NOVARTIS

Novartis Research and Development

QGE031/Ligelizumab

Clinical Trial Protocol CQGE031C2302 / NCT03580369

A multi-center, randomized, double-blind, active and placebo-controlled study to investigate the efficacy and safety of ligelizumab (QGE031) in the treatment of Chronic Spontaneous Urticaria (CSU) in adolescents and adults inadequately controlled with H1-antihistamines

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Table of contents

List of tables

List of figures

List of abbreviations

AC	Adjudication Committee
[redacted]	[redacted]
AE	Adverse Event
AH	Anti-histamine
ALT	Alanine Aminotransferase
ALP	Alkaline Phosphatase
AAS	Angioedema Activity Score
ASS7	Weekly Angioedemy Activiy Score
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
bpm	Beats per minute
BUN	Blood Urea Nitrogen
CDLQI	Children's Dermatology Life Quality Index
CU	Chronic Urticaria
CIU	Chronic Idiopathic Urticaria
CMO&PS	Chief Medical Office and Patient Safety
CO	Country Organization
COVID-19	Corona Virus Disease 2019
CRF	Case Report/Record Form
CS	Corticosteroids
CSU	Chronic Spontaneous Urticaria
CT	Computerized Tomography
CTC	Common Toxicity Criteria
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic Data Capture
eDiary	Electronic Diary
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EoT	End of treatment
EoS	End of study
eSource	Electronic Source
EU	European Union
FAS	Full Analysis Set
FcεRI	IgE receptor
FcεRII	IgE receptor
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
β-hCG	Beta-Human Chorionic Gonadotropin
HCP	Health care practitioner
HRQoL	Health-Related Quality of Life
HSS	Hives Severity Score

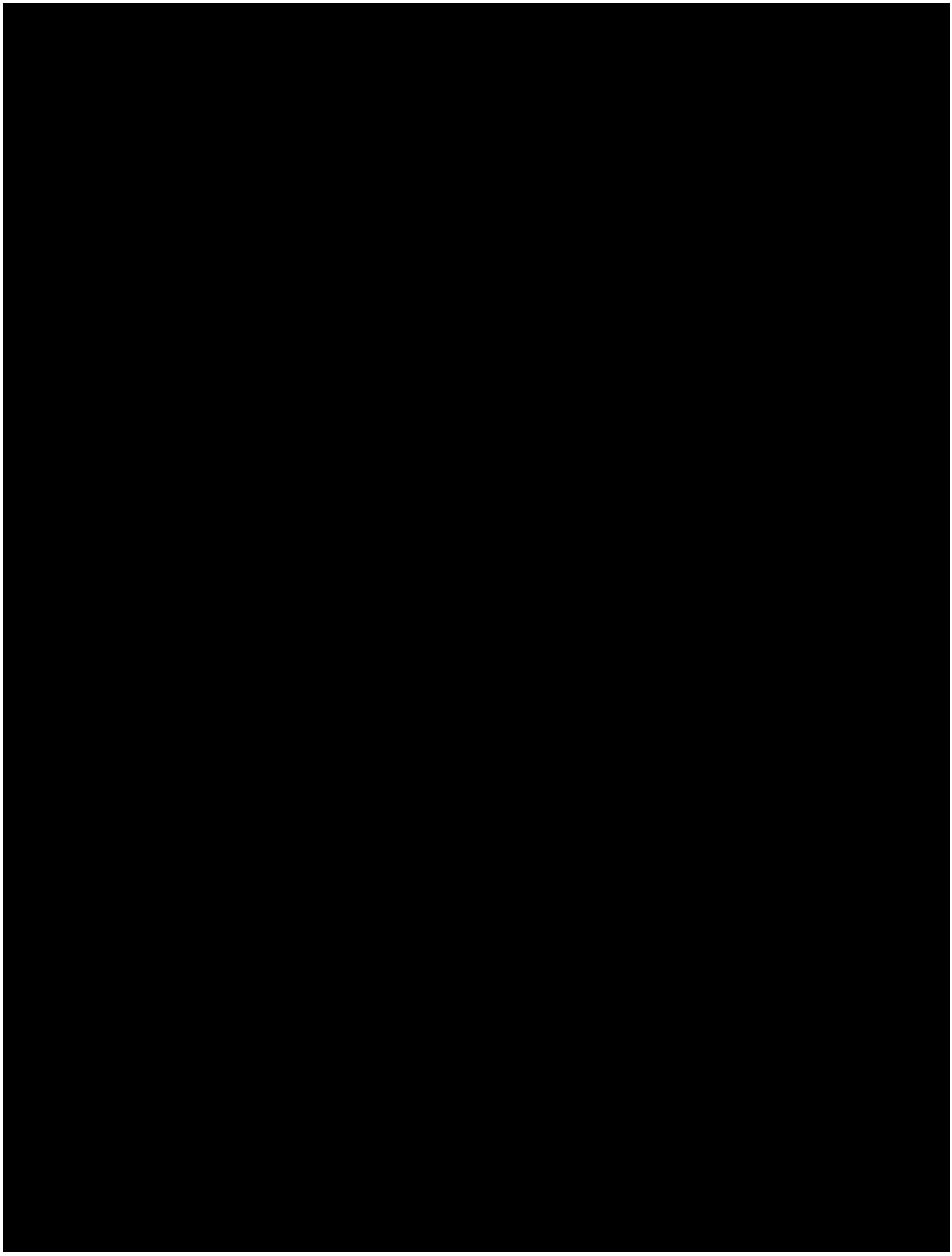
HSS7	Weekly Hives Severity Score
H1-AH	H1-antihistamines
IA	Interim Analysis
IB	Investigator's Brochure
IgE	Immunoglobulin E
IgG	Immunoglobulin G
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IM	Intra-muscular
IN	Investigator notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISS	Itch Severity Score
ISS7	Weekly Itch Severity Score
IUD	Intrauterine device
IUS	Intrauterine system
IV	Intra-venous
LFT	Liver function test
LDH	Lactate Dehydrogenase
LLOQ	Lower limit of quantification
LPLV	Last patient last visit
LoE	Lack of efficacy
LTRA	Leukotriene Receptor Antagonist
MAR	Missing at random
MCP-mod	Multiple comparison procedure modeling
MedDRA	Medical dictionary for regulatory activities
MERS	Middle Eastern respiratory syndrome
MMRM	Mixed model with repeated measures
MoA	Mechanism of action
MRI	Magnetic Resonance Imaging
NYHA	New York Heart Association
Oma	Omalizumab
PBO	Placebo
[redacted]	[redacted]
PK	Pharmacokinetic(s)
p.o.	Oral(ly)
PRO	Patient Reported Outcomes
PSD	Premature subject discontinuation
PT	Prothrombin time
QALYS	Quality-adjusted life-years
q4w	Every 4 weeks
QMS	Quality Management System
QoL	Quality of life
QTcF	QT interval corrected by Fridericia's formula
RAN	Randomized set
RBC	Red blood cell(s)

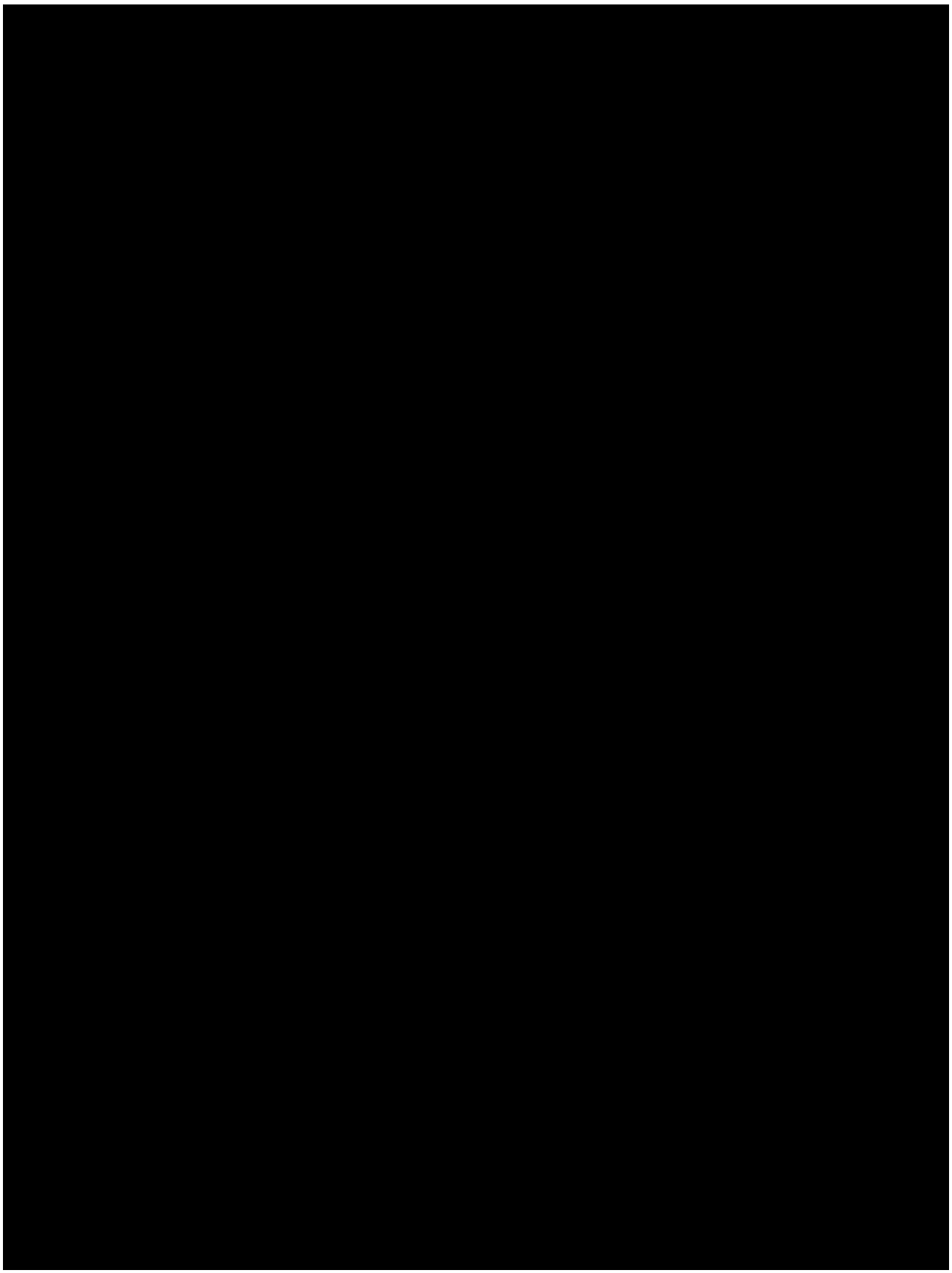
RDO	Retrieved Drop Out
RoW	Rest of world
SAE	Serious Adverse Event
SAF	Safety analysis set
sc	Subcutaneous
sCr	Serum creatinine
SOP	Standard Operating Procedure
SUSARs	Suspected Unexpected Serious Adverse Reactions
TBL	Total bilirubin
TD	Study Treatment Discontinuation
UAS7	Weekly Urticaria Activity Score
ULN	Upper limit of normal
UPDD	Urticaria patient daily device
UPV	Unplanned visit
US	United States
VAS	Visual Analog Scale
WBC	White blood cell(s)
WHO	World Health Organization
[redacted]	[redacted]

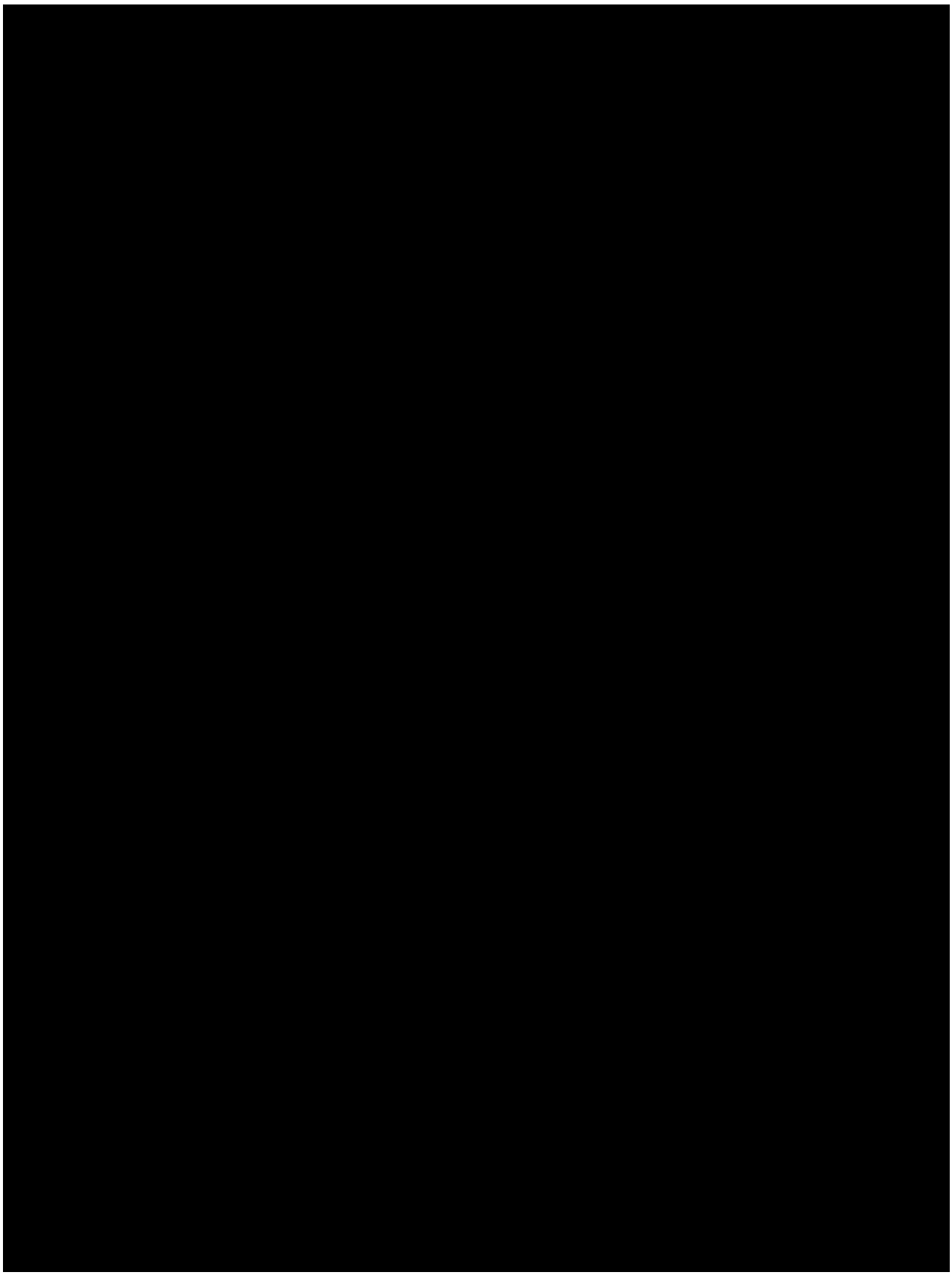
Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (eg, any background therapy)
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject
Cohort	A specific group of subjects fulfilling certain criteria and generally treated at the same time
Control drug	A study drug (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Dosage	Dose of the study treatment given to the subject in a time unit (eg, 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care.
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
eSource (DDE)	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource Platform/Applications reduce the use of paper capture source data during clinical visits. eSource combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate.
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Investigational drug/treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits
Mis-randomized subjects	Mis-randomized subjects are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study
Other treatment	Treatment that may be needed/allowed during the conduct of the study (concomitant or rescue therapy)
Part	A sub-division of a study used to evaluate specific objectives or contain different populations. For example, 1 study could contain a single dose part and a multiple dose part, or a part in subjects with established disease and in those with newly-diagnosed disease.
Patient	An individual with the condition of interest for the study
Period	The subdivisions of the trial design (eg, 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
Perpetrator drug	A drug which affects the pharmacokinetics of the other drug
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/or assessments; at this time all study drug administration is discontinued and no further assessments are planned
Randomization number	A unique identifier assigned to each randomized subject

Run-in Failure	A subject who is screened but not randomized/treated after the run-in period (where run-in period requires adjustment to subject's intervention or treatment)
UAS7	Weekly Urticaria Activity Score
Screen Failure	A subject who did not meet 1 or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource.
Stage in cancer	The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first subject.
Study treatment	Any single drug or combination of drugs or intervention administered to the subject as part of the required study procedures.
Study treatment discontinuation	When the subject permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
Subject	A trial participant (can be a healthy volunteer or a patient)
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Variable	A measured value or assessed response that is determined from specific assessments and used in data analysis to evaluate the drug being tested in the study
Victim drug	The drug that is affected by the drug-drug interaction
Withdrawal of study consent	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer and does not allow any further collection of personal data.







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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.

