NOVARTIS

Novartis Research and Development

QGE031/Ligelizumab

Clinical Trial Protocol CQGE031C2302E1 / NCT04210843

A multi-center, double-blinded and open-label extension study to evaluate the efficacy and safety of ligelizumab as retreatment, self-administered therapy and monotherapy in Chronic Spontaneous Urticaria patients who completed studies CQGE031C2302, CQGE031C2303, CQGE031C2202 or CQGE031C1301

Document type:	Amended Protocol Version
EUDRACT number:	2019-001792-37
Version number:	v01 (clean)
Clinical Trial Phase:	IIIb
Release date:	09-Apr-2021

Clinical Trial Protocol Template Version 2.0 (01-Aug-2018)

[redacted]

Table of contents

Table of contents 2
List of tables 5
List of figures 7
List of abbreviations 8
Glossary of terms 11
Amendment 1 (09-Apr-2021) 13
Protocol summary 18
1 Introduction 21
1.1 Background 21
1.2 Purpose 22
2 Objectives and endpoints 23
3 Study design 26
3.1 Screening period 29
3.2 First observation period 29
3.3 First half of the treatment period 30
3.4 Second observation period 31
3.5 Second half of treatment period 32
3.6 Follow-up period 33
4 Rationale 34
4.1 Rationale for study design 34
4.1.1 Rationale for choice of background therapy 35
4.2 Rationale for dose/regimen and duration of treatment 36
4.3 Rationale for choice of control drugs (comparator/placebo) or combination drugs 41
4.4 Purpose and timing of interim analyses/design adaptations 41
4.5 Risks and benefits 42
4.6 Rationale for Public Health Emergency mitigation procedures 44
5 Population 44
5.1 Inclusion criteria 45
5.2 Exclusion criteria 45
6 Treatment 48
6.1 Study treatment 48
6.1.1 Investigational and control drugs 48
6.1.2 Additional study treatments 48
6.1.3 Treatment arms/group 48
6.1.4 Treatment duration 49

[redacted]

6.2 Other treatment(s) 49
6.2.1 Concomitant therapy 49
6.2.2 Prohibited medication 50
6.2.3 Rescue medication 51
6.3 Subject numbering, treatment assignment, randomization 52
6.3.1 Subject numbering 52
6.3.2 Treatment assignment, randomization 53
6.4 Treatment blinding 53
6.5 Dose escalation and dose modification 56
6.5.1 Dose modifications 56
6.5.2 Follow-up for toxicities 56
6.6 Additional treatment guidance 56
6.6.1 Treatment compliance 56
6.6.2 Emergency breaking of assigned treatment code 56
6.7 Preparation and dispensation 57
6.7.1 Handling of study treatment and additional treatment 57
6.7.2 Instruction for prescribing and taking study treatment 59
7 Informed consent procedures 62
8 Visit schedule and assessments 63
8.1 Screening 74
8.1.1 Information to be collected on screening failures 75
8.2 Subject demographics/other baseline characteristics 75
8.3 Efficacy 75
8.3.1 eDiary assessments 76
8.3.2 Other Patient Reported Outcome (PRO) assessments 79
8.3.3 Appropriateness of efficacy assessments 80
8.4 Safety 80
8.4.1 Laboratory evaluations 81
8.4.2 Electrocardiogram (ECG) 82
8.4.3 Pregnancy and assessments of fertility 83
8.4.4 Assessment of parasitic infections 83
8.4.5 Anaphylaxis assessment 84
8.4.6 Assessment of cardio-cerebrovascular events 84
8.4.7 Assessment of neoplastic events 85
8.4.8 Appropriateness of safety measurements 85
8.5 Additional assessments 85
8.5.1 Resource utilization 85

[redacted]

[redacted] 85
[redacted] 86
8.5.4 Biomarkers 86
[redacted] 88
[redacted] 89
9 Study discontinuation and completion 89
9.1 Discontinuation 89
9.1.1 Discontinuation of study treatment 89
9.1.2 Discontinuation from observation periods 91
9.1.3 Withdrawal of informed consent/Opposition to use data/biological samples 91
9.1.4 Lost to follow-up 92
9.1.5 Early study termination by the sponsor 92
9.2 Study completion and post-study treatment 92
10 Safety monitoring and reporting 92
10.1 Definition of adverse events and reporting requirements 92
10.1.1 Adverse events (AEs) 92
10.1.2 Serious adverse events (SAEs) 94
10.1.3 Serious adverse event (SAE) reporting 95
10.1.4 Pregnancy reporting 96
10.1.5 Reporting of study treatment errors including misuse/abuse 96
10.2 Additional Safety Monitoring 97
10.2.1 Liver safety monitoring 97
10.2.2 Renal safety monitoring 98
10.2.3 Data Monitoring Committee (DMC) 98
10.2.4 Adjudication committee (AC) 98
11 Data Collection and Database management 98
11.1 Data collection 98
11.2 Database management and quality control 99
11.3 Site monitoring 100
12 Data analysis and statistical methods 100
12.1 Analysis sets 100
12.2 Subject demographics and other baseline characteristics 101
12.3 Treatments 101
12.4 Analysis of the primary endpoint(s) 101
12.4.1 Definition of primary endpoint(s) 101

[redacted]

12.4.2 Statistical model, hypothesis, and method of analysis 102
12.4.3 Handling of missing values/censoring/discontinuations 102
12.4.4 Sensitivity and Supportive analyses 103
12.5 Analysis of secondary endpoints 103
12.5.1 Efficacy and/or Pharmacodynamic endpoint(s) 103
12.5.2 Safety endpoints 104
[redacted] 106
[redacted] 106
12.5.5 Biomarkers 106
[redacted] 106
[redacted] 107
12.7 Interim analyses 108
12.8 Sample size calculation 108
12.8.1 Primary endpoint(s) 108
13 Ethical considerations and administrative procedures 109
13.1 Regulatory and ethical compliance 109
13.2 Responsibilities of the investigator and IRB/IEC 109
13.3 Publication of study protocol and results 110
13.4 Quality Control and Quality Assurance 110
13.5 Patient Engagement 110
14 Protocol adherence 110
14.1 Protocol amendments 111
15 References 112
16 Appendices 114
16.1 Appendix 1: Clinically notable laboratory values and vital signs 114
16.1.1 Appendix 1.1: Clinically notable vital signs – adolescent subjects 115
16.2 Appendix 2: Liver event and laboratory trigger definitions and follow-up requirements 116
16.3 Appendix 3: Specific renal alert criteria and actions and event follow-up 118
16.4 Appendix 4: PRO tools 119
[redacted] 127
[redacted] 128
16.7 Appendix 7: World allergy organization grading system 129

List of tables

Table 1-1 Urticaria disease states based on UAS7 scoring 22

[redacted]

Table 2-1 Objectives and related endpoints 23
Table 6-1 Investigational drug 48
Table 6-2 Prohibited Medication 50
Table 6-3 Blinding and unblinding plan (applies to all subjects in this study transitioning from the core studies till completion of Week 12 in the first half of the treatment period and the primary analysis has been completed) 54
Table 8-1 Assessment Schedule (Screening, First and Second half of the treatment period and Follow-up period) 64
Table 8-2 Assessment Schedule (First and Second Observation period) 72
Table 8-3 Urticaria Patient Daily Diary (UPDD) 76
Table 8-4 Hives Severity Score (HSS) 76
Table 8-5 Itch Severity Score (ISS) 77
Table 8-6 Sleep interference score 77
Table 8-7 Activity interference score 77
Table 8-8 Actions/treatments for Angioedema 78
Table 8-9 DLQI/CDLQI score bands and impact on patient's life 79
Table 8-10 Assessments & Specifications 81
Table 8-11 Laboratory assessments 82
Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse 96
Table 10-2 Base Renal Monitoring 98
Table 12-1 95% confidence interval based on number of subjects enrolled from the core studies (CQGE031C2302/2303) 109
Table 12-2 Number of subjects required at the baseline of re-treatment for each treatment arm enrolled from the core studies (CQGE031C2302/2303) 109
Table 16-1 Best Blood Pressure (BP) Measurement Practices - Pediatrics 115
Table 16-2 Upper and lower limits for adolescents' vital signs that may be considered of concern if newly identified may be identified using the following table for guidance[1] 115
Table 16-3 Liver event and laboratory trigger definitions 116
Table 16-4 Follow-up requirements for liver laboratory triggers – ALT, TBL with and without liver symptoms 116
Table 16-5 Follow-up requirements for liver laboratory triggers – isolated hyperbilirubinemia 117
Table 16-6 Specific renal alert criteria and actions 118
Table 16-7 Renal event follow-up 119

[redacted]

List of figures

Figure 3-1 Study design 28
Figure 4-1 Change from baseline in HSS7, ISS7, and UAS7 by visit 37

[redacted]

List of abbreviations

AAS	Angioedema Activity Score
AAS7	Weekly Angioedema Activity Score
AC	Adjudication Committee
[redacted]	[redacted]
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CDLQI	Children's Dermatology Life Quality Index
CFR	Code of Federal Regulation
CIU	Chronic Idiopathic Urticaria
CK	Creatine Kinase
COVID-19	Corona Virus Disease 2019
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSU	Chronic Spontaneous Urticaria
CT	Computed Tomography
CTC	Common Toxicity Criteria
CU Index	Chronic Urticaria Index
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
[redacted]	[redacted]
EC	Ethics committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
ELISA	Enzyme-Linked Immunosorbent Assay
EMA	European Medicines Agency
EOOBS1	End of Observation Period 1
EOOBS2	End of Observation Period 2
EOS	End of Study
EOT	End of Treatment
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
FcεRI	High Affinity Immunoglobulin E Receptor
FcεRII	Low Affinity Immunoglobulin E Receptor
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
GLDH	Glutamate Dehydrogenase
H1-AH	H1-Antihistamine
hCG	Human Chorionic Gonadotropin
HRQoL	Health Related Quality of Life

[redacted]

HSS	Hives Severity Score
HSS7	Weekly Hives Severity Score
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IFU	Instructions For Use
[redacted]	[redacted]
IgE	Immunoglobulin E
IgG	Immunoglobulin G
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISS	Itch Severity Score
ISS7	Weekly Itch Severity Score
LDH	Lactate Dehydrogenase
LFT	Liver Function Test
LLOQ	Lower Limit of Quantification
LTRA	Leukotriene Receptor Antagonist
MCP-Mod	Multiple Comparison Procedure Modeling
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NSD	Needle Safety Device
PD	Pharmacodynamic(s)
PFS	Pre-Filled Syringe
[redacted]	[redacted]
PK	Pharmacokinetic(s)
PRO	Patient Reported Outcome
PT	Prothrombin Time
q4w	once every 4 weeks
QoL	Quality of Life
QTcF	Fridericia QT Correction Formula
RBC	Red Blood Cell(s)
RDO	Retrieved Dropout
s.c.	Subcutaneous
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBL	Total Bilirubin
UAS	Urticaria Activity Score
UAS7	Weekly Urticaria Activity Score
[redacted]	[redacted]
ULN	Upper Limit of Normal
UPDD	Urticaria Patient Daily Diary
UPV	Unplanned Visit

[redacted]

WBC	White Blood Cell(s)
WHO	World Health Organization

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study.
Biologic sample	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject.
Control drug	A study drug 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.
Core studies	CQGE031C2302 and CQGE031C2303 studies
Dosage	Dose of the study treatment given to the subject in a time unit.
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 source data/documents used at the point of care.
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last subject or at a later point in time as defined by the protocol.
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained. The action of enrolling one or more subjects.
Investigational drug/treatment	The study drug whose properties are being tested in the study.
Medication number	A unique identifier on the label of medication kit.
Non-investigational medicinal Product (NIMP)	Products which are not the object of investigation (e.g. any background therapy administered to each of the clinical trial subjects, regardless of randomization group, rescue medication, active drug run-ins etc.).
Patient	An individual with the condition of interest for the study
Patient-Reported Outcome (PRO)	A measurement based on a report that comes directly from the patient about the status of a subject's health condition without amendment or interpretation of the patient's report by a clinician or anyone else.
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.
Preceding studies	CQGE031C2302, CQGE031C2303, CQGE031C2202 and CQGE031C1301 studies
Personal data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
Premature subject withdrawal	Point/time when the subject exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned.
Re-screening	If a subject fails the initial screening and is considered as a Screen Failure, he/she can be invited once for a new Screening visit after medical judgment and as specified by the protocol.
Screen Failure	A subject who did not meet one or more criteria that were required for participation in the study.
Self-administration	The process by which the drug is administered outside the clinic.

Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource.
Study drug discontinuation	Point/time when subject permanently stops taking investigational drug for any reason.
Study treatment	Any drug administered to the study participants as part of the required study procedures; includes investigational drug (s), control(s) or non-investigational medicinal product(s).
Study treatment discontinuation	When the subject permanently stops taking study treatment prior to the defined study treatment completion date.
Subject	A trial participant
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.
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study.
Withdrawal of study consent (WoC) / Opposition to use of data/biological samples	Withdrawal of consent from the study occurs when the subject explicitly requests to stop use of their data and biological samples (opposition to use data and biological samples) AND no longer wishes to receive study treatment, AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. Opposition to use data/biological samples occurs in the countries where collection and processing of personal data is justified by a different legal reason than consent.

[redacted]

Amendment 1 (09-Apr-2021)

Amendment rationale

CQGE031C2302E1 study is currently recruiting. This amendment primarily aims to introduce measures to allow more flexibility to the subjects successfully completing one of the preceding studies to be able to continue receiving investigational treatment. These measures include allowance of a limited amount of missing e-diary entries prior to the first treatment visit and ensuring exclusion criteria and prohibited medications are not more stringent than the original preceding study criteria.

Further, the original compliance criteria for eDairy HSS and ISS entries in the week prior to Week 52 visit has been removed. In case subjects would not meet full compliance with eDiary entries the subjects would have moved to the second observation period, however it is more appropriate for the subjects to be allowed to continue treatment even in the case of some missing eDiary entries as long as the UAS7 score is calculable as per the definition: A minimum of 4 out of 7 daily scores are needed to reliably calculate a weekly HSS7, ISS7 or UAS7 score. This is also the definition that would be used to calculate UAS7 scores for the analysis.

Additional changes in this amendment include:

- Instructions on Public Health Emergency mitigation procedures
- Protocol template updates v4.0
- Clarifications on roles and responsibilities for blinded and unblinded study personnel for handling and administering liquid in vial and prefilled syringes
- [redacted]

Changes to protocol and rationale:

Section	Changes made
List of abbreviations	Updated
Glossary of terms	Updated
[redacted]	[redacted]
Section 3	Clarification added subjects will not be allowed a gap between preceding and extension study except under specified conditions
Section 3, Section 5.2 and Table 6-2	Correction made to specify omalizumab allowed up to 16 weeks prior to Visit 101/201
Section 3.2	Clarified wording for Visit 2 assessments and eligibility
Section 3.2	Changed criterion of 100% e-diary compliance to allow for at least 12 out of 14 records for HSS and ISS respectively in one assessment week before treatment
Section 3.3	Removed the compliance criteria for score calculation prior to Week 52 to align score calculation for patient management with score calculation for statistical purposes
Section 3.5	Moved sentence concerning the discussion with the subject to the correct scenario for UAS7 score.

[redacted]

Section 4.1, Section 6.4, Table 6-3	Specified the duration of the blinding by adding “and the primary analysis has been completed”. Blinding and unblinding plan updated to specify the blinding levels of the individual team members in case of any additional analysis required to support Health Authority interactions.
Section 4.5 and Section 5	Updated numbers of subjects according to latest information Updated edition of Investigator Brochure
Section 4.5	Sentence added to confirm that based on currently available data from the ligelizumab clinical program, there is no evidence of an increased risk of infections/viral infections and that at this time there is no specific data to inform on incidence or severity of Corona Virus Disease 2019 (COVID-19) (due to severe acute respiratory syndrome coronavirus 2) in patients receiving ligelizumab. Deleted ‘sexually active males’ from requirement of contraception while receiving ligelizumab as this was incorrect.
Section 4.6	New section added to provide rationale for Public Health Emergency mitigation procedures
Section 5.1	Inclusion criterion 6 has been updated to require a minimum of 12 out of 14 records for HSS and ISS respectively must be present in the week the UAS7 score is assessed.
Section 5.2	Exclusion criteria 20: removed GGT and ALP to ensure exclusion criterion is not more stringent than the original preceding studies’ criteria
Section 5.2	Exclusion criteria 24: • Replaced “basic” with “effective” methods of contraception. • Added the word “bilateral” to tubal ligation. • Specified the wording of the exclusion criteria for post-menopausal women. • Added standard sentence: If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the informed consent form (ICF). • Added footnote (applicable for exclusion criteria #20, #21 and #22): Subjects who did not meet applicable eligibility criteria at Visit 2, will be discontinued from the study and will not enter treatment. Clarified that these subjects will not be considered screen failure subjects.
Table 6-1	Replaced “supply type” with “presentation according to Novartis protocol template v4.0.
Section 6.2.1	Concomitant H1-AH background medication: added possible exceptions for subjects to use a different H1-AH than used in the preceding study.
Table 6-2	Prohibited medication: Removed “Drugs of well-known or ill-defined mechanism of action, that are used for urticaria or allergic conditions in general (e.g. suplatast tosilate) 30 days prior to Visit 1. Since this prohibition is too vague and broad it is difficult to assess.

[redacted]

Section 6.2.3	Anti-histamine rescue medication: Added “if the medication is no longer available in the country” to allow more flexibility in case a switch of H1-AH rescue medication is required.
Section 6.4, Table 6-3	• Added sentence to specify the involvement in any other trial activities of personnel aware of treatment assignment data. • Reworded the method of blinding the liquid volume. • Removed the following redundant sentence “The study will run open-label after Week 12 (Visit 204) and once all subjects from core studies have completed Week 12 (Visit 204) in this study”.
Section 6.7	Removed redundant sentence on recording and returning of syringes and unused medication (details are available in Section 6.7.1.)
Section 6.7.1.1	Corrected sentence to remove handling and storage of liquid in vial by the unblinded pharmacist.
Section 6.7.2	Clarifications added on roles and responsibilities for blinded and unblinded study personnel for handling and administering liquid in vial and prefilled syringes.
Section 7	Added mitigation procedure of remote informed consent discussion (e.g., telephone, video conference) during a Public Health emergency.
[redacted]	[redacted]
Section 8, Section 8.4	Added mitigation procedure of phone calls, virtual contacts (e.g., tele consult) to replace on-site visits in case of a Public Health emergency
Table 8-1	• Row “height and weight” re-worded and updated to specify that for adults height measurement only required at screening. • Reminder added that for any ECG with clinically significant findings, 2 additional ECGs must be performed to confirm the finding to align with Section • Footnote 5: corrected to align with Section 3 [redacted]
Table 8-2	• Update made to allow the remote PROs collection in case the patient cannot attend the visit at site due to a Public Health emergency. • Update made to allow samples collection & analysis in a certified local laboratory in case of a Public Health emergency. [redacted]
Section 8.1	• Added clarification for assessments not taken at V1999 of preceding studies. • Clarification that a retest is allowed for transient and non-clinically significant laboratory values at Visit 2. • Added clarification regarding data collection for subjects entered first observation period and discontinue study without entering treatment period.

[redacted]

Section 8.2	Sentence added to specify the reasons for participant race and ethnicity collection and analysis.
Section 8.3 and Table 8.1	Clarification added that remote collection of eDiary assessments (DLQI/CDLQI, [redacted] is allowed if data cannot be obtained at the site due to a Public Health emergency. Sections 8.3.2.1; 8.3.2.2; updated accordingly.
Section 8.4.1 and Table 8.1	Update made to allow samples collection & analysis in a certified local laboratory in case of a Public Health emergency Guidance on local laboratory assessments are provided.
Section 8.4.3 and Table 8.1	Correction made that only female subjects of child-bearing potential are required to perform pregnancy tests. Updates made that pregnancy tests must be performed prior to investigational drug administration and post-menopausal status should be recorded in the CRF.
Section 8.4.4 and Table 8.1	Clarification added for stool sample collection at V2 and at V9999.
[redacted]	[redacted]
Section 8.5.2.3, 12.5.6	Data pooling and modeling details removed.
[redacted]	[redacted]
[redacted]	[redacted]
Section 9.1.1	Corrected units for platelets from mL to µL.
Section 9.1.3, Section 8	Updated wording around Withdrawal of informed consent/Opposition to use data/biological samples as per new Novartis protocol template
Section 9.1.4	Added clarification on withdrawn consent and oppose to the use of data/biological samples.
Section 9.1.5	In case Novartis has to terminate the study clarification added on what data needs to be collected.
Section 9.2	Added information regarding possible post trial access.
Section 10.1.3	Updated wording for reporting of SAEs.
Section 10.1.4	Updated wording for pregnancy reporting
Section 10.2.1 and Appendix 2, Section 16.2	Updates made to clarify follow up actions for abnormal liver triggers as per Novartis protocol template v4.0
Section 10.2.3	Updated minimum DMC review period.
Section 12.1	Clarified safety will be analyzed according to the actual treatment
[redacted]	[redacted]
Section 12.6	Added clarifications that DLQI and CDLQI will be analyzed separately.
Section 12.7	Minor clarification to more precisely define the time point for the first interim analysis.
Section 13.5	Added section on Patient engagement

[redacted]

Section 16.2	Revised Tables 16-3 and 16-5 and added Table 16-4 for more detailed guidance on Follow-up and management of liver safety events as per updated Novartis protocol template.
[redacted]	[redacted]

Changes to the protocol summary have been aligned with the changes as above where applicable.

Changes are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

Editorial changes have been made in the document for more clarity and to maintain consistency within the document.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities. The changes described in this amendment protocol require IRB/IEC and Health Authority approval according to local regulations prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

[redacted]

Protocol summary

Protocol number	CQGE031C2302E1
Full Title	A multi-center, double-blinded and open-label extension study to evaluate the efficacy and safety of ligelizumab as retreatment, self-administered therapy and monotherapy in Chronic Spontaneous Urticaria patients who completed studies CQGE031C2302, CQGE031C2303, CQGE031C2202 or CQGE031C1301
Brief title	Study of efficacy and safety of ligelizumab in chronic spontaneous urticaria patients who completed a previous study with ligelizumab
Sponsor and Clinical Phase	Novartis Phase IIIb
Investigation type	Biological
Study type	Interventional
Purpose and rationale	The purpose of this extension study is to establish efficacy and safety of ligelizumab. This will be assessed in adult and adolescent chronic spontaneous urticaria (CSU) patients who have completed a preceding ligelizumab study and have relapsed, following treatment in these preceding studies, despite standard of care H1-antihistamine (H1-AH) treatment. In a subset of subjects, the safety and efficacy of ligelizumab monotherapy will be assessed. This study will also fulfill the Novartis commitment to provide post-trial access to patients who have completed studies CQGE031C2302, CQGE031C2303, CQGE031C2202 or CQGE031C1301.
Primary Objective(s)	To evaluate the efficacy of ligelizumab assessed as the proportion of subjects achieving weekly urticaria activity score (UAS7) ≤6 after 12 weeks of retreatment, in subjects previously treated in CQGE031C2302/CQGE031C2303 (the core studies) as well as in the subset of subjects who previously achieved UAS7 ≤ 6 in the core studies.
Secondary Objectives	• To describe the efficacy of ligelizumab assessed as the proportion of subjects achieving UAS7 = 0 after 12 weeks of retreatment, in subjects previously treated in the core studies • To describe the efficacy of ligelizumab assessed as the reduction from extension study baseline in the UAS7 and its components (weekly itch severity score (ISS7) and weekly hives severity score (HSS7) subjects previously treated in the core studies • To describe the efficacy of ligelizumab in achieving an angioedema-free period at Week 12 previously treated in the core studies • To describe the efficacy of ligelizumab in achieving Dermatology Life Quality Index (DLQI) = 0-1 at Week 12 previously treated in the core studies • To describe the efficacy of ligelizumab in the treatment of CSU (UAS7≤6), 12 weeks after starting self-administration • To assess the safety and tolerability of ligelizumab in all subjects • To assess the safety and tolerability of ligelizumab pre-filled syringe (PFS) • To assess the safety and tolerability of ligelizumab in all subjects who self-administer
Study design	This is a Phase IIIb multi-center, double-blinded and open-label extension study to evaluate efficacy and safety of ligelizumab retreatment with H1-AHs background therapy with conditional options for monotherapy and self-administration

Population	The population will consist of male and female subjects aged ≥ 12 years who have been diagnosed with CSU and remain symptomatic despite the use of H1-AH and completed a preceding ligelizumab study.
Key Inclusion criteria	1. Written informed consent 2. Subjects who successfully completed all of the treatment period and the follow-up period in any of the following studies: CQGE031C2302, CQGE031C2303, CQGE031C2202 or CQGE031C1301 3. Male and female, adult and adolescent subjects ≥12 years of age 4. Willing and able to complete a daily symptom eDiary for the duration of the study and adhere to the study visit schedule
Key Exclusion criteria	1. Use of investigational drugs, other than those in use in the preceding studies, at the time of enrollment 2. Use of omalizumab within 16 weeks of entering treatment or observation periods 3. History of hypersensitivity to the study drug ligelizumab or its components, or to drugs of similar chemical classes 4. New onset or signs and symptoms of any form of chronic urticarias other than CSU during the preceding studies CQGE031C2302, CQGE031C2303, CQGE031C2202 5. Diseases with possible symptoms of urticaria or angioedema 6. Subjects with evidence of helminthic parasitic infection 7. Documented history of anaphylaxis 8. Pregnant or nursing (lactating) women
Study treatment	Ligelizumab with or without background H1-AH therapy
Efficacy assessments	UAS7 HSS7 ISS7
Key safety assessments	Treatment emergent adverse events, vital signs, laboratory assessments
Other assessments	Patient reported outcomes (weekly angioedema activity score (AAS7), DLQI/Children Dermatology Life Quality Index (CDLQI), [redacted] [redacted] Biomarker [redacted]
Data analysis	To show retreatment efficacy of ligelizumab in achieving well-controlled CSU after 12 weeks in subjects transitioning from the core studies, the summary statistics for the proportion of subjects achieving UAS7 ≤ 6 in this extension study will be provided. The primary analysis will be performed for subjects receiving the same dose of ligelizumab they received in the core studies. The corresponding 95% confidence interval also will be derived based on the score method including continuity correction. For the subgroup of subjects who achieved UAS7 ≤ 6 at week 12 in the core studies and who received ligelizumab, the proportion of subjects with the response of UAS7 ≤ 6 after 12 weeks of re-treatment in this extension study will be provided together with a 95% confidence interval.

