessed, where required by law or regulation), Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved informed consent.

If applicable, in cases where the subject's representative(s) gives consent (if allowed according to local requirements), the subject must be informed about the study to the extent possible given his/her understanding. If the subject is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

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 subject source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the International Council for Harmonisation of Technical Requirements for Registration for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB). This information will be included in the subject informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the subject.

Women 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 acceptable contraception requirements.

[redacted]

A copy of the approved version of all consent forms must be provided to Novartis after IRB/IEC approval.

[redacted]

8 Visit schedule and assessments

Table 8-1 lists all of the assessments. All data obtained from the assessments listed in Table 8-1 must be supported in the subject's source documentation. The table indicates which data are entered into the eCRF from the source data (X), remain in the source documents only (S) or are loaded into the database from separate source documents, i.e. outside vendors (XS).

Subjects must be seen for all visits on the designated day, or as close to it as possible. The subject should be instructed to contact the investigator if he/she is unable for any reason to attend the visit as planned and the visit should be rescheduled as close as possible to the original date. Missed or rescheduled visits should not lead to automatic treatment or study discontinuation.

All subjects who complete the treatment period will be expected to attend all follow-up visits (Visit 310 to 1999).

Subjects who discontinue treatment early will be expected to perform the Week 52 assessment (last visit in the treatment period) 4 weeks after they receive their last dose. At the final visit, all dispensed investigational product should be reconciled and the adverse event and concomitant medications reconciled on the eCRF.

[redacted]

Table 8-1 Assessment Schedule

Period	Screening	Treatment														Follow-up			Unplanned
Visit Name	**1**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**	**190**	**200**	**210**	**220**	**230**	**240/EoT/TD[1]**	**310**	**320**	**1999/EoS/PSD[2]**	**UPV[3]**
Days	**-28 to -14**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**393**	**421**	**449**	**-**
Weeks	**-4 to -2**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**-**
Informed consent	X[4]																		
[redacted]																			
Inclusion / Exclusion criteria	X	X																	
Demography	X																		
Relevant medical history (including CSU history)	X																		
Evidence of urticaria	X																		
Prior urticaria treatment	X																		
Family malignancy history (CRF to be completed if subject develops malignancy during the study)	X																		
Prior and Concomitant medication usage	X	X	X	X	X	X	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	X	X	X	X	X	X
Re-screening (re-screening eCRF should be recorded if the subject is re-screened)	X																		
[redacted]																			
Dispense H1-AH rescue medication	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S		
Dispense oral corticosteroid rescue medication[14]					S	S	S	S	S	S	S	S	S	S	S	S	S		
Study drug administration		X	X	X	X	X	X	X	X	X	X	X	X	X					

[redacted]

Period	Screening	Treatment														Follow-up			Unplanned
Visit Name	**1**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**	**190**	**200**	**210**	**220**	**230**	**240/EoT/TD[1]**	**310**	**320**	**1999/EoS/PSD[2]**	**UPV[3]**
Days	**-28 to -14**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**393**	**421**	**449**	**-**
Weeks	**-4 to -2**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**-**
ePROs should be completed prior to any other assessment and prior to administration of any medication[7]																			
Dispense Subjects' eDiary	S																		
Collect Subjects' eDiary																		S	
Subjects' eDiary (review compliance) Includes the urticaria patient daily diary (UPDD) [redacted]		XS	XS	XS	XS	XS	XS	XS	XS	XS	XS	XS	XS	XS	XS	XS	XS	XS	
DLQI (Dermatology Life Quality Index)		XS	XS	XS	XS			XS							XS	XS	XS	XS	
[redacted]																			
Laboratory evaluations																			
Stool ova and parasite evaluation[8]	X																	X	X
Hematology (*INR at Visit1, Visit 110 and UPV)	XS*	XS*	XS	XS	XS	XS	XS	XS	XS	XS	XS	XS	XS	XS	XS	XS	XS	XS	XS*
Clinical chemistry (**hCG at Visit 1 only)[9]	XS**	XS	XS	XS	XS	XS	XS	XS	XS	XS	XS	XS	XS	XS	XS	XS	XS	XS	XS
[redacted]																			
Anti-Drug(ligelizumab) antibodies (ADA)		X																X	X
[redacted]																			

[redacted]

Period	Screening	Treatment														Follow-up			Unplanned
Visit Name	1	110	120	130	140	150	160	170	180	190	200	210	220	230	240/EoT/TD[1]	310	320	1999/EoS/PSD[2]	UPV[3]
Days	-28 to -14	1	29	57	85	113	141	169	197	225	253	281	309	337	365	393	421	449	-
Weeks	-4 to -2	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	-
Urine dipstick (local) (When a dipstick evaluation is abnormal, eg positive for WBC and/or blood, a urine sample must be sent for microscopic examination to the central lab)	X							X							X			X	X
Serum β-hCG (for all pre-menopausal women who are not surgically sterile) Section 8.4.4	XS																		
Urine Pregnancy Test (local) (If positive, confirmation by serum β-hCG test should be done by central lab)		S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
Safety																			
Physical Examination[11]	S	S	S	S	S	S	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	X	X	X	X	X	X
Body Height	X																		
Body Weight	X							X							X			X	
Electrocardiogram (ECG)[12]	XS														XS				XS
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Liver safety monitoring	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
Renal safety monitoring	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
Others																			

Period	Screening	Treatment														Follow-up			Unplanned
Visit Name	1	110	120	130	140	150	160	170	180	190	200	210	220	230	240/EoT/TD[1]	310	320	1999/EoS/PSD[2]	UPV[3]
Days	-28 to -14	1	29	57	85	113	141	169	197	225	253	281	309	337	365	393	421	449	-
Weeks	-4 to -2	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	-
[redacted]																			
Treatment completion/ discontinuation form		X																	
Study completion/ discontinuation form		X																	

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[S] Assessment to be recorded in the source documentation only
[1] EoT = End of Treatment, TD = Study Treatment Discontinuation
[2] EoS = End of study, PSD = Premature Subject Discontinuation
[3] UPV = Unplanned visit (NOTE – assessments as listed should be done only at the discretion of the investigator, according to the reason for the unplanned visit)
[4] IC obtained prior to all study-specific screening procedures during or as close to the start of the screening period as possible
[redacted]
[6] XS=assessment data to be received in loaded format from separate source documents i.e. external vendors
[7] ePRO = Electronic Patient Reported Outcomes
[8] If diarrhea, or any other symptoms suggestive of parasitic infection, develops at any time between visits before end of study, additional stool sampling for assessment of parasitic conditions should be done as soon as possible. At Visit 1 and Visit 320, dispense 3 stool collection kits. Patients should collect samples, within seven days of Visit1 and in the week prior to Visit 1999/EOS/PSD.
[9] hCG = human Chorionic Gonadotropin
[10] Samples to be taken pre-dose. [redacted] ADA samples should not be collected at the End of Study (EoS) visit, if the subject takes omalizumab (outside of the study assigned treatment).
[11] Physical exam on Screening Visit 1 is comprehensive but subsequent physical exams maybe limited
[12] Single ECG to be taken at Visits 1 and 240/EoT/TD
[redacted]
[14] A subject must not have access to more than 3 doses of corticosteroids in a 30 day period or more than 9 doses of corticosteroid in total during the study period(including the follow-up period)..