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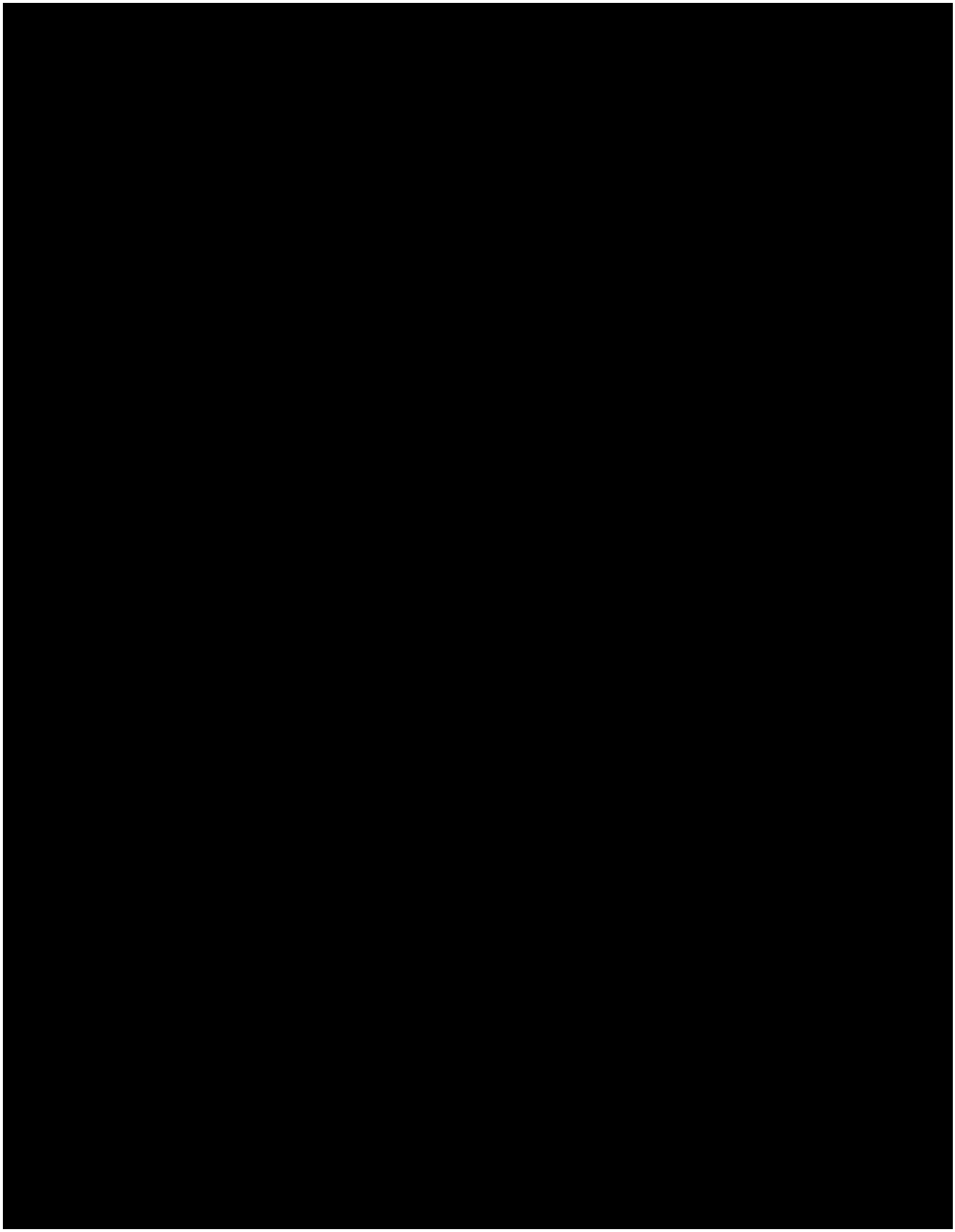
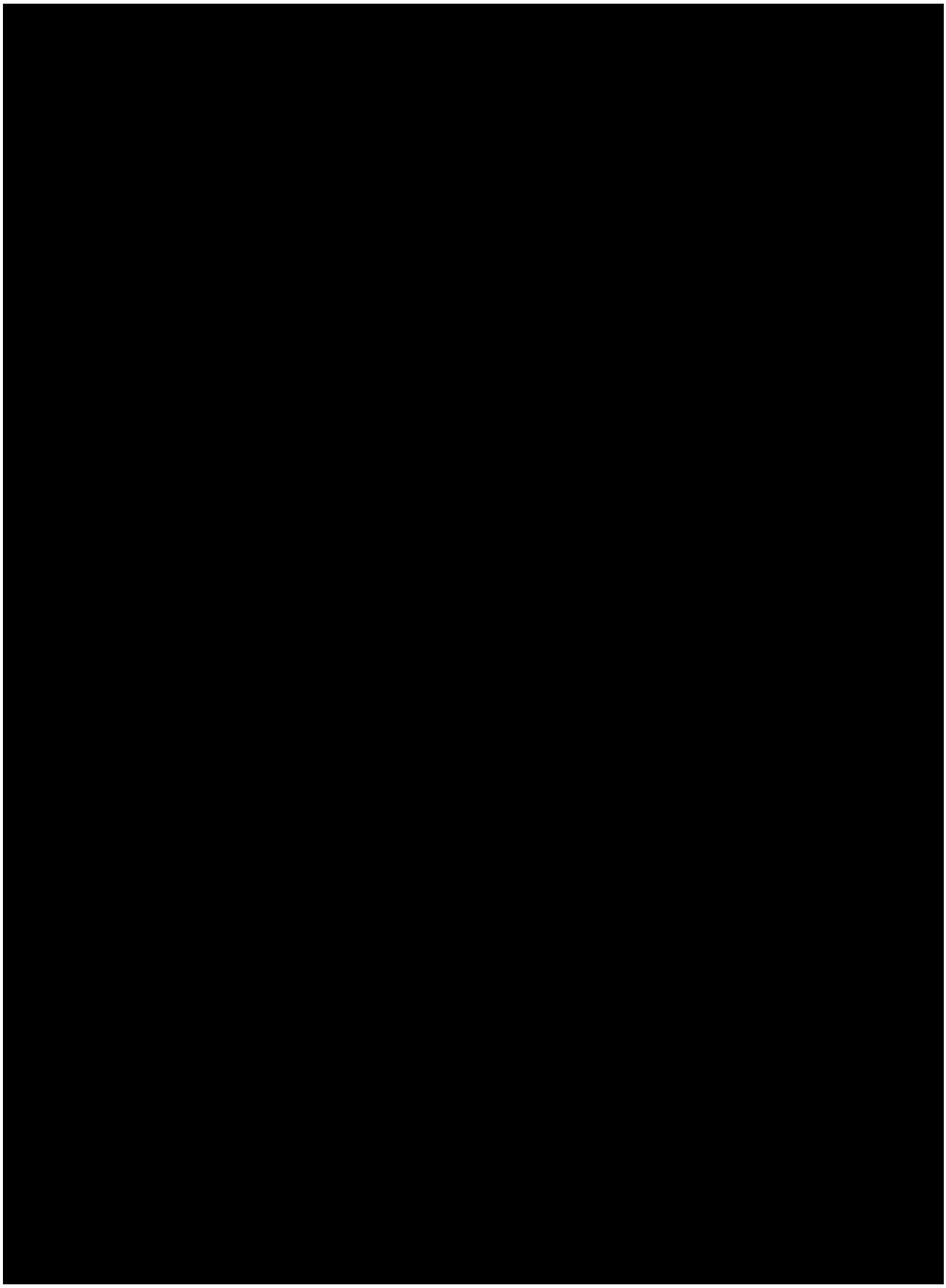




Protocol summary

Protocol number	CQGE031C2302
Full Title	A multi-center, randomized, double-blind, active and placebo-controlled study to investigate the efficacy and safety of ligelizumab (QGE031) in the treatment of Chronic Spontaneous Urticaria (CSU) in adolescents and adults inadequately controlled with H1-antihistamines
Brief title	A Phase III study of efficacy and safety of ligelizumab in the treatment of CSU in adolescents and adults inadequately controlled with H1-antihistamines
Sponsor and Clinical Phase	Novartis Phase III
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to establish efficacy and safety of ligelizumab in adolescent and adult subjects with CSU who remain symptomatic despite standard of care treatment by demonstrating better efficacy over omalizumab.
Primary Objective(s)	The primary objective of the study is to demonstrate that ligelizumab (72 mg q4w and/or 120 mg q4w) is superior to placebo and superior to omalizumab 300 mg q4w in change from baseline in UAS7 at Week 12.
Secondary Objectives	Objective 1: To demonstrate that a greater proportion of subjects achieve UAS7 = 0 at Week 12 who are treated with ligelizumab 72 mg q4w and/or 120 mg q4w compared to placebo-treated subjects and compared with omalizumab 300 mg q4w treated subjects. Objective 2: To demonstrate the superiority of ligelizumab 72 mg q4w and/or 120 mg q4w treated subjects with respect to a reduction from baseline in the weekly itch severity score at Week 12 compared to placebo-treated subjects and omalizumab 300 mg q4w treated subjects.
Study design	This is a Phase III multi-center, randomized, double-blind, active- and placebo-controlled, parallel-group study. There is a screening period of up to 28 days, a 52 week double-blind treatment period, and a 12 week post-treatment follow-up period.
Population	The study population will consist of approximately 1050 male and female subjects aged ≥ 12 years who have been diagnosed with CSU and who remain symptomatic despite the use of H1-AH. Of these, approximately 1000 adults and 50 adolescents are planned for inclusion in the study.
Key Inclusion criteria	● Signed informed consent must be obtained prior to participation in the study. The 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. ● Male and female subjects ≥ 12 years of age at the time of screening. (NOTE: Recruitment of adolescent subjects, ≥ 12 to < 18 years of age, will be in accordance with local regulatory/ethics committee requirements). ● CSU diagnosis for ≥ 6 months (defined as onset of CSU with supporting documentation). ● Diagnosis of CSU refractory to H1-AH at locally label approved doses at the time of randomization, as defined by all of the following: ● The presence of itch and hives for ≥ 6 consecutive weeks at any time prior to Visit 1 (Day - 28 to Day -14) despite current use of non-sedating H1-AH ● UAS7 score (range 0-42) ≥ 16 and Weekly hives severity score (HSS7) (range 0-21) ≥ 8 during the 7 days prior to randomization (Visit 110, Day 1) ● Subjects must be on H1-AH at only local label approved doses for treatment of CSU starting at Visit 1 (Day -28 to Day -14) ● Willing and able to complete a daily symptom eDiary for the duration of the study and adhere to the study visit schedules.

Key Exclusion criteria	● History of hypersensitivity to any of the study drugs or their excipients or to drugs of similar chemical classes (i.e. to murine, chimeric or human antibodies). ● Subjects having a clearly defined cause of their chronic urticaria, other than CSU. This includes, but is not limited to, the following: symptomatic dermographism (urticaria factitia), cold-, heat-, solar-, pressure-, delayed pressure-, aquagenic-, cholinergic- or contact-urticaria. ● Diseases, other than chronic urticaria, with urticarial or angioedema symptoms such as urticarial vasculitis, erythema multiforme, cutaneous mastocytosis (urticaria pigmentosa) and hereditary or acquired angioedema (eg, due to C1 inhibitor deficiency). ● Subjects with evidence of helminthic parasitic infection as evidenced by stools being positive for a pathogenic organism according to local guidelines. All subjects will be screened at Visit 1. If stool testing is positive for pathogenic organism, the subject will not be randomized and will not be allowed to rescreen. ● Any other skin disease associated with chronic itching that might influence in the investigators opinion the study evaluations and results (e.g. atopic dermatitis, bullous pemphigoid, dermatitis herpetiformis, senile pruritus, etc.). ● Prior exposure to ligelizumab or omalizumab and other IgE therapies. ● Any H2 antihistamine, LTRA (montelukast or zafirlukast) or H1 antihistamines use at greater than approved doses after Visit 1.
Study treatment	● Ligelizumab 120 mg sc q4w ● Ligelizumab 72 mg sc q4w ● Omalizumab 300 mg sc q4w ● Placebo 0 mg sc q4w
Efficacy assessments	● Weekly urticaria activity score (UAS7) ● Weekly hives severity score (HSS7) ● Weekly itch severity score (ISS7)
Key safety assessments	Safety evaluations include adverse events (AEs), laboratory values, vital signs and electrocardiogram (ECG).
Other assessments	● Patient reported outcomes (AAS7, Dermatology Life Quality Index(DLQI)/ Children Dermatology Life Quality Index (CDLQI), [redacted]
Data analysis	The primary endpoint is the absolute change from baseline in UAS7 score at Week 12, which is the UAS7 score at Week 12 minus the UAS7 score at baseline. The statistical hypotheses test for the primary endpoint being tested is that the absolute change from baseline in UAS7 score at Week 12 in any of the ligelizumab groups (low or high dose) is not superior to the omalizumab group and placebo group. A linear mixed model with repeated measures (MMRM) will be used to estimate treatment differences for change from baseline in UAS7 score at Week 12. The analysis of primary endpoint and the secondary endpoints included in the testing strategy will focus on the adult subjects. Due to the relatively low number of adolescent subjects for this study, the data collected for adolescent subjects will be provided in a descriptive manner separately. The adolescent subject data will be forwarded to a separate cross-study extrapolation analysis to support determination of the final posology for the treatment of adolescent patients.
Key words	Anti-IgE, chronic spontaneous urticaria, hives severity score, itch severity score, urticaria activity score

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 symptoms of urticaria and urticaria associated angioedema adversely affect daily activities and sleep (O'Donnell et al 1997). The overall burden of CSU is substantial; CSU has a negative impact on patients' lives and health related quality of life (HRQoL) and work productivity (Maurer et al 2017).

A majority of CSU patients can be treated with H1-antihistamine (H1-AH) monotherapy (Kozel and Sabroe 2004), which is frequently used at doses up to 4 fold the approved dose (Zuberbier et al 2014, Zuberbier et al 2018). The use of H2 antihistamines and Leukotriene Receptor Antagonists (LTRAs) has in the past been recommended in treatment guidelines for patients who remained symptomatic despite treatment with H1-AH (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. Systemic corticosteroids are sometimes added to the treatment regimens, however they are not recommended in treatment guidelines for long term treatment as patients are then at risk of adverse effects associated with chronic systemic corticosteroid exposure.

More recently omalizumab, a less potent monoclonal antibody than ligelizumab that also targets immunoglobulin E (IgE), has been approved in several countries including those in the European Union, the United States, Japan and Switzerland as add-on therapy in patients with CSU with symptoms despite treatment with antihistamines. Omalizumab improved the signs and symptoms of urticaria (i.e. hives and itch) in patients who failed treatment with H1-AH 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 humanized IgG-type monoclonal antibody that binds to human IgE with higher affinity than omalizumab. Upon binding to specific epitopes in the C3 region of IgE, ligelizumab is able to block the interaction of IgE with both the high and low affinity IgE receptors (FcεRI and FcεRII). Ligelizumab does not mediate IgE receptor cross-linking and consequent histamine release (i.e. is non-activating). This overall mechanism of action (MoA) is shared with omalizumab (Chang et al 2015).

When subjects are treated with ligelizumab, circulating IgE is rapidly bound by the anti-IgE antibody and becomes inaccessible to IgE receptors on mast cells and basophils (Arm et al 2014, Gauvreau et al 2016). Ligelizumab has demonstrated dose- and time-dependent suppression of free IgE, reduction in basophil FcεRI expression and thus basophil surface IgE, and inhibition of skin prick test responses to allergens, superior in extent and duration to those observed with

omalizumab (Arm et al 2014, Gauvreau et al 2016). IgE is necessary for the enhanced expression of the FcεRI seen in atopic subjects (MacGlashan et al 1997, MacGlashan et al 1998), and thus a decrease in FcεRI expression on circulating basophils accompanies ligelizumab treatment. Other potentially beneficial effects from anti-IgE therapy include decreased IgE production (Lowe and Renard 2011), reduced IgE+ B cell numbers (Ota et al 2009) and reduced cytokine production by T cells (Coyle et al 1996).

1.2 Purpose

The purpose of this study is to establish efficacy and safety of ligelizumab in adult and adolescent subjects with CSU, who remain symptomatic despite standard of care treatment by demonstrating better efficacy over Xolair® (omalizumab) when added to H1-AH at approved doses, over 12 months of treatment and a follow-up period of 12 weeks.