[redacted]

	Subjects rolling over from study CQGE031C1301 and CQGE031C2202 will not be included in this primary analysis. The efficacy data for these subjects will be analyzed separately.
Key words	Anti-IgE, chronic spontaneous urticaria, CSU, hives severity score, itch severity score, urticaria activity score, retreatment, ligelizumab

[redacted]

1 Introduction

1.1 Background

Chronic Spontaneous Urticaria (CSU), also known as Chronic Idiopathic Urticaria (CIU) is defined 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). 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 overall burden of CSU is substantial. The symptoms of urticaria and urticaria associated angioedema adversely affect daily activities and sleep resulting in a negative impact on patients' lives, health related quality of life (HRQoL) and work productivity (O'Donnell et al 1997, Maurer et al 2017).

Current treatment guidelines recommend H1-antihistamine at licensed dose as first-line therapy for CSU. If no adequate response is achieved, second line therapy should be H1-antihistamines at doses up to 4-fold the approved dose (Zuberbier et al 2018). Generally up to 50% of patients may respond (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. In addition, the current treatment guidelines suggest that while systemic corticosteroids are sometimes added to the treatment regimens for up to ten days, 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.

Omalizumab, a monoclonal antibody that targets immunoglobulin E (IgE), has been approved globally, including 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).

Ligelizumab (QGE031) is a newer humanized immunoglobulin G (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 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. Ligelizumab has demonstrated dose- and time-dependent suppression of free IgE and reduction in basophil FcεRI expression and thus basophil surface IgE, and inhibition of skin prick test responses to

[redacted]

allergens which is superior in extent and duration to those observed with omalizumab (Arm et al 2014, Gauvreau et al 2016). These studies support the scientific rationale for the development of ligelizumab in IgE driven diseases. Data from the CQGE031C2201, the first clinical study in CSU, demonstrated that ligelizumab (24, 72 and 240 mg q4w s.c.) was efficacious when added to standard of care treatment in patients with moderate to severe CSU. At Week 12, a statistically significant higher proportion of ligelizumab treated patients (72 and 240 mg q4w) achieved weekly hives severity score (HSS7) = 0 compared to omalizumab 300 mg q4w (Maurer et al 2019). Data from CQGE031C2201E1 study, an open-label extension for subjects who completed the CQGE031C2201 study and presented with active disease, demonstrate that 1 year treatment with ligelizumab 240 mg q4w results in a high rate of early onset, sustained and complete control of hives and itch (weekly urticaria activity score (UAS7) = 0), and angioedema. There were no newly identified or unexpected safety issues.

Definition of CSU Disease States

The disease activity states of CSU are commonly defined as complete control, well controlled, mild, moderate and severe (Stull et al 2017). When described by their associated UAS7 scores, the disease activity states are defined as in Table 1-1:

Table 1-1 Urticaria disease states based on UAS7 scoring

Disease State	UAS7 Score
Severe activity	28-42
Moderate activity	16-27
Mild activity	7-15
Well controlled	1-6
Urticaria free (completely controlled)	0

In this clinical trial, in addition to the inclusion and exclusion criteria, Week 52 of the treatment period is a key decision point, and is based on the CSU disease state i.e. the respective UAS7 scores (see Section 3). When scores are whole numbers the ranges and the thresholds are straightforward. However weekly scores can be fractional (e.g. 6.5) and hence to maintain accuracy, the values will not be rounded up or down. Therefore, the above noted thresholds are slightly revised to account for this (Section 3). For example in this study "Mild CSU" is defined as UAS7 > 6 and < 16.

1.2 Purpose

The purpose of this extension study (up to 104 weeks of treatment and up to 52 weeks of post-treatment follow-up) is to establish efficacy and safety of ligelizumab (QGE031) 120 mg s.c. q4w. This will be assessed in adult and adolescent CSU patients who have completed one of the studies CQGE031C2302, CQGE031C2303, CQGE031C2202 or CQGE031C1301 (the "preceding studies") and who have relapsed, following treatment in these preceding studies, despite standard of care treatment with H1-antihistamines (H1-AH) (at local label approved doses), in the following scenarios:

- re-treatment with ligelizumab 72 or 120 mg s.c. q4w following treatment in the preceding studies;
- self-administration of ligelizumab 120 mg s.c. q4w outside of the clinic setting;

[redacted]

- ligelizumab 120 mg s.c. q4w used as monotherapy, i.e. when background H1-AH medication is discontinued

In addition, this study will evaluate whether ongoing long-term treatment drives drug-mediated remission of disease. This study will also fulfill the Novartis commitment to provide post-trial access to patients who have completed studies CQGE031C2302, CQGE031C2303, CQGE031C2202 or CQGE031C1301.

2 Objectives and endpoints

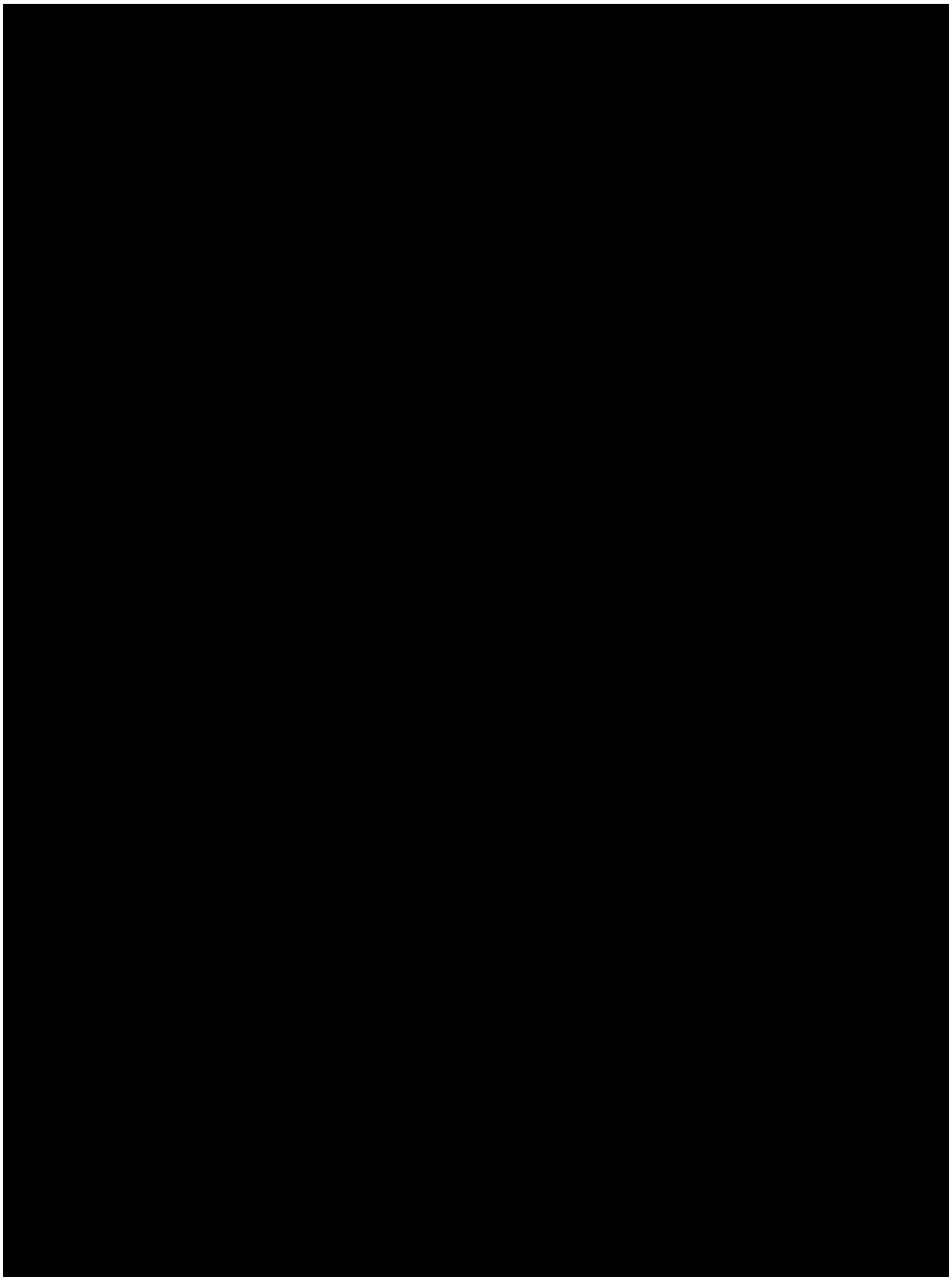
Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To evaluate the efficacy of retreatment with ligelizumab 72 mg or 120 mg q4w in subjects previously treated in the core studies (CQGE031C2302/CQGE031C2303) • To evaluate the efficacy of retreatment with ligelizumab in the subgroup of these subjects who achieved a weekly urticaria activity score (UAS7) ≤ 6 after 12 weeks of treatment in these core studies	• The proportion of subjects with well-controlled disease (UAS7 ≤ 6) at Week 12
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
For retreatment efficacy evaluation:	
• To describe the efficacy of ligelizumab 72 mg or 120 mg q4w in achieving complete control of chronic spontaneous urticaria (CSU) at Week 12 when used as retreatment for subjects previously treated in the core studies (CQGE031C2302/CQGE031C2303)	• The proportion of subjects with completely controlled disease (UAS7 = 0) at Week 12
• To describe the efficacy of ligelizumab with respect to a reduction from extension study baseline in the UAS7 and its components (weekly itch severity score (ISS7) and weekly hives severity score (HSS7) at Week 12 in all subjects receiving the same dose regimen as in the core studies, i.e. 72 mg or 120 mg q4w	• Absolute change from extension study baseline in the UAS7 and its components (ISS7 and HSS7) at Week 12
• To describe the efficacy of ligelizumab in achieving an angioedema-free period at Week 12 in all subjects receiving the same dose regimen as in the core studies, i.e. 72 mg or 120 mg q4w	• Cumulative number of weeks that subjects achieve weekly angioedema activity score (AAS7) = 0 between extension study baseline and Week 12
• To describe the efficacy of ligelizumab in achieving Dermatology Life Quality Index	• Percentage of subjects achieving DLQI = 0-1 at Week 12

Objective(s)	Endpoint(s)
(DLQI) = 0-1 at Week 12 when used as re-treatment for all subjects receiving the same dose regimen as in the core studies, i.e. 72 mg or 120 mg q4w	
For self-administration efficacy evaluation:	
• To describe the efficacy of ligelizumab in the treatment of CSU, 12 weeks after starting self-administration	• The proportion of subjects with well-controlled disease (UAS7 ≤ 6), 12 weeks after starting self-administration
For safety & tolerability evaluation:	
• To assess the safety and tolerability of ligelizumab in all subjects	In each dose group, and for each duration of treatment: • Occurrence of treatment emergent adverse events during the study • Occurrence of treatment emergent serious adverse events during the study • Vital signs • Lab assessments
• To assess the safety and tolerability of ligelizumab 120 mg q4w 1mL pre-filled syringe (PFS)	For the duration of treatment: • Occurrence of treatment emergent serious adverse events during study Week 12 onwards • Vital signs Week 12 onwards • Lab assessments Week 12 onwards
• To assess the safety and tolerability of ligelizumab 120 mg q4w in all subjects who self-administer	• Occurrence of treatment emergent adverse events • Occurrence of treatment emergent serious adverse events • Vital signs • Lab assessments

[redacted]

[redacted]



[redacted]

3 Study design

This is a Phase IIIb multi-center, double-blinded and open-label, extension study to evaluate efficacy and safety of ligelizumab 72 mg and 120 mg s.c. q4w as add-on therapy to H1-AHs with an option for monotherapy i.e. with discontinuation of background H1-AH in adult and adolescent CSU subjects who have completed one of the CQGE031C2302, CQGE031C2303, CQGE031C2202 or CQGE031C1301 studies ("preceding studies"), in the setting of retreatment and self-administration.

As per Table 1-1, the definition of the disease states for CSU, for purposes of this study protocol and used for decisions described in this section is:

- Urticaria-free (Completely controlled disease): UAS7 = 0;
- Well controlled disease: UAS7 ≤ 6;
- Mild Disease: UAS7 > 6 and < 16 and
- Moderate to severe disease: UAS7 ≥ 16.

As depicted in Figure 3-1, the study consists of 5 distinct periods

- Screening period (Day -28 to Day -7), duration 1 to 4 weeks;
- First observation period, duration up to 36 weeks;
- Treatment period, duration of 2 years (104 weeks);
- Second observation period, duration up to 52 weeks;
- Post-treatment follow-up period, duration of 12 weeks or 52 weeks.

The minimum duration of a subject's stay in the study without early discontinuation is approximately 37 weeks: 1 week screening plus 36 weeks in first observation period until the subject exists the study without a relapse.

The maximum duration of a subject's stay in the study without early discontinuation is approximately 208 weeks: 4 weeks screening, 36 weeks in first observation period, 52 weeks in first half of the treatment period, 52 weeks in the second half of the observation period, 52

[redacted]

weeks in second half of the treatment period and 12 weeks in the follow-up period until the subject exits the study.

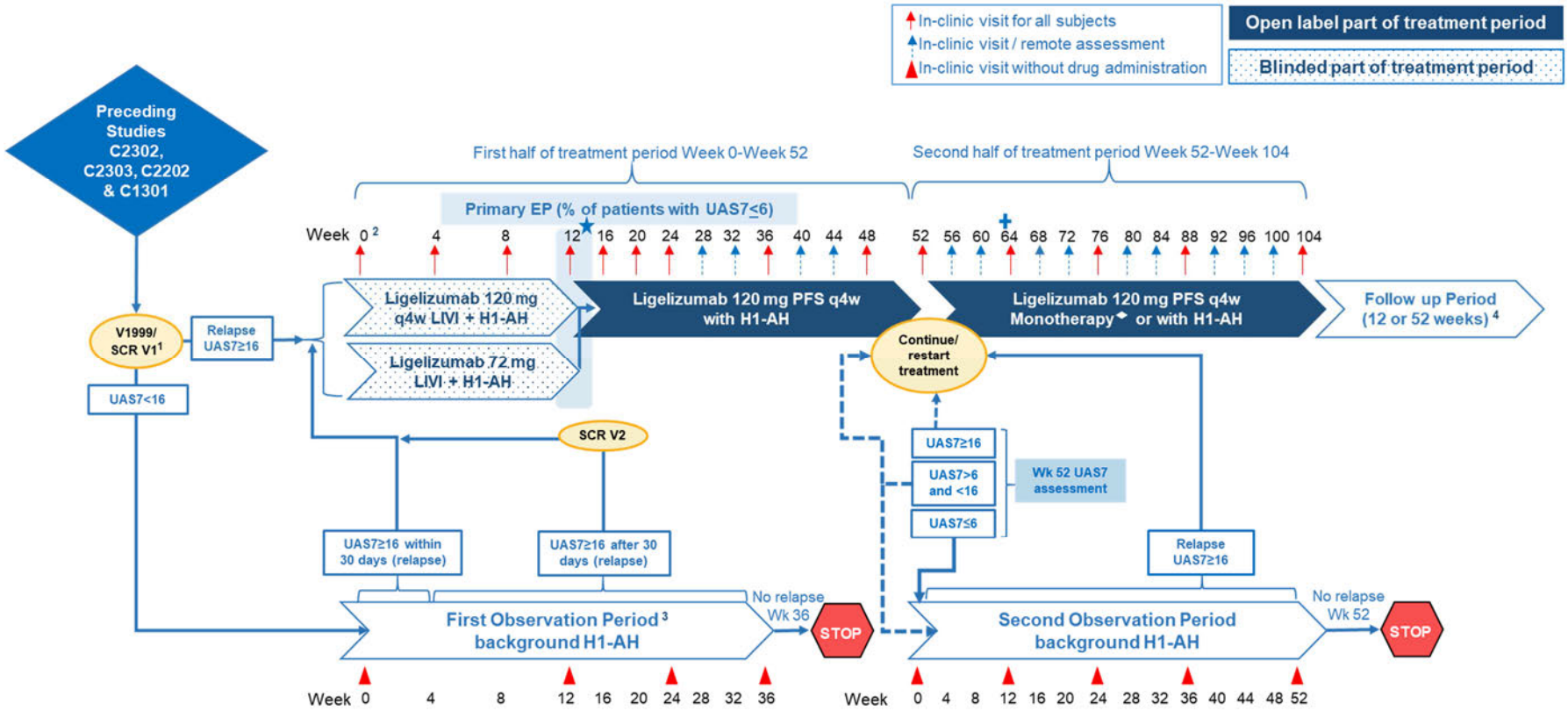
If the study site is ready to enroll subjects in the extension study, and the subject completed the preceding study's End of Study Visit (EOS, Visit 1999), the subject can "roll-over" into this extension study. When the site is ready to enroll subjects, the subject should be enrolled into the extension study in as short time-frame as possible. Subsequently, all subjects who refuse participation in the extension study at the time of V1999 will not be allowed to enter at a later time unless there are circumstances beyond their control. All assessments done as a part of Visit 1999 for preceding studies will be considered for screening for the extension study. These subjects will have their Screening Visit 1 for the extension study on the same day as Visit 1999 of the preceding study.

Subjects who complete Visit 1999 of the preceding studies prior to the study site being ready to enroll subjects in the extension study, will have a gap between their Visit 1999 and Screening Visit 1 i.e. Visit 1999 and screening Visit 1 will not occur on the same day. Informed consent for the extension study will be signed off prior to or at Screening Visit 1. If this gap between the two visits is less than or equal to 30 days, all Visit 1999 assessments can still be used to determine eligibility into the extension study. If this gap between the two visits exceeds 30 days, subjects will be re-assessed for eligibility into the trial at Screening Visit 1. During this gap between completion of preceding studies and enrolment into extension study:

- Subjects can use second generation H1-AH as per CSU treatment guidelines.
- Subjects can use omalizumab, if needed, provided there is at least 16 weeks between last dose of omalizumab and Visit 101 or V201.
- Subjects can use oral corticosteroids, if needed, provided there is at least 30 days between last dose of oral corticosteroid and Screening Visit 1 of this study.

[redacted]

Figure 3-1 Study design



[1] After screening, UAS7 score will be assessed via eDiary
[2] Subjects from C2302/2303 72 mg dose arm will receive the 72 mg; all other subjects will receive ligelizumab 120 mg
[3] Blinded to core study treatment group but unblinded to observation period
[4] Subjects completing 104 continuous weeks of treatment enter 52-week follow up; All other subjects enter 12-week follow up
EP = Endpoint; SCR = screening; LIVI = liquid in vial; PFS = prefilled syringe

Treatment continuation decision: PI reassessment in discussion with subject
★ **Week 12 Self-admin:** Qualifying subjects starts self-admin in clinic at Wk 12 and transitions at Wk 24 to out of the clinic setting
✝ **Week 64 Repeat & new self-admin:** Subjects re-starting self-admin at Week 64 and subjects who newly qualify, will start self-admin in clinic at Week 64 and transition at Week 76 to out of the clinic setting
◆ **Ligelizumab monotherapy:** Subjects with UAS7 ≤ 6 at Week 52, who re-enter 2nd half of treatment period from the 2nd observation period, will have a possibility to discontinue H1-AH background medication at Week 64, per investigator's discretion taking into account if CSU symptoms are well controlled

[redacted]

3.1 Screening period

For all study participants, the first visit of the extension phase at Visit 1 should occur on the same day as the preceding studies' EOS visit (Visit 1999), or in as short time-frame as possible after the Visit 1999 of the preceding studies, as described below.

- At or prior to Visit 1, (Visit 1999 of the preceding studies, if the subject is transitioning immediately), eligible subjects will sign an informed consent form (ICF).
- All lab assessments performed at Visit 1999 (if not more than 30 days prior to the extension screening Visit 1) and all other required assessments as per extension study protocol will be used to determine eligibility to enroll into this extension study. If the gap between the Visit 1999 of preceding studies and extension screening Visit 1 is greater than 30 days, then all lab and other required assessments will need to be re-done at extension screening Visit 1.
- Subjects must remain on the same H1-AH background medication they were taking in the preceding studies.
- Subjects should use the same H1-AH rescue medication that was agreed with the investigator at Visit 1 of this study.
- Use of oral corticosteroid rescue medication is not permitted during the screening period.
- Subjects' relevant medical conditions and concomitant medications will be reviewed at Visit 1 (Visit 1999 of the preceding studies, if the subject is transitioning immediately to the extension study).
- The subjects will continue to complete all eDiary assessments, including assessment of UAS. The 7 days prior to Week 0 will be used to calculate the UAS7 score:
  - If the subject has moderate to severe disease, defined as UAS7 $\geq$ 16, the subject will enter the treatment period immediately at Visit 201 (Week 0) to start treatment, as described in Section 3.3.
  - If the subject has a UAS7 of < 16, the subject will transition to the first observation period at Visit 101 (Week 0), as described in Section 3.2.

Rescreening may be allowed for subjects who fail initial screening (see Section 5.1 and Section 5.2 on when rescreening is allowed). Only one rescreening will be allowed. 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.

3.2 First observation period

- Visit 101 (Week 0) to 199 (Week 36 also referred to as End of Observation Period 1/EOOBS1).
- If the subject's UAS7 is < 16 at Week 0, the subject will enter the first (investigational treatment-free) observation period, performing assessments for Visit 101 after which they will be assessed remotely (i.e. outside the clinic) by a safety phone call from the site every 4 weeks, unless there is an in-clinic visit scheduled.
- Subjects will have in-clinic safety and efficacy assessments done at 12-week intervals.

[redacted]

- Subjects must remain on the same H1-AH background medication they were taking in the preceding studies.
- Subjects should use the same H1-AH rescue medication that was agreed with the investigator at Visit 1 of this study.
- Use of oral corticosteroid rescue medication is **not permitted** during this first observation period.
- Subjects will continue to complete the eDiary twice daily as per protocol, in order to monitor the activity of their disease.
- Subjects who present with moderate to severe active disease (UAS7 ≥ 16; having at least 12 out of 14 records for HSS and ISS respectively completed in one assessment week during observation) will be brought back to clinic as soon as possible:
  a. Subjects will perform the Visit 201 if they had Visit 1 in the last 30 days.
  b. Subjects for whom Visit 1 occurred more than 30 days ago will perform assessments from screening Visit 2. Assessments from Visit 2 will be used to determine eligibility as applicable (see Section 5.2).
- Subjects with UAS7 < 16 by the end of this first observation period will perform Visit 199 (EOOBS1) of this extension study to exit the study.
- Subjects who wish to discontinue from the first observation period and study, will be expected to complete Visit 199 (EOOBS1).

3.3 First half of the treatment period

- Week 0 (Visit 201) to Week 52
- Subjects receive their first dose of ligelizumab at Visit 201 (Week 0) and last dose of ligelizumab of this first half of the treatment period at Visit 213 (Week 48).
- Subjects must remain on the same H1-AH background medication they were taking in the preceding studies.
- Subjects should use the same H1-AH rescue medication that was agreed with the investigator at Visit 1 of this study.
- Oral corticosteroid rescue medication is permitted only at and after Visit 204 (Week 12) (after all assessments are completed), with the limitations as per protocol (see Section 6.2.3).
- Subjects entering the first half of the treatment period from the preceding studies will be assigned to treatment as follows:
  - Core studies CQGE031C2302 and CQGE031C2303:
    - For the first 12 weeks, the blinded treatment assignment will be determined according to the treatment group assignment during the core studies following these rules:
      - Subjects treated with ligelizumab 72 mg liquid in vial s.c. q4w in the core studies will be treated with ligelizumab 72 mg liquid in vial s.c. q4w in a double-blind manner such that their prior treatment regimen will not be unblinded.
      - All other subjects from the core studies will be treated with ligelizumab 120 mg liquid in vial s.c. q4w in a double-blind manner such that their prior treatment regimen will not be unblinded.