[redacted]

8.1 Screening

Subjects will have up to 4 week screening period to establish eligibility for the study. Subjects will be required to attend 1 visit during screening period: Visit 1 (Day -28 to Day -14). An extended screening period will be permitted only in exceptional circumstances when information concerning eligibility is outstanding (eg, pending laboratory data).

Rescreening may be allowed for subjects who failed initial screening as described in Section 3.

8.1.1 Information to be collected on screening failures

Subjects who sign an informed consent form and subsequently found to be ineligible will be considered a screen failure. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure subjects. No other data will be entered into the clinical database for subjects who are screen failures, unless the subject experienced a serious adverse event during the screening phase (see Section 10.1.3 for reporting details). Adverse events that are not SAEs will be followed by the investigator and collected only in the source data.

Subjects who sign an informed consent and are considered eligible but fail to be started on treatment for any reason will be considered a prematurely withdrawn subject. The reason for prematurely withdrawn should be captured on the appropriate disposition eCRF.

8.2 Subject demographics/other baseline characteristics

Subject demographic and baseline characteristic data to be collected on all subjects include age, sex, race and ethnicity. Relevant medical history (including CSU history)/current medical condition present before signing the informed consent will be captured. Where possible, diagnoses, and not symptoms, will be recorded. Data on subjects' family history of malignancies will be collected on the respective eCRF page, only when a subject has a malignancy event, to assess possible risk factors related to any malignancies. [redacted]

8.3 Efficacy

All subjects will be provided with an electronic device (eDiary) that contains the following assessments: Urticaria Patient Daily Diary (UPDD), [redacted] Dermatology Life Quality Index (DLQI), [redacted] will be assessed at sites at the visits described in Table 8-1.

Site and subjects will receive appropriate training and guidance on the use of the eDiary and will receive clear instructions on the completion of the assessments.

Assessments will be completed once or twice daily or monthly depending on the questions.

Site must allow subjects to complete the eDiary questionnaires on their own without any assistance from the site staff.

The eDiary assessment should be completed prior to any other assessment (except at Visit 1) and prior to administration of any investigational medication.

[redacted]

8.3.1 Electronic Diary (eDiary) assessments

8.3.1.1 Urticaria Patient Daily Diary (UPDD)

UPDD includes Urticaria Activity Score (UAS) which assesses twice daily the severity of itch and number of hives, [redacted] ection 16.4 Appendix 4, Patient Diary: Urticaria Patient Daily Diary (UPDD)). The components are presented in the Table 8-2 and the relevant weekly scores are described below.

Table 8-2 Urticaria Patient Daily Diary (UPDD)

Diary component	When assessed
Urticaria Activity Score (UAS) • Itch severity • Number of hives	Morning and evening
Sleep interference	Morning
Daily activity interference	Evening
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

8.3.1.1.1 Weekly Hives Severity Score (HSS7)

The hives severity score, defined by number of hives (wheals), will be recorded by the subject twice daily in their eDiary, on a scale of 0 (none) to 3 (see Table 8-3). A weekly score (HSS7) is derived by adding up the average daily scores of the seven preceding days. The possible range of the weekly score is therefore 0 – 21.

Complete hives response is defined as HSS7 = 0.

Table 8-3 Hives Severity Score

Score	Hives (Wheals) (every 12 hours)
0	None
1	1-6 hives/12 hours
2	7-12/12 hours
3	> 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 1 or more of the daily scores are missing, the following principles will be applied to handle the missing data:

The weekly Hives Severity Score (HSS) score will be derived based on the sum of the available eDiary score during that week. It will be considered calculable with at least 4 daily scores provided in that week, otherwise, the weekly score will be left missing.

[redacted]

Note that for the screening assessments, 14 of 14 consecutive eDiary entries are required in the 7 days prior to baseline as per inclusion criteria.

8.3.1.1.2 Weekly Itch Severity Score (ISS7)

The severity of the itch will be recorded by the subject twice daily in their eDiary, on a scale of 0 (none) to 3 (intense/severe) (see Table 8-4). A weekly score (ISS7) is derived by adding up the average daily scores of the seven preceding days. The possible range of the weekly score is therefore 0-21 (maximum itch). Partially missing diary entries will be handled in the same way as described for the weekly HSS.

Complete itch response is defined as ISS7 = 0.

Table 8-4 Itch Severity Score

Score	Pruritus (Itch) (every 12 hours)
0	None
1	Mild (minimal awareness, easily tolerated)
2	Moderate (definite awareness, bothersome but tolerable)
3	Severe (difficult to tolerate)

8.3.1.1.3 Weekly Urticaria Activity Score (UAS7)

The UAS7 is the sum of the HSS7 score and the ISS7 score. The possible range of the weekly UAS7 score is 0 – 42 (highest activity).

Complete UAS7 response is defined as UAS7 = 0.

[redacted]

[redacted]

[redacted]

[redacted]

8.3.2 Other PRO assessments

8.3.2.1 Dermatology Life Quality Index (DLQI)

The Dermatology Life Quality Index (DLQI) is a 10-item (grouped in 6 domains) dermatology-specific quality of life (QoL) measure (Finlay and Khan 1994). The DLQI was validated for patients aged 16 and above.

In this study, subjects rate their dermatology symptoms as well as the impact of their skin condition on various aspects of their lives thinking about the previous 7 days.

An overall score is calculated and ranges from 0 to 30 (higher score meaning worse dermatology QoL). For DLQI, the domain scores are calculated for: Symptoms and Feelings (0-6), Daily Activities (0-6), Leisure (0-6), Work and School (0-3), Personal Relationships (0-6) and Treatment (0-3).

The scores were split into score bands (Hongbo et al 2005) and validated in terms of their meaning/relevance to patients as follows:

Table 8-8 DLQI score bands and impact on patient's life

DLQI band	Significance of score
0-1	No effect on patients life
2-5	Small effect on patients life
6-10	Moderate effect on patients life
11-20	Very large effect on patients life
21-30	Extremely large effect on patients life

A DLQI score of > 10 is relevant for a very large impact on patients' life and usually considered as a justification for a biologic prescription for example in psoriasis (Finlay 2005). The DLQI questionnaires are administered at baseline (Visit 110, Day 1) and at Weeks 4, 8, 12, 24, 52 and every visit in the follow-up period.

[redacted]

[redacted]

8.3.3 Other assessments: Evidence of urticaria

The investigator must confirm the presence of urticaria in each subject at Screening visit (Visit 1) by direct physical examination. In the absence of active disease being visible at Visit 1, the following will be acceptable: (a) a clearly identifiable photograph of the subject showing the presence of urticaria, or (b) the investigator must have seen the subject with active CSU in the past 6 months.

8.3.4 Appropriateness of efficacy assessments

At the time the omalizumab studies were carried out, the treatment paradigm focused primarily on itch (ISS7) as a key symptom of CSU. Over the past several years the goal of therapy has evolved and the current target of therapy as described in the current CSU treatment guidelines (Zuberbier et al 2018) is to treat the disease until it is gone, i.e. complete control of the disease (UAS7 = 0). Given the current emphasis on UAS7 in the medical community and as reflected in the CSU treatment guidelines, data from the Phase II study CQGE031C2201 support the change from baseline in UAS7 (which is a composite of ISS7 and HSS7) as well as the achievement of UAS7 = 0 over time which will be assessed as secondary endpoints included in the testing strategy.