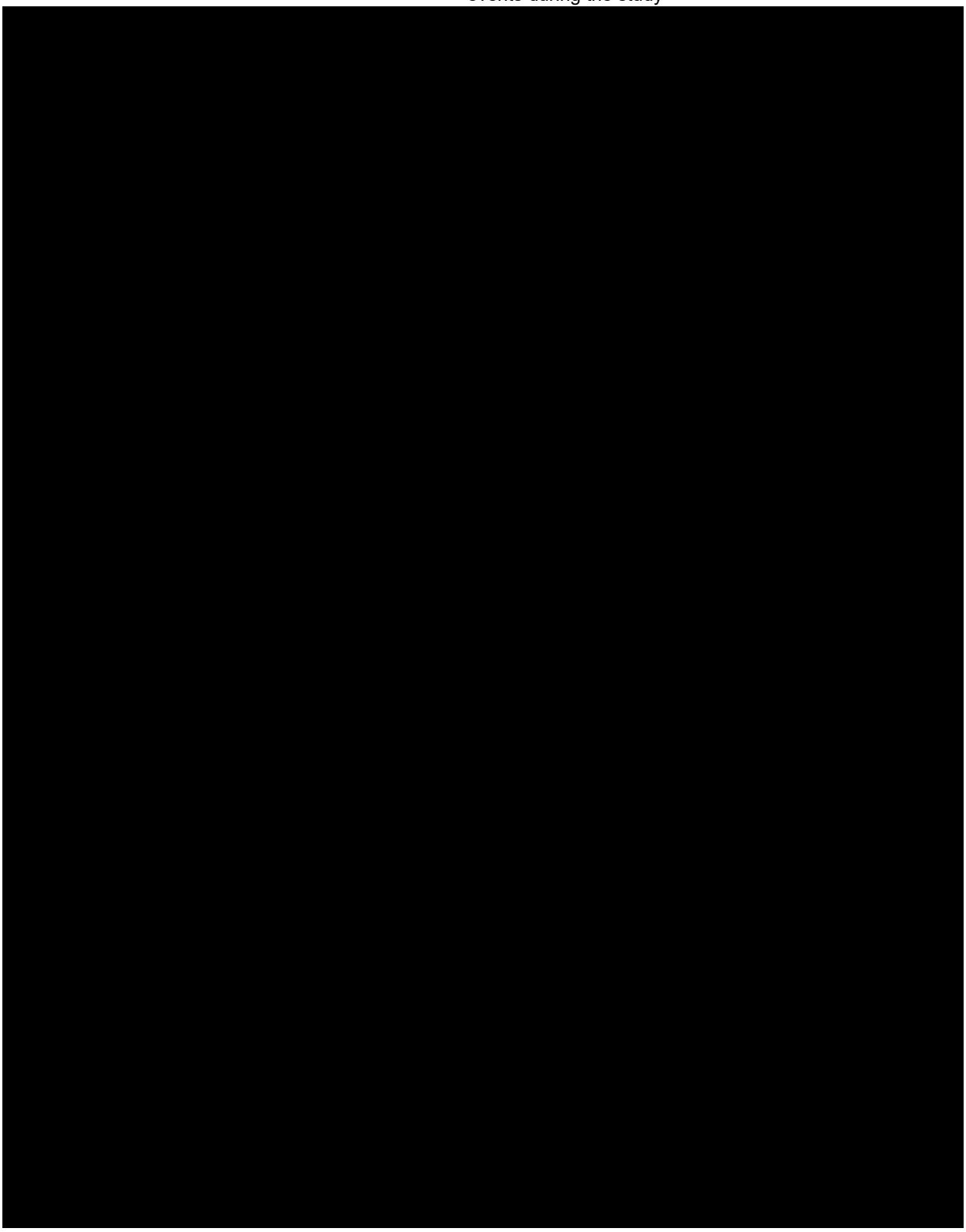
Due to the relatively low number of adolescent subjects expected to enroll in this study, [redacted]

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objectives	Endpoints
Primary objective	**Endpoint for primary objective**
● The primary objective of the study is to demonstrate that ligelizumab (72 mg q4w and/or 120 mg q4w) is superior to placebo and superior to omalizumab 300 mg q4w in change from baseline in UAS7 at Week 12	● Absolute change from baseline in UAS7 at Week 12
Secondary objectives	**Endpoints for secondary objectives**
● To demonstrate that a greater proportion of subjects achieve UAS7 = 0 at Week 12 who are treated with ligelizumab 72 mg q4w and/or 120 mg q4w compared to placebo-treated subjects and compared with omalizumab 300 mg q4w treated subjects	● Complete absence of hives and itch at Week 12, assessed as percentage of subjects achieving UAS7 = 0
● To demonstrate the superiority of ligelizumab 72 mg q4w and/or 120 mg q4w treated subjects with respect to a reduction from baseline in the weekly itch severity score at Week 12 compared to placebo-treated subjects and omalizumab 300 mg q4w treated subjects	● Improvement of severity of itch, assessed as absolute change from baseline in ISS7 score at Week 12
● To demonstrate that a greater proportion of subjects who are treated with ligelizumab 72 mg q4w and/or 120 mg q4w achieve DLQI = 0-1 at Week 12 compared to placebo-treated subjects and omalizumab 300 mg q4w treated subjects	● No impact on subjects quality of life at Week 12, assessed as % of subjects achieving DLQI = 0-1*
● To demonstrate that the ligelizumab 72 mg q4w and/or 120 mg q4w treated subjects have a longer angioedema occurrence-free period compared with placebo-treated subjects and omalizumab 300 mg q4w treated subjects.	● Cumulative number of weeks that subjects achieve AAS7 = 0 responses between baseline and Week 12

Objectives	Endpoints
● To demonstrate the safety and tolerability of ligelizumab 72 mg q4w and 120 mg q4w	● Occurrence of treatment emergent adverse events during the study ● Occurrence of treatment emergent serious adverse events during the study



[redacted]

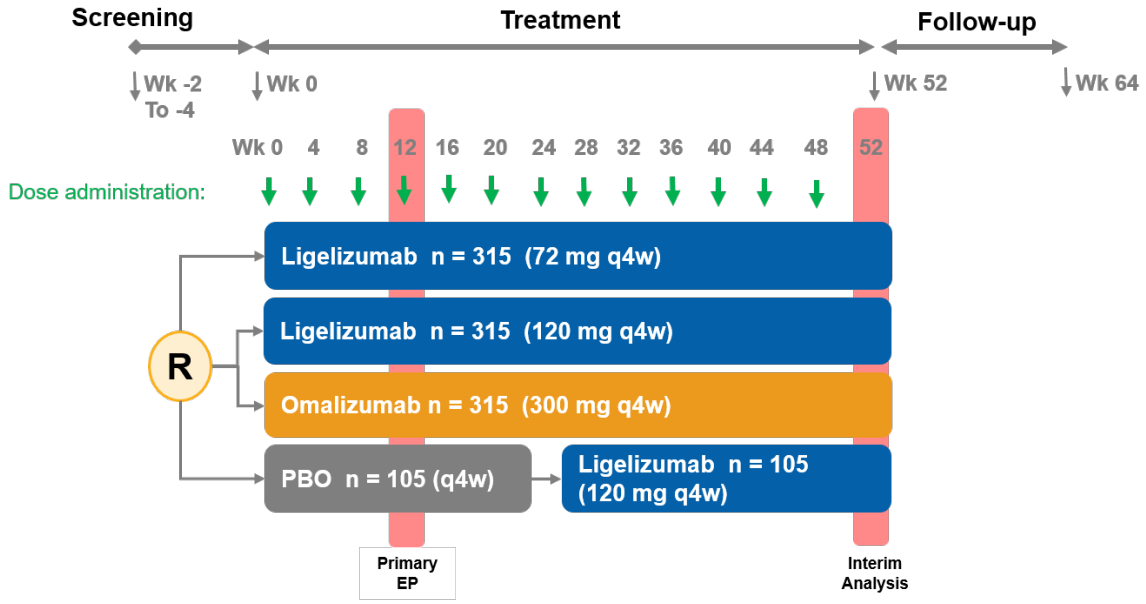
*For the adolescents subgroup analyses, CDLQI will be used for the objective/endpoint assessments.

3 Study design

This is a Phase III multi-center, randomized, double-blind, active- and placebo-controlled, parallel-group study. The study consists of 3 distinct periods:

- Screening period (Day - 28 to Day 1): Duration of up to 4 weeks in which subjects who have given informed consent are assessed for eligibility.
- Double-blind treatment period (52 weeks): The subjects will be seen in the clinic every 4 weeks.
- Post-treatment follow-up period (12 weeks): This period consists of 3 visits (every 4 weeks) with the final visit occurring 16 weeks after the last dose at Week 48.

Figure 3-1 Study design



Screening period

Subjects will have a screening period of up to 4 weeks to establish eligibility for the study. Subjects will be required to attend 2 visits during screening period: Visit 1 (Day -28 to Day - 14) and Visit 20 (Day -7). An extended screening period will be permitted only in exceptional circumstances when information concerning eligibility is outstanding (eg, pending laboratory data).

Rescreening may be allowed for subjects who failed initial screening. Only 1 rescreening will be allowed (see Section 5.1 and Section 5.2). If a subject is rescreened for the study, the subject must sign a new informed consent and will be issued a new subject number. Informed consent

for a rescreened subject must be obtained prior to performing any study-related assessments or collecting any data for the Screening visit.

Double-blind treatment period

On Day 1, eligible subjects will be randomly assigned to receive ligelizumab 72 mg or 120 mg sc q4w, omalizumab 300 mg sc q4w or placebo sc q4w. During the double blind treatment period the first dose of study drug will be administered on Day 1 (Visit 110). The last dose in the ligelizumab 72 mg or 120 mg or omalizumab 300 mg group will be administered on Day 337 (Week 48, Visit 230) study visit.

Subjects randomized to the placebo group will receive the first dose of placebo on Day 1 (Visit 110) and the last dose of placebo on Day 141 (Week 20, Visit 160) study visit. From Week 24 to Week 48 these subjects will receive ligelizumab 120 mg sc q4w.

Approximately 315 subjects will be allocated to each of the ligelizumab 72 mg q4w, 120 mg q4w and omalizumab 300 mg q4w arms, respectively. Approximately 105 subjects will be allocated to the placebo/ligelizumab 120 mg q4w arm. Subjects are expected to attend all site visits based on the assessment schedule (Table 8-1).

Follow-up period

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

Eligible subjects may roll-over into an extension study (CQGE031C2302E1), once the study is locally approved and implemented. Subjects will be eligible to enroll in the extension study, after succesfully completing the current study and fulfilling the enrollment criteria defined in the extension study protocol.

4 Rationale

4.1 Rationale for study design

Data from the dose-range finding Study CQGE031C2201 suggest that ligelizumab treatment improves itch and hives in adult subjects with CSU who have failed treatment with H1-AH and those who failed treatment with a combination of H1 and H2 antihistamines and LTRA. This Phase III study is designed to further evaluate the efficacy and safety of ligelizumab in adult and adolescent CSU subject's refractory to antihistamines.

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

Only ligelizumab- and omalizumab-naïve subjects will be enrolled. This avoids any potential issue of a prior treatment with an anti-IgE antibody having an unknown persistent influence in the study population, and avoids potential selection bias based on results of prior exposure.

Although the signs and symptoms of CSU are burdensome to subjects, placebo controlled trials have been safely and successfully conducted in this indication (Kaplan et al 2013, Maurer et al 2013). Subjects have been allocated across the treatment arms according to statistical consideration and sample size requirements. Comparison to placebo will provide a background incidence in the study population for possible safety findings.

As CSU appears to be the same condition with the same unmet need in both adult and pediatric populations, adolescents will be included in this study. The symptoms, natural course and the various subtypes of CSU are very similar in both age groups. Furthermore, the disease classification is the same for both adult and adolescent subjects, with an autoimmune etiology as the main identifiable cause of CSU in both adolescents and adults. [redacted]

All subjects in the placebo arm will receive ligelizumab 120 mg q4w from Week 24 onwards. A switch to ligelizumab before Week 24 is not allowed. In addition to continuing their background medication (locally approved doses of H1-AH), subjects in the placebo group may receive rescue therapy (for details, see Section 6.2.3). The drop-out rate in the placebo arm of the CQGE031C2201 study over a 6-month treatment duration was [redacted] Therefore, with a similar expected drop-out rate, a 6-month placebo duration in the current study is anticipated to be feasible.

The number of subjects receiving placebo has been limited as far as possible while still allowing statistical comparison and maintenance of blinding to active versus placebo treatment.

This study will use ligelizumab placebo only. [redacted]

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 emphasis and target of therapy as described in the CSU treatment guidelines (Zuberbier et al 2014, Zuberbier et al 2018) have evolved and focus on UAS7 which is a composite of ISS7 and HSS7 rather than only ISS7. In addition to the current emphasis on UAS7 in the medical community, as reflected in the CSU treatment guidelines, data from the Phase II study CQGE031C2201 also support the change from baseline in UAS7 at week 12 being assessed as the primary endpoint. Change from baseline in ISS7 and achievement of UAS7 = 0 will be evaluated as secondary endpoints included in the testing strategy.

After the completion of the double-blind treatment period, subjects will enter a post-treatment follow-up period [redacted]

4.1.1 Rationale for choice of background therapy

This study requires concurrent use of one second generation-H1-AH at doses approved by the local Health Authority as background medication. All subjects, regardless of what treatment arm they are randomized to, will receive standard of care therapy (H1-AH at (locally label approved doses) as background medication. Subjects must remain on a stable treatment regimen (type and dose of H1-AH) throughout the study. If a subject must switch to another background H1-AH (at approved dose) as a result of an AE, the subject will be considered to have remained on stable treatment.

4.2 Rationale for dose/regimen and duration of treatment

Rationale for dose/regimen

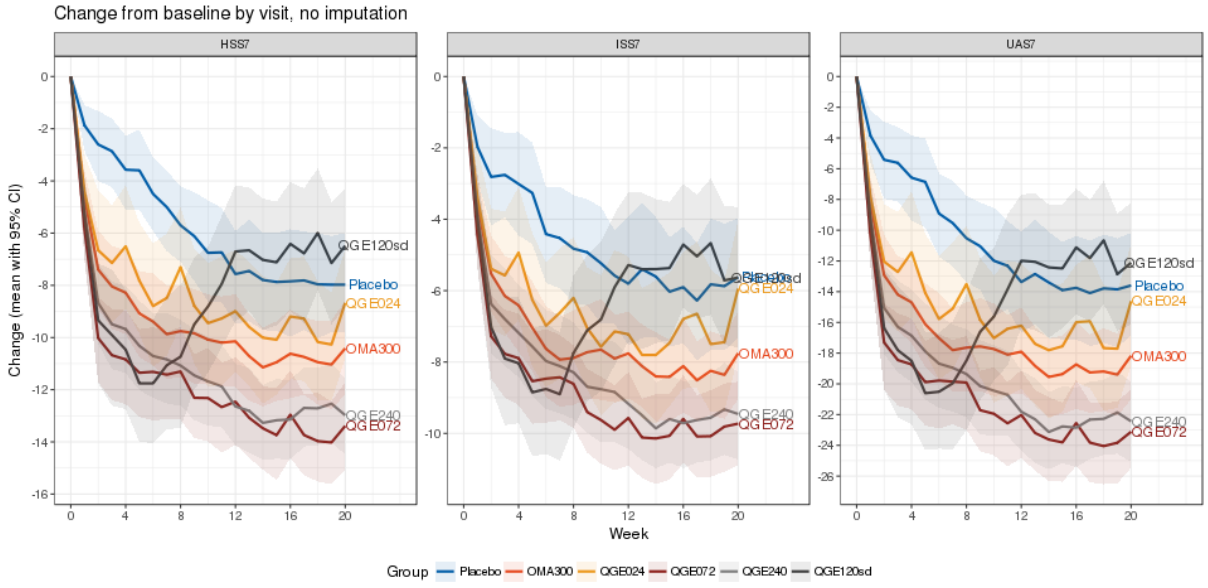
Two ligelizumab doses, 72 and 120 mg, will be tested in this Phase III study. These doses are selected based on the totality of observed clinical data in the Phase IIb CQGE031C2201 study, the lack of any safety concerns across the doses tested and modeling and simulation data.

Overview of Phase II clinical data

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 III program, and for HSS7 and ISS7 are shown in Figure 4-1.

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 throughout the dosing interval such that relapse of symptoms is minimal. These data also imply that treating subjects at a monthly interval is more beneficial in achieving a meaningful sustained clinical response.

During the phase II study there was no evidence of dose related safety signals up to Week 20 except for a trend in injection site reactions, which were mostly non-serious, mild to moderate 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 CQGE031C2201E1 study 240mg q4w did not result in any new safety signals.

Doses of 72 and 120 mg are considered safe dose levels for phase III with a substantial safety window. There have been no new or unexpected safety findings in the CQGE031C2201 study, across all the doses assessed.

[redacted]

Rationale for route of administration

In the CQGE031C2201 study, ligelizumab was 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.

Rationale for duration of treatment

The double blind treatment period will be 52 weeks in duration, with the primary endpoint assessed at Week 12. Current treatment guidelines recommend re-evaluating the necessity for continued or alternative drug treatment every 3–6 months (Zuberbier et al 2014, Zuberbier et al 2018). However, it is recognized that patients with a longer history of CSU are more likely to have persistence of disease and therefore, in clinical practice, often require many months to years of treatment. The planned 52 week treatment period is not only consistent with such actual clinical practice; it will also be more likely to allow effective treatment of subjects who have both a shorter and longer history of CSU.

The study will evaluate the efficacy of ligelizumab in controlling angioedema as well as evaluate the burden of angioedema. While many patients with CSU suffer from angioedema, the episodes may be infrequent and are unpredictable. Thus a 1 year period of time provides a greater probability of observing its clinical course and the potential reduction in the occurrence of angioedema as a result of treatment [redacted].

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

Omalizumab has been selected as an active comparator for the following reasons:

- it is the only drug in the same class as ligelizumab currently approved as add-on therapy in CSU subjects with inadequate response to H1-AH.
- it is recommended as a third line option in the current treatment algorithm for management of CSU (Zuberbier et al 2018) after failure of higher dose antihistamines.
- to confirm the efficacy and safety of ligelizumab versus omalizumab that was noted in the CQGE031C2201 study.