[redacted]

  - Studies CQGE031C1301 and CQGE031C2202:
    - All subjects from these studies will be treated with ligelizumab 120 mg liquid in vial s.c. q4w in an open-label manner for the first 12 weeks.
- If the subject in the screening period or first observation period presents with moderate to severe disease, defined as UAS7 ≥ 16, the subject will enter the treatment period at Visit 201 (Week 0), and start the treatment assigned as above.
- At Visit 204 (Week 12), all subjects will be switched to ligelizumab 120 mg s.c. pre-filled syringe (PFS) q4w in an open-label manner.
- At Visit 204 (Week 12) subjects will be offered an opportunity to administer ligelizumab outside the clinic. For details regarding self-administration outside of the clinic and monitoring post ligelizumab administration, see Section 6.7.2.
- All subjects, whether in the clinic-administered or outside the clinic self-administered group will continue to complete the eDiary twice daily as per protocol.
- All subjects should complete their eDiary for the 7 days prior to Visit 214 (Week 52) to ensure the UAS7 thresholds are available for evaluation at Visit 214 (Week 52).
- At Week 52 UAS7 needs to be assessed:
  - Subjects who have achieved a **UAS7 ≤ 6** will transition to the second observation period Visit 301 (see Section 3.4).
  - Subjects who have achieved a **UAS7 > 6 and < 16** will continue treatment without interruption into the second half of the treatment period (Visit 214), unless a decision to stop treatment is made based on a risk-benefit discussion between the investigator and subject, in which case the subject would move to the second observation period Visit 301).
  - For subjects with a **UAS7 ≥ 16**, the investigator must reassess the risk-benefit with the subject and decide whether the subject will continue with the investigational treatment (Visit 214) or move to the follow-up period and perform Visit 9998 (see Section 4.2 – Rationale for duration of treatment).

3.4 Second observation period

- Visit 301 (Week 0) to 399 (Week 52 also referred to as End of Observation Period 2, EOOBS2).
- If the subject's UAS7 is ≤ 6 at Week 52, the subject will enter the second (investigational treatment-free) observation period Visit 301 (Week 0) and will be assessed remotely (i.e. outside the clinic) by a safety phone call from the site every 4 weeks, unless there is an in-clinic visit scheduled.
- Subjects will have in-clinic safety and efficacy assessments done at 12 or 16 week intervals.
- Subjects must remain on the same H1-AH background medication they were taking in the preceding studies.
- Subjects should use the same H1-AH rescue medication that was agreed with the investigator at Visit 1 of this study.
- Use of oral corticosteroid rescue medication is **not permitted** during this second observation period.

[redacted]

- Subjects will continue to complete the eDiary twice daily as per protocol, in order to monitor the activity of their disease. All subjects should complete their eDiary for the 7 days prior to Visit 214 (i.e. one assessment-week) to ensure the UAS7 thresholds are available.
- Subjects who present with moderate to severe active disease (UAS7 ≥ 16) will be brought back to clinic to be treated as soon as possible to perform Visit 214 (Week 52) in the second half of the treatment period) and restart treatment with ligelizumab 120 mg PFS q4w.
- Subjects with a UAS7 < 16 by the end of this second observation period will perform Visit 399 (EOOBS2) of this extension study to exit the study.
- Subjects who wish to discontinue from this observation period will be expected to complete at least Visits 301, 302 and 303 (Week 0, 4 and 8), and perform Visit 399 (Week 52/EOOBS2) and exit the study.

3.5 Second half of treatment period

- Visit 214 to 9998 (Week 52 to Week 104)
- At Week 52:

  Subjects who have achieved **UAS7 of > 6 and < 16** will be assessed based on a risk-benefit discussion between the subject and the investigator on whether to continue treatment without interruption into the second half of the treatment period, or, move to the second observation period.

  - These subjects, with an uninterrupted treatment period of 104 weeks will complete the second half of the treatment period at Visit 9998 (Week 104/EOT (End of Treatment)), and transition to the 52-week follow-up period Visit 501 (Week 116).
  - These subjects will not be allowed to discontinue H1-AH background medication.

  For subjects who have achieved a **UAS7 ≥ 16,** the investigator must reassess the risk-benefit with the subject. This discussion with the individual subject will include whether or not the subject has had enough improvement from their initial disease state at the start of the treatment period, even though they still have moderate to severe disease, to justify continuing in the treatment period.

  Based on this benefit risk assessment and discussion with the subject, the subject and investigator will decide whether to

  - continue with the investigational treatment (ligelizumab 120 mg s.c. q4w PFS) in the second half of the treatment period **or**
  - discontinue the treatment, and complete Visit 9998 (Week 104/EOT) and transition to the 12-week follow-up period Visit 9999 (Week 156/EOS).
  - These subjects will not be allowed to discontinue H1-AH background medication.

  For the sub-group of subjects who achieved a **UAS7 ≤ 6** at Week 52, and re-entering treatment (second half of the treatment period) from the second observation period due to a relapse (UAS7 ≥ 16):

  - These subjects must enter the second half of the treatment period at Visit 214 (Week 52).
  - At Visit 403 (Week 64), only this sub-group of subjects will be offered the opportunity, after discussion with the investigator, to discontinue their H1-AH background medication (i.e. ligelizumab 120 mg s.c. q4w PFS monotherapy).

[redacted]

- To support the investigator in making the decision for monotherapy, subjects should complete their eDiary for the 7 days prior to Visit 403 (i.e. one assessment-week) to ensure the UAS7 thresholds are available.
- The investigator will decide whether monotherapy is appropriate considering the UAS7 score. It is recommended that only subjects with UAS7 ≤ 6 at Visit 403 (Week 64) discontinue H1-AH.
- These subjects must be advised that, if needed to use their H1-AH background medication, they must then remain on their H1-AH background medication for the rest of the study. Any worsening of CSU symptoms can be managed with the use of H1-AH rescue medication without the need to resume H1-AH background medication.

- All subjects completing the second half of the treatment period will complete the Visit 9998 (Week 104/EOT), and transition to the 12-week follow-up period Visit 9999 (Week 156/EOS).

- All subjects, whether in the clinic-administered or outside the clinic self-administered group will continue to complete the eDiary twice daily as per protocol.
- Subjects should use the same H1-AH rescue medication that was agreed with the investigator at Visit 1 of this study.
- Use of oral corticosteroid rescue medication is permitted during the second half of the treatment period, with the limitations as per Section 6.2.3.
- For details regarding monitoring post ligelizumab administration and self-administration outside of the clinic, see Section 6.7.2.

3.6 Follow-up period

- Visit 501 to 9999 (Week 116 to Week 156)
- Subjects who do not complete a continuous 104-week treatment will enter the follow-up period for 12 weeks duration and will only perform Visit 9999 (Week 156).
- Subjects who have completed the full 104-week treatment period without interruption will enter the follow-up period of 52 weeks duration and will perform Visit 501 to Visit 9999 (Week 116 to Week 156).
- After completion of the follow-up period, subjects will perform the EOS visit (Visit 9999) and exit the study.
- Subjects will continue to complete the eDiary twice daily as per protocol (see Table 8-1), in order to monitor the activity of their disease.
- Subjects who decided to remain on H1-AH background medication will continue to use H1-AH background medication. Subjects who decided to go off H1-AH background medication should continue to remain off.
- Subjects should use the same H1-AH rescue medication that was agreed with the investigator at Visit 1 of this study.
- Use of oral corticosteroid rescue medication is permitted during the follow-up period, with the limitations as per protocol (see Section 6.2.3).

[redacted]

4 Rationale

4.1 Rationale for study design

Data from the dose-range finding Study CQGE031C2201 demonstrated 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 a LTRA. [redacted]

This Phase 3 extension study is designed to build on [redacted] previous and ongoing study data by further evaluating longer-term safety and efficacy, keeping in mind that many patients with CSU will have their disease for many years, and there is currently a knowledge gap in long-term management of CSU with ligelizumab.

The target population for this study consists of all CSU adult and adolescent subjects who have completed studies CQGE031C2302, CQE031C2303, CQGE031C2202 or CQGE031C1301. In these ongoing Phase 3 and CQGE031C2202 adolescent studies, the population consists of patients who remain symptomatic despite treatment with H1-AHs at locally approved doses. In the CQGE031C2302 and CQE031C2303 studies, subjects were randomized (3:3:3:1) to receive ligelizumab 72 or 120 mg q4w or omalizumab 300 mg q4w for 52 weeks treatment period or placebo for 24 weeks then ligelizumab 120 mg q4w for the rest of the 52 week treatment period. In the CQGE031C2202 adolescent study, subjects are randomized (1:2:1) to receive ligelizumab 120 mg q4w for 24 weeks, ligelizumab 24 mg q4w for 24 weeks or placebo for 12 weeks followed by 120 mg q4w for the following 12 weeks. In the CQGE031C1301 open label Japan safety study, subjects receive ligelizumab 120 mg q4w for the 52 weeks treatment period.

Subjects from the core studies (CQGE031C2302 and CQGE031C2303) and the CQGE031C2202 adolescent study will not be unblinded in order to enter this extension study.

This study will remain blinded until all subjects who have transitioned from the Phase 3 core studies have completed Visit 204 (Week 12) in this study, and the primary analysis has been completed after which it will be open-label. Such a study design was chosen to maintain the blind in the Phase 3 core studies and to avoid any bias in primary efficacy assessments due to knowing the dose the subjects received in the Phase 3 core studies.

Adolescents will be included in this study, as they make up all, or part of the, study population in the CQGE031C2202 and CQGE031C2302 / CQGE031C2303 studies, respectively, and as CSU appears to be the same condition with the same unmet medical need in both adult and pediatric populations. The symptoms and natural course of CSU are very similar in both age groups (Church et al 2011), (Caffarelli et al 2013). This Phase 3 extension study will provide further support for long-term efficacy and safety in the adolescent population.

The timepoint for the primary endpoint analysis (Week 12, Visit 204) in this study is chosen to align with that in the Phase 3 core studies, allowing the comparison of retreatment efficacy following 72 mg and 120 mg s.c. q4w.

[redacted]

The 52-week post-treatment follow-up period (12-weeks for subjects completing less than 104 weeks of continuous treatment) will assess safety following treatment discontinuation, as well as evaluate long-term treatment outcome including sustained remission.

To allow an adequate follow-up of approximately 5 half-lives following the last dose administration, a 12-week follow-up period is expected for:

- Subjects discontinuing in the treatment periods
- Subjects discontinuing in the second observation period

This Phase 3 double-blind and open-label extension study will evaluate the efficacy of ligelizumab in the management of CSU from three aspects:

- First, in order to evaluate the retreatment, long-term efficacy and safety with ligelizumab, subjects with moderate to severe disease (defined as UAS7 $\geq$ 16) will be enrolled directly after the screening period as described in Section 3.3. If subjects do not have moderate to severe disease at the time of screening, they will move to the first observation period (see Section 3.2). During this period, they will be monitored for disease activity and safety assessments through a combination of safety phone calls from the sites and in-clinic visits, as per the assessment / visit schedule (Table 8-2). Once they reach the threshold of UAS7 $\geq$ 16, they will return to the site as soon as possible to be enrolled to treatment as described in Section 3.3. In this way, all subjects eligible to transition from the preceding studies will be assessed in the screening period and start treatment within as short a time as possible once they present with moderate to severe disease, or they will be closely followed until they qualify for treatment.
- Second, to evaluate the efficacy and safety of self-administration, subjects who express interest in self-administration outside the clinic setting and fulfill the suitability requirements will undergo training at Visit 204, 205 and 206 (Week 12, 16 and 20). At Visit 207 (Week 24), they will be provided with medication kits and will perform their first outside of clinic self-administration at this time. In addition, subjects who did not self-administer in the first half of the treatment period will be evaluated for self-administration at the start of the second half of the treatment period (Visit 214, Week 52). The same evaluation and training will be followed as at the start of the first half of the treatment period. Subjects who start self-administering in the second half of the treatment period will carry out in-clinic visits at Visits 214, 401, 402, 403, 404 and 405 (Weeks 52, 56, 60, 64, and 72), and at Visit 406 (Week 76) will be provided with medication kits and will perform their first outside of clinic self-administration at this time.
- Third, to obtain ligelizumab monotherapy efficacy data, the subgroup of subjects who achieved a UAS7 $\leq$ 6 at Visit 214 (Week 52), and are re-entering treatment (second half of the treatment period) from the second observation period due to a relapse will be offered the opportunity after discussion with the investigator to discontinue their background H1-AH at Visit 403 (Week 64).

4.1.1 Rationale for choice of background therapy

[redacted], this extension study requires concurrent use of one second generation H1-AH at local label approved doses as

[redacted]

background medication. All subjects will initially receive standard of care therapy (H1-antihistamines at approved doses, per local label) as background medication.

Subjects being kept on background H1-AH medication must remain on a stable treatment regimen (type and dose of H1-AH) throughout the study, including the observation periods.

Subjects who achieved UAS7 ≤ 6 at Week 52 in the treatment period and re-entering the second half of the treatment period from the second observation period, will be considered for discontinuation of their background H1-AH use after three doses of ligelizumab in the second half of the treatment period. The rationale for selecting this subgroup of subjects to evaluate ligelizumab monotherapy is that this population is considered to be more responsive to treatment and thus eligible for evaluation of ligelizumab monotherapy. Ligelizumab monotherapy will be offered to this sub-group at Visit 403 (Week 64). The rationale for selecting this timepoint is based on data from the Phase IIb study CQGE031C2201 study where it was noted that, following administration of the third dose of ligelizumab 72 mg slightly higher numbers of subjects achieved UAS7 = 0 compared to following the first and second dose administrations (44.0% compared to 29.8 and 40.5%, respectively). A similar trend was noted with regards to numbers of subjects achieving UAS7 ≤ 6 following administration of ligelizumab 72 mg (60.5 % compared to 48.8 and 54.2%). In choosing this time point of 12 weeks after re-entering second half of the treatment period and receiving 3 doses of ligelizumab on standard background therapy, it was considered that the effect of ligelizumab would be well-established, and the likelihood of experiencing a flare-up of CSU would be notably diminished by this time.

4.2 Rationale for dose/regimen and duration of treatment

Rationale for dose/regimen

The doses of 72 and 120 mg s.c. q4w [redacted] are selected based on the totality of observed clinical data in the Phase IIb CQGE031C2201 study and the lack of any safety concerns across the doses tested and modeling and simulation data (overview of Phase 2 clinical data provided below). The 72 mg s.c. q4w dose was tested in the CQGE031C2201 study and demonstrated efficacy while the 120 mg s.c. q4w dose was only administered as a single dose and modeled to be an efficacious q4w dose based on dose-response and exposure-response modeling.

In this extension study, until Week 12 (Visit 204) both 72 mg and 120 mg s.c. q4w will be evaluated. Subjects who received 72 mg liquid in vial s.c. q4w in the core studies will continue to receive 72 mg until Week 12 (Visit 204) in this extension study. All other subjects from the other treatment arms in the Phase 3 studies, subjects from CQGE031C2202 and CQGE031C1301 studies will receive ligelizumab 120 mg s.c. q4w in this extension study. This dose i.e. 120 mg is the higher of the two doses being evaluated in the Phase 3 core studies and is the only dose being evaluated in the CQGE031C1301 study. The rationale for including the 72 mg dose until Week 12 (Visit 204) is to allow ligelizumab retreatment efficacy comparison between the Phase 3 core studies and the extension study until primary endpoint at Week 12 (Visit 204).

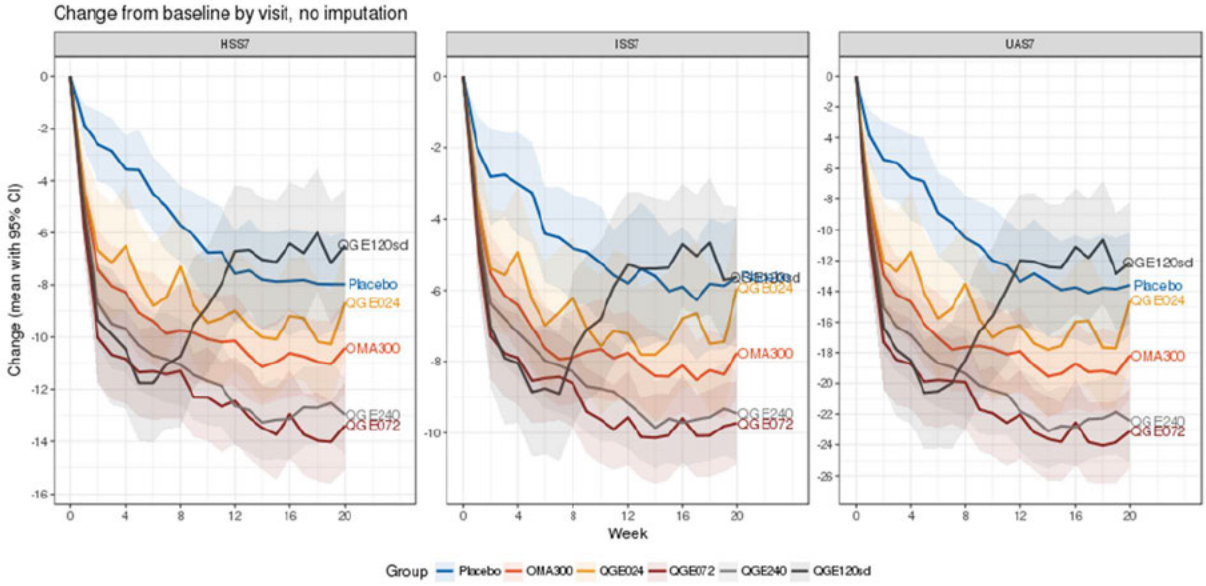
Overview of Phase 2 clinical data

[redacted]

The following ligelizumab doses were tested in the CQGE031C2201 study: 24, 72 and 240 mg q4w over 20 weeks, as well as 120 mg in a single administration. Data for the 120 mg single dose was collected to enable further exposure response analysis, to support dose selection and frequency, based on duration of effect.

The treatment responses for UAS7 change from baseline (the primary endpoint (Week 12) for the Phase 3 program) and for HSS7 and ISS7 are shown in Figure 4-1 below.

Figure 4-1 Change from baseline in HSS7, ISS7, and UAS7 by visit



The strongest treatment responses across all 3 endpoints at Week 4 were seen with 72 mg and 120 mg and appeared to be comparable. Beyond Week 4, data is available for 24 mg, 72 mg and 240 mg. The response for the 72 mg and 240 mg doses appear to be similar up to Week 20. With doses of 24 or 72 mg q4w a partial relapse of symptoms towards the end of the dosing interval can be observed. These data imply that the 72 mg q4w dose achieves rapid and good control of symptoms and a dose higher than 72 mg q4w can provide enough drug exposure so that relapse of symptoms throughout the dosing interval is minimal. These data also imply that treating subjects at a monthly interval is beneficial in achieving a meaningful sustained clinical response.

During the Phase 2 study, there was no evidence of dose related safety signals up to Week 20 except for a potential trend in injection site reactions, which were mostly non-serious, mostly mild in severity, reversible and did not lead to treatment discontinuations. This observation is further supported by data from adult asthma trials where doses up to 240 mg q2w were administered. Furthermore, in the CSU Phase 2 extension study CQGE031C2201E1 which uses 240 mg q4w, no new safety signals have been observed.

[redacted]

[redacted]

Summary

[redacted]

A dose of 120 mg is considered a safe dose level for this Phase 3 extension study, with a substantial safety window. To allow for retreatment efficacy comparison, a dose of 72 mg is included in this extension study until Week 12 (Visit 204). There have been no new or unexpected safety findings in the completed and ongoing studies CQGE031C2201, CQGE031C2201E1, CQGE031C2302 and CQGE031C2303 studies to date, across all the doses assessed.

Rationale for observation periods

In clinical practice, many patients with CSU require chronic treatment for their disease. In this extension study, subjects transitioning from the preceding studies who have not yet relapsed to moderate to severe disease (UAS7 $\geq$ 16) will move to the first observation period of up to 36 weeks, remaining on their background and rescue H1-AH medication. Based on the Phase IIb CQGE031C2201/E1 study data, some subjects may not relapse for many weeks after

[redacted]

extended treatment of ligelizumab. Hence, this will allow observation of subjects from the preceding studies for relapse of disease over an extended period of time. Those presenting with a relapse of moderate to severe disease will be enrolled directly to a 104 week (2 year) treatment period with a decision branch point at Week 52. Subjects who have not relapsed by the end of the first observation period will exit from the study.

Rationale for treatment period duration

In order to parallel clinical practice, where patients with long-term CSU are likely to be treated for up to 6 or 12 months then reassessed for ongoing disease and the need for ongoing treatment, the treatment period has been designed with a three-way branch point at the half-way mark, i.e. Week 52. Here the subject will be assessed by the investigator. Depending on the results of the UAS7 scores and a discussion between the investigator and the subject, the subject will either continue treatment or stop and transition to the second observation period, move to the follow-up period or exit the study. The three options are:

- Subjects with a UAS7 $\leq$ 6:

  These subjects, having reached the state of their CSU being well-controlled, will transition to the second observation period, to permit a drug "holiday" and following the subject for evidence of persistent remission / control of disease or relapse.
- Subjects with a UAS7 > 6 and < 16:

  These subjects have improved from their original enrollment status of moderate-to-severe disease to the level of mild disease. Nonetheless, the persistence of active disease demonstrates the need for ongoing treatment to keep their disease suppressed. These subjects will continue uninterrupted treatment unless a decision is made, based on a risk-benefit discussion with the investigator, to move the subject to the second observation period.
- Subjects with a UAS7 $\geq$ 16:

  As these subjects still have moderate-to-severe disease, yet also may have had significant improvement from their enrollment status, it is important that they are given the opportunity to be evaluated on an individual basis by the investigator. Evidence from the literature supports the opinion that these subjects will have had more severe and longstanding disease prior to initiating anti-IgE therapy and require long-term treatment (Vadasz et al 2017). Therefore, the investigator must reassess the risk-benefit with the subject and decide whether to continue or discontinue treatment (see Section 9.1.1). This discussion with the individual subject will include whether or not the subject has had enough improvement from their initial disease state at the start of the treatment period, even though they still have moderate to severe disease, to justify continuing in the treatment period.
  - One example of this scenario: a subject enters the screening period with a UAS7 of 36 (severe urticaria) and at Week 52, has a UAS7 of 18 (moderate urticaria). In this scenario, the subject may feel that this has been a significant enough improvement to warrant continuation of treatment to Visit 9998 (Week 104/EOT). Here the investigator must review the risk-benefit with the subject to ensure that all efficacy and safety factors are reviewed and the investigator is in agreement with the subject to continue without any undue risk. This may include a review of any adverse events

[redacted]

(AEs)/serious adverse events (SAEs) that the subject may have reported up to this point, and any other relevant information from the investigator's perspective.

As always, subject may discontinue treatment or from the study at any time, including at this Week 52 branch point.

This two-year overall treatment period, with flexibility for two observation periods closely reflects the practicing physician's treatment plan for the long-term management of patients with this chronic relapsing disease.

In addition, the duration of this study with its long-term treatment period and observation periods will support Novartis' commitment to post trial access for patients completing pivotal Phase 3 studies.

Rationale for route of administration

In the completed CQGE031C2201, CQGE031C2201E1 studies, the ongoing CQGE031C2302, CQGE031C2303, CQGE031C2202 and CQGE031C1301 studies, ligelizumab was/is administered subcutaneously. The subcutaneous (s.c.) 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 and tolerability.

Rationale for using pre-filled syringes (PFS)

In this extension study, after Visit 204 (Week 12), all subjects will be administered ligelizumab in X100L pre-filled syringes (ligelizumab 120 mg PFS preassembled with an off-the shelf needle safety device). The rationale for using pre-filled syringes is to allow easy administration of a single fixed dose of ligelizumab 120 mg for any drug administrator in clinic or outside the clinic. To allow any efficacy comparison at Week 12 (Visit 204) (the primary endpoint) between the preceding studies (CQGE031C2302, CQGE031C2303, CQGE031C2202, CQGE031C1301), all of which use ligelizumab liquid in vial, and this extension study, ligelizumab administration in PFS will begin only at Week 12 (Visit 204).

Rationale for self-administration option

In this study protocol, the term "self-administration" refers to the process by which the investigational drug is actually administered to the subject in any setting outside of the clinic, and may take any of the following forms:

- An adult subject who is appropriately trained (see Section 6.7.2) and takes complete responsibility for the injection;
- an adult subject whose adult lay caregiver is appropriately trained (see Section 6.7.2), takes complete responsibility of preparing the subject for the injection and carries out the actual injection of the adult subject with ligelizumab; or
- an adolescent subject whose adult lay parent / caregiver is appropriately trained, takes complete responsibility of preparing the subject for the injection and carries out the actual injection of the adolescent subject with ligelizumab.