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

Data collected during this study will be used to provide information that will support selection of doses for further evaluation and patient reported outcome (PRO) tools and potential biomarkers which may be included in future studies.

[redacted]

8.4 Safety

Main safety and tolerability assessments include:

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

Table 8-9 Assessments & Specifications

Assessment	Specification
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, and extremities and vascular and neurological systems. 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. A short physical exam will be conducted at all visits starting from Visit 1 except where a complete physical examination is required (see Table 8-1). Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate eCRF that captures medical history. Significant findings made after signing the informed consent which meet the definition of an Adverse Event must be recorded as an Adverse Event.
Vital signs	Vital signs include blood pressure and pulse measurements. After the subject has been sitting for 5 minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured 3 times using an automated validated device with an appropriately sized cuff. The repeat sitting measurements will be made at 1 – 2 minute intervals and the mean of the 3 measurements will be used. In case the cuff sizes available are not large enough for the subject's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used. Clinically notable vital signs are defined in Section 16.1 Appendix 1.
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 as specified in Table 8-1.

8.4.1 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.

[redacted]

Clinically notable laboratory findings are defined in Section 16.1 Appendix 1. In case of lab abnormalities, an additional re-draw for central laboratory assessment is allowed during the screening period to confirm eligibility criteria.

Clinically significant abnormalities must be recorded on the relevant section of the Case report/Record Forms (CRFs) capturing medical history/Current medical conditions/AEs.

A sample for serum β-hCG assessment will be collected at screening Visit 1 for all pre-menopausal women who are not surgically sterile.

Table 8-10 Laboratory Assessments

Test Category	Test Name
Hematology	Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential and platelet count will be measured.
Coagulation	At Visits 1 and 110 coagulation will be assessed by International Normalized Ratio (INR).
Chemistry	Albumin, total bilirubin, alkaline phosphatase, AST, ALT, LDH, GGT, chloride, sodium, potassium, magnesium, calcium, inorganic phosphorus, creatinine, urea/BUN and uric acid 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. Serum hCG is assessed at Visit 1 only.
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. Semi-quantitative “dipstick” evaluation for specific gravity, glucose, protein, bilirubin, ketones, leukocytes, blood and pH will be performed at site. When a dipstick evaluation is abnormal, eg, positive for WBC and/or blood, a urine sample must 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.)
Parasite screening	Assessment of stool samples for parasitic infections (refer to Assessment of parasitic infections Section 8.4.3)
Pregnancy Test	Serum / Urine pregnancy test (refer to Pregnancy and assessments of fertility Section 8.4.4). If urine preganancy test is positive, confirmation by serum β-hCG test should be done by central lab.

WBC: white blood cell(s); RBC: red blood cell(s); LDH: lactate dehydrogenase; GGT: gamma-glutamyl transferase

8.4.2 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.

Single ECGs will be collected at Visits 1 and Visit 240/End of treatment (EoT)/Sudy Treatment Discontinuation (TD).

The original ECG will be sent electronically to the Clinical Research Organization (CRO) directly from the provided ECG machine. Two “identical” duplicate print-outs will be generated

[redacted]

on non-heat sensitive paper 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 must be labeled with study number, subject initials, subject number, date and time, and signed and archived in the study site source documents.

Clinically significant ECG findings prior to dosing with investigational treatment must be discussed with the sponsor. Clinically significant abnormalities must be recorded on the relevant section of the CRFs capturing Medical history/Current medical conditions/AE as appropriate.

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

For any ECGs with subject safety concerns, 2 additional ECGs must be performed to confirm the safety finding.

8.4.3 Assessment of parasitic infections

[redacted].

All subjects will be given three stool sample collection kits at screening Visit 1 and Visit320 by the site or site's local laboratory. Subjects will take the stool sample kits home and collect stool samples, from three different bowel movements, ideally on three different days, within seven days of Visit 1 and in the week prior to Visit 1999. Subjects will return the three stool samples to the site as soon as possible after Visit 1 (in order to allow processing within the screening period) and at Visit 1999.

Stool samples for parasitic disease will be examined for ova and parasites by the local laboratory. The identification of organisms in positive stools will be made by local laboratory. If stool testing is positive for pathogenic organisms (pathogenic as defined by the local laboratory), the result must be recorded in the eCRF and the subject will not enter treatment period and will not be allowed to rescreen. Stool samples negative for pathogenic organisms must be recorded in the eCRF before Visit 110.

Subjects must be advised that if diarrhea, or any other symptoms suggestive of parasitic infection, develops at any time before the end of study, three additional stool samples must be collected at next visit or sooner and sent to local laboratory for analysis.

8.4.4 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have sample for serum β-hCG test collected at screening Visit 1. Post-menopausal status should be recorded in the CRF.

At Visit 110 and subsequent study visits until Visit 1999/EOS/PSD, all pre-menopausal women who are not surgically sterile will have urine pregnancy testing performed BEFORE administration of the study medication. A positive urine test needs to be confirmed with a central lab serum test prior to study drug administration. If positive, the subject must be discontinued from study treatment.

[redacted]

Additional pregnancy testing might be performed if requested by local regulatory/ethics committee requirements.

Assessments of fertility

Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents. Subsequent hormone level assessment to confirm the woman is not of child bearing potential must also be available as source documentation in the following cases:

1. Surgical bilateral oophorectomy without a hysterectomy
2. Reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

In the absence of the above medical documentation, Follicle Stimulating Hormone (FSH) testing is required at screening/baseline.

8.4.5 Anaphylaxis assessment

An adjudication committee (AC) will be put in place to determine whether cases of hypersensitivity identified through a search algorithm based on the Standardized Medical dictionary for regulatory activities (MedDRA) Queries may represent cases of anaphylaxis. Further details regarding the AC will be documented in the AC charter. See Section 10.2.3 for details.

8.4.6 Assessment of cardio-cerebrovascular 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 10.2.3 for details.

8.4.7 Assessment of neoplastic events

An AC will be put in place to review all cases identified through a search algorithm based on the Standardized MedDRA Queries of neoplastic events. The clinical presentation and association of these events with pre-existing risk factors will be part of the assessment. See Section 10.2.3 for details.

8.4.8 Appropriateness of safety measurements

In addition to safety assessments that are standard in this population, the potential of selected biomarkers will be evaluated for monitoring subjects' safety. Events of special interest such as anaphylaxis, malignancies, and cardio-cerebrovascular events will be monitored and will be adjudicated by expert ACs.

8.5 Additional assessments

[redacted]

[redacted]

[redacted]

8.5.3 Anti-ligelizumab antibody in serum

The presence of anti-ligelizumab antibodies will be assayed using a 3-tiered testing strategy consisting of a screening assay, a confirmatory assay and a titration of anti-ligelizumab responses by a titration assay for samples confirmed positive. A specific assay will be used to determine if ADAs are neutralizing in nature.

The detailed method to assess immunogenicity will be described in the bioanalytical raw data of the study and in the bioanalytical data report.

[redacted]

[redacted]

9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

Discontinuation of investigational treatment for a subject occurs when investigational treatment is stopped earlier than the protocol planned duration, and can be initiated by either the subject or the investigator.