Placebo is used in this study for the following reasons:

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

- to allow the assessment of safety of ligelizumab on top of background medication compared to background medication alone.

The use of combination drugs is not applicable to this trial.

4.4 Purpose and timing of interim analysis

An interim analysis will be performed after all adult subjects have completed the treatment period (Week 52 visit). The interim analysis at the time of this Week 52 database lock would be utilized for the primary efficacy analysis for this study. [redacted] An unblinded study team will conduct the Week 52 primary efficacy analysis and a separate blinded study team will oversee the conduct of the study until the final database lock, after all the subjects have completed end of study participation. All investigators, site personnel, subjects, and the blinded study team will remain blinded until the final database lock has occurred. No access to patient level data will be provided to the investigators, site personnel, subjects, and blinded study team.

4.5 Risks and benefits

Women of child bearing potential and sexually active males must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the basic (acceptable effective) 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.

In the overall ligelizumab clinical program, approximately 923 subjects have been exposed across 12 studies, covering the indications of CSU, asthma, atopic dermatitis, and bullous pemphigoid The longest individual continuous exposure to ligelizumab is 12 months (CQGE031C2201E1 and CQGE031B2201E1). Cumulative (continuous and interrupted) human duration of exposure to ligelizumab is approximately 16 and 20 months (across the CQGE031B2201/CQGE031B2201E1 asthma studies and the CQGE031C2201/ CQGE031C2201E1 CSU studies, respectively). The following doses have been tested in the clinical programs: 12 mg, 24 mg, 36 mg, 72 mg, 180 mg and 240 mg s.c. q4w, 280 mg q2w and 120 mg s.c. single dose. To date in the CSU program alone, 254 subjects have been exposed to ligelizumab at doses up to 240 mg s.c. q4w.

Overall, no apparent dose-dependent safety signals (except for a trend in injection site reactions, which can be easily managed clinically) have been observed to date, although the number of subjects studied is relatively small, in line with the development phase of the CSU program. In the 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 exceptions were AEs related to injection site reactions, where a possible trend of dose dependency for ligelizumab was observed. All cases of injection site reactions (except 1 case of medical significance) regardless of treatment group or doses were non-serious, mild to moderate in severity, reversible, and did not lead to discontinuation of study treatment.

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

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 class as omalizumab and therefore, in theory, carries the same 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, 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, through target mediated disposition, the half-life of ligelizumab 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) or Middle Eastern respiratory syndrome (MERS) in patients receiving omalizumab or ligelizumab.

Therefore, based on the cumulative data available across all clinical studies in different patient populations for ligelizumab, the current evidence demonstrates 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 study in adults.

The data from CQGE031C2201 demonstrates that ligelizumab administration results in significant improvement of CSU symptoms including itch, hives, angioedema and quality of

life (QoL) [redacted]. 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.

Regarding the choice of omalizumab as an active comparator, the Phase III studies for omalizumab included adolescents, based on which omalizumab is approved for use in adolescents. It is safe and well-tolerated for use in this population.

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 [redacted].

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

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 study population will consist of approximately 1050 male and female subjects aged ≥ 12 years who have been diagnosed with CSU and who remain symptomatic despite the use of H1-AH. Of these, approximately 1000 adults and 50 adolescents are planned for inclusion in the study.

It is anticipated that approximately 1616 subjects will need to be screened (an estimated screening failure rate of 35%) in order to randomize approximately 1050 subjects into the 52 week treatment period (see Figure 3-1).

Since both adults and adolescent subjects will be enrolled into this study, randomization will be stratified by age group. In addition, randomization for adults will be stratified by region and/or country to ensure a balanced assignment to each treatment group. Considering the relative small sample size of adolescent subjects, there will be no additional stratification for adolescent subjects.

5.1 Inclusion criteria

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

1. Signed informed consent must be obtained prior to participation in the study.

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. Male and female subjects ≥ 12 years of age at the time of screening.
(NOTE: Recruitment of adolescent subjects, ≥ 12 to <18 years of age, will be in accordance with local regulatory/ethics committee requirements).
4. CSU diagnosis for ≥ 6 months (defined as onset of CSU with supporting documentation).
5. Diagnosis of CSU refractory to H1-AH at locally label approved doses at the time of randomization, as defined by all of the following:
   a. The presence of itch and hives for ≥ 6 consecutive weeks at any time prior to Visit 1 (Day -28 to Day -14) despite current use of non-sedating H1-AH
   b. UAS7 score (range 0–42) ≥ 16 and HSS7 score (range 0–21) ≥ 8 during the 7 days prior to randomization (Visit 110, Day 1)
   c. Subjects must be on H1-AH at only locally label approved doses for treatment of CSU starting at Visit 1 (Day -28 to Day -14)
6. Willing and able to complete a daily symptom eDiary for the duration of the study and adhere to the study visit schedules.
7. Subjects must not have had any missing eDiary entries in the 7 days (twice a day) prior to randomization (Day 1, Visit 110), i.e. 14 eDiary entries required. 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.

No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible subjects.

1. Use of other investigational drugs within 5 half-lives, or within 30 days (for small molecules) prior to Visit 1 or until the expected pharmacodynamic effect has returned to baseline (for biologics), whichever is longer.
2. History of hypersensitivity to any of the study drugs or their excipients or to drugs of similar chemical classes (i.e. to murine, chimeric or human antibodies).
3. Subjects having a clearly defined cause of their chronic urticaria, other than CSU. This includes, but is not limited to, the following: symptomatic dermographism (urticaria factitia), cold-, heat-, solar-, pressure-, delayed pressure-, aquagenic-, cholinergic- or contact-urticaria.
4. Diseases, other than chronic urticaria, with urticarial or angioedema symptoms such as urticarial vasculitis, erythema multiforme, cutaneous mastocytosis (urticaria pigmentosa) and hereditary or acquired angioedema (eg, due to C1 inhibitor deficiency).
5. Subjects with evidence of helminthic parasitic infection as evidenced by stools being positive for a pathogenic organism according to local guidelines. All subjects will be screened at Visit 1 (see Section 8.4.3). If stool testing is positive for pathogenic organisms, the subject will not be randomized and will not be allowed to rescreen.

6. Any other skin disease associated with chronic itching that might influence, in the investigator's opinion, the study evaluations and results (eg, atopic dermatitis, bullous pemphigoid, dermatitis herpetiformis, senile pruritus, etc.).
7. Prior exposure to ligelizumab, omalizumab and other IgE therapies.
8. Any H2 antihistamine use after Visit 1.
9. Any LTRA (montelukast or zafirlukast) use after Visit 1.
10. Any H1-AH used as background medication at greater than local label approved doses after Visit 1.
11. History or evidence of ongoing alcohol or drug abuse, within the last 6 months prior to randomization.
12. Inability to comply with study and follow-up procedures.
13. Use of prohibited treatment detailed in protocol (Table 6-2).
14. Contraindications to or hypersensitivity to study drugs including but not limited to fexofenadine, loratadine, desloratadine, cetirizine, levocetirizine, rupatadine, epinephrine or any of their ingredients.
15. Documented history of anaphylaxis.
16. History of malignancy of any organ system within the past 5 years (except for basal cell carcinoma 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).
17. Presence of clinically significant cardiovascular (such as but not limited to myocardial infarction, unstable ischemic heart disease, NYHA Class III/IV left ventricular failure, arrhythmia and uncontrolled hypertension within 12 months prior to Visit 1), neurological, psychiatric, metabolic or other pathological conditions (such as but not limited to cerebrovascular disease, neurodegenerative or other neurological diseases, uncontrolled hypo- and hyperthyroidism and other autoimmune diseases, hypokalemia, hyperadrenergic state or ophthalmologic disorder) that could interfere with or compromise the safety of the subjects, interfere with evaluation or interpretation of the study results, or preclude completion of the study.
18. Medical examination or laboratory findings that suggest the possibility of decompensation of co-existing conditions for the duration of the study. Any items that are cause for uncertainty will be reviewed with the investigator.
19. History of, or current treatment for, hepatic disease including but not limited to acute or chronic hepatitis, cirrhosis or hepatic failure or Aspartate Aminotransferase (AST)/ Alanine Aminotransferase (ALT) levels of more than 1.5 x upper limit of normal (ULN) or International Normalized Ratio (INR) of more than 1.5 at Visit 1.
20. History of renal disease or creatinine level above 1.5x ULN at Visit 1.
21. Platelets < 100 000/µL at Visit 1.
22. History of long QT syndrome or whose QTcF (Fridericia) measured at Visit 1 is prolonged (> 450 ms for males or > 460 ms for females) and confirmed by a central assessor (these subjects should not be rescreened).
23. Pregnant or nursing (lactating) women.

24. Female subjects, including adolescent females of 12 to less than 18 years of age, of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using basic (acceptable effective) methods of contraception for the duration of the study (approx. 4 months, i.e. 5 half-lives, after last dose of ligelizumab or omalizumab). Basic (acceptable effective) contraception methods include:
    a. Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable effective methods of contraception
    b. Female sterilization (surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least 6 weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment
    c. Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject
    d. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps). For UK: with spermicidal foam/gel/film/cream/ vaginal suppository
    e. Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS)

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

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (eg, age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least 6 weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment is she considered not of child bearing potential.

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

6 Treatment

6.1 Study treatment

6.1.1 Investigational and control drugs

Table 6-1 Investigational and control drugs

Investigational/ Control Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Supply type	Sponsor (global or local)
Ligelizumab 120 mg per 1 mL	Liquid in vial	s.c.	Open label subject packs; vials	Sponsor global
Omalizumab 150 mg per 1.2mL	Lyophilized powder for solution in vial	s.c.	Open label subject packs; vials	Sponsor global
Ligelizumab Placebo 0 mg per 1 mL	Liquid in vial	s.c.	Open label subject packs; vials	Sponsor global

6.1.2 Additional study treatments

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

6.1.3 Treatment arms

Subjects will be assigned at Visit 110 to one of the following 4 treatment arms. Each subject will receive a total of 2 injections every 4 weeks:

a. Ligelizumab 120 mg arm: 1 injection of 1.0 mL ligelizumab + 1 injection of 1.0 mL ligelizumab placebo
b. Ligelizumab 72 mg arm: 1 injection of 0.6 mL ligelizumab + 1 injection of 1.0 mL ligelizumab placebo
c. Omalizumab 300 mg arm: 2 injections of 1.2 mL omalizumab
d. Placebo / ligelizumab arm: 2 injections of 1.0 mL ligelizumab placebo from Week 0 through Week 20; 1 injection of 1.0 mL ligelizumab + 1 injection of 1.0 mL ligelizumab placebo from Week 24 through Week 48

During the double-blind treatment period, study drug will be administered for 13 visits as per Table 6-3 and Table 8-1. Due to the specifics of the blinding procedure in this trial, the dispensing and administration of the study treatments must be performed by suitable authorized site personnel who are otherwise not involved in study conduct. Further details are provided in Section 6.3.2, Section 6.4 and Section 6.7.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

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

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

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

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt the investigator should contact the Novartis medical monitor before randomizing a subject or allowing a new medication to be started.

6.2.2 Prohibited medication

Use of the class of treatments displayed in Table 6-2 is NOT allowed after start of screening. The minimum required period without prohibited treatment before Visit 1 is also listed in Table 6-2. Each concomitant drug must be individually assessed against all exclusion criteria and the table below to see if it is allowed. If in doubt, the investigator should contact Novartis or delegate before randomizing a subject or allowing a new medication to be started.

Table 6-2 Prohibited medication

Medication	Minimum required period without medications
Omalizumab	No prior use allowed
Ligelizumab	No prior use allowed
Routine (more than 3 doses over a 5 day period) oral corticosteroids *	30 days prior to Visit 1
IV/IM/Intra-Articular corticosteroids	30 days prior to Visit 1
Beta-blocker therapy	7 days prior to Visit 1
Leukotriene antagonists	Stop at Visit 1
H2-antihistamines	Stop at Visit 1
First generation H1-antihistamines	Stop at Visit 1
Hydroxychloroquine or chloroquine	30 days prior to Visit 1
Other immunosuppressive medication with or without known effect on CSU including but not limited to Methotrexate, cyclosporine A, cyclophosphamide, tacrolimus and mycophenolate mofetil	30 days prior to Visit 1
Intravenous immunoglobulin G	30 days prior to Visit 1
Plasmapheresis	30 days prior to Visit 1
Regular (daily or every other day) doxepin (oral)	14 days prior to Visit 1
Vaccination with inactivated viruses	48 hours prior to each dosing visit (i.e. Visit 110 to Visit 230)

Medication	Minimum required period without medications
Live attenuated vaccine	30 days prior to Visit 1

* Allowed only as rescue therapy only after Week 12, on an as-needed basis for unbearable symptoms as per Section 6.2.3. Other preparations of corticosteroids (CS) with limited systemic exposure for non-CSU indications can be used (e.g. Intra nasal or any topical CS) as-needed basis.

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

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

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

6.2.3 Rescue medication

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

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

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 electronic Case Report Form (eCRF).

6.3 Subject numbering, treatment assignment, randomization

6.3.1 Subject numbering

Each subject is identified in the study by a Subject Number (Subject No.) that is assigned when the patient is first enrolled for screening (Interactive Response Technology (IRT) to be contacted at screening Visit 1) and is retained as the primary identifier for the subject throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No.; as assigned by Novartis to the investigative site) with a sequential subject number suffixed to it, so that each subject is numbered uniquely across the entire database. Upon signing the informed consent form, the patient is assigned to the next sequential Subject No. available.

6.3.2 Treatment assignment and randomization

At Visit 110 all eligible subjects will be randomized via IRT to one of the treatment arms. The investigator or his/her delegate will inform the independent unblinded site personnel (pharmacist or authorized delegate) to contact the IRT after confirming that the subject fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the subject, which will be used to link 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 and will specify the volume of dose. The randomization number will not be communicated to the caller.

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

Since both adults and adolescent subjects will be enrolled into this study, randomization will be stratified by age group. In addition, randomization for adults will be stratified by region and/or country to ensure a balanced assignment to each treatment group. Considering the relative small sample size of adolescent subjects, there will be no additional stratification for adolescent subjects.

The randomization scheme 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 will remain blinded to the identity of the treatment from the time of randomization until final database lock. An unblinded study monitor will visit the study site to monitor study drug related administration (see Section 11.3).

Blinding will be maintained using the following methods:

1. Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study with the following exceptions:
   - Bioanalyst (PK): to enable identification of samples from the ligelizumab treatment arms of the study to facilitate bioanalysis;
   - Independent personnel (external to Novartis) involved in monitoring anaphylaxis, neoplastic and cerebro-cardiovascular events (Adjudication Committee members), if needed; and
   - An independent Data Monitoring Committee (DMC; see Section 10.2.3) and the independent statistician supporting the DMC activities (Table 6-4).
2. The following measures will be applied to keep the subject and study personnel blinded despite differences of the investigational treatments in appearance, viscosity and volume:
   - The study drug must be prepared by an independent unblinded pharmacist (or authorized delegate) and administered by an independent unblinded administrator who are both not involved in any of the study assessments. If an unblinded pharmacist is not available, preparation and administration of drug may also be performed by a single independent unblinded site person if he/she is authorized to do both.
   - Preparation of the investigational drug must be done in a separate space/room where subjects and study personnel have no access during time of preparation.
   - To blind the liquid volume in the syringe, the syringe must be covered by a strip of opaque tape. The differences in length of the syringe plunger, related to the differences in the volume, should also be covered by the way of administration (see Pharmacist Manual).
   - The 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 appearance, 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.

In each treatment group, subjects receive 2 injections at every visit (Table 6-3). Subjects in the placebo arm will have placebo administered for 6 visits, then will be switched to ligelizumab 120 mg for rest of the treatment period. All subjects will be observed following the recommendation by the National Heart, Lung, and Blood Institute and by the American Academy of Allergy, Asthma & Immunology and the American College of Allergy, Asthma and Immunology Executive Committees Joint Task Force (Cox et al 2007) for the anti-IgE therapy currently available (omalizumab). All subjects in all treatment arms will need to remain at the site for a 2 hour observation at randomization and Weeks 4, 8, 24, 28 and 32 and for a 30 minute observation period for the remaining treatment visits. This approach will help maintain the blind for subjects and site staff.

After the Week 52 database lock for the interim analysis, an unblinded study team will perform the primary efficacy analysis. Treatment assignment will remain blinded to all investigators,

site personnel, subjects and blinded study team until all patients have completed the entire study participation and the final database lock has occurred.

Interim analysis data will not be shared with the blinded study team overseeing the conduct of the ongoing study until all subjects have completed the entire study and the final database lock has occurred. Interim analysis results and reports generated prior to the final database lock that would reveal subject-level data will be kept in a secure and restricted area until the end of the study.

Unblinding of investigator, site personnnel and patients will only occur in the case of subject emergencies and at the conclusion of the study.

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

Table 6-3 Drug administration

				Placebo/ligelizumab arm	
Treatment	**Ligelizumab 120 mg arm**	**Ligelizumab 72 mg arm**	**Omalizumab 300 mg arm**	**Placebo period**	**Ligelizumab period**
Ligelizumab 120 mg/mL liquid in vial	1 x 1.0 mL	1 x 0.6 mL	0	0	1 x 1.0 mL
Omalizumab 150 mg/1.2mL Lyophilized powder for reconstitution	0	0	2 x 1.2 mL	0	0
Ligelizumab Placebo[1] 0 mg/mL liquid in vial	1 x 1.0 mL	1 x 1.0 mL	0	2 x 1.0 mL	1 x 1.0 mL
Total # of injections	2	2	2	2	2
Total volume injected	2.0 mL	1.6 mL	2.4 mL	2.0 mL	2.0 mL

[1] Placebo for blinding between ligelizumab doses.