A. The benefits of self-administration of medication (Richardson et al 2014)

- Significantly reduces the burden on patients, caregivers, healthcare professional and the overall health care systems, as well as direct and indirect costs for the patient and the healthcare system

[redacted]

- Improves patients' knowledge about the disease and medication and increases sense of responsibility and independence of managing their conditions
- Patients are more careful and responsible in administering the investigational drug
- Sense of ownership may decrease the chance of medication errors
- Better compliance leading to improved effectiveness of disease management
- Specifically regarding *self-injection* (Collier et al 2017; Keininger and Coteur 2011):
  - increased treatment adherence; reduced frequency of hospital visits, convenience; economic benefits (patient and the healthcare system)
  - control of their treatment schedule (within the limits imposed by the product label) and their treatment setting; greater independence and freedom in their social, domestic and professional lives; psychological benefits including improved self-esteem; improved therapeutic outcomes and improved HRQoL

B. The importance of studying self-administration in this Phase 3 extension study

In addition to the benefits detailed above, offering subjects self-administration will:

[redacted]

- significantly reduce the burden required for subjects to make on-site visits, with all the associated benefits described above and in addition, will permit more time for subjects' daily life activities.

Rationale for starting points of self-administration

As self-administration can only be done with PFS and to allow sufficient training to subject, the first self-administration outside of the clinic starts at Week 24 in the first half of the treatment period. There is a second opportunity to start self-administration outside of the clinic in the second half of the treatment period at Week 76. This time point is chosen in order that monotherapy initiation at Week 64 does not coincide with self-administration outside of the clinic, as efficacy and safety assessments of monotherapy and self-administration may be confounded (e.g. in case there is an increase in injection site reactions due to discontinuation of H1-AH).

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

The first interim analysis is planned once all subjects of the CQGE031C2302 and CQGE031C2303 have completed Week 12 (Visit 204) in the first half of the treatment period to evaluate the primary endpoint of retreatment efficacy (or discontinued the trial or completed the first observation period without relapse).

The second interim analysis will be performed at the end of the first half of the treatment period at Week 52 to evaluate endpoints up to the end of 1 year treatment.

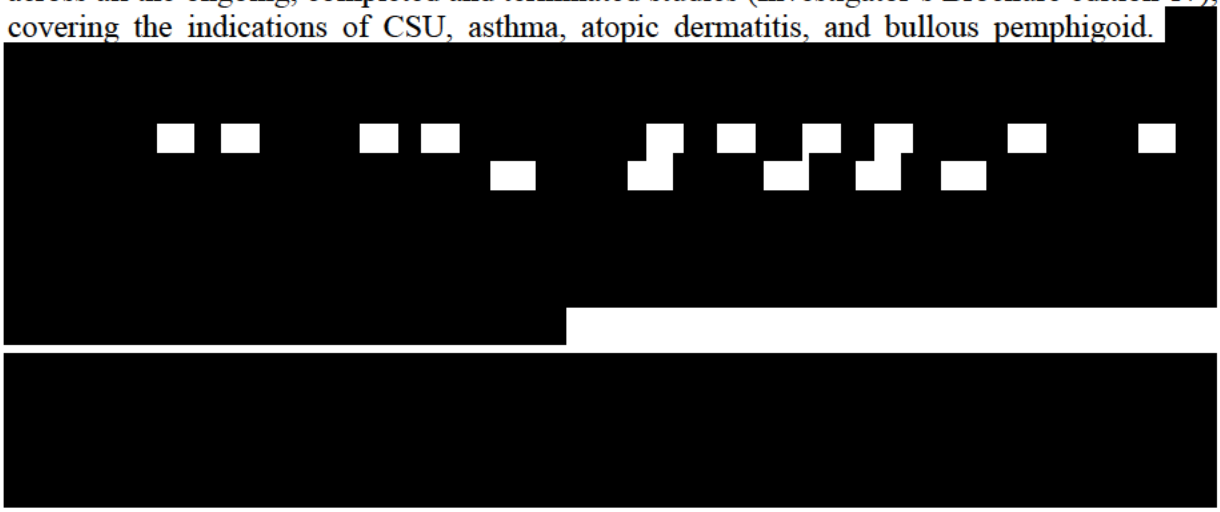
Additional analyses may be performed to support health authority interactions as necessary.

[redacted]

At the End of Study, a final analysis of all data collected up to last study visit will be performed when all subjects have completed the last study visit.

4.5 Risks and benefits

In the overall ligelizumab clinical program, approximately 3607 subjects have been exposed across all the ongoing, completed and terminated studies (Investigator's Brochure edition 17), covering the indications of CSU, asthma, atopic dermatitis, and bullous pemphigoid.



Overall, no apparent dose-dependent safety signals (except for a potential trend in injection site reactions) 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 asthma clinical study CQGE031B2201, 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 single dose), omalizumab and placebo. The frequency of injection site reactions was noted to be common with a potential trend towards dose dependency, however, the sample size of subjects for the different dose levels was too small to reach a definitive conclusion. The incidence was higher with ligelizumab 72mg and 240mg as compared to omalizumab 300mg and placebo arms. In all studies, the majority of injection site reactions were non-serious, mostly mild in severity, reversible, and did not lead to discontinuation of study treatment.

With regard to 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).

Risk associated with omalizumab is well characterized. Potential risks to omalizumab are hypersensitivity-type allergic reactions (i.e., anaphylaxis, angioedema and urticaria), immune complex associated allergic reactions (i.e., serum sickness), Churg-Strauss syndrome, and hyper eosinophilia. In clinical trials, the most commonly reported adverse reactions are injection site reactions (including injection site pain, swelling, erythema and pruritus) and headaches.

Additional information on risks associated with omalizumab is found in the local health authority approved product information. Severe thrombocytopenia has been reported in preclinical studies in cynomolgus monkeys with high doses of omalizumab. Although thrombocytopenia has not been observed with ligelizumab in the toxicology studies in non-human primates or in the clinical program conducted so far, the current protocols include monitoring of platelets as part of the hematology assessment. Ligelizumab is in the same class as omalizumab and therefore, in theory, carries the similar risks as omalizumab.

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, screening will be carried out for the presence of parasitosis, particularly helminthic infections and these subjects will be excluded prior to enrollment. In addition, 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. The resulting increase of IgE production would decrease the half-life of ligelizumab, through target mediated disposition, hence restoring normal IgE levels more rapidly.

Based on currently available data from the ligelizumab clinical program, there is no evidence of an increased risk of infections/viral infections. At this time there are no specific data to inform on incidence or severity of Corona Virus Disease 2019 (COVID-19) (due to severe acute respiratory syndrome coronavirus 2) in patients receiving ligelizumab.

Therefore, based on the cumulative data available across all clinical studies in different patient populations for ligelizumab, the current evidence indicates that ligelizumab is safe and well tolerated and thus appropriate for further development.

The non-clinical safety evaluation for ligelizumab supports a clinical treatment of children down to the age of 2 years. There is no evidence to suggest that ligelizumab will have a different mode of action or will be cleared differently in pediatric versus adult subjects. No new or unexpected safety signals were identified in the CQGE031C2201 or CQGE031C2201E1 studies in adults.

The data from CQGE031C2201 and CQGE031C2201E1 demonstrates that ligelizumab administration results in significant improvement of CSU symptoms including itch, hives, angioedema and quality of life (QoL) irrespective of chronic urticaria (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 including periodic review of data by an independent Data Monitoring Committee (DMC), the use of an electronic diary at home to monitor symptoms and the use of rescue medication. Furthermore, a dedicated clinical safety team at Novartis will actively monitor the safety of subjects and take proper actions to address any safety concerns that may emerge during the study.

[redacted]

To manage worsening of disease during the course of this study, including when subjects may discontinue their background medication, the study allows use of selected H1-AH as rescue medication as per CSU treatment guidelines.

In the overall clinical program for ligelizumab in CSU, ligelizumab efficacy is always evaluated with H1-AH as background medication. Allowing a subgroup of subjects, who are considered more responsive to treatment, to stop H1-AH background medication, gives the opportunity to collect ligelizumab efficacy data when administered as monotherapy. Given that this sub-group of subjects would have responded well to treatment in the first half of the treatment period, they would be more accommodated to stop their background medication. Further, any potential worsening of CSU symptoms in this sub-group, can be managed with the use of H1-AH rescue medication as per treatment guidelines.

The provision for use of rescue medications has been designed to minimize interference with efficacy assessment of the study drug, and investigators should instruct subjects on its use with this purpose in mind (see Section 6.2.3).

After Visit 204 (Week 12), ligelizumab will be administered (in-clinic and outside the clinic) in X100L Plus PFSs which is a single-use, disposable combination product, intended for the s.c. application of a fixed dose of ligelizumab. [redacted]

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 must agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the subject will not reliably comply, they should not be entered or continue in the study.

4.6 Rationale for Public Health Emergency mitigation procedures

During a Public Health emergency as declared by Local or Regional authorities, i.e., pandemic, epidemic or natural disaster, mitigation procedures to ensure participant safety and trial integrity are listed in relevant sections. Notification of the Public Health emergency should be discussed with Novartis prior to implementation of mitigation procedures and permitted/approved by Local or Regional Health Authorities and Ethics Committees as appropriate.

5 Population

The population will consist of male and female subjects aged $\geq$ 12 years who have been diagnosed with CSU and remain symptomatic despite the use of H1-AH and completed any of the preceding studies. These preceding studies are planned to enroll a total of 2267 subjects who in the case of completion of the respective study will have the possibility to consent and enter this extension study.

[redacted]

The majority of subjects will be adults, as only about 5% of subjects completing the Phase 3 pivotal studies are expected to be adolescents, only the 49 subjects in the CQGE031C2202 study are adolescents and there are no adolescents in the CQGE031C1301 Japan safety study.

All the enrolled subjects will be assigned to the treatment groups according to the preceding study treatment group.

5.1 Inclusion criteria

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

1. Written informed consent must be obtained before any assessment is performed.
2. Subject's, parent's or legal guardian's signed written informed consent and child's assent, if appropriate, must be obtained before any assessment is performed. Of note, if the subject reaches age of consent (age as per local law) during the study, they will also need to sign the corresponding study Informed Consent Form (ICF) at the next study visit.
3. Subjects who successfully completed all of the treatment period and the follow-up period of any of the following studies: CQGE031C2302, CQGE031C2303, CQGE031C2202 or CQGE031C1301.
    a. Subjects who had completed the preceding studies prior to start of this extension study are also allowed to participate, provided they perform the full Screening Period as soon as the extension study had been initiated at their study site.
4. Male and female, adult and adolescent subjects ≥12 years of age (NOTE: Recruitment of adolescent subjects, ≥ 12 to < 18 years of age, will be in accordance with local regulatory/ethics committee requirements).
5. Willing and able to complete a daily symptom eDiary for the duration of the study and adhere to the study visit schedule.
6. Subjects must not have had missing eDiary entries in the 7 days prior to the first visit of the first half of the treatment period* or first visit of the first observation period (at least 12 out of 14 records for HSS and ISS respectively must be present in the week the UAS7 score is assessed).

    *Subjects must reach UAS7 score ≥16 prior to treatment.

    For subjects entering treatment directly from the screening period the score will be assessed in the 7 days prior to first treatment visit.

Rescreening may be considered only once.

5.2 Exclusion criteria

Subjects meeting any of the following criteria are not eligible for inclusion in this study.

1. Use of investigational drugs, other than those in use in the preceding studies, at the time of enrollment, or within 30 days or 5 half-lives prior to Visit 1 (Screening visit), whichever is longer.
2. Use of omalizumab within 16 weeks of Visit 101 or 201 (whichever occurs first).
3. History of hypersensitivity to the study drug ligelizumab or its components, or to drugs of similar chemical classes (i.e. to murine, chimeric, or human antibodies).
4. New onset or signs and symptoms of any form of chronic urticarias other than CSU during the preceding studies CQGE031C2302, CQGE031C2303 or CQGE031C2202.

[redacted]

- This includes, but is not limited, to the following:
  - Inducible urticaria: symptomatic dermographism (urticaria factitia), cold-, heat-, solar-, pressure-, delayed pressure-, aquagenic-, cholinergic-, or contact-urticaria.

5. Diseases with possible symptoms of urticaria or angioedema such as urticarial vasculitis, erythema multiforme, cutaneous mastocytosis (urticaria pigmentosa), and hereditary or acquired angioedema (e.g., due to C1 inhibitor deficiency).
6. Subjects with evidence of helminthic parasitic infection as evidenced by stools being positive for a pathogenic helminth according to local guidelines. All subjects should have been assessed for evidence of parasitic infection at Visit 1999 of the preceding studies (see Section 8.4.3 of respective preceding study's protocol). If stool testing is positive for pathogenic helminthic organisms, the subject will not be enrolled in to this extension study and will not be allowed to rescreen.
   - In the event that stool samples from Visit 1999 of the preceding studies were not collected or the results from these are not available, subjects will be assessed for evidence of parasitic infection at Visit 1 (see Section 8.4.4). If stool testing is positive for pathogenic helminthic organisms, the subject will not be enrolled to this extension study and will not be allowed to rescreen.
7. Any other skin disease associated with chronic itching that might in the opinion of the investigator, confound the study evaluations and results (e.g. atopic dermatitis, contact dermatitis, bullous pemphigoid, dermatitis herpetiformis, senile pruritus etc.).
8. Any H2-antihistamine use after Visit 1 in this study.
9. Any LTRA (e.g. montelukast or zafirlukast) use after Visit 1 in this study.
10. Any H1-antihistamine background medication used at greater than the local label approved doses after Visit 1.
    - H1-antihistamine rescue medication may be used at up to 4 times the local label approved doses after Visit 1, at the discretion of the investigator (see Section 6.2.3).
11. Prior exposure to any anti-IgE antibody therapy other than omalizumab and ligelizumab.
12. History or evidence of ongoing alcohol or drug abuse, within the last 6 months prior to enrollment.
13. Inability to comply with study and follow-up procedures.
14. Subjects taking medications prohibited by the protocol (see Section 6.2.2, Table 6-2).
15. Contraindications to or hypersensitivity to study drugs including but not limited to fexofenadine, loratadine, desloratadine, cetirizine, levocetirizine, rupatadine or epinephrine or any of their ingredients.
16. Documented history of anaphylaxis.
17. Onset of malignancy of any organ system within the past 5 year (except for basal cell carcinoma or actinic keratoses or Bowen disease (carcinoma in situ) that have been treated with no evidence of recurrence in the past 12 weeks; carcinoma in situ of the cervix or non-invasive malignant colon polyps that have been removed).
18. Presence of clinically significant cardiovascular (such as but not limited to myocardial infarction, unstable ischemic heart disease, New York Heart Association Class III/IV left ventricular failure, arrhythmia, uncontrolled hypertension within 12 months prior to Visit 1), neurological, psychiatric, metabolic or other pathological conditions (such as but not

[redacted]

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 subject, interfere with evaluation or interpretation of the study results or preclude completion of the study.

19. 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.
20. History of, or current treatment for, hepatic disease including but not limited to acute or chronic hepatitis, cirrhosis or hepatic failure or AST (aspartate aminotransferase)/ALT (alanine aminotransferase)/albumin/TBL (total bilirubin) levels of more than 1.5x upper limit of normal (ULN) at Visit 1 or Visit 2*.
21. History of renal disease or creatinine level above 1.5 x ULN at Visit 1 or Visit 2*.
22. Platelets < 100,000/µL at Visit 1 or Visit 2*.
23. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test.
24. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, **unless** they are using effective methods of contraception during dosing of investigational drug (and approx. 4 months, i.e. 5 half-lives, after last dose of ligelizumab). Effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable effective methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or bilateral 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
    - 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
    - Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps). For UK: with spermicidal foam/gel/film/cream/vaginal suppository
    - 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 or intrauterine system

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

Women are considered post-menopausal if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms). Women are considered not of child bearing potential if they are post-menopausal or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy

[redacted]

or bilateral 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 childbearing potential.

If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the informed consent form (ICF).

*Subjects who did not meet applicable eligibility criteria at Visit 2, as listed above, will be discontinued from the study and will not enter treatment. Since these subjects have been initially eligible at Visit 1 and participated in the first observation period, they will not be considered screen failure subjects if they do not enter treatment.

6 Treatment

6.1 Study treatment

Novartis Global Clinical Supply will supply Ligelizumab (QGE031) 120 mg per 1 mL liquid in vial and 120 mg per 1 mL as PFS with a needle safety device (NSD).

6.1.1 Investigational and control drugs

Table 6-1 Investigational drug

Investigational (Name and strength)	Pharmaceutical Dosage Form	Route of Administration	Presentation	Sponsor (global or local)
Ligelizumab 120 mg per 1 mL	Liquid in vial	s.c.	Open-label subject kits; vials	Sponsor global
Ligelizumab (QGE031) 120 mg per 1 mL	Solution for injection in a pre-filled syringe	s.c	Open-label subject kits; pre-filled syringe	Sponsor global

No placebo or active comparator will be used.

6.1.2 Additional study treatments

No additional treatment beyond investigational treatment (ligelizumab) is requested for this trial. Subjects will continue to use their background medication (H1-AH at local label-approved doses) with a stable regimen during the study except for those on monotherapy. For rescue medication, see Section 6.2.3.

6.1.3 Treatment arms/group

First half of the treatment period

For subjects rolling over from the core studies CQGE031C2302 and CQGE031C2303:

a. Blinded treatment period (Week 0, 4 and 8; Visits 201, 202, 203 respectively):
   - Ligelizumab 120 mg arm: 1 injection of 1.0 mL ligelizumab (120 mg/mL) liquid in vial s.c. q4w
   - Ligelizumab 72 mg arm: 1 injection of 0.6 mL ligelizumab (120 mg/mL) liquid in vial s.c. q4w

[redacted]

b. Open-label treatment period (Week 12 through Week 52; Visits 204 to 214):
   - Ligelizumab 120 mg arm: 1 PFS injection of 1.0 mL ligelizumab s.c. q4w

For subjects rolling over from CQGE031C2202 and CQGE031C1301:

a. Open-label treatment period (Week 0, 4 and 8; Visits 201, 202, 203 respectively):
   - Ligelizumab 120 mg arm: 1 injection of 1.0 mL ligelizumab (120 mg/mL) liquid in vial s.c. q4w

b. Open-label treatment period (Week 12 through Week 52; Visits 204 to 214):
   - Ligelizumab 120 mg arm: 1 PFS injection of 1.0 mL ligelizumab s.c. q4w

Second half of the treatment period

For all subjects:

a. Open-label treatment period (Week 52 to Week 104; Visits 214 to 9998/EOT)
   - Ligelizumab 120 mg arm: 1 PFS injection of 1.0 mL ligelizumab s.c. q4w

Further details are provided in Section 6.3.2, Section 6.7 and Table 8-1.

6.1.4 Treatment duration

As described above in Section 3 and Section 4.2, the longest possible treatment is 104 weeks however this treatment might not be continuous and might span over a period of 156 weeks due to possibly entering the observation period.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

Concomitant H1-AH background medication

This study requires concurrent use of one second generation H1-AH at local label approved doses as background medication except for the subgroup of subjects who will be offered a choice to go off background medication in the second half of the treatment period.

Subjects must remain on the same H1-AH background medication they were taking in the preceding studies (exceptions may apply, e.g., subjects experienced an AE related to the specific antihistamine or due to unavailability). Subjects must remain on the same H1-AH while taking background H1-AH and will only be allowed to switch to another background H1-AH (at approved dose) due to an AE.

If a subject must switch to another background H1-AH 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 (eCRFs).

[redacted]

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact the Novartis monitor before enrolling a subject or allowing an enrolled subject to start a new medication.

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 is also listed in Table 6-2. Each concomitant drug must be individually assessed against all exclusion criteria and Table 6-2 to see if it is allowed. If in doubt, the investigator should contact Novartis or delegate before enrolling a subject or allowing an enrolled subject to start a new medication.

Table 6-2 Prohibited Medication

Medication or Treatment	Minimum required period without medication or treatment
Omalizumab*	At least 16 weeks prior to V101 or V201 (whichever occurs first)
Any anti-IgE antibody therapy other than omalizumab and ligelizumab	No prior use allowed
Routine oral corticosteroids (more than 3 doses over a 5 day period)**	30 days prior to Visit 1
Intramuscular /intra-articular /intravenous - injections of 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
Any second generation (non-sedating) H1-antihistamine at greater than local label approved dose(s)***	Stop at Visit 1
Hydroxychloroquine or chloroquine	30 days prior to Visit 1
Dapsone	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
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
Live attenuated vaccine	30 days prior to Visit 1

*If a subject takes concomitant omalizumab during the study the subject must discontinue from the study, in which case, [redacted]

[redacted]

** Allowed only as rescue therapy, in the form of oral corticosteroids, on an as-needed basis for unbearable symptoms as per Section 6.2.3. Other preparations of corticosteroids (e.g. intra-nasal or topical corticosteroids) with limited systemic exposure for non-CSU indications can be used on an as needed basis.
*** Applies to H1-antihistamines used as background medication, or as a concomitant medication for non-CSU indication. The six H1-AH permitted as rescue medications may be used at up to 4 times local label approved dose at the discretion of the investigator (see Section 6.2.3).

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

Table 6-2 is not considered all inclusive. Medication should be assessed for adherence to the indication and other inclusion/exclusion criteria.

6.2.3 Rescue medication

If unbearable symptoms occur during the study, Investigators must instruct subjects on the acceptable treatment for managing their disease with the use of rescue medication, thereby allowing subjects to continue in the study as long as possible. At the same time, the provision for use of rescue medications has been designed to minimize interference with efficacy assessment of the investigational drug. Therefore, investigators must instruct subjects on rescue medication use with this purpose in mind, i.e. to assess the need for rescue medication on a day-by-day basis, and following the limitations below for both H1-AH and oral corticosteroid rescue medications.

Anti-histamine rescue medication

Fexofenadine, loratadine, desloratadine, cetirizine, levocetirizine and rupatadine H1-AHs, in addition to being allowed as background medication, will be allowed as rescue medication and used on an as-needed basis during screening, observation, treatment and follow-up periods for treatment of unbearable symptoms. The six H1-AH permitted as rescue medications may be used at up to 4 times local label approved dose at the discretion of the investigator. The selection of the H1-AH rescue medication should be made once for an individual subject at Visit 1. A switch of the H1-AH rescue medication for an individual subject will only be permitted in the event of an associated AE that prevents the subject from taking the original H1-AH rescue medication or if the medication is no longer available in the country. The reason for the change of H1-AH rescue medication must be clearly documented in detail in the appropriate eCRF.

Corticosteroid rescue medication

In addition, after the Week 12 (Visit 204) primary endpoint, subjects will be permitted to use oral corticosteroids such as prednisone and its equivalents as rescue medication if needed, for treatment of unbearable symptoms.

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, in

[redacted]

order to minimize any confounding suppression of signs and symptoms of CSU, oral corticosteroid use will be restricted to after the Week 12 (Visit 204) assessments for all subjects.

In addition, for all subjects, the number of doses of oral corticosteroids will be limited to:

- a maximum of 3 days per 30 days;
- a maximum of 9 doses total (i.e. a maximum of 9 days of corticosteroids in total) in the first half of the treatment period after Week 12
- a maximum of 9 doses total in the second half of the treatment period;
- a maximum of 9 doses total in the 52-week follow-up period;
- a maximum of 3 doses total in the 12-week follow-up period.

Use of oral corticosteroid rescue medication is **not** permitted during the first and second observation periods, in order to avoid masking the signs and symptoms of CSU that would make the subject eligible to start / re-start treatment with ligelizumab. If a subject uses more than allowable doses of corticosteroids in each half of the treatment period, then the subject will be discontinued from study treatment.

While the dose of oral corticosteroid should be individualized for subject comfort, it is suggested that the investigator consider a maximum daily dose, in order to minimize the risk of significant interference with the quality of data. Using oral prednisone as an example, this might be in the range of 0.5 mg/kg. If a subject requires prednisone in excess of 0.5 mg/kg as a daily dose of rescue medication on an ongoing basis, it is suggested that that they might not be considered suitable subjects for the study as they would likely exceed the allowed corticosteroid doses.

The selection of the oral corticosteroid rescue medication should be made once for an individual subject. A switch of the oral corticosteroid rescue medication for an individual subject will only be permitted in the event of an associated AE that prevents the subject from taking the original oral corticosteroid rescue medication. The change of oral corticosteroid rescue medication must be clearly documented in detail in the appropriate eCRF.

Rescue medication will be sourced locally. Use of H1-AH and oral corticosteroids rescue medication (number of tablets taken and name of rescue medication) only for CSU will be recorded on the eDiary by the subject. The rescue medication information will be captured on the appropriate eCRF.

6.3 Subject numbering, treatment assignment, randomization

6.3.1 Subject numbering

Each subject is identified in the study by a Subject Number that will be assigned in the electronic data capture system (EDC) when the subject is first enrolled for screening Visit 1. The Subject Number is retained as the primary identifier for the subject throughout his/her participation in the entire trial. The Subject Number consists of the Center Number (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 ICF, the subject is assigned to the next sequential Subject Number available.