The investigator must discontinue investigational treatment for a given subject if, he/she believes that continuation would negatively impact the subject's well-being.

Investigational treatment must be discontinued under the following circumstances :

- Subject decision
- Adverse events for which continued exposure to the study drug would be detrimental
- Abnormal renal laboratory results requiring discontinuation (see Section 16.3 Appendix 3)
- Abnormal liver laboratory results requiring discontinuation (see Section 16.2 Appendix 2)
- Platelets < 75,000/ μ L

[redacted]

- Pregnancy (See Section 8.4.4 and Section 10.1.4)
- Subject develops a medical condition that requires use of prohibited treatment as per Section 6.2.2, or if subject exhibits a behavior of non-compliance regarding prohibited medications
- Subject received a live virus vaccination during the study
- Subject experiences an unexpected hypersensitivity reaction of grade 5, as defined by the World Allergy Organization Grading System (Cox et al 2017), see Section 16.6 Appendix 6:
  - Lower or upper respiratory: Respiratory failure with or without loss of consciousness; or
  - Cardiovascular: Hypotension with or without loss of consciousness
- Emergency use of epinephrine due to anaphylactic or anaphylactoid reaction
- Any other protocol deviation that results in a significant risk to the subject's safety
- Any situation in which study participation might result in a safety risk to the subject
- If a subject uses rescue oral corticosteroids for CSU more than 3 doses in a 30 day period or more than 9 doses of in total after week 12 during the study period (including the follow-up period).

If discontinuation of investigational treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the subject's premature discontinuation of study treatment and record this information. Always consider reasons which are related to safety and efficacy first.

Subjects who discontinue investigational treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see Section 9.1.2, withdrawal of informed consent). They will be expected to perform the Wk 52/Visit 240/EoT/TD assessments 4 weeks after their last dose and will be expected to perform all follow-up assessments (Visits 310-1999). If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the subject/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

At the final visit, all dispensed investigational product should be reconciled and the adverse event and concomitant medications reconciled on the appropriate eCRF.

If subjects discontinue from investigational treatment and are administered Xolair® (omalizumab) in the follow-up period, the subject should be discontinued from the study and no efficacy or safety assessments should be collected from the subject at the EOS visit.

9.1.2 Withdrawal of informed consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent (WoC) occurs only when a subject:

- Does not want to participate in the study anymore

and

- Does not allow further collection of personal data

[redacted]

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject'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 subject 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 subject's study withdrawal should be made as detailed in the assessment table.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's sample until the time of withdrawal) according to applicable law.

All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

9.1.3 Lost 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 subject should not be considered as lost to follow-up until due diligence has been completed. Follow-up is recommended until the end of the study.

9.1.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination:

- Unexpected, significant, or unacceptable safety risk to subjects enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data
- Discontinuation of study drug development

In taking the decision to terminate, Novartis will always consider the subject's welfare and safety. Should early termination be necessary, subjects must be seen as soon as possible and treated as a prematurely withdrawn subject. 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 subject's interests. The investigator or sponsor, depending on the local regulation, will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Study completion is defined as when the last subject finishes their Study Completion visit, and any repeat assessments associated with this visit have been documented and followed-up

appropriately by the Investigator, or in the event of an early study termination decision, the date of that decision.

Patients will be eligible for post-trial access after completion of the study.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 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 in the appropriate CRF 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 10.1.2):

1. The Common Toxicity Criteria (CTC) AE grade (version 5 or higher);
2. its relationship to the study treatment and other investigational treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected'. The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single subject;
3. its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported;
4. whether it constitutes a SAE (see Section 10.1.2 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

[redacted]

- 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 or end of study visit, whichever is longer.

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 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 Section 16.1 Appendix 1.

For lab values provided without related clinical information, the Common Terminology Criteria for Adverse Events (CTCAE) scale must be used to determine the seriousness. Any value of Grade 4 and above on this CTCAE scale must be considered serious.

10.1.2 Serious adverse events

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

- fatal
- life-threatening

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

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect

[redacted]

- 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 ICH-E2D Guidelines).

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met and the malignant neoplasm is not a disease progression of the study indication.

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 or not.

10.1.3 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject 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. Any SAEs reported up to the subject's last visit will be reported in the eCRF. SAEs beyond that date will only be recorded in the Novartis Safety database.

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

[redacted]

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 the study treatment (if the 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 reoccurrence, compilation, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the investigational treatment, a Chief Medical Office and Patient Safety (CMO & PS) 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.

Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

Consider the following 3 categories (as applicable) to determine SAE reporting timeframes:

1. To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days after the last study visit must be reported to Novartis within 24 hours of learning of its occurrence.
2. Any SAEs experienced after the 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.
3. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

10.1.4 Pregnancy reporting

Pregnancies

To ensure subject 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.

[redacted]

Pregnancy should be recorded and reported by the investigator to the Novartis/ Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. The follow-up should be for up to 12 months following the birth of the baby. Any SAE experienced during pregnancy must be reported.

10.1.5 Reporting of study treatment errors including misuse/abuse

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

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 recorded on 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 within 24 hours of Investigator's awareness.

Table 10-1 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.

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

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

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

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

[redacted]

Please refer to Table 16-1 in Section 16.2 Appendix 2 for complete definitions of liver laboratory triggers and liver events.

Every liver event defined in Table 16-1 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 16-2. Repeat liver chemistry tests (i.e. ALT, AST, total bilirubin (TBL), prothrombin time (PT)/INR, ALP and GGT) to confirm elevation.

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

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

10.2.2 Renal safety monitoring

The following base monitoring for renal laboratory values, as per the Novartis Drug-Induce Nephrotoxicity Guidelines (July 2013; Table 10-2 below) of abnormal renal laboratory values, will be carried out as part of the assessment schedule (Table 8-1) during the course of the study:

Table 10-2 Base Renal Monitoring

Assessments	Assessment Frequency
Serum Creatinine, Electrolytes (Na, Ca, K) Urine Dipstick (Spot urine sample)	1. Single baseline 2. Steady State assessment 3. 6-monthly during study 4. Final visit ≥ 48 h after last dose

Every renal laboratory trigger or renal event as defined in Table 16-3 should be followed up by the investigator or designated personnel at the trial site as summarized in Table 16-4.

[redacted]

10.2.3 Adjudication committee

To enhance the safety assessment, more specifically relative to 1) anaphylactic events, 2) neoplastic events, and 3) major cardio-cerebrovascular events, 3 Adjudication Committees, independent panels of experts external to Novartis, will provide reviews of identified potential events in a blinded manner. Adjudication will be performed on a regular basis.

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

11 Data Collection and Database management

11.1 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. Designated investigator site staff will not be given access to the Electronic Data Capture (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 (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner.

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

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

11.2 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered into the CRFs 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 are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical (ATC) classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.
Laboratory samples except for stool samples and other locally processed laboratory samples will be processed centrally and the results will be sent electronically to Novartis. Stool samples will be processed by local labs and the results will be collected by Novartis via eCRFs.
ECG readings will be processed centrally and results will be sent electronically to Novartis. Patients will fill in their daily diary data on a device at home. PROs will be completed by patients on site on the day of applicable visits. The system will be supplied by a vendor(s) who will also manage the database. The database will be sent electronically to Novartis.