Table 6-4 Blinding and unblinding plan

	Time or Event				
Role	**Randomization list generated**	**Treatment allocation & dosing**	**Safety event (single subject unblinded)**	**DMC Analysis**	**Week 52 Interim Analysis (IA)**
Subjects	B	B	B	B	B
Investigator and Site staff	B	B	UI	B	B
Unblinded site staff eg, pharmacy staff and study drug administrator	B	UI	NA	B	B
Global Clinical Supply and Randomization Office	UI	UI	UI	UI	UI

Role	Time or Event			DMC Analysis	Week 52 Interim Analysis (IA)
	Randomization list generated	Treatment allocation & dosing	Safety event (single subject unblinded)		
Unblinded sponsor staff eg, 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	NA
Independent committees used for assessing interim results, if required (eg, DMC)	B	UI	UI	UI	B
Adjudication committee	B	B	B*	B	B
Bioanalyst (PK)	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 week 52 IA as defined in the Charter for maintaining data integrity for interim lock	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					

6.5 Dose escalation and dose modification

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

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

6.6 Additional treatment guidance

6.6.1 Treatment compliance

Subjects will receive 2 subcutaneous injections every 4 weeks at 13 visits during the double-blind treatment period. Compliance is assured as study drug must / will be administered by independent unblinded study personnel via subcutaneous injection at the site. Administration of study drug must be recorded in the source documents and the corresponding eCRF for each administration.

6.6.2 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the subject safely. 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. If the IRT system is not available for technical reasons, the IRT help desk can facilitate emergency code break requests. 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 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
- study drug name
- subject number

In addition, oral and written information to the subject must be provided on how to contact the investigator's backup in cases of emergency, or when he/she is unavailable, the local Novartis Country Organization (CO) (or any entity to which it has delegated responsibility for emergency code breaks) 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.

Study treatment must be discontinued after emergency unblinding.

6.7 Preparation and dispensation

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

For drug preparation of omalizumab prior to administration, please refer to the Pharmacy Manual.

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

An independent unblinded pharmacist (or authorized delegate) will identify the study medication kits to dispense to the subject by contacting the IRT and obtaining the medication number(s) and volume of dose. The study medication has a 2-part label (base plus peel-off label). Immediately before preparing study treatment, the unblinded pharmacist (or authorized delegate) will detach the outer part of the label from the packaging and affix it to the source document.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

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

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

The independent unblinded site personnel must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by unblinded monitors during site visits or remotely and at the completion of the trial.

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

6.7.1.2 Handling of additional treatment

Not applicable.

6.7.2 Instruction for prescribing and taking study treatment

The independent study drug administrator will administer the study treatment to the subject during the study visit without engaging in any unnecessary interactions that may have the potential to unblind the subject or any of the study site personnel.

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

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

Subjects will remain on-site for observation for a period of 2 h post-dose for the first 3 study drug administrations at Visits 110, 120 and 130 and the 3 study drug administrations at Visits 170, 180 and 190 and 30 min post-dose for all other drug administrations. These observation periods follow the recommendation suggested by the National Heart, Lung, and Blood Institute and by the American Academy of Allergy, Asthma & Immunology and the American College of Allergy, Asthma and Immunology Executive Committees Joint Task Force (Cox et al 2007) for the anti-IgE therapy currently available (omalizumab). As described in the Investigator Brochure (IB), the site needs to ensure readiness to react to anaphylactic events (eg, have available injectable epinephrine, antihistamine, corticosteroids, intravenous supplies, oxygen, an oral airway, Ambu bag and the ability to transport a subject rapidly to an emergency department/hospital).

The dose for individual subjects will be the same within a treatment arm and will be assigned at randomization (Visit 110).

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.

The investigator must promote compliance by instructing the subject to ensure scheduled visits are made to the site in order to take the study treatment as prescribed and by stating that compliance is necessary for the subject's safety and the validity of the study. 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 Institutional Review Board/Independent Ethics Committee (IRB/IEC)-approved informed consent (witnessed, where required by law or regulation).

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

Informed consent must be obtained before conducting any study-specific procedures (eg, all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the subject's 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 informed consent form and child's assent form that complies with the ICH GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

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

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the basic (acceptable effective) contraception requirements.

After IRB/IEC approval, a copy of the approved version of all consent forms must be provided to Novartis.

8 Visit schedule and assessments

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

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

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

Subjects who discontinue treatment early will be expected to perform the Week 52 assessment (last visit in the double blinded treatment period) 4 weeks after they receive their last dose. 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 140 (Week 12). At the final visit, all dispensed investigational product should be reconciled and the AE and concomitant medications reconciled on the eCRF.

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.

Table 8-1 Assessment schedule

Period	**Screening**		**Double-blind treatment**														**Post-treatment follow-up**			
Visit	**1**	**20**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**	**190**	**200**	**210**	**220**	**230**	**240/ EoT/ TD**	**310**	**320**	**1999/ EoS/ PSD**	**UPV[6]**
Day	**-28 to -14**	**-7**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**393**	**421**	**449**	
Week (R = randomization week)	**-4 to -2**	**-1**	**R**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	
Obtain Informed Consent	X[1]																			
[redacted]																				
Inclusion/exclusion criteria	X	X	X																	
Demographic data	X																			
Relevant medical history (including CSU history)	X																			
Evidence of urticaria	X	X																		
Prior urticaria treatment	X																			
Family malignancy history (CRF to be completed if subject develops malignancy during the study)		X																		
Prior and Concomitant medication usage	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Period	**Screening**		**Double-blind treatment**														**Post-treatment follow-up**			
Visit	**1**	**20**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**	**190**	**200**	**210**	**220**	**230**	**240/ EoT/ TD**	**310**	**320**	**1999/ EoS/ PSD**	**UPV[6]**
Day	**-28 to -14**	**-7**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**393**	**421**	**449**	
Week (R = randomization week)	**-4 to -2**	**-1**	**R**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	
Surgery and procedures	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																			
[redacted]																				
Dispense H1-AH rescue medication	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S		
Dispense oral corticosteroid rescue medication[4]						S	S	S	S	S	S	S	S	S	S	S	S	S		
Study drug/placebo administration			X	X	X	X	X	X	X	X	X	X	X	X	X					
Randomization			XS																	
Contact IRT	XS		XS	XS	XS	XS	XS	XS	XS	XS	XS	XS	XS	XS	XS					
ePROs should be completed prior to any other assessment and prior to administration of any medication																				

Period	**Screening**		**Double-blind treatment**														**Post-treatment follow-up**			
Visit	**1**	**20**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**	**190**	**200**	**210**	**220**	**230**	**240/ EoT/ TD**	**310**	**320**	**1999/ EoS/ PSD**	**UPV[6]**
Day	**-28 to -14**	**-7**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**393**	**421**	**449**	
Week (R = randomization week)	**-4 to -2**	**-1**	**R**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	
Dispense Subjects' eDiary	S																			
Collect Subjects' eDiary																			S	
Subjects' eDiary (review compliance) Includes the urticaria subject daily diary (UPDD) and AAS (Angioedema activity score)		XS	XS	XS	XS	XS	XS	XS	XS	XS	XS	XS	XS	XS	XS	XS	XS	XS	XS	
DLQI (Dermatology Life Quality Index)/CDLQI (Children's DLQI)			XS	XS[7]	XS[7]	XS[7]			XS[7]							XS[7]	XS[7]	XS[7]	XS[7]	
[redacted]																				

Period	**Screening**		**Double-blind treatment**														**Post-treatment follow-up**			
Visit	**1**	**20**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**	**190**	**200**	**210**	**220**	**230**	**240/ EoT/ TD**	**310**	**320**	**1999/ EoS/ PSD**	**UPV[6]**
Day	**-28 to -14**	**-7**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**393**	**421**	**449**	
Week (R = randomization week)	**-4 to -2**	**-1**	**R**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	
Laboratory tests																				
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 as soon as possible	X																		X[5]	X
Hematology (*INR at Visit 1, V110 and UPV)	XS*		XS*	XS[8]	XS[8]	XS[8]	XS[8]	XS[8]	XS[8]	XS[8]	XS[8]	XS[8]	XS[8]	XS[8]	XS[8]	XS[8]	XS[8]	XS[8]	XS[8]	XS[8] *
Clinical chemistry (FSH to be done only if indicated as per Section 8.4.4)	XS		XS	XS[8]	XS[8]	XS[8]	XS[8]	XS[8]	XS[8]	XS[8]	XS[8]	XS[8]	XS[8]	XS[8]	XS[8]	XS[8]	XS[8]	XS[8]	XS[8]	XS[8]

Period	Screening		Double-blind treatment														Post-treatment follow-up			
Visit	1	20	110	120	130	140	150	160	170	180	190	200	210	220	230	240/ EoT/ TD	310	320	1999/ EoS/ PSD	UPV[6]
Day	-28 to -14	-7	1	29	57	85	113	141	169	197	225	253	281	309	337	365	393	421	449	
Week (R = randomization week)	-4 to -2	-1	R	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	
[redacted]																				

Period	**Screening**		**Double-blind treatment**														**Post-treatment follow-up**			
Visit	**1**	**20**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**	**190**	**200**	**210**	**220**	**230**	**240/ EoT/ TD**	**310**	**320**	**1999/ EoS/ PSD**	**UPV[6]**
Day	**-28 to -14**	**-7**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**393**	**421**	**449**	
Week (R = randomization week)	**-4 to -2**	**-1**	**R**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	
Urine dipstick (local) (When a dipstick evaluation is abnormal, eg positive for WBC and/or blood, a urine sample must be sent for microscopic examination to the central lab)		X							X[9]							X			X	X
Serum β-hCG (for all pre-menopausal women who are not surgically sterile) Section 8.4.4	XS																			
Urine Pregnancy Test (local) (If positive, confirmation by serum β-hCG test should be done by central lab)			S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
Safety																				

Period	**Screening**		**Double-blind treatment**														**Post-treatment follow-up**			
Visit	**1**	**20**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**	**190**	**200**	**210**	**220**	**230**	**240/ EoT/ TD**	**310**	**320**	**1999/ EoS/ PSD**	**UPV[6]**
Day	**-28 to -14**	**-7**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**393**	**421**	**449**	
Week (R = randomization week)	**-4 to -2**	**-1**	**R**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	
Physical Exam (Physical exam on Screening Visit 1 is comprehensive but subsequent physical exams maybe limited)	S		S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
Vital signs	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height (For adolescents, height to be collected at each visit. For adults height will be collected at screening only)	X		S	S	S	S	S	S	X	S	S	S	S	S	S	X	S	S	X	S
Weight	X								X							X			X	
ECG (single ECG to be taken at Visits 1 and 240/EoT/TD)	XS[10]															XS[10]				XS[10]
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Liver safety monitoring	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
Renal safety monitoring	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S

Period	**Screening**		**Double-blind treatment**														**Post-treatment follow-up**			
Visit	**1**	**20**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**	**190**	**200**	**210**	**220**	**230**	**240/ EoT/ TD**	**310**	**320**	**1999/ EoS/ PSD**	**UPV[6]**
Day	**-28 to -14**	**-7**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**393**	**421**	**449**	
Week (R = randomization week)	**-4 to -2**	**-1**	**R**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	
Others																				
Treatment completion/ discontinuation form			X																	
Study completion/ discontinuation form	X																			

TD = Study treatment discontinuation; PSD = Premature subject discontinuation
X = assessment to be recorded on eCRF
S = assessment to be recorded on source documentation only
XS = assessment data to be received in loaded format from separate source documents i.e. external vendors
UPV = Unplanned visit (NOTE – assessments as listed should be done only at the discretion of the investigator, according to the reason for the unplanned visit)

[1] IC obtained prior to all study specific screening procedures during or as close to the start of the screening period as possible

[redacted]

[3] Samples to be taken pre-dose [redacted] samples should not be collected at the End of Study (EoS) visit, if the subject takes omalizumab (outside of the study assigned treatment).

[4] A subject must not have access to more than 3 doses of corticosteroids at any 30 day period.

[5] At Visit 320, dispense 3 stool collection kits. Patients should collect samples prior to Visit 1999/EoS/PSD (no later than 7 days after Visit 1999/EoS in unavoidable circumstances).

[6] Assessments listed under unplanned visit column can be chosen as required

[7] Remote PROs collection is possible in case the patient cannot attend the visit at site due to a Public Health emergency

[8] Samples can be collected & analyzed in a certified local laboratory due to a Public Health emergency

[9] If V170 has already occurred prior to the amendment 1 approval & the urine dipstick was not collected, it should be collected as an unscheduled assessment at the patient's next scheduled visit.

[10] For any ECG with subject safety concern, 2 additional ECGs must be performed to confirm the finding.

8.1 Screening

Subjects will have up to 4 week screening period to establish eligibility for the study. Subjects will be required to attend 2 visits during screening period: Visit 1 (Day -28 to Day -14) and Visit 20 (Day -7). An extended screening period will be permitted only in exceptional circumstances when information concerning eligibility is outstanding (eg, pending laboratory data).

Rescreening may be allowed for subjects who failed initial screening. Only 1 rescreening will be allowed (Section 5.1 and Section 5.2). If a subject rescreens 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.

8.1.1 Information to be collected on screening failures

Subjects who sign an informed consent form and subsequently found to be ineligible prior to randomization 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). Adverse events that are not SAEs will be followed by the investigator and collected only in the source data. If the subject fails to be randomized, the IRT must be notified within 2 days of the screen failure that the subject was not randomized.

Subjects who are randomized and fail to start treatment, eg, subjects randomized in error, will be excluded from the analysis sets, both Full Analysis Set (FAS) and Safety Analysis Set (SAF)

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), (Children's) Dermatology Life Quality Index ((C)DLQI), Work [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 should be completed prior to any other assessment (except at Visit 1 and 20) 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 at Weeks 4, 8, 12, 24, 52 or any visit(s) in the follow-up period.

8.3.1 eDiary assessments

8.3.1.1 Urticaria Patient Daily Diary (UPDD)

UPDD includes Urticaria Activity Score (UAS) which assesses twice daily the severity of itch and number of hives, use of rescue medication once daily, sleep and activity interference, angioedema occurrence and its management and records the calls to a health care practitioner (HCP) (Appendix 4, Patient Diary: Urticaria Patient Daily Diary (UPDD)). The components are presented in the Table 8-2 and the relevant weekly scores are described below.

Table 8-2 UPDD

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

8.3.1.1.1 Weekly Hives Severity Score (HSS7),

The hives severity score, defined by number of hives (wheals), will be recorded by the subject twice daily in their eDiary, on a scale of 0 (none) to 3 (see Table 8-3). A weekly score (HSS7) is derived by adding up the average daily scores of the 7 days preceding the visit. The possible range of the weekly score is therefore 0 – 21.

Complete hives response is defined as HSS7 = 0.

Table 8-3 Hives Severity Score

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

When either the morning or evening score is missing, the non-missing score for that day (morning or evening) will be used as the daily score. When 1 or more of the daily scores are missing, the following principles will be applied to handle the missing data:

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

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

8.3.1.1.2 Weekly Itch Severity Score (ISS7)

The severity of the itch will be recorded by the subject twice daily in their eDiary, on a scale of 0 (none) to 3 (intense/severe) (see Table 8-4). A weekly score (ISS7) is derived by adding up the average daily scores of the 7 days preceding the visit. The possible range of the weekly score is therefore 0-21 (maximum itch). Partially missing diary entries will be handled in the same way as described for the weekly HSS.

Complete itch response is defined as ISS7 = 0.

Table 8-4 Itch Severity Score

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

8.3.1.1.3 Weekly Urticaria Activity Score (UAS7)

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

Complete UAS7 response is defined as UAS7 = 0.

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 8-5). The possible range of the weekly sleep interference score is therefore 0-21 (maximum interference).

Table 8-5 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 8-6), once daily in the evening in the eDiary. Daily activities could include, school, sports, hobbies and activities with friends and family. The possible range of the weekly activity interference score is therefore 0-21 (maximum interference).

Table 8-6 Activity interference score

Score	Activity interference
0	No interference
1	Mild, little interference with daily activities
2	Moderate, some interference with daily activities
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 8-7).

Table 8-7 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)). 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.

8.3.2 Other PRO assessments

8.3.2.1 Dermatology Life Quality Index (DLQI)

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

In this study, DLQI will be administered only in adult subjects (18 years and older). 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). The rationale of this approach relies on the following reasons:

- As a good practice rule, the same PRO should be administered to the same subjects consistently over a study period;
- The data will be analyzed separately for adults (≥ 18 years old) and adolescents (≥ 12 to < 18 years old) and the same analysis group of subjects needs to have the same PRO (Patient Reported Outcomes) in the study;
- There is no mapping possible between DLQI and CDLQI and the developers do not recommend changing between the 2 versions during a study; and
- Published data show a good correlation between DLQI and CDLQI scores in the group of patients 16-17 years old. (van Geel et al 2016).