[redacted]

6.3.2 Treatment assignment, randomization

No randomization will be performed in this study. The assignment of treatment will depend on the previous study treatment assignment.

At Visit 201 (Week 0), all eligible subjects will be assigned to investigational treatment via Interactive Response Technology (IRT). All subjects will receive 120 mg s.c. q4w except subjects treated with 72 mg s.c. q4w in the core studies CQGE031C2302 or CQGE031C2303, who will continue to receive 72 mg s.c. q4w in this extension study for the first 12 weeks (see Section 3.3 and Section 6.1.3). The investigator or his/her delegate will contact the IRT after confirming that the subject fulfills all the inclusion/exclusion criteria. The IRT will assign the subject, to a treatment arm and will specify a unique medication number for the package of investigational treatment to be dispensed to the subject. All kits of study treatment assigned by the IRT will be recorded in the IRT system.

The treatment assignment list for subjects will be reviewed and approved by a member of the Randomization Office.

6.4 Treatment blinding

Subjects, investigator staff and personnel performing the study assessments for studies CQGE031C2302 and CQGE031C2303 will remain blinded to the identity of the treatment from the time of enrollment (Visit 201, Week 0) until all subjects in this study have completed Week 12 in the first half of the treatment period and the primary analysis has been completed. An unblinded study monitor will visit the study site to monitor study drug related administration (see Section 11.3).

Should additional analysis be required to support Health Authority interactions (prior to the primary analysis), sponsor team members may be unblinded for such analysis. These unblinded team members will not be further involved in the study conduct until the primary analysis has been completed.

No blinding is required for subjects transitioning from study CQGE031C2202 and CQGE031C1301, as all subjects will receive 120 mg s.c. q4w ligelizumab.

Treatment blinding will be maintained at Visits 201, 202 and 203 (Weeks 0, 4 and 8) when subjects are being administered with liquid in vial (see Section 3.3) using the following methods:

1. Treatment assignment data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study with the following exceptions:
   - Bioanalyst ([redacted]): to enable identification of samples from the ligelizumab treatment arms of the study to facilitate bioanalysis;
   - Independent personnel (external to Novartis) involved in monitoring anaphylaxis, neoplastic and cerebro-cardiovascular events (Adjudication Committee members), if needed; and
   - An independent DMC (see Section 10.2.3) and the independent statistician supporting the DMC activities (Table 6-3).
   - These personnel will not be involved in any other trial activities.

[redacted]

2. The following measures will be applied to keep the subject and study personnel blinded despite differences of the investigational treatments in volume:
   - The investigational drug must be prepared by an independent unblinded pharmacist (or authorized delegate) and administered by an independent unblinded administrator who are both not involved in any of the study assessments. If an unblinded pharmacist is not available, preparation and administration of the investigational drug may also be performed by a single independent unblinded site person if he/she is authorized to do both.
   - Preparation of the investigational drug must be done in a separate space/room where subjects and blinded study personnel have no access during time of preparation.
   - To blind the liquid volume in the syringe, one method is to cover the syringe by a strip of opaque tape. The differences in length of the syringe plunger, related to the differences in the volume, should also be covered by the way of administration (see Pharmacist Manual).
   - The prepared syringes must be placed on a tray which is covered by an opaque towel to ensure the syringes are not visible to the subject at any time.
   - The independent unblinded authorized site persons (pharmacist/administrator) should not communicate the volume and any perceived sensation associated with the administration of the investigational drug.
   - The subject will be instructed to look away, from the tray of prepared syringes (whenever the tray is uncovered) and from the injection site.

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

Unblinding will occur in the case of subject emergencies.

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

Table 6-3 Blinding and unblinding plan (applies to all subjects in this study transitioning from the core studies till completion of Week 12 in the first half of the treatment period and the primary analysis has been completed)

	Time or Event				
Role	**Treatment assignment list generated**	**Treatment allocation & dosing**	**Safety event (single subject unblinded)**	**DMC Analysis**	**Any additional analyses to support health authority interactions prior to primary analysis**
Subjects	B	B	B	B	B
Investigator and Site staff	B	B	UI	B	B

[redacted]

Role	Time or Event			DMC Analysis	Any additional analyses to support health authority interactions prior to primary analysis
	Treatment assignment list generated	Treatment allocation & dosing	Safety event (single subject unblinded)		
Unblinded site staff e.g., pharmacy staff and investigational drug administrator	B	UI	NA	B	B
Global Clinical Supply and Randomization Office	UI	UI	UI	UI	UI
Unblinded sponsor staff e.g., for study treatment re-supply, unblinded monitor(s)	B	UI	NA	B	B
Unblinded Pharmacovigilance sponsor staff	B	B	UI	B	B
Trial Statistician/statistical programmer	B	B	B	B	B
Independent Statistician/statistical programmer	B	B	B	UI	UI
Independent committees used for assessing interim results, if required (e.g., DMC)	B	UI	UI	UI	UI
Adjudication committee	B	B	B*	B	B
Bioanalyst ([redacted])	B	UI	B	B	B
All other sponsor staff not identified above (trial team, project team, management & decision boards, support functions)	B	B	B	B	B
Unblinded sponsor team for additional analyses (if needed)	B	B	B	B	UI

UI: Allowed to be unblinded on individual subject level
B: Remains blinded
NA: Not applicable to role

*Unblinded if needed

[redacted]

6.5 Dose escalation and dose modification

6.5.1 Dose modifications

Investigational drug dose adjustments are not permitted.

Any interruption of investigational drug administration should be discussed with Novartis or delegate regarding the subject's eligibility to continue investigational treatment.

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

6.5.2 Follow-up for toxicities

Not applicable.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

Subjects will have one s.c. injection every 4 weeks at 13 visits during the first half of the treatment period and for 48 weeks at 13 visits during the second half of the treatment period. For the first 3 treatment visits, the subjects will receive the injection as liquid in vial and thereafter as PFS.

The investigator must promote compliance by instructing the subject to take the study treatments (investigational, background and rescue medications) exactly as prescribed, by stating that compliance is necessary for the subject's safety and the validity of the study data. The subject must also be instructed to contact the investigator if he/she is unable, for any reason, to take the study treatment as prescribed.

For subjects receiving investigational treatment at the site, compliance is assured, as study drug must be administered by study personnel via s.c. injection.

For subjects self-administering investigational treatment, compliance will be assessed by the investigator and/or study personnel at each in-clinic visit (see Table 8-1) using medication package counts and information provided by the subject. This information should be captured in the source document and corresponding eCRF at each in-clinic visit. All study treatment dispensed and returned must be recorded as per Section 6.7.1.

6.6.2 Emergency breaking of assigned treatment code

Emergency breaking of treatment code is only applicable for all subjects from the two core studies CQGE031C2302 and CQGE031C2303 until they complete Visit 204 (Week 12).

Emergency code breaks must only be undertaken when it is required in the interest of subject safety. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a subject, he/she must provide the requested subject identifying information and confirm the necessity to break the treatment code for the subject. The investigator will then receive details of the investigational drug treatment for the specified

[redacted]

subject and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the study team that the code has been broken.

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

- protocol number
- investigational drug name
- subject number

In addition, oral and written information to the subject must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that un-blinding can be performed at any time.

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

Investigational treatment must be discontinued after emergency unblinding.

6.7 Preparation and dispensation

Each study site will be supplied with investigational study drug in kits as described under Section 6.7.1.1.

Please refer to the Pharmacist Manual and Instructions For Use (IFU) for drug preparation and administration.

A unique medication number is printed on the study medication label.

Investigator staff will identify the study medication kits to dispense to the subject by contacting IRT and obtaining the medication number(s). The study medication has a 2-part label (base plus tear-off label). Immediately before dispensing the study medication kit to the subject, site personnel will detach the outer part of the label from the packaging and affix it to the source document.

From Visit 207 (Week 24), selected subjects will perform outside of clinic administrations at the protocol specified time points. For these cases, the investigator (or authorized delegate) will dispense, via IRT, an appropriate number of investigational treatment kits for outside of clinic administrations and detach the outer part of the label from the packaging in order to adhere it on the drug accountability log. Please refer to Section 6.7.1 for returning and recording study treatment.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

Subjects transitioning from CQGE031C2302 and CQGE031C2303

Ligelizumab liquid in vial and ligelizumab PFS 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

[redacted]

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 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 except for the medication number.

For ligelizumab liquid in vial, an accurate record of the shipment, dispensing and collection/destruction of study treatment must be maintained in a drug accountability log by the independent unblinded site personnel.

For PFS, an accurate record of the shipment, dispensing and collection/destruction of study treatment must be maintained in a drug accountability log by the study site personnel.

Monitoring of drug accountability will be performed by unblinded monitors (for liquid in vial) and monitors (for PFS) during site visits or remotely and at the completion of the trial.

Subjects who do outside of clinic investigational drug administration will record the date(s) of administration on a diary/form and will be asked to return all used and unused investigational treatment, syringes and packaging as well as unused rescue medication at each in-clinic visit and the end of the study or at the time of discontinuation of study treatment. Site staff will record in the appropriate documents the dates of the administration. Detailed instructions will be provided separately.

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

Subjects transitioning from CQGE031C2202 and CQGE031C1301

Investigational treatment (liquid in vial or PFS) 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 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 except for the medication number.

The study site personnel must maintain an accurate record of the shipment, dispensing and collection/destruction 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.

Subjects who do outside of clinic investigational drug administration will record the date(s) of administration on a diary/form and will be asked to return all used and unused investigational

[redacted]

treatment syringes and packaging as well as unused rescue medication at each in-clinic visit and the end of the study or at the time of discontinuation of study treatment. Site staff will record in the appropriate documents the dates of the administration. Detailed instructions will be provided separately.

At the conclusion of the study, and as appropriate during the course of the study, the study site personnel will return all used and unused investigational treatment syringes, unused rescue medication**,** 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

For all subjects transitioning from the core studies receiving treatment administration in the clinic setting, study treatment will be administered as follows to ensure blinding in the core studies:

- Blinded personnel involved in the core studies cannot at the same time act as unblinded personnel in the extension study.
- Unblinded pharmacist or designee of the core studies can prepare and administer both blinded (i.e. liquid in vial injection) and open label (i.e. PFS) investigational treatment in the extension study.
- Blinded personnel involved in the core studies can prepare and administer open label ligelizumab prefilled syringes from Week 12 onwards.

Since all subjects transitioning from CQGE031C1301 or CQGE031C2202 receive open label ligelizumab 120 mg (liquid in vial injection and PFS) there is no blinding restrictions and any site staff including blinded site staff can prepare and administer investigational treatment for these subjects throughout this study.

The liquid in vial injection at Visits 201, 202, 203 (Weeks 0, 4 and 8) and the PFS injection from Visit 204 (Week 12) onwards will be administered in the deltoid region on the right or left arm, or in the right 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.

Please refer to the Pharmacist Manual and IFU for drug preparation and administration.

Please refer to Section 6.4 for treatment blinding.

All subjects will be monitored in accordance with the recommendations for omalizumab, the currently available anti-IgE therapy, from 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 Omalizumab Joint Task Force (Cox et al 2011).

[redacted]

All subjects receiving treatment at the sites, in all treatment arms, must remain at the site and monitored for 2 hours for the first three treatment administration visits, when starting or re-starting treatment and for 30 minutes for the remaining treatment visits.

Therefore, whether they are in the clinic-administered or self-administered group:

- subjects starting treatment at Visit 201 (Week 0) and subsequent visits 202 and 203 (Weeks 4 and 8) will be monitored at the site for 2 hours after administration, and for 30 minutes for all remaining visits as long as their treatment is not interrupted during the full 104 week treatment period; and
- subjects who are entering the second half of the treatment period (Visit 214, Week 52) from the second observation period will be monitored at the site for 2 hours after administration for the first three Visits 214, 401 and 402 (Weeks 52, 56 and 60).
    - All subjects receiving treatment in clinic will remain in clinic for a 30 min observation period for all remaining treatment visits.
    - All subjects self-administering ligelizumab in their out-of-clinic setting should remain in a quiet environment for 30 minutes after administration for self-observation for all remaining treatments.

Self-administration outside of clinic

PFS injections should only be administered by adults or adult caregivers.

Subject will be given the option to start self-administration at Visit 204 (Week 12) or Visit 403 (Week 64). During these visits subjects who are willing to self-administer, should be evaluated according to the below criteria. If the criteria are satisfied, then the IFU will be provided and the subjects or caregiver who will perform the administration will undergo training.

The clinical criteria for self-administering ligelizumab is below:

- The subject should not have experienced any severe/serious hypersensitivity reactions (including during the preceding studies)
- The subject should know how to recognize symptoms/signs of severe hypersensitivity reactions
- The subject should be capable and willing to self-administer ligelizumab

For the first and second use of PFS at Visit 204 (Week 12) / Visit 403 (Week 64) and Visit 205 (Week 16) / Visit 404 (Week 68) respectively, the self-injection will take place as a site staff assisted injection i.e. with the help of the site staff performing the injection steps. At the third use of PFS at Visit 206 (Week 20) / Visit 405 (Week 72), the self-injection will take place under supervision however without the help of the site staff, i.e. the site staff only observes and does not help in performing the injection steps. The training for each injection, be it assisted or under supervision, will be provided individually by the site staff to the subject.

Subjects who self-administered in the first half of treatment period and continuing straight into the second half of treatment (i.e. without transitioning into the second observation period) will continue to self-administer in the second half of treatment. These subjects do not have to be re-evaluated or re-trained at Week 64.

Visit 204 (Week 12) or Visit 403 (Week 64) – assisted

[redacted]

- The site staff will show the subject how to use the PFS based on the instructions provided in the IFU, with emphasis on specific checks for device use evaluation.
- The subject will be given the opportunity to raise questions if any
- The subject will perform the injection into an appropriate injection site of the body with the site staff **actively assisting** them during the injection. If the site staff observes that the subject is performing an action that may jeopardize the subject's safety, site staff will intervene to prevent any potential harm and guide/correct the subject.

Visit 205 (Week 16) or Visit 404 (Week 68) - assisted

- Study staff should ask the subject whether they wish to be retrained prior to injection. If needed, site staff will retrain the subject.
- The subject will perform the injection into the appropriate injection site of the body with the site staff **actively assisting** them during the injection.

Visit 206 (Week 20) or Visit 405 (Week 72) - supervised

- The subject will perform the injection into the appropriate injection site of the body mimicking an outside of clinic administration i.e. **without the active assistance** of the site staff but under their supervision.
- If the site staff observes that the subject is performing an action that may jeopardize the subject's safety, site staff will intervene to prevent any potential harm and guide/correct the subject.
- The site staff will observe that the dose is administered in accordance to the steps indicated in the self-injection assessment list and the potential hazard assessment list as described in the pharmacist manual. The site staff will observe the subject actions as per the lists to evaluate if the subject is capable of self-administration outside of clinic.

Thereafter, outside of clinic administrations should be done at pre-defined time points as per assessment schedule (Table 8-1). If self-administration is not chosen, these administrations can be performed by a trained caregiver who will then be trained as outlined above.

Subjects carrying out self-administration **outside the clinic** setting will:

- have in-clinic safety and efficacy assessments done at 12 to 16 week intervals and will be provided with three/four kits for self-administration outside of the clinic; and
- be assessed remotely (i.e. outside of clinic) by safety phone call from the site every 4 weeks, unless there is an in-clinic visit scheduled (at 12 to 16 week intervals per protocol).

During outside of clinic administrations, subjects are expected to contact the investigator/site staff in case they are experiencing any AE/SAEs or have any concerns.

At any time during the study, should a self-administering subject, caregiver or investigator decide not to continue with self-administration, the subject must contact the site, or the site staff must contact the subject, to arrange for all subsequent visits and treatments to be administered at the site.

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.

All kits of study treatment assigned by the IRT will be recorded in the IRT system. The investigator must promote compliance by instructing the subject to take the study treatment

[redacted]

exactly as prescribed and by stating that compliance is necessary for the subject's safety and the validity of the study. The subject must also be instructed to contact the investigator if he/she is unable, for any reason, to take the study treatment as prescribed.

7 Informed consent procedures

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

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities, i.e., pandemic, epidemic or natural disaster, that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, Investigator may conduct the informed consent discussion remotely (e.g., telephone, videoconference) if allowable by a local Health Authority. Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g., the presence of an impartial witness, sign/dating separate ICFs by trial participant and person obtaining informed consent, etc.).

Novartis will provide to investigators in a separate document a proposed ICF that complies with the ICH E6 GCP (International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice) 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. 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 Investigator's Brochure 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 contraception requirements.

[redacted]

[redacted]

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

8 Visit schedule and assessments

The first visit of the extension study, if it cannot occur on same day as the last visit (Visit 1999) of the preceding studies, as described in Section 3.1 and Section 8.1, should occur within as short time as possible from the last visit of the preceding studies. In this case, the Investigator must perform a thorough review of new medical histories and concomitant medication changes from the time of the last visit of the preceding studies until the first visit of this extension study.

Assessment schedule (Table 8-1 and Table 8-2) lists all of the assessments and when they are performed. All data obtained from these assessments must be supported in the subject's source documentation.

Subjects should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1 and Table 8-2) or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Subjects who prematurely discontinue the study or withdraw their consent/oppose the use of their data/biological samples for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit (Visit 9999/EOS) will be performed. At this final visit, all dispensed investigational product should be reconciled, and the AE and concomitant medications recorded on the CRF.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities, i.e., pandemic, epidemic or natural disaster that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the investigator as the situation dictates. If allowable by a local Health Authority and depending on operational capabilities, phone calls or virtual contacts (e.g., tele consult), can replace on-site study visits, for the duration of the disruption until it is safe for the participant to visit the site again.

[redacted]

Table 8-1 Assessment Schedule (Screening, First and Second half of the treatment period and Follow-up period)

Epoch	Screening		<----------First half of the Treatment---------->													<----------Second half of the Treatment---------->												
Visit Numbers[1]	**1**[2]	**2**[3]	**201**	**202**	**203**	**204**	**205**	**206**	**207**	**208**	**209**	**210**	**211**	**212**	**213**	**214**[4,5]	**401**	**402**	**403**	**404**	**405**	**406**	**407**	**408**	**409**	**410**	**411**	**412**	**9998**
Days	**-28 to -7**	**-14 to -1**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**393**	**421**	**449**	**477**	**505**	**533**	**561**	**589**	**617**	**645**	**673**	**701**	**729/ EOT**
Weeks	**-4 to -1**	**-2 to -1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**	**104**
Informed Consent	X[6]																												
[redacted]																													
Inclusion / Exclusion criteria	X	X	X																										
Demography	X																												
Relevant medical history (including CSU history)[8]	X																												
Prior urticaria treatment	X																												
Prior urticaria non-drug therapy	X																												
Family malignancy history[9]	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	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	X	X	X	X	X	X	X	X	X	X
Rescreening (rescreening eCRF should be recorded if the subject is rescreened)	X																												
Rescue medication usage	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense H1-AH rescue medication[10]	S	S	S	S	S	S	S	S	S	S[11]	S[11]	S	S[11]	S[11]	S	S	S[11]	S[11]	S	S[11]	S[11]	S	S[11]	S[11]	S	S[11]	S[11]	S[11]	S
Dispense oral corticosteroid rescue medication[12]						S	S	S	S	S[11]	S[11]	S	S[11]	S[11]	S	S	S[11]	S[11]	S	S[11]	S[11]	S	S[11]	S[11]	S	S[11]	S[11]	S[11]	S
Dispense Subjects' eDiary	S																												
Collect Subjects' eDiary																													
Visit at the site	X	X	X[14]	X[14]	X[14]	X	X	X	X[15]	X[13]	X[13]	X	X[13]	X[13]	X	X[14]	X[14]	X[14]	X	X[13]	X[13]	X	X[13]	X[13]	X	X[13]	X[13]	X[13]	X

[redacted]

Epoch	Screening		<----------First half of the Treatment---------->														<----------Second half of the Treatment---------->											
Visit Numbers[1]	**1**[2]	**2**[3]	**201**	**202**	**203**	**204**	**205**	**206**	**207**	**208**	**209**	**210**	**211**	**212**	**213**	**214**[4,5]	**401**	**402**	**403**	**404**	**405**	**406**	**407**	**408**	**409**	**410**	**411**	**412**	**9998**
Days	**-28 to -7**	**-14 to -1**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**393**	**421**	**449**	**477**	**505**	**533**	**561**	**589**	**617**	**645**	**673**	**701**	**729/ EOT**
Weeks	**-4 to -1**	**-2 to -1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**	**104**
Safety phone call[15]										X	X		X	X			X	X		X	X		X	X		X	X	X	
Contact IRT	X		X	X	X	X	X	X	X[16]	X	X	X[16]	X	X	X	X[16]	X	X	X[16]	X	X	X[16]	X	X	X[16]	X	X	X	X
Liquid in vial investigational study drug administration			X	X	X																								
PFS investigational study drug administration						X	X	X	X	X	X	X	X	X	X	X[17]	X	X	X	X	X	X	X	X	X	X	X	X		
Self-administration training						X	X	X											X[27]	X[27]	X[27]								
PFS outside of clinic administration									X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Subjects' eDiary (review compliance) includes the urticaria subject daily diary (UPDD) and AAS (Angioedema activity score)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
DLQI (Dermatology Life Quality Index/CDLQI (Children's DLQI)			X	X[28]	X[28]	X[28]			X[28]			X[28]			X[28]	X			X[28]			X[28]			X[28]				X[28]
[redacted]																													
Stool ova and parasite evaluation: 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 asap	X[18,19]	X[3]																											
Hematology (INR only at Visit 201 and unscheduled Visit)	X[20]	X	X	X[29]	X[29]	X[29]			X[29]			X[29]			X[29]	X[29]			X[29]			X[29]			X[29]				X[29]

[redacted]

Epoch	Screening		<----------First half of the Treatment---------->														<----------Second half of the Treatment---------->											
Visit Numbers[1]	**1**[2]	**2**[3]	**201**	**202**	**203**	**204**	**205**	**206**	**207**	**208**	**209**	**210**	**211**	**212**	**213**	**214**[4,5]	**401**	**402**	**403**	**404**	**405**	**406**	**407**	**408**	**409**	**410**	**411**	**412**	**9998**
Days	**-28 to -7**	**-14 to -1**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**393**	**421**	**449**	**477**	**505**	**533**	**561**	**589**	**617**	**645**	**673**	**701**	**729/ EOT**
Weeks	**-4 to -1**	**-2 to -1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**	**104**
Clinical chemistry (FSH to be done only if indicated in Section 8.4.3)	X[20]	X	X	X[29]	X[29]	X[29]			X[29]			X[29]			X[29]	X[29]			X[29]			X[29]			X[29]				X[29]
Serum β-hCG	X[22]																												
[redacted]																													
IgE-autoantibodies (Marker of hypersensitivity)			X																										
Chronic urticaria (CU) index panel (CU index, thyroid peroxidase IgG, thyroglobulin IgG)			X																										
Total tryptase			X																										
[redacted]																													
Urine dipstick (local) (When a dipstick evaluation is abnormal, e.g. positive for WBC and/or blood, a urine sample must be sent for microscopic examination to the central lab)	X[20]	X				X						X				X			X						X				X

[redacted]

Epoch	Screening		<----------First half of the Treatment---------->													<----------Second half of the Treatment---------->											
Visit Numbers[1]	**1[2]**	**2[3]**	**201**	**202**	**203**	**204**	**205**	**206**	**207**	**208**	**209**	**210**	**211**	**212**	**213**	**214[4,5]**	**401**	**402**	**403**	**404**	**405**	**406**	**407**	**408**	**409**	**410**	**411**	**412**	**9998**
Days	**-28 to -7**	**-14 to -1**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**393**	**421**	**449**	**477**	**505**	**533**	**561**	**589**	**617**	**645**	**673**	**701**	**729/ EOT**
Weeks	**-4 to -1**	**-2 to -1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**	**104**
Urine Pregnancy Test (local) (If positive, confirmation by serum β-hCG test should be done by central lab)	S[18]	S	S	S	S	S	S	S	S	S[24]	S[24]	S	S[24]	S[24]	S	S	S[24]	S[24]	S	S[24]	S[24]	S	S[24]	S[24]	S	S[24]	S[24]	S[24]	S
Physical Examination (Physical exam on Screening Visit 1 and 2 is comprehensive but subsequent physical exams maybe limited)	S[18]	S	S	S	S	S			S			S			S	S			S			S			S				S
Vital signs	X[18]		X	X	X	X			X			X			X	X			X			X			X				X
Height and Weight (for adult subjects after screening, only body weight will be measured)	X[25]								X							X													X
Electrocardiogram (ECG)	X[30]															X[30]													X[30]
Adverse Events	As required																												
Liver safety monitoring	S[18]	S	S	S	S	S			S			S			S	S			S			S			S				S
Renal safety monitoring	S[18]	S	S	S	S	S			S			S			S	S			S			S			S				S
Treatment completion/discontinuation form			X																										
Study completion/discontinuation form	X																												

[redacted]