[redacted]

The occurrence of relevant protocol deviations will be determined. Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked 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.

11.3 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. 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 subject 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 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 subject 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 subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

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 subjects will be disclosed.

12 Data analysis and statistical methods

The analysis will be conducted on all subject 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.

12.1 Analysis sets

The following analysis sets will be used in this trial:

Safety Set includes all subjects who received at least one dose of study treatment. Subjects will be analyzed according to the study treatment received. Safety Set will be used for all safety analyses and also for efficacy analyses.

[redacted]

12.2 Subject demographics and other baseline characteristics

Demographic and other baseline data will be listed and summarized descriptively for the Safety set.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation (SD), median, minimum, and maximum will be presented.

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term. Summary for urticaria specific medical history will also be provided.

12.3 Treatments

The Safety set will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

The number of patients and the length of time in weeks exposed to ligelizumab will be summarized by means of descriptive statistics.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system. Prior medications for CSU will be summarized separately by pre-specified categories and preferred term.

12.4 Analysis of the primary endpoint(s)

The primary variable will be analyzed descriptively. No formal statistical analysis will be provided.

12.4.1 Definition of primary endpoint(s)

As the study objective is to assess the safety with no specific safety hypothesis, treatment emergent adverse events during the study will be considered as a primary variable. Treatment emergent adverse events are defined as adverse events which start after the first dose of study medication, or events present prior to the first dose of study medication but increased in severity based on preferred term. All adverse events onset in the follow-up period will also be considered as treatment emergent.

[redacted]

12.4.2 Statistical model, hypothesis, and method of analysis

The number of subjects who had a treatment-emergent adverse event will be summarized overall, by system organ class (SOC) and preferred term descriptively. No statistical model will be applied for the primary endpoints.

12.4.3 Handling of missing values/censoring/discontinuations

For the subject who discontinued treatment or study, no imputation or adjustment will be considered for counting the number of subjects who have a treatment emergent AE/SAE. All subjects will be treated equally when the data is summarized, regardless of the treatment duration and/or study duration of each subject.

12.4.4 Sensitivity and Supportive analyses

No sensitivity or supportive analyses are planned.

12.5 Analysis of secondary endpoints

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

All efficacy variables listed below will be analyzed in Safety Set. Summary tables will be presented by visit or week using descriptive statistics. Categorical variables will be presented as frequencies and percentages. For continuous variables, mean, standard deviation, median, minimum, and maximum will be presented. Mean differences of the change from baseline (UAS7, HSS7, ISS7 and DLQI) will be shown descriptively with 95% confidence interval based on one-sample t-test. Proportion of subjects (UAS7=0, HSS7=0, ISS7=0 and DLQI=0/1) will also be shown with 95% confidence interval based on Fisher's exact test. All analyses will be provided descriptively and no formal statistical testing will be applied.

- Absolute change from baseline of UAS7, ISS7 and HSS7
- Proportion of subjects with HSS7 = 0, ISS7 =0 and UAS7=0 response
- Absolute change from baseline of DLQI
- Proportion of subjects with DLQI = 0/1

12.5.2 Safety endpoints

For all safety analyses, the safety set will be used.

Adverse events

All information obtained on adverse events will be displayed by subject.

All treatment emergent adverse events which started after first drug dose and within 4 weeks after the last dose will also be summarized as adverse events in the treatment phase. In addition to what is described in the primary endpoints section, 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:

- Serious adverse events
- Adverse events by maximum severity

[redacted]

- Adverse events suspected by the investigator as study drug related
- Adverse events leading to permanent discontinuation of study drug

The number of subjects with adverse events of special interest will be listed.

A subject with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

Vital signs

All vital signs data will be listed by subject and visit with the abnormalities flag based on the notable criteria. The number of patients with notable abnormal vital signs will be summarized.

12-lead ECG

All ECG data will be listed by subject and visit with abnormalities flag based on the notable criteria. The number of patients with notable abnormal vital signs will be summarized.

Clinical laboratory evaluations

All laboratory data will be listed by subject and visit with abnormalities flag based on normal ranges. Shift tables using the low/normal/high classification will be used to compare baseline to the worst on-treatment value. For the parameters with clinically notable abnormal criteria, newly occurred or worsening abnormality will also be summarized.

Anti-ligelizumab antibody

All data of anti-ligelizumab antibodies will be listed. Number of patients who have positive anti-ligelizumab antibodies will be summarized by visit.

[redacted]

[redacted]

12.7 Interim analyses

Not Applicable.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

No formal statistical power calculations to determine sample size were performed for this study. The sample size is determined based on the regulatory requirement by Pharmaceuticals and Medical Devices Agency (PMDA) to fulfill the long term safety data for Japanese patients. Considering 10% drop out rate based in the QGE031C2201 study, the planned sample size (N=65) in this study will have 58 patients with 1 year exposure, and it is expected to have 100 Japanese patients exposed to ligelizumab with 1 year in the total ligelizumab CSU program, together with QGE031C2201/E1 and QGE031C2303 studies. With the total sample size (N=100) exposed to ligelizumab in Japanese patients, one can expect to see at least one patient with a specific AE with 95% probability, assuming the occurrence rate of an AE is 3%, aligned with ICH E1 guideline. Safety data from the study will also be evaluated together with Japanese patients from other ligelizumab studies in the submission dossier.

[redacted]

12.8.2 Secondary endpoint(s)

The expected half-width of 95% confidence interval for the change from baseline in UAS7 would be 3.3, assuming 58 patients (10% missing) are available of post-baseline UAS7 data and SD=13. If the mean change from baseline in UAS7 for ligelizumab group is -22.0 (based on C2201 study at Week 12), 95% confidence interval of the mean change from baseline in UAS7 will be (-25.3, -18.7).

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

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

13.2 Responsibilities of the investigator and IRB/IEC

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, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to 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.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (defined as last patient last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT etc.).

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard

[redacted]

Operating Procedures (SOPs) as well as applicable global/local GCP regulations and ICH Guidelines.

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

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

14 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 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 prohibition, 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.

14.1 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 required for subject safety 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 subject included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

[redacted]

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16 Appendices

16.1 Appendix 1: Clinically notable laboratory values and vital signs

Refer to Section 16.2 Appendix 2 for clinically notable laboratory values for hepatotoxicity.

Refer to Section 16.3 Appendix 3 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 has 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.

Notable values for adults are defined as follows: heart rate of < 60 and > 100 beats per minute (bpm); systolic blood pressure of < 90 and ≥ 140 mmHg; diastolic blood pressure of < 60 and ≥ 90 mmHg.

For ECGs a notable QTc value is defined as a QTcF (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. For adolescent subjects, the Central CRO will use age-and gender-specific reference values.