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).

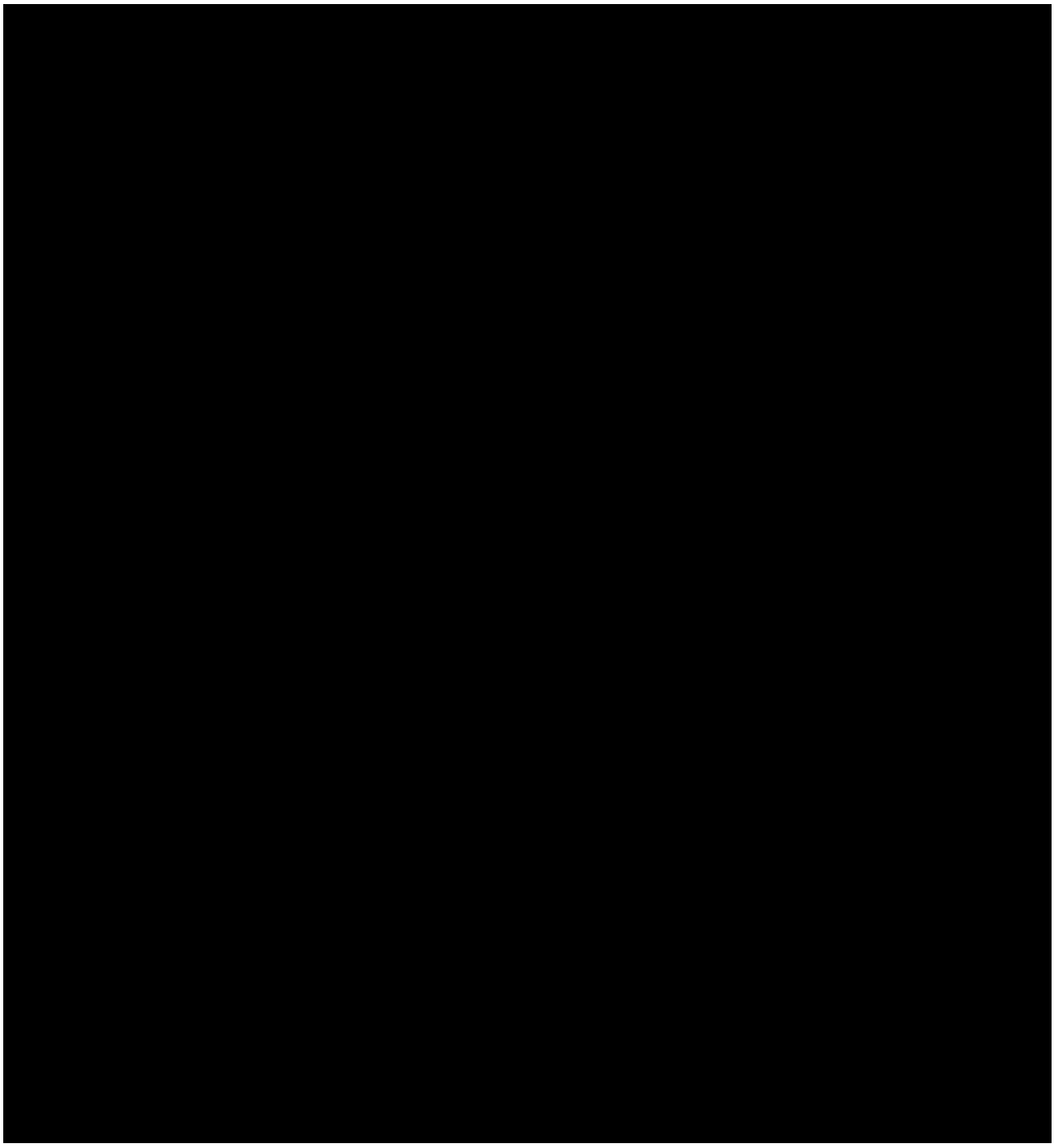
The scores were split into score bands (Hongbo et al 2005, Waters et al 2010) and validated in terms of their meaning/relevance to patients as follows:

Table 8-8 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 2005). The DLQI and CDLQI questionnaires are administered at randomization and at Weeks 4, 8, 12, 24, 52 and every visit in the follow-up period.

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 at Weeks 4, 8, 12, 24, 52 or any visit(s) in the follow-up period.



[redacted]

8.3.3 Other assessments: Evidence of urticaria

The investigator must confirm the presence of urticaria in each subject, at one of the Screening visits (Visit 1 or Visit 20) by direct physical examination. In the absence of active disease being visible at Visit 1 or Visit 20, the following will be acceptable: (a) a clearly identifiable photograph of the subject showing the presence of urticaria, or (b) the investigator must have seen the subject with active CSU in the past 6 months.

8.3.4 Appropriateness of efficacy assessments

At the time the omalizumab studies were carried out, the treatment paradigm focused primarily on itch (ISS7) as a key symptom of CSU. Over the past several years the goal of therapy has evolved and the current target of therapy as described in the current CSU treatment guidelines (Zuberbier et al 2018) is to treat the disease until it is gone, i.e. complete control of the disease (UAS7 = 0). Given the current emphasis on UAS7 in the medical community and as reflected in the CSU treatment guidelines, data from the Phase II study CQGE031C2201 support the change from baseline in UAS7 (which is a composite of ISS7 and HSS7) at Week 12 being assessed as the primary endpoint. Change from baseline in ISS7 and achievement of UAS7 = 0 will be assessed as secondary endpoints included in the testing strategy.

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

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

8.4 Safety

Main safety and tolerability assessments include:

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

Table 8-9 Physical Assessments

Assessment	Specification
Physical examination	A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, and extremities and vascular and neurological systems. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. A short physical exam will include the examination of general appearance and vital signs. A short physical exam will be conducted at all visits starting from Visit 1 except where a complete physical examination is required (see Table 8-1). Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate eCRF that captures medical history. Significant findings made after signing the informed consent which meet the definition of an 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 centimeters (cm) and body weight (to the nearest 0.1 kilogram (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 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. In case of lab abnormalities, an additional re-draw for central laboratory assessment is allowed during the screening period to confirm eligibility criteria.

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

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

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 8-10 Laboratory Assessments

Test Category	Test Name
Hematology	Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential and platelet count will be measured.
Coagulation	At Visits 1 and 110,coagulation will be assessed by International Normalized Ratio (INR).
Chemistry	Albumin, total bilirubin, alkaline phosphatase, AST, ALT, LDH, GGT, chloride, sodium, potassium, magnesium, calcium, inorganic phosphorus, creatinine, urea/BUN and uric acid will be measured. If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reacting bilirubin should be differentiated.
Urinalysis	A midstream urine sample (approximately 30 mL) will be obtained, in order to avoid contamination with epithelial cells and sediments, and allow proper assessments. Semi-quantitative “dipstick” evaluation for specific gravity, glucose, pH, protein, bilirubin, ketones, leukocytes and blood will be performed at site. When a dipstick evaluation is abnormal, eg, positive for WBC and/or blood, a urine sample must be sent to the Central Lab for microscopic examination including RBC and WBC. (Details on collection of urine for analysis by central laboratory are provided to investigators in the laboratory manual.)
Parasite screening	Assessment of stool samples for parasitic infections (refer to Assessment of parasitic infections Section 8.4.3
Pregnancy Test	Serum / Urine pregnancy test (refer to Pregnancy and assessments of fertility Section 8.4.4)

8.4.2 Electrocardiogram (ECG)

Standard 12 lead ECGs must be recorded after 10 minutes rest in the supine position to ensure a stable baseline. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood sampling. The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

Single ECGs will be collected at Visits 1 and Visit 240/EoT/TD.

The original ECG will be sent electronically to the Clinical Research Organization (CRO) directly from the provided ECG machine. Two “identical” duplicate print-outs will be generated on non-heat sensitive paper and kept at the investigator site as source documentation and as back-up for submission to the vendor in case of problems with the electronic transmission. The “identical” duplicates must be labeled with study number, subject initials, subject number, date and time, and signed and archived in the study site source documents.

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

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

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

8.4.3 Assessment of parasitic infections

Reduction in IgE levels may confer increased susceptibility to parasitic infections. The risk of acquiring or activating infections with helminthes during or after treatment with anti-IgE

therapy such as ligelizumab and omalizumab is suspected to be low. Data from the Phase II CQGE031C2201 study in this regard was unremarkable but limited due to study sample size.

All subjects will be given three stool sample collection kits at screening Visit 1 and Visit 320 by the site or site's local laboratory. Subjects will take the stool sample kits home and collect stool samples from three different bowel movements, ideally on three different days, within seven days of Visit 1 and in the week prior to Visit 1999. Subjects will return the three stool samples to the site or local laboratory as soon as possible after Visit 1 (in order to allow processing within the screening period) and at Visit 1999 (no later than 7 days after Visit 1999/EoS in unavoidable circumstances).

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

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

8.4.4 Pregnancy and assessments of fertility

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

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

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

Assessments of fertility

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

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

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

8.4.5 Anaphylaxis assessment

An adjudication committee (AC) will be put in place to determine whether cases of hypersensitivity identified through a search algorithm based on the Standardized MedDRA Queries may represent cases of anaphylaxis. Further details regarding the AC will be documented in the AC charter. See Section 10.2.4 for details.

8.4.6 Assessment of cardio-cerebrovascular events

An AC will be put in place to review all cases identified through a search algorithm based on the Standardized MedDRA Queries of cardio-cerebrovascular events. The clinical presentation and association of these events with pre-existing risk factors will be part of the assessment. See Section 10.2.4 for details

8.4.7 Assessment of neoplastic events

An AC will be put in place to review all cases identified through a search algorithm based on the Standardized MedDRA Queries of neoplastic events. The clinical presentation and association of these events with pre-existing risk factors will be part of the assessment. See Section 10.2.4 for details.

8.4.8 Appropriateness of safety measurements

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

8.5 Additional assessments

[redacted]

8.5.2 Pharmacokinetics and pharmacodynamics

[redacted]

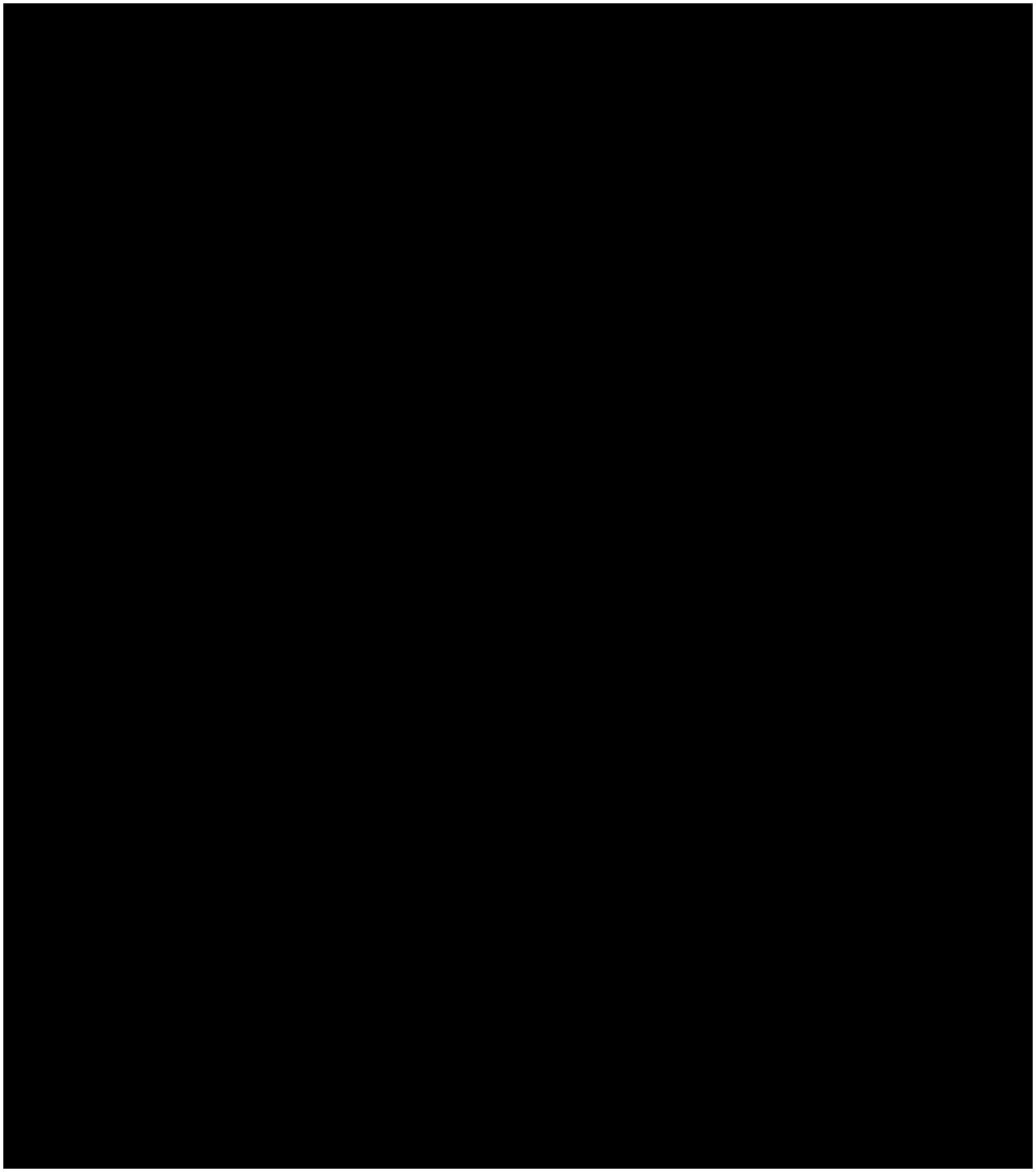
8.5.2.1 Blood collection and processing

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

All samples will be given a unique sample number. The actual sample collection date and time will be entered on the appropriate eCRF page. Sampling problems will be noted in the Notes field of the eCRFs.

Detailed instructions for blood sample collection, processing, storage and shipment are provided in the blood log (Section 16.5), lab manual and flow charts prepared by the Central Laboratory.

[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 8.4.4 and Section 10.1.4)
- Unblinding of study treatment other than to authorized personnel (see Section 6.4) for any reason
- Subject develops a medical condition that requires use of prohibited treatment as per Section Section 6.2.2, or if subject exhibits a behavior of non-compliance regarding prohibited medications
- Subject received a live virus vaccination during the study
- Subject experiences an unexpected hypersensitivity reaction of grade 5, as defined by the World Allergy Organization Grading System (Cox et al 2017), see Appendix 6:
  - Lower or upper respiratory: Respiratory failure with or without loss of consciousness; or
  - Cardiovascular: Hypotension with or without loss of consciousness
- Emergency use of epinephrine due to anaphylactic or anaphylactoid reaction
- Any other protocol deviation that results in a significant risk to the subject's safety
- Any situation in which study participation might result in a safety risk to the subject
- Following emergency unblinding
- If a subject uses rescue corticosteroids for CSU more than 3 doses in a 30 day period or more than 9 doses of in total after week 12 during the study period (including the follow-up period).
- If a subject misses 3 consecutive doses.

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

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

For subjects who wish to prematurely discontinue treatment prior to the primary endpoint (Visit 140/Wk 12) for any reason, every effort should be made to have them continue study visits as per the assessment schedule, at least until Visit 140 (Week 12). At the final visit, all dispensed investigational product should be reconciled and the AE and concomitant medications reconciled on the appropriate eCRF.

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

If discontinuation occurs because treatment code has been broken, please refer to Emergency breaking of treatment code section.

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

9.1.2 Withdrawal of informed consent

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

- Does not want to participate in the study anymore

and

- Does not allow further collection of personal data

In this situation, the investigator should make a reasonable effort (eg, telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information.

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

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

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

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

For United States (US) and Japan: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

For EU and Rest of World (RoW): All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

9.1.3 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, eg, dates of telephone calls, registered letters, etc. A subject should not be considered as lost to follow-up until due diligence has been completed. Follow-up is recommended until the end of the study.

9.1.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/ risk assessment of participating in the study, practical reasons (including slow enrollment) or for regulatory or medical reasons. In taking the decision to terminate, Novartis will always consider the subject's welfare and safety. Should early termination be necessary, subjects must be seen as soon as possible and treated as a prematurely withdrawn subject. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator or sponsor, depending on the local regulation, will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Study completion is defined as when the last subject finishes their Study Completion visit, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator, or in the event of an early study termination decision, the date of that decision.

Patients may be eligible to roll-over into an extension study (CQGE031C2302E1) after completion of the study.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (eg, 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.

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 during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination findings, laboratory test findings or other assessments.

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

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

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

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

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

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

Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment or end of study visit, whichever is longer.

Once an AE is detected, it must be followed until its resolution or until it is judged to be permanent (eg, Continuing at the end of the study), and assessment must be made at each visit

(or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

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

Abnormal laboratory values or test results constitute AE 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

An SAE is defined as any adverse event, eg, 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, eg, defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

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

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

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

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective of whether a clinical event has occurred or not.

10.1.3 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days after the last patient last visit (LPLV) must be reported to Novartis Safety within 24 hours of learning of its occurrence. Any SAEs experienced after the 30 day period should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment. Any SAEs reported up to the subject's last visit will be reported in the eCRF. SAEs beyond that date will only be recorded in the Novartis Safety database.