Epoch	Follow-Up[26]				
Visit Numbers[1]	**501**	**502**	**503**	**9999**	
Days	**813**	**897**	**981**	**1093/ EOS**	**UPV**
Weeks	**116**	**128**	**140**	**156**	**-**
Informed Consent					
[redacted]					
Inclusion / Exclusion criteria					
Demography					
Relevant medical history (including CSU history)[8]					
Prior urticaria treatment					
Prior urticaria non-drug therapy					
Family malignancy history[9]					
Prior and Concomitant medication usage	X	X	X	X	X
Surgery and procedures	X	X	X	X	X
Rescreening (rescreening eCRF should be recorded if the subject is rescreened)					
Rescue medication usage	X	X	X	X	
Dispense H1-AH rescue medication[10]	S	S	S		
Dispense oral corticosteroid rescue medication[12]	S	S	S		
Dispense Subjects' eDiary					
Collect Subjects' eDiary				S	
Visit at the site	X	X	X	X	X
Safety phone call					
PFS outside of clinic administration					
Contact IRT					
Liquid in vial investigational study drug administration					
PFS investigational study drug administration					
Subjects' eDiary (review compliance) includes the urticaria subject daily diary (UPDD) and AAS (Angioedema activity score)	X	X	X	X	
DLQI (Dermatology Life Quality Index/CDLQI (Children's DLQI)	X[28]	X[28]	X[28]	X[28]	
[redacted]					

[redacted]

Epoch	Follow-Up[26]				
Visit Numbers[1]	**501**	**502**	**503**	**9999**	
Days	**813**	**897**	**981**	**1093/ EOS**	**UPV**
Weeks	**116**	**128**	**140**	**156**	**-**
Stool ova and parasite evaluation: 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 asap				X	X
Hematology	X[29]	X[29]	X[29]	X[29]	X[21,29]
Clinical chemistry	X[29]	X[29]	X[29]	X[29]	X[29]
[redacted]					
IgE-autoant bodies (Marker of hypersensitivity)					X
Chronic urticaria (CU) index panel (CU index, thyroid peroxidase IgG, thyroglobulin IgG)					X
Total tryptase					X
[redacted]					
Urine dipstick (local) (When a dipstick evaluation is abnormal, e.g. positive for WBC and/or blood, a urine sample must be sent for microscopic examination to the central lab)				X	X
Urine Pregnancy Test (local) (If positive, confirmation by serum β-hCG test should be done by central lab)	S	S	S	S	S
Physical Examination (Physical exam on Screening Visit 1 and 2 is comprehensive but subsequent physical exams maybe limited)	S	S	S	S	S
Vital signs	X	X	X	X	X
Height and Weight (for adult subjects, only body weight will be measured)				X	
Electrocardiogram (ECG)					X[30]
Adverse Events	As required				X
Liver safety monitoring	S	S	S	S	S
Renal safety monitoring	S	S	S	S	S
Treatment completion/discontinuation form					
Study completion/ discontinuation form	X				

[redacted]

[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] Visit structure given for internal programming purpose only
[2] Subjects who become eligible to enroll into the extension study at Visit 1999 of the preceding studies must complete all lab assessments done as a part of end of preceding study visit (Visit 1999) and all lab and other required assessments as per this extension study protocol. Refer to the latest version of the preceding protocols regarding assessments related to Visit 1999.
[3] Only for subjects in the observation period who have not had these assessment completed in the past 30 days. Stool samples should be collected at Visit 2 unless the subject has not had any symptoms indicative of parasitic infection including diarrhea since Visit 1 and the subject has not travelled to an area of higher risk of parasitic infection since Visit 1.
[4] (1) Continuation of treatment for (i) subjects who have UAS7 >6 and <16, or (ii) subjects who have UAS7 ≥ 16 when the investigator has reassessed the risk-benefit with the subject and decided to continue the subject's treatment. (2) Restarting of treatment for subjects relapsing in the second observation period.
[5] The first task at Week 52 in the treatment period must be to check the UAS7 score: If the subject enters the second observation period, then the assessment must be done for Visit 301 (Week 0) and recorded on eCRF for Visit 301. If the subject continues in the second half of the treatment period, then the assessment must be done for Visit 214 (Week 52) and recorded for eCRF Visit 214 (Week 52).
[6] Informed consent can also be obtained prior to or at Visit 1999 of the preceding studies.

[redacted]

[8] Relevant ongoing medical conditions that were already present at the time of informed consent should be recorded in medical history eCRF. Medical history that are ongoing from the preceding studies will be transcribed.
[9] Completed Family malignancy history CRFs from the preceding studies should be transcribed to the extension Family malignancy history CRF. Family malignancy history CRF in this extension study should be completed if the subject develops malignancy during this study.
[10] For subjects self-administering investigational drug, the dispensing of H1-AH rescue medication will take place as needed at each scheduled in-clinic visit.
[11] For subjects who do not perform self-administration of investigational drug, H1-AH and oral corticosteroid rescue medication may be dispensed as needed at each visit.
[12] For subjects self-administering investigational drug, the dispensing of oral corticosteroids will take place as needed at each scheduled in-clinic visit.
[13] For subjects who do NOT perform self-administration of investigational drug, these visits will be used for drug administration and local urine pregnancy test only.
[14] All subjects will remain in-clinic for 2 hours observation after ligelizumab administration at Visits 201, 202, 203 (Weeks 0, 4 and 8). Subjects transitioning from the second observation period to re-start treatment at Visits 214, 401 and 402 (Weeks 52, 56 and 60) will remain in-clinic for 2 hours observation after ligelizumab administration.
[15] Detailed arrangements for safety phone calls on a regular basis per protocol must be planned at Visit 207 (Week 24) for all subjects self-administering investigational drug and safety phone call will replace visits at site for these subjects.
[16] IRT to dispense kits to take with them for subjects who do self-administration.
[17] (a) Continuation of treatment and (b) Restarting of treatment for subjects relapsing in the second observation period

[redacted]

[18] Transcribe results from Visit 1999 of the preceding studies to screening eCRF if Visit 1999 date and Screening Visit 1 date are less than or equal to 30 days apart. If Visit 1999 date and Screening Visit 1 date are more than 30 days apart assessment has to be repeated.
[19] In the event that the 3 stool samples from Visit 1999 of the preceding studies were not collected, or the results from these are not available, or Visit 1999 date and Screening Visit 1 date are more than 30 days apart, subjects must be assessed at Visit 1 (see Section 8.4.4).
[20] Hematology and chemistry results will be transcribed automatically by central lab from Visit 1999 to Visit 1. Urine dipstick results need to be transcribed to the respective eCRF.
[21] INR (International Normalized Ratio) at Visit 201 and unscheduled Visit only
[22] hCG for all female subjects of child-bearing potential at Visit 1 only

[redacted]

[24] Urine pregnancy tests will be provided to all self-administration subjects who are women of child-bearing age, for home use. In the event that the home test is positive, the subject must call site and arrange for an immediate visit to perform a serum pregnancy test.
[25] Transcribe weight for adults and adolescents from Visit 1999 of the preceding studies to screening eCRF; If Visit 1999 date and Screening Visit 1 date are more than 30 days apart assessment has to be repeated. Transcribe height for adolescents from Visit 1999 of the core phase 3 studies and CQGE031C2202 to screening eCRF; If Visit 1999 date and Screening Visit 1 date are more than 30 days apart assessment has to be repeated. Measure height for adult subjects and record on screening eCRF.
[26] (a) Subjects who complete all visits on investigational drug during the 104 weeks treatment period without interruption will complete a 52 weeks post-treatment follow-up period. (b) all other subjects will complete a 12 week post-treatment follow-up period. For all subjects last visit is EOS/9999.
[27] Subjects who do self-administration in the first half of the treatment period and continue uninterrupted in the second half of the treatment period with self-administration are not required to re-do the training.
[28] Remote PROs collection is possible in case the patient cannot attend the visit at site due to a Public Health emergency
[29] Samples can be collected & analyzed in a certified local laboratory (if feasible) due to a Public Health emergency
[30] For any ECG with subject safety concern, 2 additional ECGs must be performed to confirm the finding.
[31] For subjects who only performed self-administration in the second half of the treatment period

[redacted]

[redacted]

Table 8-2 Assessment Schedule (First and Second Observation period)

Epoch	First Observation										Second Observation														
Visit Numbers[1]	**101**	**102**	**103**	**104**	**105**	**106**	**107**	**108**	**109**	**199**	**301**	**302**	**303**	**304**	**305**	**306**	**307**	**308**	**309**	**310**	**311**	**312**	**313**	**399**	
Days	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253/ EOOBS1**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365/ EOOBS2**	**UPV**
Weeks	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**-**
Visit at the site	X[3]			X			X			X	X			X			X			X				X	
[redacted]																									
Safety phone call		X	X		X	X		X	X			X	X		X	X		X	X		X	X	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	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	X	X	X	X	X	X
Rescue medication usage	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense H1-AH rescue medication	S			S			S				S			S			S			S					
Collect Subjects' eDiary										X[2]														X[2]	
Subjects' eDiary (review compliance) includes the urticaria subject daily diary (UPDD) and AAS (Angioedema activity score)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
DLQI (Dermatology Life Quality Index/CDLQI (Children's DLQI)	X			X[4]			X[4]			X[4]	X[4]			X[4]			X[4]			X[4]				X[4]	
[redacted]																									
Stool ova and parasite evaluation: 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 asap																								X	X
Hematology				X[5]			X[5]			X[5]	X[5]			X[5]			X[5]			X[5]				X[5]	X[5]
Clinical chemistry				X[5]			X[5]			X[5]	X[5]			X[5]			X[5]			X[5]				X[5]	X[5]
[redacted]																									

[redacted]

Epoch	First Observation										Second Observation														
Visit Numbers[1]	101	102	103	104	105	106	107	108	109	199	301	302	303	304	305	306	307	308	309	310	311	312	313	399	
Days	1	29	57	85	113	141	169	197	225	253/ EOOBS1	1	29	57	85	113	141	169	197	225	253	281	309	337	365/ EOOBS2	UPV
Weeks	0	4	8	12	16	20	24	28	32	36	0	4	8	12	16	20	24	28	32	36	40	44	48	52	-
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
Urine dipstick (local) (When a dipstick evaluation is abnormal, e.g. positive for WBC and/or blood, a urine sample must be sent for microscopic examination to the central lab)				X			X			X	X			X			X			X				X	X
Physical Examination (Physical exam on Screening Visit 1 and 2 is comprehensive but subsequent physical exams maybe limited)				S			S			S	S			S			S			S				S	S
Liver safety monitoring	S			S			S			S	S			S			S			S				S	S
Renal safety monitoring	S			S			S			S	S			S			S			S				S	S
Electrocardiogram (ECG)																									X
Vital signs				X			X			X	X			X			X			X				X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	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] Visit structure given for internal programming purpose only
[2] Applies to subjects who are not eligible to start treatment
[3] Detailed arrangements for safety phone calls on a regular basis per protocol must be planned at Visit 101 (Week 0) of the first observation period.
[4] Remote PROs collection is possible in case the patient cannot attend the visit at site due to a Public Health emergency
[5] Samples can be collected & analyzed in a certified local laboratory (if feasible) due to a Public Health emergency

[redacted]

[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 one visit during screening period, Visit 1 (Day -28 to Day -7) which is equivalent to Visit 1999 of the preceding studies or in as short time-frame as possible after the Visit 1999 of the preceding studies. An extended screening period will be permitted only in exceptional circumstances when information concerning eligibility is outstanding (e.g., pending laboratory data).

- All lab assessments performed at Visit 1999 (if not more than 30 days prior to the extension screening Visit 1) and all additional other required assessments as per extension study protocol (e.g. serum pregnancy tests) will be used to determine eligibility to enroll into this extension study. If the gap between the Visit 1999 of preceding studies and extension screening Visit 1 is greater than 30 days, then all lab and other required assessments will need to be re-done at extension screening Visit 1.
- Subjects' relevant medical conditions and concomitant medications will be reviewed at Visit 1 (Visit 1999 of the preceding studies, if the subject is transitioning immediately to the extension study).
- The subjects will continue to complete all eDiary assessments (for the UAS7 score calculation), between Visit 1 (Visit 1999 of the preceding studies, if the subject is transitioning immediately) and start of treatment.
- Start of treatment should occur approximately 7 to 28 days after Visit 1 assessments (Visit 1999 of the preceding studies if subject is transitioning immediately).

Once all screening assessments are done:

- If the subject has moderate to severe disease (defined as UAS7 $\geq$ 16), the subject will enter the treatment period immediately at Visit 201 (Week 0).
- If the subject has a UAS7 of < 16, the subject will transition to the first observation period. Once UAS7 $\geq$ 16 has been met in the first observation period the subject will have to complete screening Visit 2 (Day -14 to -1) if the required assessments at that visit had not been completed in the past 30 days (e.g. during a regular visit as per assessment schedule Table 8-2).

Rescreening may be allowed for subjects who fail initial screening (see Section 5.1 and Section 5.2 on when rescreening is allowed). Only 1 rescreening will be allowed. 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.

Subjects who did not meet applicable eligibility criteria at Visit 2, will be discontinued from the study and will not enter treatment. These subjects are not considered screen failure subjects.

For subjects who did not meet applicable eligibility criteria at Visit 2 due to a transient and non-clinically significant lab abnormality one re-test (AST, ALT, albumin, TBL, creatinine, platelets) can be performed.

[redacted]

8.1.1 Information to be collected on screening failures

Subjects who sign an ICF and subsequently found to be ineligible prior to start of treatment will be considered a screen failure. The reason for screen failure should be recorded on the appropriate eCRF. 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 SAE during the screening phase (see Section 10.1.3 for reporting details). AEs that are not SAEs will be followed by the investigator and collected only in the source data. If the subject fails to enter the treatment period, the IRT must be notified within 2 days of the screen failure i.e. that the subject did not enter treatment.

Subjects who enter the treatment period and fail to start treatment, e.g., subject entered treatment period in error, subject was transitioned from observation period to treatment period in error, the local Country Organization is to be contacted whether subject should continue to remain in the study. In case of early termination, the reason should be recorded on the appropriate 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. Participant race and ethnicity, as required by some Health Authorities, are collected to assess the diversity of the study population and to evaluate their impact on the safety and efficacy parameters in the study. 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.

8.3 Efficacy

All subjects will be provided with an electronic device (eDiary) that contains the following assessments: Urticaria Patient Daily Diary (UPDD), Angioedema Activity Score (AAS), Dermatology Life Quality Index (DLQI) for adults and Children Dermatology Life Quality Index (CDLQI) for adolescents [redacted]

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 must be completed prior to any other assessment and prior to administration of any investigational medication.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities, i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, patient reported outcome assessments (DLQI/CDLQI, [redacted] may be collected remotely as per Assessment Schedule Table 8-1 and Table 8-2.

[redacted]

8.3.1 eDiary assessments

8.3.1.1 Urticaria Patient Daily Diary (UPDD)

Urticaria Patient Daily Diary (UPDD) includes UAS which assesses twice daily the severity of itch and number of hives, and once-daily the use of rescue medication, sleep and activity interference, angioedema occurrence and its management and records the calls to a health care practitioner (Appendix 4, Patient Diary - Urticaria Patient Daily Diary (UPDD)) Urticaria Patient Daily Diary (UPDD)). The components are presented in the Table 8-3 and the relevant weekly scores are described below.

Table 8-3 Urticaria Patient Daily Diary (UPDD)

Diary component	When assessed
Urticaria Activity Score (UAS)	Morning & evening
• Itch severity	
• Number of hives	
Sleep interference	Morning
Daily activity interference	Evening
Rescue medication use	Evening
Angioedema	Evening
• Whether patient had an episode	
• If patient had an episode, how did they manage it	
Contact health care provider	Evening

8.3.1.1.1 Weekly Hives Severity Score (HSS7)

The HSS, 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 8-4). A weekly score (HSS7) is derived by adding up the average daily scores of the 7 preceding days. The possible range of the weekly score is therefore 0 – 21.

Complete hives response is defined as HSS7 = 0.

Table 8-4 Hives Severity Score (HSS)

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 HSS7 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]

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 8-5). A weekly score (ISS7) is derived by adding up the average daily scores of the 7 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 HSS7.

Complete itch response is defined as ISS7 = 0.

Table 8-5 Itch Severity Score (ISS)

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).

8.3.1.1.4 Weekly Sleep interference score

Sleep interference will be assessed by the subject, once daily in the morning in the eDiary. It is scored on a scale from 0 to 3 (see Table 8-6). The weekly sleep interference score ranges from 0 to 21 (Table 8-6).

Table 8-6 Sleep interference score

Score	Sleep interference
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

8.3.1.1.5 Weekly Activity interference score

Activity interference will be assessed by the subjects on a scale of 0 to 3 (Table 8-7), once daily in the evening in the eDiary. Daily activities could include, school, sports, hobbies and activities with friends and family. The weekly activity interference score ranges from 0-21 (Table 8-7).

Table 8-7 Activity interference score

Score	Activity interference
0	No interference
1	Mild, little interference with daily activities
2	Moderate, some interference with daily activities

[redacted]

Score	Activity interference
3	Substantial, severe interference with daily activities

8.3.1.1.6 H1-AH rescue medication use

The number of tablets of rescue medication used over the past 24 hours to control conditions such as itch or hives is recorded once daily in the eDiary by the subject. The dose per day of rescue medication will be calculated as the daily number of tablets times the dose of each tablet and then the dose per week of rescue medication will be calculated as the sum of the dose per day, over 7 days.

8.3.1.1.7 Angioedema occurrence

Angioedema occurrence is recorded once daily in the evening in the eDiary by the subject. Angioedema will be reported as number of days with angioedema. Actions and/or treatments related to those angioedema occurrences will be also recorded in the eDiary (Table 8-8).

Table 8-8 Actions/treatments for Angioedema

Actions/treatments
Did nothing
Took some prescription or non-prescription medication
Called my doctor, nurse or nurse practitioner
Went to see my doctor, nurse or nurse practitioner
Went to the emergency room at the hospital
Was hospitalized

8.3.1.1.8 Number of calls to doctor or nurse

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

8.3.1.2 Angioedema Activity Score (AAS)

Angioedema activity score is recorded once daily in the evening in the eDiary by the subject. This validated tool assesses occurrence of episodes of angioedema by an opening question. If "yes" is the answer to the opening question the subject will continue to answer questions about the duration, severity and impact on daily functioning and appearance of the angioedema (Appendix 4, Patient Diary - Angioedema Activity Score (AAS)) Angioedema Activity Score (AAS)). A score between 0 and 3 is assigned to every answer field. The AAS score in this study will be reported as weekly AAS (AAS7). The possible range of the AAS7 score is 0−105. Higher score means higher severity. The opening question will be used to count the number of angioedema affected days during the AAS documentation period but has no score.

[redacted]

8.3.2 Other Patient Reported Outcome (PRO) assessments

8.3.2.1 Dermatology Life Quality Index (DLQI)

The DLQI is a 10-item (grouped in 6 domains) dermatology-specific QoL measure (Finlay AY and Khan GK 1994). The DLQI was validated for patients aged 16 and above.

In this study, DLQI will be administered only in adult subjects (18 years and older, Appendix 4, Dermatology Life Quality Index (DLQI)). These 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.

In this study, subjects of age 17 at the time of consenting are considered in the adolescent group and therefore they, along with the subjects aged 12 through 16, will be administered the CDLQI, which was designed initially for use in children from age 4 to age 16 (Lewis-Jones and Finlay AY 1995, Appendix 4, Children's Dermatology Life Quality Index (CDLQI)). At Visits 201 and 214 (Weeks 0 and 52), if an adolescent has turned 18, they will be considered in the adult group and administered DLQI.

An overall score is calculated and ranges from 0 to 30 for both instruments (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). For CDLQI, the domain scores are calculated for: Symptoms and Feelings (0-6), Leisure (0-9), School and holidays (0-3), Personal Relationships (0-6), Sleep (0-3) and Treatment (0-3).

The scores were split into score bands (Hongbo et al 2005, Waters et al 2010) and validated in terms of their meaning/relevance to patients as follows:

Table 8-9 DLQI/CDLQI score bands and impact on patient's life

DLQI band	CDLQI band	Significance of score
0-1	0-1	No effect on patients life
2-5	2-6	Small effect on patients life
6-10	7-12	Moderate effect on patients life
11-20	13-18	Very large effect on patients life
21-30	19-30	Extremely large effect on patients life

A DLQI/CDLQI score of > 10 is relevant for a very large impact on patients' life and justification for a biologic prescription for example in psoriasis (Finlay AY 2005). The DLQI and CDLQI questionnaires are administered according to Table 8-1 and Table 8-2.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities, i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, the DLQI and CDLQI questionnaires may be collected remotely as per Assessment Schedule Table 8-1 and Table 8-2.

[redacted]

[redacted]

8.3.3 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 2 study CQGE031C2201 supported the change from baseline in UAS7 (which is a composite of ISS7 and HSS7) at Week 12 being assessed as the primary endpoint in the ongoing Phase 3 core studies. In this Phase 3 extension study, which is reflective of long-term real world management of CSU, the primary endpoint is well-controlled urticaria at Week 12 in the first half of the treatment period, assessed as percentage of subjects achieving UAS7 $\leq$ 6. This is consistent with the longer-term realistic clinical goal of achieving well-controlled disease (UAS7 $\leq$ 6), which also includes completely controlled disease (UAS7 = 0).

Disease recurrence after investigational drug is withdrawn will be measured during the post-treatment follow-up periods. Disease worsening, after well-controlled disease (UAS7 $\leq$ 6) will be measured during the second observation period.

For all subjects, symptom scores will be measured during the observation, treatment and post-treatment follow-up periods.

8.4 Safety

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed.

For details on AE collection and reporting, refer to Section 10.1.1.

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

[redacted]

- Vital signs
- Laboratory evaluations
- ECG (Electrocardiogram)

Table 8-10 Assessments & Specifications

Assessment	Specification
Physical examination	A comprehensive 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 comprehensive physical examination is required (see Table 8-1 / Table 8-2). 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 AE must be recorded as an AE.
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 Appendix 1.
Height and Weight	Height in cm and Body weight (to the nearest 0.1 kg in indoor clothing, but without shoes) will be measured.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities, i.e., pandemic, epidemic or natural disaster, that limits or prevents required on-site study visits, regular phone or virtual calls can occur (every 4 weeks or more frequently if needed) for safety monitoring and discussion of the participant´s health status until it is safe for the participant to visit the site again.

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.

Clinically notable laboratory findings are defined in Appendix 1.

Clinically significant abnormalities must be recorded on the relevant section of the eCRFs capturing medical history/Current medical conditions/AEs.

[redacted]

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities, i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, an alternative lab (local) collection site may be used for protocol specified safety lab assessments. It is recommended to use certified local laboratories, if feasible. If a local laboratory is used during a Public Health emergency, local laboratory reports need to be collected, reviewed, filed in the patient medical record or chart at the site, and entered into the CRF.

Table 8-11 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.
Chemistry	Albumin, total bilirubin, ALP, AST, ALT, LDH (lactate dehydrogenase), GGT, chloride, sodium, potassium, magnesium, calcium, inorganic phosphorus, creatinine, urea/BUN (blood urea nitrogen) and uric acid will be measured. If the TBL concentration is increased above 1.5 times ULN, direct and indirect reacting bilirubin should be differentiated.
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, pH, glucose, protein, bilirubin, ketones, leukocytes and blood will be performed at site. When a dipstick evaluation is abnormal, e.g., positive for WBC (white blood cells) and/or blood, a urine sample must be sent to the Central Lab for microscopic examination including RBC (red blood cells) and WBC. (Details on collection of urine for analysis by central laboratory are provided to investigators in the laboratory manual.)
Coagulation	At Visit 201 coagulation will be assessed by INR (international normalized ratio).
Parasite screening	Local laboratory assessment of stool samples for parasitic infections (see Section 8.4.4)
Pregnancy Test	Serum / Urine pregnancy test (see Section 8.4.3)

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 Screening (Visit 1), Visit 214 (Week 52), Visit 9998/EOT (Week 104) and unscheduled as required.

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 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

[redacted]

"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.

For any ECGs with clinically significant findings, two additional ECGs must be performed to confirm the abnormal findings.

Clinically significant ECG findings prior to dosing with investigational treatment must be discussed with the sponsor. Clinically significant abnormalities must be recorded on the CRF as either medical history/current medical conditions or AEs 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.

8.4.3 Pregnancy and assessments of fertility

A serum β-hCG will be collected at Screening Visit 1 for all female subjects of child-bearing potential before entering the treatment period.

All pre-menopausal women who are of child-bearing potential will have urine pregnancy testing during the treatment and observation period. A positive urine test needs to be confirmed with a central lab serum test during all study periods. If positive, the subject must be discontinued from study treatment.

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

Pregnancy tests must be performed prior to investigational drug administration.

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 testing is required at screening. If the Follicle Stimulating Hormone level is available from the preceding studies, and subject is of confirmed post-menopausal status, a repeat FSH is not needed.

Post-menopausal status should be recorded in the CRF.