[redacted]

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

Table 16-1 Liver Event and Laboratory Trigger Definitions

	Definition/ threshold
LIVER LABORATORY TRIGGERS	• 3 x ULN < ALT / AST ≤ 5 × ULN • 1.5 x ULN < TBL ≤ 2 × ULN
LIVER EVENTS	• ALT or AST > 5 × ULN
	• ALP > 2 × ULN (in the absence of known bone pathology)
	• TBL > 2 × ULN (in the absence of known Gilbert syndrome)
	• ALT or AST > 3 × ULN and INR > 1.5

	• Potential Hy's Law cases defined as
	  ◦ subjects showing ALT or AST > 3 x ULN, combined with elevation of serum TBL to > 2 x ULN, without initial findings of cholestasis (no ALP elevation), and
	  ◦ Absence of any alternative cause likely explaining the combination of increased ALT or AST and TBL, such as viral hepatitis A, B, C, or E; preexisting or acute liver disease; or another drug capable of causing the observed injury

	• Any clinical event of jaundice (or equivalent term)
	• ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, right upper quadrant pain or tenderness, fever, nausea, vomiting, rash and/or eosinophilia(5%)
	• 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

Table 16-2 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 • Hospitalize, if clinically appropriate • Establish causality • Record the AE and contributing factors (eg, conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
ALT or AST		

[redacted]

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

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

[redacted]

Criteria	Actions required	Follow-up monitoring
[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, right upper quadrant pain or tenderness fever, nausea, vomiting, rash and/or eosinophilia(5%) [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; LFT: Liver function test * 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		

Based on investigator's discretion investigation(s) for contributing factors for the liver event can include: 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.

[redacted]

16.3 Appendix 3: Specific Renal Alert Criteria and Actions and Event Follow-up

Refer to Section 10.2.2

Table 16-3 Specific Renal Alert Criteria and Actions

Renal Event	
Confirmed serum creatinine increase 25% – 49%	Consider causes and possible interventions Follow up within 2-5 days
Serum creatinine increase ≥ 50% [+]	Consider causes and possible interventions Repeat assessment within 24-48 h if possible Consider drug interruption or discontinuation unless other causes are diagnosed and corrected Consider patient hospitalization and specialized treatment
New onset dipstick proteinuria ≥3+ or Protein-creatinine ratio (PCR)≥1 g/gCr (or mg/mmol equivalent as converted by the measuring laboratory)	Consider causes and possible interventions Assess serum albumin & serum protein Repeat assessment to confirm Consider study drug interruption or discontinuation unless other causes are diagnosed and corrected
New onset hematuria ≥ 3+ on urine Dipstick [+] Corresponds to KDIGO criteria for Acute Kidney Injury	Assess & document • Repeat assessment to confirm • Distinguish hemoglobinuria from hematuria • Urine sediment microscopy • Assess sCr • Exclude infection, trauma, bleeding from the distal urinary tract/bladder, menstruation • Consider bleeding disorder

Whenever a renal event is identified, a detailed patient history and examination are indicated to identify and potentially eliminate risk factors that may have initiated or contributed to the event:

- Blood pressure assessment (after 5-minute rest, with an appropriate cuff size)
- Signs and symptoms like fever, headache, shortness of breath, back or abdominal pain, dysuria or hematuria, dependent or periorbital edema
- Changes in blood pressure, body weight, fluid intake, voiding pattern, or urine output
- Concomitant events or procedures such as trauma, surgical procedures, cardiac or hepatic failure, contrast media or other known nephrotoxin administration, or other diseases or causes, e.g., dehydration due to delirium, tumor lysis

[redacted]

Table 16-4 Renal event follow-up

FOLLOW-UP OF RENAL EVENTS
Assess, document and record in CRF • Urine dipstick and sediment microscopy evidence of DIN: crystals, red blood cells (dysmorphic/glomerular vs. non-dysmorphic/non-glomerular), white blood cells, tubular epithelial cells • Blood pressure and body weight • Serum creatinine, BUN, electrolytes (sodium, potassium, phosphate, calcium), bicarbonate and uric acid • Urine output
Review and record possible contributing factors to the renal event (co-medications, other co-morbid conditions) and additional diagnostic procedures (MRI etc) in the CRF
Monitor patient regularly (frequency at investigator's discretion) until: • Event resolution: (sCr within 10% of baseline or protein-creatinine ratio <1 g/g Cr, or ACR <300 mg/g Cr) or • Event stabilization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months • Analysis of urine markers in samples collected over the course of the DIN event

sCR: serume creatinine

16.4 Appendix 4: PRO tools

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

Patient Diary: Urticaria Patient Daily Diary (UPDD)

General Instructions

Please answer each question to the best of your ability.

There are no right or wrong answers.

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

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

Instructions for Counting the Number of Hives

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

[redacted]

Today's Date 

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

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

Itch (severity)

0 = none

1 = mild

2 = moderate

3 = severe

Hives (number)

0 = none

1 = between 1 and 6 hives

2 = between 7 and 12 hives

3 = greater than 12 hives

Today's Date 

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

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

Itch (severity)

0 = none

1 = mild

2 = moderate

3 = severe

Hives (number)

0 = none

1 = between 1 and 6 hives

2 = between 7 and 12 hives

3 = greater than 12 hives

[redacted]

Today's Date 

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

(Please circle only one response.)

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

   0 = No interference

   1 = Mild, little interference with sleep

   2 = Moderate, awoke occasionally, some interference with sleep

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

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

   0 = No interference

   1 = Mild, little interference with daily activities

   2 = Moderate, some interference with daily activities

   3 = Substantial, severe interference with daily activities

[redacted]