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

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

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

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

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

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

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

10.1.4 Pregnancy reporting

Pregnancies

To ensure subject safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

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

10.1.5 Reporting of study treatment errors including misuse/abuse

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

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

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

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

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

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

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

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

The following 2 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 and liver events.

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, PT/INR, ALP and GGT) to confirm elevation.

- These liver chemistry repeats will be performed using the central laboratory. If results will not be available from the central laboratory, then the repeats can also be performed at a local laboratory to monitor the safety of the subject. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results recorded on the appropriate CRF.

- If the initial elevation is confirmed, close observation of the subject will be initiated, including consideration of
  - Treatment interruption if deemed appropriate
  - Discontinuation of the investigational drug (refer to the Discontinuation of study treatment section), if appropriate
  - Hospitalization of the subject if appropriate
  - Causality assessment of the liver event
  - A thorough follow-up of the liver event should include (based on investigator's discretion) serology tests, imaging and pathology assessments, gastroenterologist or hepatologist's consultancy, obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease, imaging such as abdominal ultrasound, CT or MRI scans and obtaining a history of exposure to environmental chemical agents

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

10.2.2 Renal safety monitoring

The following base monitoring for renal laboratory values, as per the Novartis Drug-Induce Nephrotoxicity Guidelines (Nov-2017; Table 10-2 below) of abnormal renal laboratory values, will be carried out as part of the assessment schedule (Table 8-1) during the course of the study:

Table 10-2 Base Renal Monitoring

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

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

Specific details regarding composition, responsibilities, data monitoring, 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

To enhance the safety assessment, more specifically relative to 1) anaphylactic events, 2) neoplastic events, and 3) major cardio-cerebrovascular events, 3 Adjudication Committees,

independent panels of experts external to Novartis, will provide reviews of identified potential events in a blinded manner. Adjudication will be performed on a regular basis.

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

11 Data collection and database management

11.1 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms using fully validated software that conforms to US Code of Federal regulations (CFR) 21 Part 11 requirements. Designated investigator site staff will not be given access to the Electronic Data Capture (EDC) system until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to the CRO working on behalf of Novartis. After final database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

The investigator/designee is responsible for assuring that the data entered into eCRF is complete and accurate, and that entry and updates are performed in a timely manner.

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 staff or CRO working on behalf of Novartis review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff are required to respond to the query and confirm or correct the data.

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

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis. Stool samples will be processed by local labs and the results will be collected by Novartis via eCRFs.

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

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

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

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

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

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 & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

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

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

12 Data analysis and statistical methods

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

Due to the relatively low number of adolescent subjects for this study, the data collected for adolescent subjects will be provided in a descriptive manner separately.

12.1 Analysis sets

The following analysis sets will be used in this trial:

Randomized set (RAN): The RAN set will include all randomized subjects, regardless of whether or not they receive a dose of study drug. Subjects will be analyzed according to the treatment they are assigned.

Full analysis set (FAS): The FAS set will include all randomized subjects who received at least 1 dose of study drug. Subjects will be analyzed according to the treatment to which they are assigned at randomization. FAS will be used for all efficacy variables, unless otherwise stated.

Safety analysis set (SAF): The SAF set will include all subjects who received at least 1 dose of study drug whether or not being randomized. Subjects will be analyzed according to the treatment they received. The safety set will be used in the analysis of all safety variables. 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.

12.2 Subject demographics and other baseline characteristics

Summary statistics will be presented for continuous demographic and baseline characteristic variables for each treatment group and for all subjects in the randomized set (RAN). The number and percentage of subjects in each category will be presented for categorical variables for each treatment group and all subjects.

Medical history

Any condition entered as medical history or current medical conditions at baseline will be coded using the MedDRA dictionary. They will be summarized by system organ class and preferred term of the MedDRA dictionary for RAN. Summaries for cardiovascular and urticaria specific medical history will also be provided.

12.3 Treatments

Study Treatment

The analysis of study treatment data will be based on the safety set.

The number of patients and the length of time (in weeks) exposed to each study drug and dose will be summarized by treatment. In addition, the number of doses, total cumulative dose, and number of missed doses will be presented. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, SD, median, 25th and 75th percentiles, minimum, and maximum will be presented.

Prior and concomitant medications

Prior medications are defined as medications taken and stopped prior to first dose of study treatment. Prior medications will be summarized based on RAN. Prior medications for CSU will be summarized by type of therapy, preferred term and treatment group. Prior medications

non-related to CSU will be summarized by Anatomical Therapeutic Chemical (ATC) code and preferred term.

Concomitant medications will be summarized by treatment for the safety set separated for urticaria related background medications and non-urticaria related medications. Urticaria related background medications will be summarized by type of therapy, preferred term and treatment group. Non-urticaria related concomitant medications will be summarized by preferred term.

12.4 Analysis of the primary endpoint(s)

This section will detail the statistical analysis of the primary endpoint. Details of the hypothesis testing strategy including primary and secondary endpoints to handle multiplicity are provided in Section 12.5.1.

The analysis of primary endpoint and the secondary endpoints included in the testing strategy will focus on the adult subjects.

The aim is to estimate the treatment effect of the investigational drug (ligelizumab) compared to omalizumab and placebo, for the target population of adults on the primary endpoint. The detailed definition of the primary estimand is provided in Section 12.4.1 and the justification of the corresponding primary estimand, as well as the definition of the supplementary estimands will be provided in the statistical analysis plan.

The efficacy information for adolescents will be presented descriptively for this study. The adolescent subject data will be forwarded to a separate cross-study extrapolation analysis to support determination of the final posology for the treatment of adolescent patients.

12.4.1 Definition of primary endpoint(s)

The primary endpoint is the absolute change from baseline in UAS7 score at Week 12, which is the UAS7 score at Week 12 minus the UAS7 score at baseline.

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.

The primary estimand will account for two categories of intercurrent events which will be treated in different ways. We will distinguish between intercurrent events unrelated to the COVID-19 pandemic and intercurrent events that happened due to operational complications caused by the COVID-19 pandemic, e.g. patients missed their dose as they were not able to receive their study medication due to regional lockdowns. Intercurrent events due to non-operational reasons during the COVID-19 pandemic will be treated analogously to intercurrent events unrelated to the COVID-19 pandemic and will therefore be classified as intercurrent events unrelated to the COVID-19 pandemic for the primary efficacy analysis. In order to distinguish between these two categories, protocol deviations arising due to the COVID-19 pandemic will be collected in addition to the original list of protocol deviations. Hence, the COVID-19 pandemic related protocol deviations complete the set of protocol deviations already in place and will coexist with those. The COVID-19 pandemic related protocol deviations will identify intercurrent events due to COVID-19, which will then be split into operational complications due to COVID-19 (e.g., a missed dose because the patient was not able to reach

the site because of a local lockdown due to COVID-19, etc.) and non-operational complications due to COVID-19 (e.g., lack of efficacy and adverse events).

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 drop-out (RDO) subjects. The definition of primary estimand is described by the following attributes, and the detail handling of intercurrent events descriptions will be provided in Section 12.4.2.

- **Population**: Adult participants receiving H1-antihistamines therapy at local-approved dose level as background medication suffering from chronic spontaneous urticaria and meeting study inclusion/exclusion criteria (as listed in Section 5.1 and Section 5.2). Further details about the population are provided in Section 5.
- **Endpoint**: absolute change from baseline in UAS7 score at Week 12
- **Treatment of interest**: ligelizumab or the placebo or omalizumab treatment with stable H1-antihistamines (H1-AH) at local-approved doses as background medication + allowed rescue medication if needed.
- **Handling of remaining intercurrent events**:

Intercurrent events unrelated to the COVID-19 pandemic :

1. Discontinuation of initially assigned study treatment prior to Week 12 due to adverse events (AE) or lack of efficacy (LoE) or any other reasons unrelated to the COVID-19 pandemic: Participants who discontinue from study treatment early will be encouraged to stay in the study as detailed in Section 9.1.1. Retrieved drop out (RDO) data collected after study treatment discontinuation will be used for analysis. (treatment policy strategy).
2. Use of rescue medication prior to Week 12 unrelated to the COVID-19 pandemic: ignore (treatment policy strategy).

Intercurrent events related to the COVID-19 pandemic due to operational complications:

1. Discontinuation of study treatment prior to Week 12 due to the COVID-19 pandemic: had participants not discontinued study treatment prior to Week 12 due to the COVID-19 pandemic (hypothetical strategy).
2. Missed treatment prior to Week 12 due to the COVID-19 pandemic: had participants not missed treatment prior to Week 12 due to the COVID-19 pandemic (hypothetical strategy)

- **The summary measure**: difference in mean absolute change from baseline in UAS7 score at Week 12 between treatments (ligelizumab 72 mg q4w vs placebo/omalizumab and ligelizumab 120 mg q4w vs placebo/omalizumab)

For all the intercurrent events occurred during the COVID-19 pandemic period which are not due to operational complications, they will be classified as intercurrent events unrelated to COVID-19 pandemic and handled by the treatment policy strategy.

12.4.2 Statistical model, hypothesis, and method of analysis

The statistical hypotheses test for the primary endpoint being tested is that the absolute change from baseline in UAS7 score at Week 12 in any of the ligelizumab groups (low or high dose) is not superior to the omalizumab group and placebo group. i.e.

$H_{01}: \mu_{ligelizumab} \geq \mu_{Placebo}$ versus $H_{A1}: \mu_{ligelizumab} < \mu_{Placebo}$
$H_{01}': \mu_{ligelizumab} \geq \mu_{omalizumab}$ versus $H_{A1}': \mu_{ligelizumab} < \mu_{omalizumab}$

where μ is the mean change from baseline of UAS7 at Week 12.

Stating these formulae in another way gives the following:

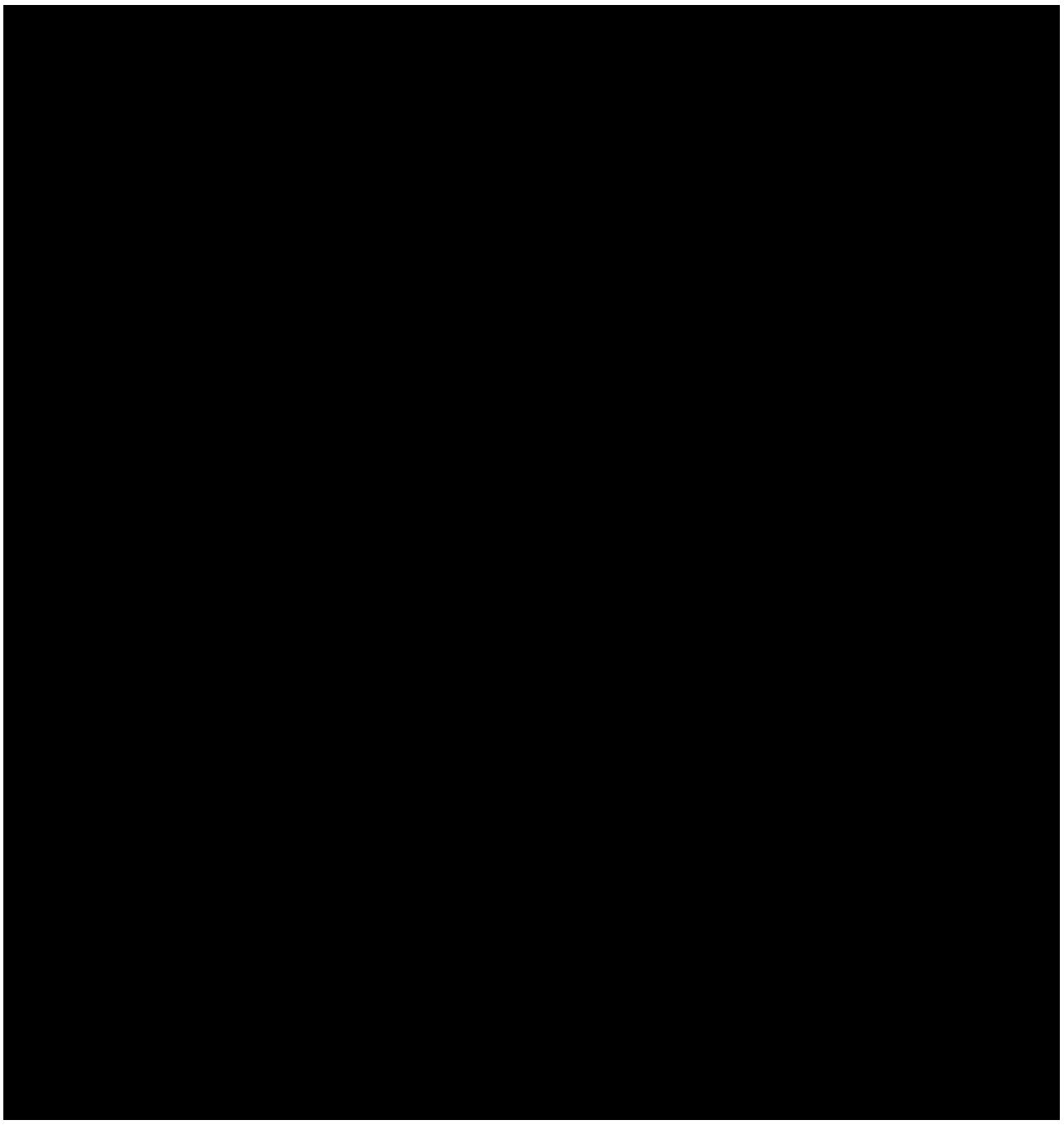
H_{1l}, H_{1h}: Ligelizumab low or high dose is not superior to placebo with respect to absolute change from baseline at Week 12;

H_{1l}', H_{1h}': Ligelizumab low or high dose is not superior to omalizumab with respect to absolute UAS7 change from baseline at Week 12.

A linear mixed model with repeated measures (MMRM) will be used to estimate treatment differences for change from baseline in UAS7 score at Week 12, based on the FAS. [redacted] epeated measures within subject are modeled using an unstructured covariance of the error terms. Additional important covariates may be added to the model.

The detailed testing strategy including the primary endpoint analysis is provided in Section 12.5.

[redacted]



Multiple intercurrent events occuring prior to Week 12

In general, if there are multiple intercurrent events occurring prior to Week 12 with different relations to the COVID-19 pandemic, that is, at least one of the intercurrent event is classified as being unrelated to COVID-19 and one is classified as being related to COVID-19 operational complications, the treatment policy strategy will be applied. That is, multiple intercurrent events occurring prior to Week 12 will be handled by the hypothetical strategy only if all of them are classified as being due to COVID-19 operational complications.

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.

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 daily data:

- If a patient 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.

[redacted]

[redacted]

12.5 Analysis of secondary endpoints

12.5.1 Efficacy and/or pharmacodynamic endpoint(s)

- Complete absence of hives and itch at Week 12, assessed as % of subjects achieving UAS7 = 0.

The proportion of subjects with UAS7 = 0 at Week 12 will be analyzed using a logistic regression model including treatment group, region and baseline UAS7 score. Missing data will be considered as non-responder in the analysis.

- Improvement of severity of itch, assessed as absolute change from baseline in ISS7 score at Week 12.

The absolute change from baseline in ISS7 score at Week 12 will be analyzed analogously to absolute change from baseline in UAS7 score at Week 12, i.e. using MMRM modeling.

- No impact on subjects' quality of life at Week 12, assessed as % 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 analyzed using a logistic regression model which includes treatment group, region and baseline UAS7 score. Missing data will be considered as non-responder in the analysis.

- Cumulative number of weeks that subjects achieve AAS7 = 0 responses between 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. If the AAS7 assessment 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 number of weeks achieving AAS7 = 0 response between baseline and Week 12 will be modelled using a negative binomial regression model with log link, using treatment group, region and baseline AAS7 = 0 status.

Testing strategy

The efficacy analysis of secondary variables listed in the testing strategy will focus on adult subjects. The efficacy information for adolescent subjects will be provided in a descriptive manner over time.
The following null hypotheses (H_0) will be tested against the respective alternative hypotheses (H_A) in a closed testing procedure (Bretz et al 2009), thus controlling the family-wise type I error which is set to 0.025 (one-sided) at the level of the individual studies, and for the pooled dataset of both studies as listed in Figure 12-1 Multiple testing strategy:

Primary endpoint

UAS7 change from baseline at Week 12

$H_{01}: \mu_{ligelizumab} \geq \mu_{Placebo}$ versus $H_{A1}: \mu_{ligelizumab} < \mu_{Placebo}$

H_{01}': $\mu_{ligelizumab} \geq \mu_{omalizumab}$ versus H_{A1}': $\mu_{ligelizumab} < \mu_{omalizumab}$

where μ is the mean change from baseline in UAS7 at Week 12, as described in Section 12.4.2.

Secondary endpoints

UAS7 = 0 at Week 12

H_{02}: $\pi_{ligelizumab} \leq \pi_{Placebo}$ versus H_{A2}: $\pi_{ligelizumab} > \pi_{Placebo}$
H_{02}': $\pi_{ligelizumab} \leq \pi_{omalizumab}$ versus H_{A2}': $\pi_{ligelizumab} > \pi_{omalizumab}$

where π is the proportion of subjects achieving UAS7 = 0 at Week 12.