8.4.4 Assessment of parasitic infections

Reduction in IgE levels may confer increased susceptibility to parasitic infections. The risk of acquiring or activating infections with helminths during or after treatment with anti-IgE therapy such as ligelizumab and omalizumab is suspected to be low. Data from the Phase 2 CQGE031C2201 study in this regard was unremarkable but limited due to the small study sample size.

Subjects should have had three stool samples analyzed from Visit 1999 of the preceding studies, except subjects from CQGE031C2202, and these results must be transcribed to the appropriate

[redacted]

screening eCRF for this extension study. In the event that three stool samples from Visit 1999 were not collected, (i.e. all subjects from CQGE031C2202 and subjects from the other preceding studies who missed collection of three stool samples), or the results from these are not available, these subjects will be given stool sample collection kits at screening Visit 1. Stool sample kits will be provided by the site or site's local laboratory. Subjects will take the stool sample kits home. Three stool samples will be collected, as per instructions from the local laboratory. Subjects will return the three stool samples to the site or the local lab, according to arrangements made by the site, as soon as possible after Visit 1 in order to allow processing within the screening period.

Stool samples should be collected at Visit 2 unless, since the time of Visit 1:

- the subject has not had any symptoms indicative of a parasitic infection, including diarrhea and
- the subject has not travelled to an area of higher risk for parasitic infection

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 local laboratory), the result must be recorded in the source document and the subject will not be enrolled and will not be allowed to rescreen. Stool samples negative for pathogenic helminthic infections must be recorded in the source document before enrollment.

Subjects must be advised that if diarrhea, or any other symptoms suggestive of parasitic infection, develops at any time between visits before end of study, three additional stool sampling for assessment of parasitic conditions should be done at the next visit or sooner if possible, following the above process. In addition, subjects will also be asked to provide three stool samples for analysis at the last study visit (Visit 9999/Week 156/EOS) (no later than 7 days after Visit 9999/EOS in unavoidable circumstances).

Subjects who develop stools positive for pathogenic helminthic infections during the study should be discontinued from treatment, have their infection treated according to current local practice and transition to the follow-up period for all scheduled assessments.

8.4.5 Anaphylaxis assessment

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

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.

[redacted]

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.

8.4.8 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/subject population. Events of special interest such as anaphylaxis, malignancies, and cardio-cerebrovascular events will be monitored and will be adjudicated by independent expert ACs.

8.5 Additional assessments

8.5.1 Resource utilization

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

[redacted]

[redacted]

[redacted]

[redacted]

8.5.4 Biomarkers

8.5.4.1 Chronic Urticaria (CU) index panel

The CU index panel consists of the CU Index®, thyroid peroxidase IgG and thyroglobulin IgG assays.

The CU Index® is an *in vitro* basophil histamine release assay in which a subject's serum is mixed with donor basophils and the released histamine levels are measured through a quantitative enzyme immunoassay. Biagtan et al found that a positive or elevated CU Index value suggested an increased severity of chronic urticaria. In addition, a CU Index value of greater than or equal to 10 indicated that the subject had either an autoimmune basis for their disease or an alternate histamine-releasing factor (Biagtan et al 2011).

In a number of common autoimmune disorders, the presence of other autoantibodies would be considered not usual. Several independent studies have reported that a significant number of subjects with CSU (up to 33% in some studies) exhibit high levels of autoantibodies to thyroid antigens like thyroid peroxidase IgG and thyroglobulin IgG. Interestingly, subjects with significant amounts of thyroid antigens have also significantly higher IgE levels (Chang et al 2015). Although the pathophysiology behind this association remains unclear, there is some consensus among allergists that it likely represents an epiphenomenon (Viswanathan et al 2012).

[redacted]

8.5.4.2 Total Tryptase

Tryptase is a neutral serine protease and is the most abundant mediator stored in mast cell granules. Measuring a subject's tryptase levels at baseline, and again in the event of a suspected anaphylactic reaction is reported to be helpful in assessing whether the event was indeed an anaphylactic reaction. It is a specific biomarker of mast-cell activation and plays a part in the allergic inflammation and is reported to be elevated in anaphylactic events. Although individual baseline levels and levels during / following acute hypersensitivity events may vary greatly, serum tryptase levels in blood samples taken 15–180 min after symptom onset can support the clinical diagnosis of anaphylaxis in some but not all subjects. However, reliance on elevation of only one mediator of inflammation to confirm the clinical diagnosis of anaphylaxis is likely to be insufficient (Simons et al 2015). Serial measurement of tryptase levels during an anaphylactic episode, and measurement of a baseline level after recovery are reported to be more useful than measurement at only one point in time (Simons et al 2011). In this study, total tryptase will be measured at Visit 201 (Week 0) and again, whenever possible, at the time of a suspect hypersensitivity event.

[redacted]

[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/guardian decision
- AEs for which continued exposure to the study drug would be detrimental
- Abnormal renal laboratory results requiring discontinuation (see Appendix 3)
- Abnormal liver laboratory results requiring discontinuation (see Appendix 2)
- Platelets < 75000/µL
- Pregnancy (see Section 8.4.3 and Section 10.1.4)
- Subject develops stools positive for pathogenic helminthic infections

[redacted]

- 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 receives 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 Appendix 7
  - 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
- Use of prohibited treatment as per protocol in Section 6.2.2, when subject safety is compromised and / or there is potential for significant impact on data integrity. Instances of this nature should be discussed as soon as possible with a member of the Global Study Team.
- If a subject uses rescue corticosteroids for CSU more than 3 doses in a 30 day period or more than 9 doses after week 12 in first half of the treatment period or more than 9 doses in the second half of the treatment period.
- Any other protocol deviation that results in a significant risk to the subject's safety
- Any situation in which continued study participation might result in a safety risk to the subject

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 investigational 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 9.1.3). They will be expected to perform the Visit 9998/EOT (Week 104) assessments 4 weeks after their last dose and will be expected to perform assessments at follow-up Visit 9999, 12 weeks after Visit 9998/EOT. 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 Section 9.1.4. This contact should preferably be done according to the study visit schedule.

For subjects who wish to prematurely discontinue treatment prior to the primary endpoint for any reason, every effort should be made to have them continue study visits as per the assessment schedule, at least until Visit 204 (Week 12). At the final visit, all dispensed investigational product should be reconciled and the AE and concomitant medications reconciled on the appropriate eCRF.

If the subject cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the subject, or with a person pre-designated by the subject. This telephone contact should preferably be done according to the study visit schedule until a decision is made to return to the site for discussion about ongoing treatment, or to discontinue treatment/study.

[redacted]

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

9.1.2 Discontinuation from observation periods

Subjects who wish to discontinue from the first observation period will be expected to complete Visit 199 (EOOBS1).

Subjects who wish to discontinue from the second observation period will be expected to complete at least Visits 301, 302 and 303 (Week 0, 4 and 8), and perform Visit 399 (Week 52/EOOBS2) 16 weeks after the last investigational drug administration and exit the study.

9.1.3 Withdrawal of informed consent/Opposition to use data/biological samples

Withdrawal of consent/opposition to use data/biological samples occurs when a subject:

- Explicitly requests to stop use of their biological samples and/or data (opposition to use subject's data and biological samples)

and

- No longer wishes to receive study treatment

and

- Does not want any further visits or assessments (including further study-related contacts)

This request should be in writing (depending on local regulations) and recorded in the source documentation.

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/opposition to use data/biological samples and record this information.

Where consent to the use of Personal and Coded Data is not required in a certain country's legal framework, the subject therefore cannot withdraw consent. However, they still retain the right to object to the further collection or use of their Personal Data.

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.

If the participant agrees, a final evaluation at the time of the participant's withdrawal of consent/opposition to use data/biological samples should be made as detailed in the assessment table (refer to Section 8).

Novartis will continue to retain and use all research results (data) that have already been collected for the study evaluation, including processing of biological samples that has already started at time of consent withdrawal/opposition. No new Personal Data (including biological samples) will be collected following withdrawal of consent/opposition.

[redacted]

9.1.4 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 consent/oppose to the use of their data/biological samples, 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.

9.1.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time. Reasons for early termination may include.

- 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 subject welfare and safety. Should early termination be necessary, subjects must be seen as soon as possible and treated as a subject who discontinued from study treatment. 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 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.

Should the subject complete this extension study prior to the investigational treatment becoming available in the country of the participant and is in the opinion of the investigator still deriving clinical benefit from ligelizumab, every effort will be made to continue provision of study treatment.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events (AEs)

An 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 AEs.

[redacted]

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

The occurrence of AEs must be sought by non-directive questioning of the subject at each visit **or, for self-administering subjects at each scheduled safety phone call,** during the study. AEs also may be detected when they are volunteered by the subject during or between visits **or telephone calls** or through physical examination findings, laboratory test findings, or other assessments.

AEs must be recorded under the signs, symptoms or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

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

   All AEs must be treated appropriately. Treatment may include 1 or more of the following:

   - Dose not changed
   - Dose Reduced/increased
   - Drug interrupted/permanently discontinued; and
6. its outcome i.e., its recovery status or whether it was fatal.

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

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

AE 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 AE 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.

[redacted]

Abnormal laboratory values or test results constitute AEs 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. See Appendix 1 for alert ranges for laboratory and other test abnormalities.

For lab values provided without related clinical information, the 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 (SAEs)

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

- fatal
- life-threatening
  - Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - 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

[redacted]

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.

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 SAE irrespective of whether a clinical event has occurred or not.

10.1.3 Serious adverse event (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 subject's last study visit, must be reported to Novartis safety immediately, without undue delay, under no circumstances later than within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site. 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.

To comply with regulations, all suspected, unexpected, serious adverse reactions (SUSARs) occurring in a clinical trial must be reported in an expedited timeframe (7 or 15 days) to competent authorities.

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

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

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

Any SAEs experienced after the 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to study treatment, unless otherwise specified by local law/regulations.

[redacted]

10.1.4 Pregnancy reporting

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.

Pregnancy should be recorded and reported by the investigator to the Novartis Chief Medical Office and Patient Safety. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the investigational treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported. After consent is provided, the pregnancy reporting will occur up to one year after the estimated date of delivery.

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 they are 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.

[redacted]

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 must be followed.

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

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

Please refer to Table 16-3 in Appendix 2 for complete definitions of liver laboratory triggers.

Once a subject is exposed to study treatment, every liver event defined in Table 16-3 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 16-4 and Table 16-5. Repeat liver chemistry tests (ALT, AST, 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 Section 9.1.1), if appropriate
  - Hospitalization of the subject if appropriate
  - Causality assessment of the liver event
  - A thorough follow-up of the liver event: Assessments should be based on investigator's discretion and can include 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, computed 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.

[redacted]

10.2.2 Renal safety monitoring

The following base monitoring for renal laboratory values, as per the Novartis Drug-Induced Nephrotoxicity (DIN) Guidelines (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)	1. Single baseline
Urine Dipstick (Spot urine sample)	2. Steady State assessment
	3. 6-monthly during study
	4. Final visit ≥ 48h after last dose

Every renal laboratory trigger or renal event as defined in Table 16-6 should be followed up by the investigator or designated personnel at the trial site as summarized in Table 16-7.

10.2.3 Data Monitoring Committee (DMC)

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

The DMC will review clinical trial data from this extension study at least until all subjects completed the Week 12 time-point after which all subjects will be receiving open label treatment.

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

10.2.4 Adjudication committee (AC)

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

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

11 Data Collection and Database management

11.1 Data collection

Designated investigator staff will enter the data required by the protocol into the eCRFs. The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR (Code of Federal Regulation) Part 11 requirements, Investigator site staff will not be given access to EDC system until they have been trained. Automatic validation programs check for

[redacted]

data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

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

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

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 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 classification system. Concomitant procedures, non-drug therapies, medical history/current medical conditions and AEs will be coded using the MedDRA terminology.

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 captured by Novartis via eCRFs.

ECG readings will be processed centrally and results will be sent electronically to Novartis.

Subjects will fill in their daily diary data on a smart phone device at home. PROs will be completed by subjects on site on the day of applicable visits. The system will be supplied by a vendor(s) who will also manage the database. The source data collected by the vendor will be sent electronically to Novartis.

[redacted]

At selected sites digital photos will be taken as per Section 8.5.6. These photographs will be sent electronically by the site to the central dermatology-imaging vendor and from there electronically to Novartis.

Data about study treatment dispensed to the subject will be tracked using IRT. The system will be supplied by a vendor, who will also manage the database. The source data collected by the vendor will be sent electronically to Novartis.

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

[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. 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 or delegated CRO 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. Additionally, a central analytics organization may analyze data and identify risks and trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

The investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, ECGs, 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 ICF 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

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

12.1 Analysis sets

The Full Analysis Set comprises all enrolled subjects who received at least one dose of study treatment. Subjects will be analyzed according to the treatment group they have been assigned to.

The Safety Set includes all subjects who received at least one dose of study treatment. Subjects will be analyzed according to the study treatment received (i.e. actual treatment). The actual treatment will be defined as the treatment received over the study. In case of error in dispensation, the actual treatment will correspond to the treatment which was given most often.

[redacted]

12.2 Subject demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be summarized descriptively by treatment group for the subjects included in the Full Analysis Set. Information from all enrolled subjects; which includes subjects who complete only first observation period and do not transition into the first half of the treatment period, will be included in the listing. Information on screen-failed subjects will not be included.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. For selected parameters, 25^{th} and 75^{th} percentiles will also be presented.

Relevant medical histories and current medical conditions collected from preceding study baseline before patients receiving any study drug will be summarized by system organ class and preferred term, by treatment group.

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, 25^{th} and 75^{th} percentiles, minimum, and maximum will be presented.

The number of subjects and the duration of exposure to investigational drug and dose will be summarized by treatment. Duration of exposure is defined as the date of the last treatment minus the date of first investigational drug administration plus 4 weeks (28 days).

In addition, the number of doses, total cumulative dose, and number of missed doses will be presented. A partial dose will be considered as if 100% of the dose of the assigned treatment has been administered.

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. Concomitant medications will be summarized for the safety set separated for urticaria related background medications and non-urticaria related medications. Similarly, use of rescue medication will also be summarized.

12.4 Analysis of the primary endpoint(s)

12.4.1 Definition of primary endpoint(s)

The primary endpoint is the proportion of subjects with well-controlled urticaria at Week 12 (Visit 204) in the first half of the treatment period based on the UAS7 score. Well-controlled urticaria at Week 12 is assessed as achieving UAS7 ≤ 6 at Week 12.

The UAS7 is the sum of the HSS7 score and the ISS7 score, and ranges from 0-42. Weekly scores (HSS7 and ISS7 scores) will be derived by adding up the average daily scores of the 7 days preceding the visit.

Regardless of the use of rescue medication or discontinuation of the study assigned-treatment due to any reason up to the assessment time point, all available data collected for UAS7 scores will be used for primary endpoint calculation.

[redacted]

12.4.2 Statistical model, hypothesis, and method of analysis

To show retreatment efficacy of ligelizumab 120 mg q4w or 72 mg q4w in achieving well-controlled CSU at Week 12 in the first half of the treatment period in subjects transitioning from the core studies, the summary statistics for the proportion of subjects achieving UAS7 $\leq$ 6 at Week 12 of the first half of the treatment period in this extension study will be provided. The primary analysis will be performed for subjects receiving the same dose of ligelizumab they received in the core studies, i.e. 72 mg or 120 mg for one year. The corresponding 95% confidence interval also will be derived based on the score method including continuity correction.

For the subgroup of subjects who achieved UAS7 $\leq$ 6 at Week 12 in the core studies, and who received either 72 mg or 120 mg ligelizumab, the proportion of subjects with the response of UAS7 $\leq$ 6 at Week 12 of the first half of the treatment period in this extension study will be provided together with a 95% confidence interval.

Subjects rolling over from study CQGE031C1301, who received ligelizumab 120 mg, will not be included in this primary analysis. As this is an open-label Japan safety study, the efficacy data for these subjects will be analyzed separately to avoid potential confounding issues.

Subjects rolling over from the adolescent PK/PD study CQGE031C2202 will also not be included in this primary analysis, as they received treatment doses of ligelizumab of 24 mg or 120 mg for different treatment times. The efficacy data for these subjects will be analyzed separately.

12.4.3 Handling of missing values/censoring/discontinuations

The UAS7 score is derived from the sum of the HSS7 score and the ISS7 score, as noted above. The HSS7 and ISS7 score will be derived by adding up the daily HSS and ISS scores of the 7 days preceding the visit, respectively. The daily score (HSS and ISS) will be calculated by averaging the morning and evening HSS and ISS score, respectively. If one of the morning or evening scores is missing, the non-missing score for that day (morning or evening) will then be used as the daily score.

A minimum of 4 out of 7 daily scores are needed to reliably calculate a weekly HSS7, ISS7 or UAS7 score. For each weekly score from UPDD (i.e. HSS7, ISS7 and UAS7 score), if one or more of the daily scores are missing, the following principles will be applied to handle the missing data:

- If a subject has at least 4 “non-missing” daily scores within the 7 days prior to the study visit, the weekly score will be calculated as the sum of the available eDiary scores of that week, divided by the number of non-missing days, multiplied by 7.
- If there are less than 4 “non-missing” daily scores within the prior 7 days, then the weekly score will be considered as missing for that week.

Subjects who discontinue from study treatment early will be encouraged to stay in the study following the procedures described in Section 9.1.1. These are considered as retrieved dropout (RDO) subjects.

The primary analysis will account for different post-dosing events for missing data handling as follows:

[redacted]

- Discontinuation of initially assigned study treatment prior to Week 12 (Visit 204) due to AEs or lack of efficacy or any other reasons:

Retrieved dropout (RDO) data collected after study treatment discontinuation will be used for analysis. If no RDO data was collected after study treatment permanent discontinuation, non-responder imputation will be applied for missing data imputation.

- Use of rescue medication prior to Week 12 of the first half of the treatment period (V204):

Efficacy data collected during intake of rescue medication will not be excluded from the analysis.

H1-AH is being used as rescue medication in addition to background medication. Considering that, the patient population are refractory to H1-AHs and that ligelizumab efficacy is being evaluated on top of H1-AH therapy, all data collected will be used for analysis.

12.4.4 Sensitivity and Supportive analyses

Sensitivity analyses

Not applicable.

Supportive analyses

To provide relevant insight into efficacy of subject with different features, additional supportive analyses will be provided for the following subgroups, if applicable:

- Adolescent subjects (12 - 17 years) versus adult subjects (≥18 years)

12.5 Analysis of secondary endpoints

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

- Complete control of urticaria at Week 12 after retreatment of ligelizumab for subjects receiving the same dose regimen as in the core studies, assessed as percentage of subjects achieving UAS7 = 0.

  The proportion of subjects with UAS7 = 0 at Week 12 will be summarized in a descriptive manner, it will be provided together with 95% confidence interval. Missing data will be considered as non-responder in the analysis.

- Absolute change from extension study baseline in UAS7 at Week 12 after retreatment of ligelizumab for subjects receiving the same dose regimen as in the core studies.

  The absolute change from extension study baseline in UAS7 score at Week 12 will be summarized descriptively, it will be provided together with 95% confidence interval. The change from extension study in UAS7 components (ISS7 and HSS7) will also be provided in descriptive manner at Week 12.

- No impact on subjects QoL at Week 12 after retreatment of ligelizumab for subjects receiving the same dose regimen as in the core studies, assessed as percentage of subjects achieving DLQI = 0-1.

  An overall score will be calculated according to the scoring manual. The proportion of subjects with overall DLQI scores ≤ 1 at Week 12 will be summarized in a descriptive

[redacted]

manner, it will be provided together with a 95% confidence interval. Missing data will be considered as non-responder in the analysis.

- Cumulative number of weeks that subjects achieve AAS7 = 0 between extension study baseline and Week 12

  The cumulative number of weeks achieving AAS7 = 0 response between baseline and Week 12 will be derived based on the AAS eDiary. A weekly AAS7 score will be derived by adding up the daily scores of the 7 days preceding the visit, and ranges from 0 to 105. For a weekly AAS7 score, if one or more of the daily scores are missing, the same principles as handling the weekly score from UPDD will be applied to handle the missing data. If the AAS7 score is missing, it will be considered as a non-response for the cumulative number of weeks that subjects achieve AAS7 = 0 response calculation. The cumulative frequency plot will be provided together with the summary statistics.

- Well-controlled urticaria at 12 weeks after starting self-administration in the first half of the treatment period, assessed as percentage of subjects achieving UAS7 $\leq$ 6 at 12 weeks after starting self-administration.

  The proportion of subjects with UAS7 $\leq$ 6, 12 weeks after starting self-administration will be summarized in a descriptive manner, and it will be provided together with 95% confidence interval. Missing data will be considered as non-responder in the analysis.

12.5.2 Safety endpoints

For all safety analyses, the safety set will be used. All subjects enrolled into the extension study, regardless of which preceding studies they came from will be included in the safety analysis. All listings and tables will be presented by treatment group. All data will be included in the analysis regardless of rescue medication use.

Adverse events (AEs)

Treatment emergent AEs will be summarized by treatment group. Treatment emergent AEs are defined as the events started after the first dose of study treatment within 16 weeks of last dose of study treatment, or events present prior to the first dose of study treatment but increased in severity based on preferred term within 16 weeks after the last dose of the study treatment.

The number (and percentage) of subjects with treatment emergent AEs will be summarized in the following ways:

- by treatment, primary system organ class and preferred term.
- by treatment, primary system organ class, preferred term and maximum severity.

Separate summaries will be provided for study medication related AEs, death, SAEs, other significant AEs leading to discontinuation. The number (and proportion) of subjects with AEs of special interest/related to identified and potential risks will be summarized by treatment. A subject with multiple AEs within a primary system organ class is only counted once towards the total of the primary system organ class.

AEs which will be counted for a specific treatment period are those which are treatment-emergent. These events are those with an onset after the start of the treatment period, or which

[redacted]

were present prior to the start of the treatment period but increased in severity, and developed into SAEs after the start of the treatment period.

For safety and tolerability of ligelizumab for all subjects during the study, a summary table will be provided for the two subgroups of subjects below:

- Subjects who receive two years continuous ligelizumab treatment.
- Subjects who receive one year ligelizumab treatment and move to the second observation period before move to the second half of the treatment.

To investigate the safety and tolerability of ligelizumab 120 mg PFS, a summary table will be provided to include the AEs after the first dose of PFS use. Only the subjects who receive at least one dose of ligelizumab 120 mg PFS use will be included in this analysis.

To investigate the safety and tolerability of ligelizumab 120 mg in all subjects who will be self-administered, a summary table will be provided to include the information after the first dose using self-administration. Subjects who move from self-administration back to in- clinic administration during the study, they will be included in this analysis if majority (>50%) of drug use is based on self-administration.

SAE summaries will be provided in a similar manner.

Vital signs

Analysis of the vital sign measurements using summary statistics for the change from baseline for each post-baseline visit will be performed. These descriptive summaries will be presented by vital sign and treatment group. Change from baseline will only be summarized for subjects with both baseline and post-baseline values. Subjects with notable vital signs as defined in Appendix 1 will be listed.

12-lead electrocardiogram (ECG)

All ECG data will be listed by treatment group, subject and visit/time, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Clinical laboratory evaluations

The summary of laboratory evaluations will be presented for 2 groups of laboratory tests (hematology and serum chemistry). Descriptive summary statistics for the change from baseline to each study visit will be presented. These descriptive summaries will be presented by laboratory test and treatment group. Change from baseline will only be summarized for subjects with both baseline and post baseline values. Shift tables using the low/normal/high/ (low and high) classification will be used to compare baseline to the worst on-treatment value.

Other safety evaluations

[redacted]

[redacted]

[redacted]

[redacted]

Resource utilization

Data relating to resource utilization will be used for the purpose of economic evaluation and will be carried out and reported as a separate activity.

[redacted]

[redacted]

[redacted]

12.5.5 Biomarkers

Available biomarker data will be listed by treatment group, subject and visit. Summary statistics will be provided by treatment and visit. The number of values outside of the limits of quantification will be reported in each table.

[redacted]

[redacted]

[redacted]

[redacted]

12.7 Interim analyses

The first interim analysis is planned once all subjects of the CQGE031C2302 and CQGE031C2303 have completed Week 12 (Visit 204) in the first half of the treatment period to evaluate the primary endpoint of retreatment efficacy (or discontinued the trial or completed the first observation period without relapse).

The second interim analysis will be performed at the end of the first half of the treatment period at Week 52 to evaluate endpoints up to the end of 1 year treatment.

Additional analyses may be performed to support health authority interactions as necessary.

At the End of Study, a final analysis of all data collected up to last study visit will be performed when all subjects have completed the last study visit.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

The total number of subjects enrolled will be determined by the drop-out rate prior to the Phase 3 extension study from studies CQGE031C2302, CQGE031C2303, CQGE031C2202 and CQGE031C1301.

Based on interim results from CQGE031C2201, it is assumed that the proportion of subjects achieving UAS7 ≤ 6 at Week 12 is around 55% for ligelizumab 72 mg q4w. It is assumed that the well-controlled response for ligelizumab 120 mg q4w will be similar. The corresponding

[redacted]

95% confidence interval is listed based on different assumptions of number of subjects who will be enrolled for each treatment arm.