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

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

   ☐

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

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

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

   1 = Yes

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

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

   1 = Took some prescription or non-prescription medication

   2 = Called my doctor, nurse or nurse practitioner

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

   4 = Went to the emergency room at the hospital

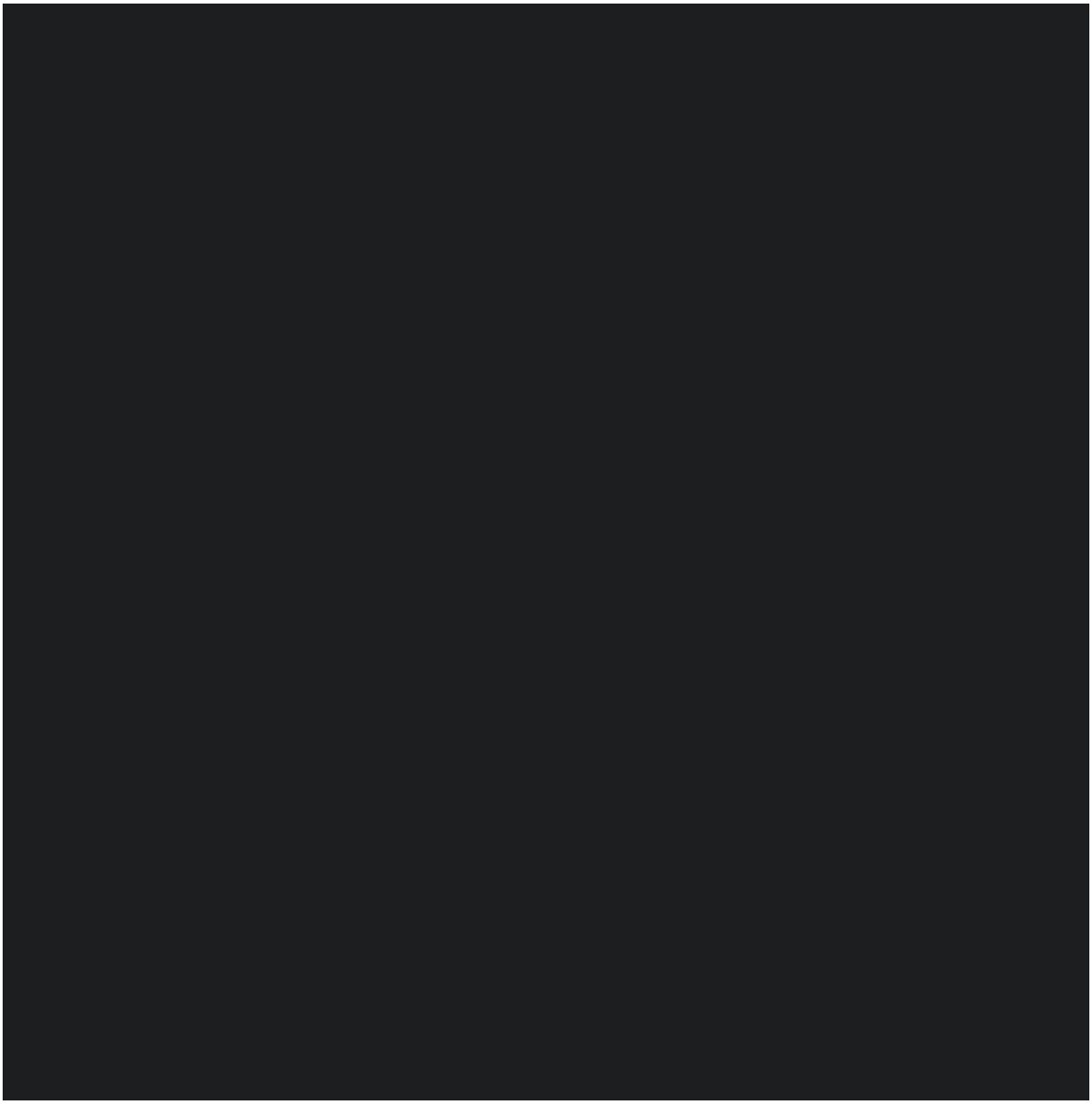
   5 = Was hospitalized

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

   0 = No

   1 = Yes

[redacted]



Dermatology Life Quality Indec (DLQI):

DERMATOLOGY LIFE QUALITY INDEX

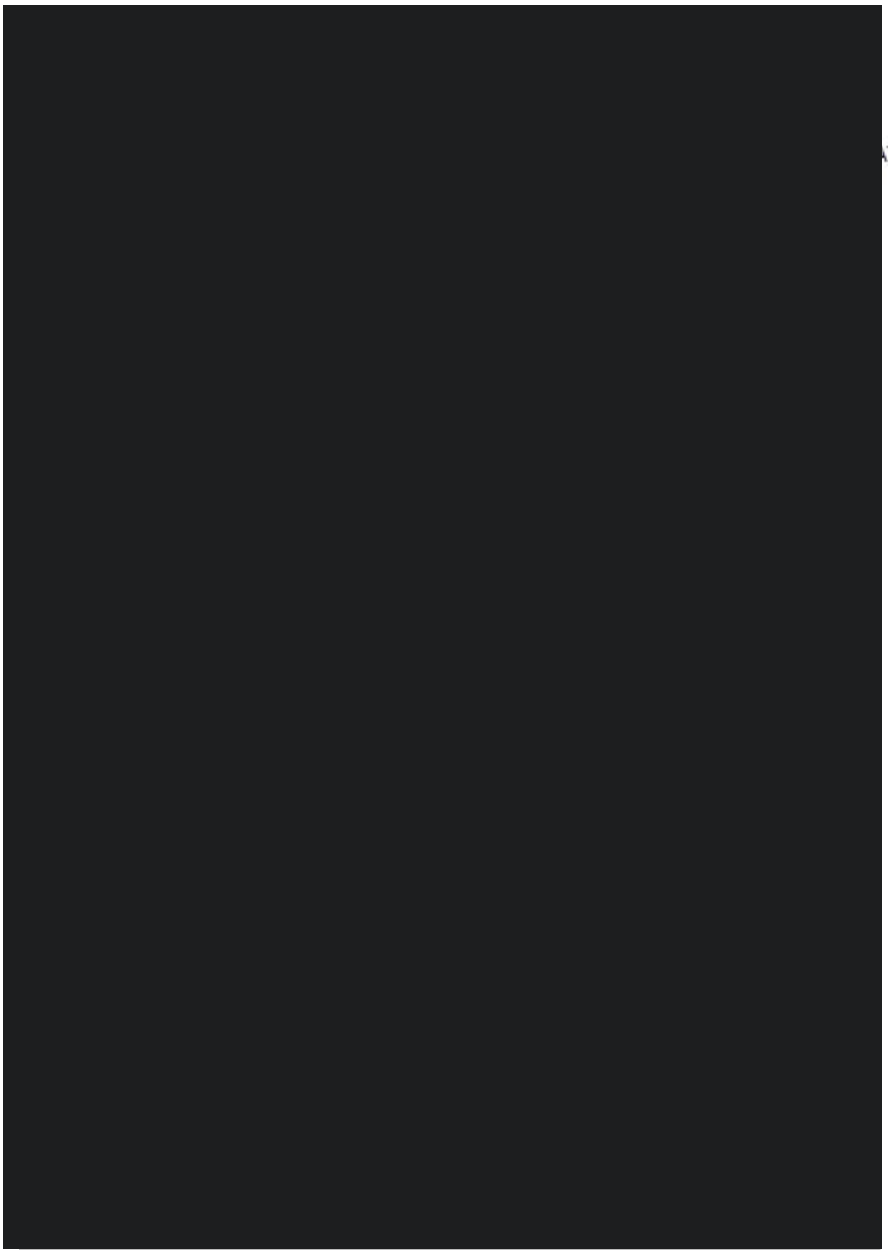
DLQI

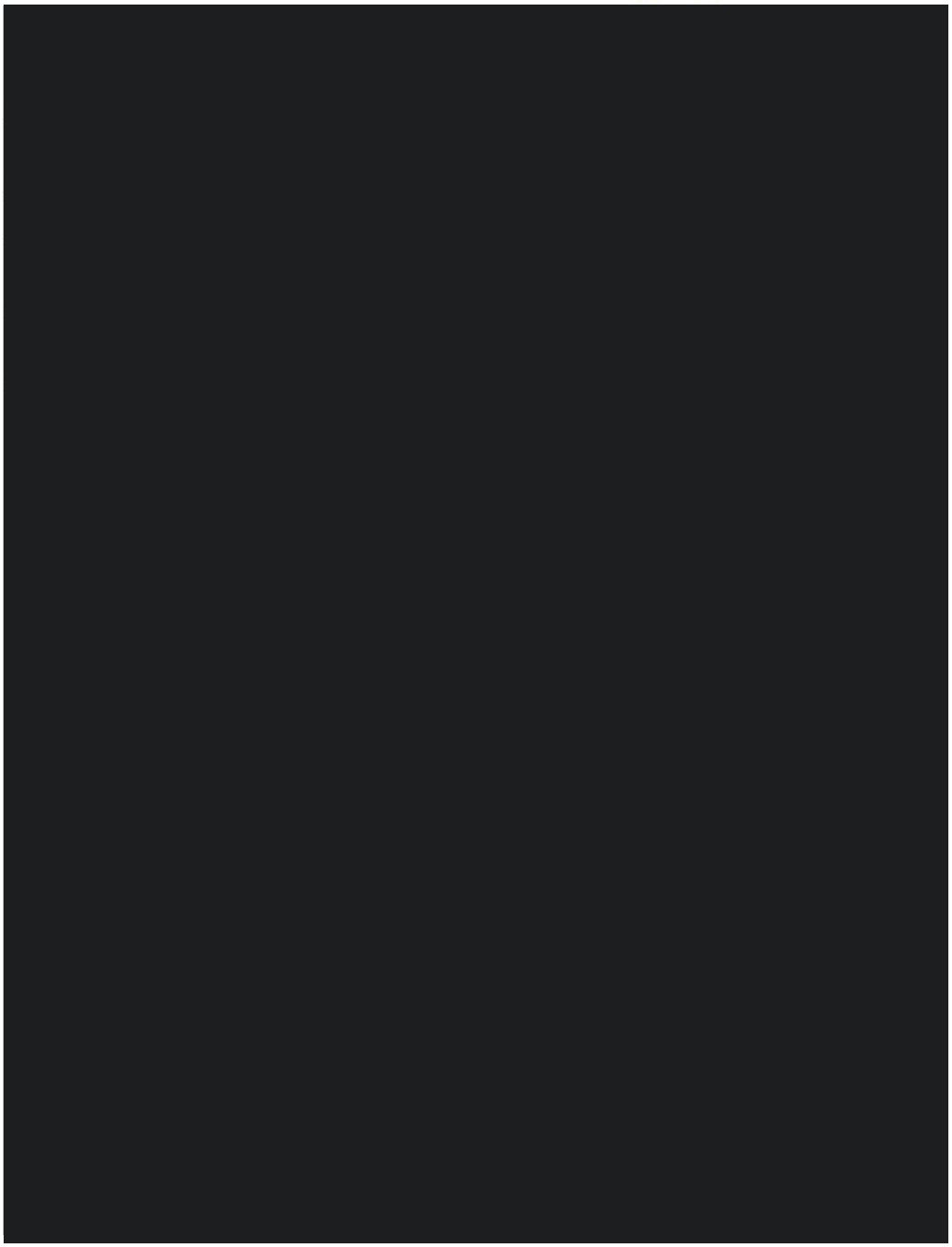
Hospital No: Date:
Name: Score:
Address: Diagnosis:

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick ■ one box for each question.

1.	Over the last week, how **itchy, sore, painful** or **stinging** has your skin been?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes No	❒ ❒	Not relevant ❒
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	❒ ❒ ❒	
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒

Please check you have answered EVERY question. Thank you.





16.5 Appendix 5 [redacted]/ADA Log

Period	Visit Name	Days	Weeks	[redacted]	Anti-Drug antibodies (ADA)	
					3 x 0.5 mL serum	Sample No
Screening	1	-28 to -14	-4 to -2			
Treatment	110	1	0		X	301
	120	29	4			
	130	57	8			
	140	85	12			
	150	113	16			
	160	141	20			
	170	169	24			
	180	197	28			
	190	225	32			
	200	253	36			
	210	281	40			
	220	309	44			
	230	337	48			
	240/EOT/TD	365	52			
Follow up	310	393	56			
	320	421	60			
	1999/EOS/PSD	449	64		X	302
	UPV				X	3001, 3002...

[redacted]

16.6 Appendix 6: World allergy organization grading system

World allergy organization subcutaneous immunotherapy systemic reaction grading system

Grading system for SARs				
			Grade 4	Grade 5
Grade 1	Grade 2	Grade 3	Anaphylaxis	
Symptom(s)/sign(s) from 1 organ system present Cutaneous • Urticaria and/or erythema-warmth and/or pruritus, other than localized at the injection site And/or • Tingling, or itching of the lips* or • Angioedema (not laryngeal)[b] Or Upper respiratory • Nasal symptoms (eg, sneezing, rhinorrea, nasal pruritus, and/or nasal congestion) And/or • Throat-clearing (itchy throat)* And/or • Cough not related to bronchospasm Or Conjunctival • Erythema, pruritus, or tearing Or Other • Nausea • Metallic taste	Symptom(s)/sign(s) from ≥2 organ symptoms listed in grade 1	Lower airway • Mild bronchospasm, eg, cough, wheezing, shortness of breath which responds to treatment And/or Gastrointestinal • Abdominal cramps* and/or vomiting/diarrhea Other • Uterine cramps • Any symptom(s)/sign(s) from grade 1 would be included	Lower airway • Severe bronchospasm, eg, not responding or worsening in spite of treatment And/or Upper airway • Laryngeal edema with stridor • Any symptom(s)/sign(s) from grades 1 or 3 would be included	Lower or upper airway • Respiratory failure and/or Cardiovascular • Collapse/hypotension† And/or Loss of consciousness (vasovagal excluded) • Any symptom(s)/sign(s) from grades 1, 3, or 4 would be included

The final grade of the reaction is not determined until the event is over, regardless of the medication administered to treat the reaction. The final report should include the first symptom(s)/sign(s) and the time of onset after the causative agent exposure and a suffix reflecting if and when epinephrine was or was not administered: a, ≤5 min; b, >5 min to ≤10 min; c, >10 to ≤20 min; d, >20 min; z, epinephrine not administered.

Final report: Grade 1-5; a-d, or z; First symptom(s)/sign(s); Time of onset of first symptom(s)/signs(s).

Case example. Within 10 min of receiving an AIT injection, a patient develops generalized urticaria followed by a tickling sensation in the posterior pharynx. Intramuscular epinephrine is administered within 5 min of symptoms(s)/sign(s) resulting in complete resolution of the reaction. The final report would be: Grade 2; a; Urticaria; 10 min.

*Application-site reactions would be considered local reactions. Oral mucosa symptoms, such as pruritus, after SLIT administration, or warmth and/or pruritus at a subcutaneous immunotherapy injection site would be considered a local reaction. However, tingling or itching of the lips or mouth could be interpreted as a SAR if the known allergen, eg, peanut, is inadvertently placed into the mouth or ingested in a subject with a history of a peanut-induced SAR. Gastrointestinal tract reactions after SLIT or oral immunotherapy (OIT) would also be considered local reactions, unless they occur with other systemic manifestations. SLIT or OIT reactions associated with gastrointestinal tract and other systemic manifestations would be classified as SARs. SLIT local reactions would be classified according to the WAO grading system for SLIT local reactions.[6] A fatal reaction would not be classified in this grading system but rather reported as a serious adverse event.

†Hypotension is defined per the National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Expert Panel criteria[3]: "Reduced blood pressure after exposure to known allergen for that subject (minutes to several hours)

A) Infants and children: low systolic blood pressure (age-specific) or greater than 30% decrease in systolic blood pressure.
   Low systolic blood pressure for children is defined as follows:
   - 1 mo to 1 y: <70 mm Hg
   - 1-10 y: <70 mm Hg + [2 × age]
   - 11-17 y: <90 mm Hg

B) Adults: systolic blood pressure of less than 90 mm Hg or greater than 30% decrease from that person's baseline.

[redacted]

[32] [redacted]