Table 12-1 95% confidence interval based on number of subjects enrolled from the core studies (CQGE031C2302/2303)

Number of subjects enrolled	Number of subjects for each treatment group	Drop out rate at Week 12	Assumed proportion of subjects achieving UAS7 ≤ 6 at Week 12	Corresponding 95% confidence interval
500	250	10%	55%	(48.6% - 61.6%)
900	450	10%	55%	(50.2% - 59.9%)
1200	600	10%	55%	(50.8% - 59.2%)

To evaluate the retreatment efficacy in the subgroup of subjects who achieved UAS7 ≤ 6 at Week 12 after the retreatment on the same ligelizumab dose, the 95% confidence interval of the response rate will be provided for each treatment group. It is assumed that 50% of subjects enrolled into this extension study were well-controlled responders during the core studies for each ligelizumab treatment group. A 15% drop out rate is assumed for each treatment group before Week 12. The number of subjects required at the baseline of re-treatment for each treatment arm is listed in Table 12-2 below, based on different assumptions of the retreatment response rates and the corresponding precision levels (width of the 95% confidence interval).

Table 12-2 Number of subjects required at the baseline of re-treatment for each treatment arm enrolled from the core studies (CQGE031C2302/2303)

	Precision		
Response rate after retreatment	10%	12%	15%
70%	191	135	85
80%	146	102	66
90%	83	59	38

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 IRB/IEC for the trial protocol, written ICF, 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

[redacted]

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 European Union Drug Regulating Authorities Clinical Trials Database (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 at the trial investigator meetings.

13.4 Quality Control and Quality Assurance

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

13.5 Patient Engagement

The following patient engagement initiatives are included in this study and will be provided as available, for distribution to study participants at the time points indicated. If compliance is impacted by cultural norms or local laws and regulations, sites may discuss modifications to these requirements with Novartis.

- Thank You letter – end of trial
- Plain language trial summary – after Clinical Study Report publication

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.

15 References

References are available upon request

Arcara K, Tschudy M (eds) (2011) The Harriet Lane Handbook. The Johns Hopkins Hospital. Philadelphia:Mosby.

Arm JP, Bottoli I, Skerjanec A, et al (2014) Pharmacokinetics, pharmacodynamics and safety of QGE031 (ligelizumab), a novel high-affinity anti-IgE antibody, in atopic subjects. Clin Exp Allergy; 44(11):1371-85.

Bernstein JA, Lang DM, Khan DA, et al (2014) The diagnosis and management of acute and chronic urticaria: 2014 update. J Allergy Clin Immunol; 133(5):1270-7.

Biagtan MJ, Viswanathan RK, Evans MD, et al (2011) Clinical utility of the Chronic Urticaria Index. J Allergy Clin Immunol; 127(6):1626-7.

Bretz F, Pinheiro JC, Branson M, et al (2005) Combining multiple comparisons and modeling techniques in dose-response studies. Biometrics; 61(3):738-48.

Chang TW, Chen C, Lin CJ, et al (2015) The potential pharmacologic mechanisms of omalizumab in patients with chronic spontaneous urticaria. J Allergy Clin Immunol; 135(2):337-42.

Church M, Weller K, Stock P, et al (2011) Chronic spontaneous urticaria in children: Itching for insight. Pediatric Allergy Immunology; 22 (1 Pt 1):1-8.

Collier DH, Bitman B, Coles A, et al. (2017) A novel electromechanical autoinjector, AutoTouch™, for self-injection of etanercept: real-world use and benefits. Postgrad Med; 129(1):118-25.

Cox L, Lieberman P, Wallace D, et al (2011) American Academy of Allergy, Asthma & Immunology/American College of Allergy, Asthma & Immunology Omalizumab-Associated Anaphylaxis Joint Task Force follow-up report. J Allergy Clin Immunol; 128(1):210-2.

Cox LS, 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.

EMA (2014) Qualification Opinion on MCP-Mod as an efficient statistical methodology for model-based design and analysis of Phase II dose finding studies under model uncertainty.

FDA (2016) guidance document: <https www fda.gov/drugs/development-approval-process-drugs/drug-development-tools-fit-purpose-initiative>.

Finlay AY, Khan GK (1994) Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use. Clin Exp Dermatol; 19(3):210-6.

Finlay AY (2005) Current severe psoriasis and the Rule of Tens. Br J Dermatol; 152(5):861-7.

Gauvreau GM, Arm JP, Boulet LP, et al (2016) Efficacy and safety of multiple doses of QGE031 (ligelizumab) versus omalizumab and placebo in inhibiting allergen-induced early asthmatic responses. J Allergy Clin Immunol; 138(4):1051-9.

[redacted]

Gober LM, Sterba PM, Eckman JA (2008) Effect of Anti-IgE (Omalizumab) in Chronic Idiopathic Urticaria (CIU) in patients. J Allergy and Clin Immonol; 121(2):S147.

Greaves MW (2003) Chronic idiopathic urticaria. Curr Opin Allergy Clin Immunol; 3(5):363-8.

Hongbo Y, Thomas CL, Harrison MA, et al (2005) Translating the science of quality of life into practice: What do dermatology life quality index scores mean? J Invest Dermatol; 125(4):659-64.

Lewis-Jones MS, Finlay AY (1995) The Children's Dermatology Life Quality Index (CDLQI): initial validation and practical use. Br J Dermatol; 132(6):942-9.

Kaplan A, Ferrer M, Bernstein JA, et al (2016) Timing and duration of omalizumab response in patients with chronic idiopathic/spontaneous urticaria. J Allergy Clin Immunol; 137(2):474-81.

Kaplan A, Ledford D, Ashby M, et al (2013) Omalizumab in patients with symptomatic chronic idiopathic/spontaneous urticaria despite standard combination therapy. J Allergy Clin Immunol; 132(1):101-9.

Kaplan AP, Joseph K, Maykut RJ, et al (2008) Treatment of chronic autoimmune urticaria with omalizumab. J Allergy Clin Immunol; 122(3):569-73.

[redacted]

Maurer M, Abuzakouk M, Berard F, et al (2017) The burden of chronic spontaneous urticaria is substantial: Real-world evidence from ASSURE-CSU. Allergy; 72(12):2005-16.

Maurer M, Gimenez-Arnau AM, Sussman G, et al (2019) Ligelizumab for Chronic Spontaneous Urticaria. N Engl J Med; 381(14):1321-32.

Maurer M, Rosen K, Hsieh HJ, et al (2013) Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. N Engl J Med; 368(10):924-35.

O'Donnell BF, Lawlor F, Simpson J, et al (1997) The impact of chronic urticaria on the quality of life. Br J Dermatol; 136(2):197-201.

[redacted]

Pickering TG, Hall JE, Appel LJ, et al (2005) Recommendations for blood pressure measurement in humans and experimental animals: part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. Circulation; 111(5):697-716.

Powell RJ, Du Toit GL, Siddique N, et al (2007) BSACI guidelines for the management of chronic urticaria and angio-oedema. Clin Exp Allergy; 37(5):631-50.

[redacted]

Richardson SJ, Brooks HL, Bramley G, et al (2014) Evaluating the effectiveness of self-administration of medication (SAM) schemes in the hospital setting: a systematic review of the literature. PLos One; 9(12): e113912.

Simons FE, Ardusso L, Bilo B, et al (2011) World Allergy Organization Guidelines for the Assessment and Management of Anaphylaxis. World Allergy Organ J; 4(2):13-37.

Simons FE, Ebisawa M, Sanchez-Borges M, et al (2015) 2015 update of the evidence base: World Allergy Organization anaphylaxis guidelines. World Allergy Organ J; 8(1):32.

Stull D, McBride D, Tian H, et al (2017) Analysis of disease activity categories in chronic spontaneous/idiopathic urticaria. Br J Dermatol; 177(4):1093-101.

Vadasz Z, Tal Y, Rotem M, et al (2017) Omalizumab for severe chronic spontaneous urticaria: Real-life experiences of 280 patients. J Allergy Clin Immunol Pract; 5(6):1743-5.

Viswanathan RK, Biagtan MJ, Mathur SK (2012) The role of autoimmune testing in chronic idiopathic urticaria. Ann Allergy Asthma Immunol; 108(5):337-41.

Waters A, Sandhu D, Beattie P, et al (2010) Severity stratification of Children's Dermatology Life Quality Index (CDLQI) scores. Br J Dermatol; 163(1):121.

[redacted]

Zuberbier T, Aberer W, Asero R, et al (2014) The EAACI/GA2LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. Allergy; 69(7):868-87.

Zuberbier T, Asero R, Bernstein JA, et al (2018) The EAACI/GA²LEN/EDF/WAO Guideline for the Definition, Classification, Diagnosis and Management of Urticaria. The 2017 Revision and Update. Allergy; 73(7):1393-414.

Zuberbier T, Asero R, Bindslev-Jensen C, et al (2009) EAACI/GA2LEN/EDF/WAO guideline: management of urticaria. Allergy 64:1427-43.

16 Appendices

16.1 Appendix 1: Clinically notable laboratory values and vital signs

Refer to Appendix 1.1 for clinically notable vital sign values for adolescents.

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

Refer to 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 have platelets < 75 000/μL after being randomized should discontinue study treatment.

[redacted]

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 as an AE.

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 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 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.

16.1.1 Appendix 1.1: Clinically notable vital signs – adolescent subjects

16.1.1.1 Guideline for pediatric blood pressure measurements:

Table 16-1 Best Blood Pressure (BP) Measurement Practices - Pediatrics

1. The child should be seated in a quiet room for 3–5 min before measurement, with the back supported and feet uncrossed on the floor.
2. BP should be measured in the right arm for consistency, for comparison with standard tables, and to avoid a falsely low reading from the left arm in the case of coarctation of the aorta. The arm should be at heart level, supported, and uncovered above the cuff. The patient and observer should not speak while the measurement is being taken.
3. The correct cuff size should be used. The bladder length should be 80%–100% of the circumference of the arm, and the width should be at least 40%.
4. For an auscultatory BP, the bell of the stethoscope should be placed over the brachial artery in the antecubital fossa, and the lower end of the cuff should be 2–3 cm above the antecubital fossa. The cuff should be inflated to 20–30 mm Hg above the point at which the radial pulse disappears. Overinflation should be avoided. The cuff should be deflated at a rate of 2–3 mm Hg per second. The first (phase I Korotkoff) and last (phase V Korotkoff) audible sounds should be taken as systolic blood pressure and diastolic blood pressure. If the Korotkoff sounds are heard to 0 mm Hg, the point at which the sound is muffled (phase IV Korotkoff) should be taken as the diastolic BP, or the measurement repeated with less pressure applied over the brachial artery. The measurement should be read to the nearest 2 mm Hg.
5. To measure BP in the legs, the patient should be in the prone position, if possible. An appropriately sized cuff should be placed midthigh and the stethoscope placed over the popliteal artery. The systolic BP in the legs is usually 10%–20% higher than the brachial artery pressure.

Adapted from Pickering TG et al 2005

Table 16-2 Upper and lower limits for adolescents' vital signs that may be considered of concern if newly identified may be identified using the following table for guidance[1]

Age	Systolic BP[2,3]	Diastolic BP[2,3]	HR[3]
12 yrs	101-135	59-91	60-110
13 yrs	104-137	60-91	60-110

[redacted]

Age	Systolic BP[2,3]	Diastolic BP[2,3]	HR[3]
14 yrs	106-140	60-92	60-110
15 yrs	107-142	61-93	60-110
16 yrs	108-145	63-94	60-110
17 yrs	108-147	64-97	60-100
18 yrs	-	-	60-100

[1] The table above was developed from multiple resources listed below. The normal values for vital signs in children vary greatly with age, growth and development. The purpose of these values is to guide investigators to identify or screen for values of concern in pediatric patients by age. These are not normal values, which can be found in sources such as the Harriet Lane Pediatric Handbook but rather are upper and lower limits for children's vital signs that may be considered of concern if newly identified. The significance of these findings must be considered in view of the patient's disease, time course and overall clinical condition.

[2] Based on percentiles by height (50th - 99th)

[3] (Arcara K and Tschudy M 2011). The Harriet Lane Handbook
who.int/childgrowth/standards/w_f_a_tables_p_girls/en/index.html
who.int/childgrowth/standards/second_set/hcfa_girls_p_exp.txt
who.int/childgrowth/standards/second_set/hcfa_boys_p_exp.txt

16.2 Appendix 2: Liver event and laboratory trigger definitions and follow-up requirements

Table 16-3 Liver event and laboratory trigger definitions

	Definition/ threshold
LIVER LABORATORY TRIGGERS if ALT, AST and TBL normal at baseline	• ALT or AST >5 × ULN • ALP > 2 × ULN (in the absence of known bone pathology) • TBL > 3 × ULN (in the absence of known Gilbert syndrome) • ALT or AST > 3 × ULN and (TBL > 2 x ULN or INR > 1.5) • Potential Hy's Law cases defined as ALT or AST > 3 x ULN, combined with elevation of serum TBL to > 2 x ULN (mainly conjugated fraction), without notable increase of ALP to > 2 ULN • Any clinical event of jaundice (or equivalent term) • ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia • Any adverse event potentially indicative of a liver toxicity
If ALT or AST abnormal at baseline:	• ALT or AST > 3 x baseline or > 300 U/L (whichever occurs first)

Table 16-4 Follow-up requirements for liver laboratory triggers – ALT, TBL with and without liver symptoms

ALT	TBL	Liver Symptoms	Actions
ALT increase without bilirubin increase:			
If normal at baseline: ALT > 3 × ULN **If elevated at baseline:** ALT > 2 × baseline or > 300 U/L (whichever	Normal For patients with Gilbert's syndrome: No change in	None	• **No change to study treatment** • Measure ALT, AST, ALP, GGT,

[redacted]

	ALT	TBL	Liver Symptoms	Actions
	occurs first)	baseline TBL		TBL, INR, albumin, CK, and GLDH in 48-72 hours. • Follow-up for symptoms.
	If normal at baseline: ALT > 5 × ULN for more than two weeks **If elevated at baseline:** ALT > 3 × baseline or > 300 U/L (whichever occurs first) for more than two weeks	Normal For patients with Gilbert's syndrome: No change in baseline TBL	None	• **Interrupt study drug** • Measure ALT, AST, ALP, GGT, TBL, INR, albumin, CK, and GLDH in 48-72 hours. • Follow-up for symptoms. • Initiate close monitoring and workup for competing etiologies. • Study drug can be restarted only if another etiology is identified and liver enzymes return to baseline.
	If normal at baseline: ALT > 8 × ULN	Normal	None	
ALT increase with bilirubin increase:				
	If normal at baseline: ALT > 3 × ULN **If elevated at baseline:** ALT > 2 × baseline or > 300 U/L (whichever occurs first)	TBL > 2 x ULN (or INR > 1.5) For patients with Gilbert's syndrome: Doubling of direct bilirubin	None	
	If normal at baseline: ALT > 3 x ULN **If elevated at baseline:** ALT > 2 x baseline or > 300 U/L (whichever occurs first)	Normal or elevated	Severe fatigue, nausea, vomiting, right upper quadrant pain	

Table 16-5 Follow-up requirements for liver laboratory triggers – isolated hyperbilirubinemia

Criteria	Actions required	Follow-up monitoring
TBL (isolated)		
>1.5 – 3 × ULN	Maintain treatment Repeat LFTs within 48-72 hours	Monitor LFTs weekly until resolution to ≤ Grade 1 or baseline
> 3 - 10 × ULN (in the absence of known Gilbert syndrome)	Interrupt treatment Repeat LFT within 48-72 hours Hospitalize if clinically appropriate Establish causality Record the AE and contributing factors (eg, conmeds, med hx, lab) in the appropriate CRF	Monitor ALT, AST, TBL, Alb, PT/INR, ALP and GGT weekly until resolution to ≤ Grade 1 or baseline Test for hemolysis (eg, reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 10 × ULN	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 (frequency at investigator discretion)

[redacted]

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

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.

16.3 Appendix 3: Specific renal alert criteria and actions and event follow-up

Refer to Section 10.2.2.

Table 16-6 Specific renal alert criteria and actions

Renal Event	Actions
Confirmed serum creatinine increase 25% – 49%	• Consider causes and possible interventions • Follow up within 2-5 days
Serum creatinine increase ≥ 50% [+] **OR** **if <18 years old,** eGFR < 35mL/min/1.73 m2	• Consider causes and possible interventions • Repeat assessment within 24-48h 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) ≥ 1g/g Cr (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 drug interruption or discontinuation unless other causes are diagnosed and corrected
New onset hematuria ≥ 3+ on urine dipstick	• 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

[+] Corresponds to KDIGO (Kidney Disease Improving Global Outcomes) criteria for Acute Kidney Injury

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:

[redacted]

- Blood pressure assessment (after 5-min 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

Table 16-7 Renal event follow-up

Follow-up of renal events
1. Assess, document and record in CRF • Urine dipstick and sediment microscopy evidence of drug induced nephrotoxicity: 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
2. 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
3. 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 of baseline) or • Event stabilization: SCR level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months
4. Analysis of urine markers in samples collected over the course of the drug induced nephrotoxicity event

16.4 Appendix 4: PRO tools

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

[redacted]

Patient Diary: Urticaria Patient Daily Diary (UPDD)

URTICARIA PATIENT DAILY DIARY (UPDD)

General Instructions

Please answer each question to the best of your ability.

There are no right or wrong answers.

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

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

Instructions for Counting the Number of Hives

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

Today's Date day month year

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

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

Itch (severity)

0 = none

1 = mild

2 = moderate

3 = severe

Hives (number)

0 = none

1 = between 1 and 6 hives

2 = between 7 and 12 hives

3 = greater than 12 hives

[redacted]

Today's Date day month year

Please complete this section 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

Today's Date day month year

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]

Patient Diary: Angioedema Activity Score (AAS)

Instructions: Please document your symptoms retrospectively once a day. Refer to the last 24 hours in each case. Please answer all questions as fully as possible

		Day						
		1	2	3	4	5	6	7
Have you had a swelling episode in the last 24 hours?	no							
	yes							
Please answer the questions below about this swelling episode during the last 24 hours. If you did not have a swelling episode, leave them blank.								
At what time(s) of day was this swelling episode(s) present? (please select all applicable times)	midnight - 8 a.m.							
	8 a.m. - 4 p.m.							
	4 p.m. - midnight							
How severe is / was the physical discomfort caused by this swelling episode(s) (e.g., pain, burning, itching?)	no discomfort							
	slight discomfort							
	moderate discomfort							
	severe discomfort							
Are / were you able to perform your daily activities during this swelling episode(s)?	no restriction							
	slight restriction							
	severe restriction							
	no activities possible							
Do / did you feel your appearance is / was adversely affected by this swelling episode(s)?	no							
	slightly							
	moderately							
	severely							
How would you rate the overall severity of this swelling episode?	negligible							
	mild							
	moderate							
	severe							

[redacted]

Dermatology Life Quality Index (DLQI)

DERMATOLOGY LIFE QUALITY INDEX

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please check 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 **yard?**	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.

[redacted]

Children Dermatology Life Quality Index (CDLQI)

CHILDREN'S DERMATOLOGY LIFE QUALITY INDEX

Hospital No
Name: Diagnosis: CDLQI SCORE:
Age:
Address: Date:

The aim of this questionnaire is to measure how much your skin problem has affected you OVER THE LAST WEEK. Please tick 4 one box for each question.

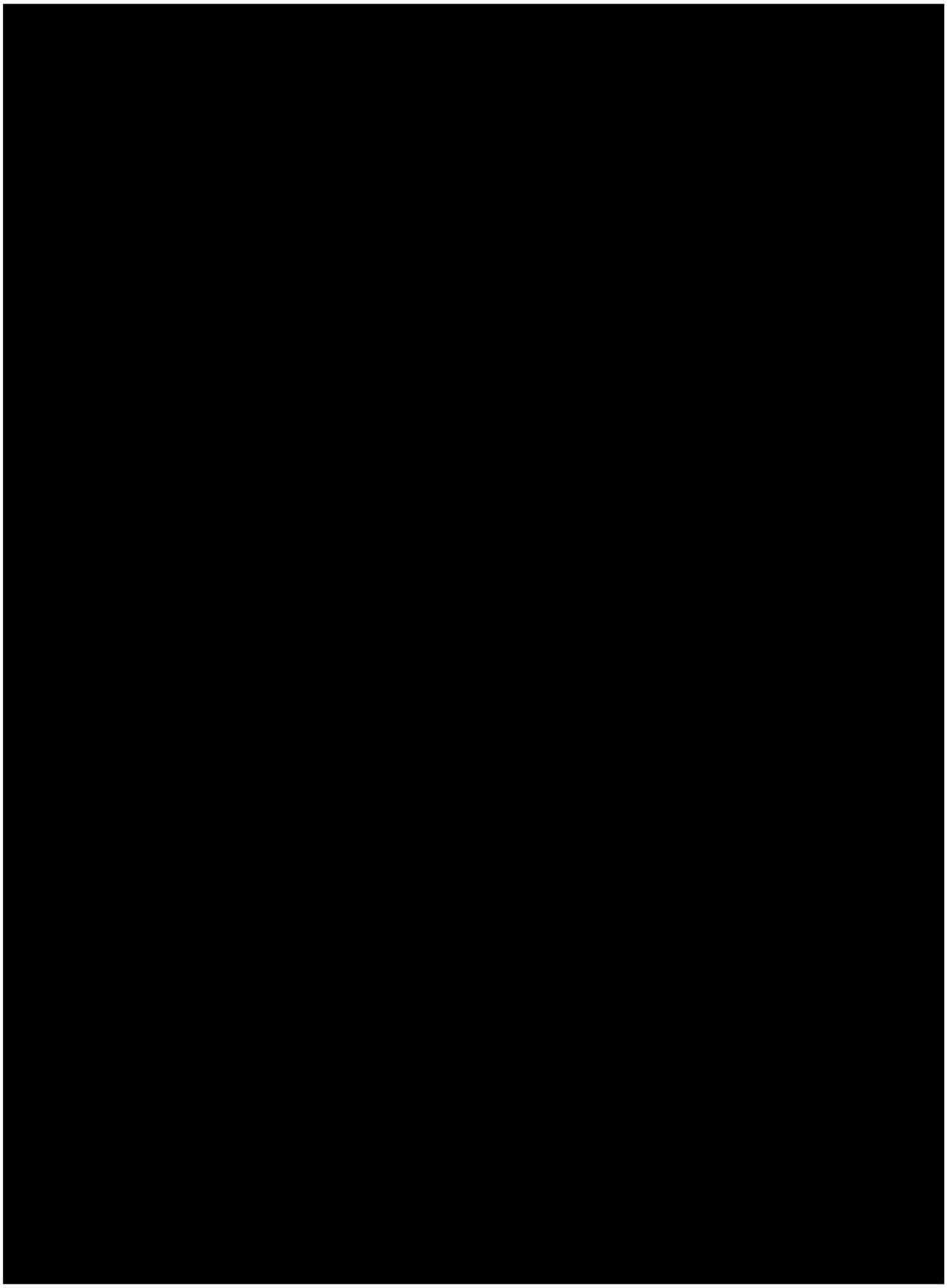
1.	Over the last week, how **itchy, "scratchy", sore or painful** has your skin been?	Very much Quite a lot Only a little Not at all	r r r r
2.	Over the last week, how **embarrassed or self conscious, upset or sad** have you been because of your skin?	Very much Quite a lot Only a little Not at all	r r r r
3.	Over the last week, how much has your skin affected your **friendships?**	Very much Quite a lot Only a little Not at all	r r r r
4.	Over the last week, how much have you changed or worn **different or special clothes/shoes** because of your skin?	Very much Quite a lot Only a little Not at all	r r r r
5.	Over the last week, how much has your skin trouble affected **going out, playing, or doing hobbies?**	Very much Quite a lot Only a little Not at all	r r r r
6.	Over the last week, how much have you **avoided swimming or other sports** because of your skin trouble?	Very much Quite a lot Only a little Not at all	r r r r
7.	Last week, was it **school time?** ⇨ **If school time**: Over the last week, how much did your skin affect your **school work?**	Prevented school Very much Quite a lot Only a little Not at all	r r r r r
	OR		
	was it **vacation time?** ⇨ **If vacation time**: How much over the last week, has your skin problem interfered with your enjoyment of the **vacation?**	Very much Quite a lot Only a little Not at all	r r r r
8.	Over the last week, how much trouble have you had because of your skin with other people **calling you names, teasing, bullying, asking questions or avoiding you?**	Very much Quite a lot Only a little Not at all	r r r r
9.	Over the last week, how much has your **sleep** been affected by your skin problem?	Very much Quite a lot Only a little Not at all	r r r r
10.	Over the last week, how much of a problem has the **treatment** for your skin been?	Very much Quite a lot Only a little Not at all	r r r r

Please check that you have answered EVERY question. Thank you.

[redacted]

[redacted]

[redacted]



[redacted]

[redacted]

[redacted]

16.7 Appendix 7: World allergy organization grading system

World allergy organization subcutaneous immunotherapy systemic reaction grading system

Grading system for SARs

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
			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)* 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