Stating these formulae in another way gives the following:

H_{2l}, H_{2h}: Ligelizumab low or high dose is not superior to placebo with respect to UAS7 = 0 response at Week 12;
H_{2l}', H_{2h}': Ligelizumab low or high dose is not superior to omalizumab with respect to UAS7 = 0 response at Week 12.

ISS7 change from baseline at Week 12

H_{03}: $\mu_{ligelizumab} \geq \mu_{Placebo}$ versus H_{A3}: $\mu_{ligelizumab} < \mu_{Placebo}$
H_{03}': $\mu_{ligelizumab} \geq \mu_{omalizumab}$ versus H_{A3}': $\mu_{ligelizumab} < \mu_{omalizumab}$

where μ is the mean change from baseline in ISS7 to Week 12.

Stating these formulae in another way gives the following:

H_{3l}, H_{3h}: Ligelizumab low or high dose is not superior to placebo with respect to the absolute change from baseline to Week 12 of ISS7;
H_{3l}', H_{3h}': Ligelizumab low or high dose is not superior to omalizumab with respect to the absolute change from baseline to Week 12 of ISS7.

DLQI = 0-1 at Week 12

H_{04}: $\pi_{ligelizumab} \leq \pi_{Placebo}$ versus H_{A04}: $\pi_{ligelizumab} > \pi_{Placebo}$
H_{04}': $\pi_{ligelizumab} \leq \pi_{omalizumab}$ versus H_{A4}': $\pi_{ligelizumab} > \pi_{omalizumab}$

where π is the proportion of subjects achieving DLQI = 0 or 1 at Week 12.

Stating these formulae in another way gives the following:

H_{4l}, H_{4h}: Ligelizumab low or high dose is not superior to placebo with respect to the DLQI = 0 or 1 response at Week 12;
H_{4l}', H_{4h}': Ligelizumab low or high dose is not superior to omalizumab with respect to the DLQI = 0 or 1 response at Week 12.

Cumulative number of weeks that subjects achieve AAS7=0 responses between baseline and Week 12

H_{05}: $\mu_{ligelizumab} \leq \mu_{Placebo}$ versus H_{A5}: $\mu_{ligelizumab} > \mu_{Placebo}$

H_{05}': $\mu_{ligelizumab} \leq \mu_{omalizumab}$ versus H_{A5}': $\mu_{ligelizumab} > \mu_{omalizumab}$

where μ is the mean cumulative number of weeks achieving AAS7 = 0 during 12 weeks.

Stating these formulae in another way gives the following:

H_{5l}, H_{5h}: Ligelizumab low or high dose is not superior to placebo with respect to the cumulative number of weeks achieving AAS7 = 0 during 12 weeks;
H_{5l}', H_{5h}': Ligelizumab low or high dose is not superior to omalizumab with respect to the cumulative number of weeks achieving AAS7 = 0 during 12 weeks.

A testing procedure is proposed with type-I-error control in the planned submission package which consists of studies C2302 and C2303 (both with identical design). Hypotheses can only be tested in the order as indicated by the arrows for alpha propagation for each individual study as listed in Figure 12-1. If the primary endpoint has demonstrated the superiority versus placebo and versus omalizumab, the alpha could be passed to the tests for all of the secondary endpoints. For the secondary endpoints, if an endpoint demonstrates superiority versus placebo based on each of the individual studies, the same endpoint can be tested based on the pooled dataset as pre-specified.
For the comparison versus placebo based on each individual study, the initial alpha level for each branch is set to $\alpha/2 = 0.0125$ (one-sided). The first hypothesis (H_{1h} and H_{1l}) is tested with

$\alpha/2 = 0.0125$ (one-sided) of high/low dose ligelizumab versus placebo regarding the primary endpoint. If either of the hypotheses is rejected, the corresponding second hypothesis (H_{1h}' and/or H_{2l}') of high/low dose ligelizumab versus omalizumab is tested with $\alpha/2$. The same principle applies for moving from the second to the third hypothesis. If either H_{3h} and/or H_{3l} is rejected, $\alpha/4$ is passed to the other dose on primary endpoint testing together with the initial $\alpha/2$. The rest $\alpha/4$ is passed to test H_{4h} and/or H_{4l} for the same ligelizumab dose versus placebo. The testing within each sequence is strictly hierarchical, so that null hypotheses can be tested along the pre-defined order at the level assigned to the respective sequence until a null hypothesis cannot be rejected, at which point the testing in that sequence stops. If all null hypotheses in either of the sequence can be rejected, the "unused" type I error is transferred to the other sequence, so that the initial level in the other sequence is increased. Thus, the family-wise type I is controlled at $\alpha = 0.025$ (one-sided).

[redacted]

12.5.2 Safety endpoints

All safety endpoints (i.e. AEs, laboratory data, vital signs, and ECG) will be summarized by treatment for all subjects of the safety set. All data will be included in the analysis regardless of rescue medication use. In addition safety endpoints for adults and adolescents will each be presented separately.

Adverse events

Treatment emergent adverse events (events started after the first dose of study treatment or events present prior to the first dose of study treatment but increased in severity based on preferred term) will be summarized. AEs will be summarized by presenting, for each treatment group, the number and percentage of subjects having any AE, having an AE in each primary system organ class and having each individual AE (preferred term). Summaries will also be presented for AEs by severity and for study treatment related AEs. If a subject reported more than 1 AE with the same preferred term, the AE with the greatest severity will be presented. If a subject reported more than 1 AE within the same primary system organ class, the subject will be counted only once with the greatest severity at the system organ class level, where applicable. Serious adverse events will also be summarized. Separate summaries will be provided for death, SAE, and other significant AEs leading to discontinuation.

All AEs with onset in the follow-up period will be considered as treatment emergent. Only AEs occurring in the follow-up period will be included in the follow-up report. Data from the placebo arm after switching to ligelizumab will be summarized separately.

Adverse events of special interest for ligelizumab treatment will also be summarized.

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 below will be listed.

For adults:

- Hypertension (systolic blood pressure of ≥ 140 mmHg and/or diastolic blood pressure of ≥ 90 mmHg) or hypotension (systolic blood pressure of < 90 mmHg and/or diastolic blood pressure of < 60 mmHg).
- Pulse rate below 60 bpm (bradycardia) or above 100 bpm (tachycardia).

For adolescents:

- See Appendix 1 for upper and lower limits for children's vital signs that may be considered of concern if newly identified.

12-lead 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

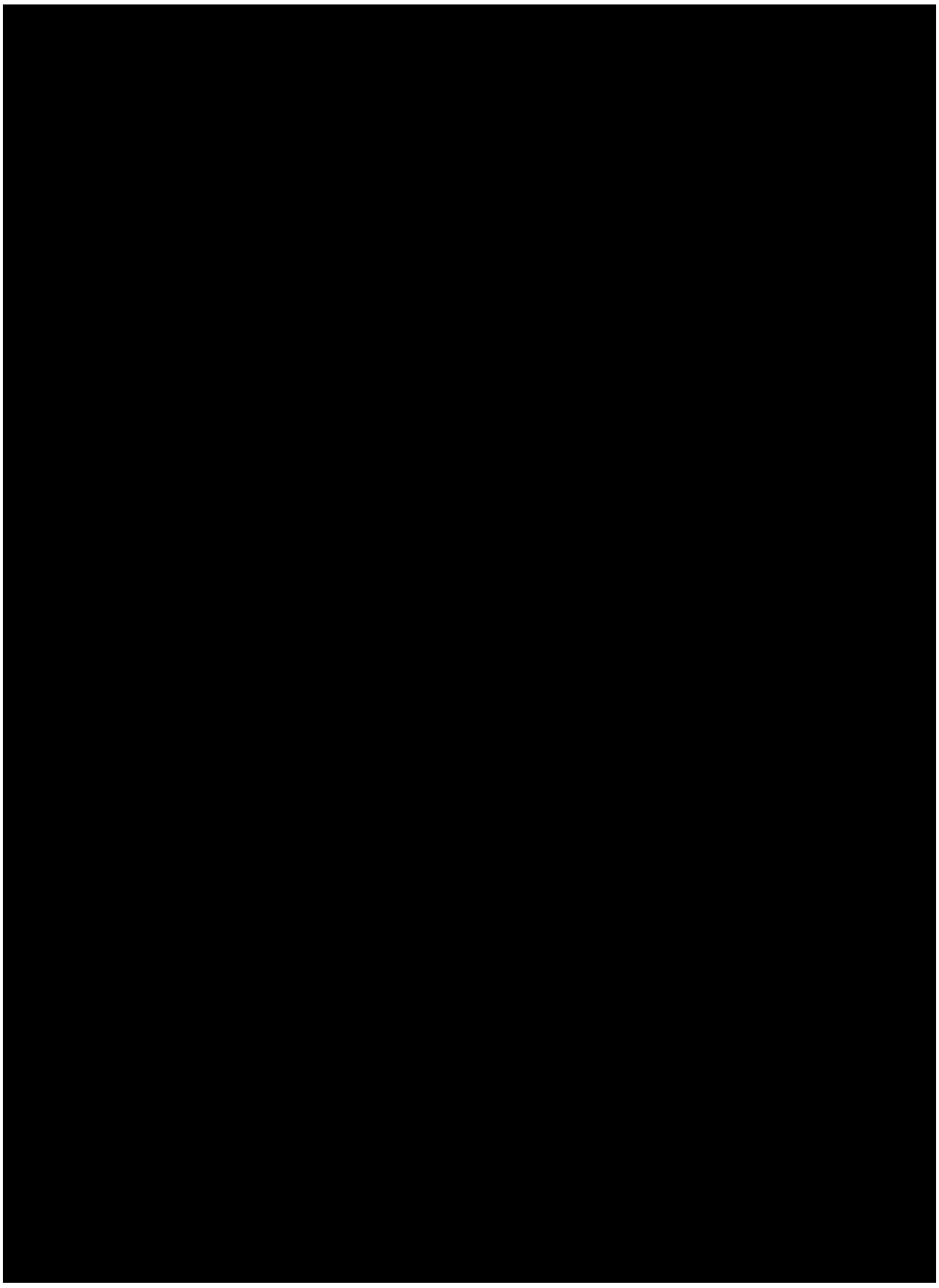
The summary of laboratory evaluations will be presented for 2 groups of laboratory tests (hematology and serum chemistry). Descriptive summary statistics for the change from baseline to each study visit will be presented. These descriptive summaries will be presented by test group, laboratory test and treatment group. Change from baseline will only be summarized for subjects with both baseline and post baseline values.

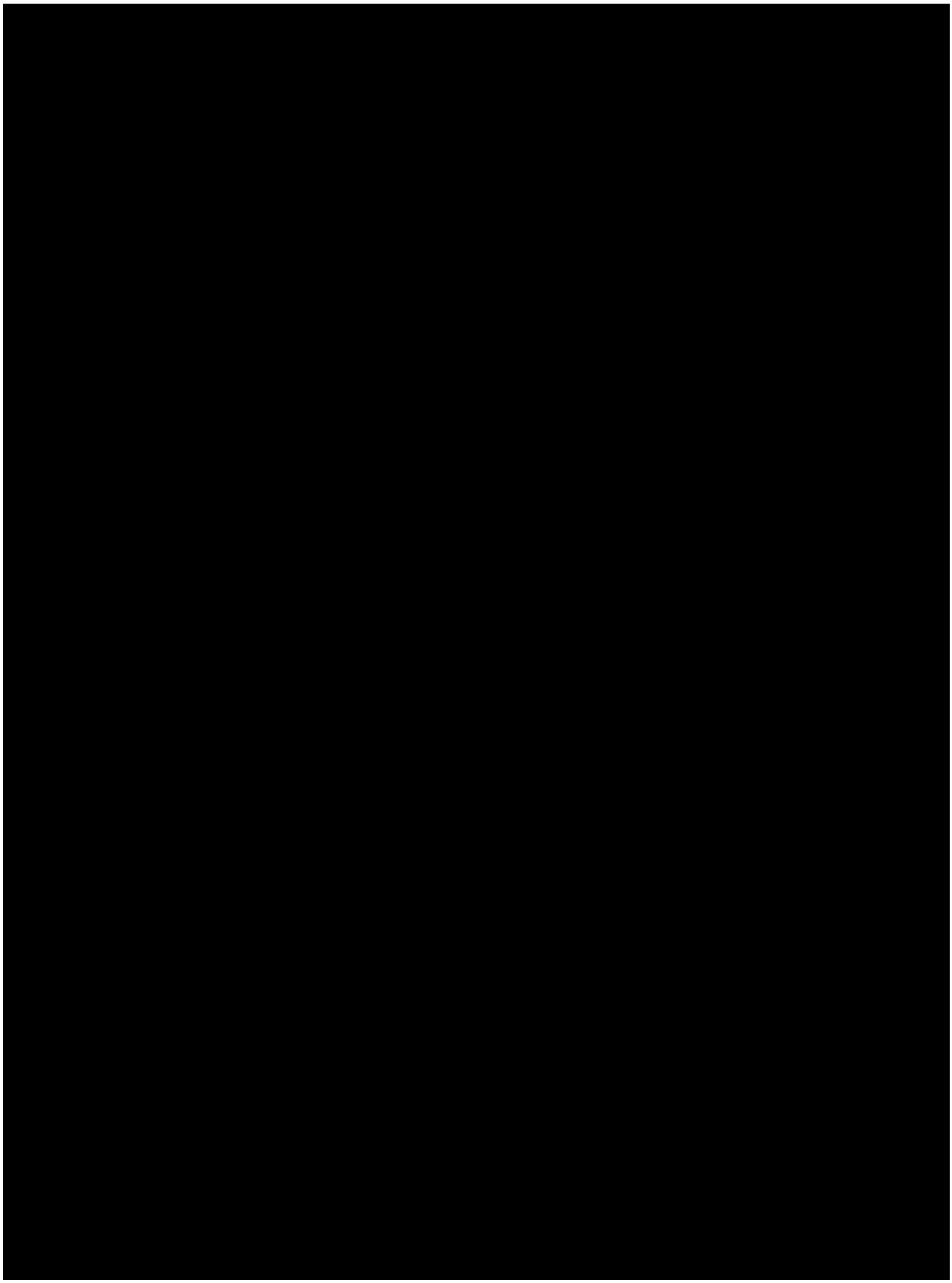
[redacted]

Resource utilization

Data relating to resource utilization is collected and reported by the subject in the daily eDiary and may be used for the purpose of economic evaluation.

[redacted]





[redacted]

12.7 Interim analysis (primary efficacy analysis)

An interim analysis is planned when all adult subjects have completed the treatment period (Week 52 visit). The interim analysis at the time of this Week 52 database lock would be utilized for the primary efficacy analysis for this study. A separate unblinded study team will perform the interim analysis. [redacted] A blinded study team will oversee the study conduct until all subjects have completed the entire study participation and the final database lock has occurred. All investigators, study personnel, subjects, and the blinded study team will remain blinded to the interim results and to the individual treatment assignment until all subjects have completed the entire study participation and the final database lock has occurred.

12.8 Sample size calculation

Sample size justification for adult subjects

The sample size justification is based on UAS7 change from baseline and achievement of UAS7 = 0. Due to the much larger effect sizes versus placebo, the sample sizes are driven by the assumptions underlying the comparisons of ligelizumab versus omalizumab 300 mg. To avoid assigning an unnecessary large number of subjects to placebo, subjects will be randomized in a 3:3:3:1 ratio to ligelizumab high dose, ligelizumab low dose, omalizumab and placebo, respectively.

All calculations were performed with nQuery Advisor 7.0.

UAS7 change from baseline at Week 12

Based on interim results from CQGE031C2201, it is assumed that the difference between ligelizumab and omalizumab 300 mg mean change of UAS7 from baseline to Week 12 is at least 3.5 in favor of ligelizumab, with common standard deviation of approximately 13 based on the Phase IIb study. Although it is planned to use a repeated measures model for the analysis, an approximate sample size can be based on a simple t-test, assuming type I error 0.025 (one-sided) and power 90%, which results in 291 per group. This will give > 99% power for the same comparison versus placebo, if the placebo sample size is only 97 and the assumed difference is 8.

Achievement of UAS7 = 0 at Week 12

A sample size of 291 per group, which is required for the UAS7 change from baseline, will provide more than 90% power based upon a 2 group continuity corrected $\chi 2$ test with a 0.025 one-sided significance level to detect the difference between a proportion of 0.30 (omalizumab 300 mg) and a proportion of 0.45 (ligelizumab, odds ratio of 1.909). As for the change from baseline, the power for the comparison versus placebo is > 99% even if the placebo sample size is only 97 and the proportion of placebo treated subjects achieving UAS7 = 0 responses is around 10%. These power calculations are an approximation of the power achieved with the logistic regression approach.

Despite the intention of convincing study subjects to stay in the study and providing eDiary information even if they will be discontinued early from the study treatment, the early discontinuation rate from study at Week 12 is only assumed to be around 5% based on the phase II study data.

In summary, the required adult sample size in each of the ligelizumab and omalizumab 300 mg arms is approximately 300, while the placebo sample size can be reduced to approximately 100 for efficacy comparisons.

It was also confirmed that the assigned sample size calculated above is sufficient to maintain the power of the overall multiple testing strategy (at least 90%) for the primary endpoint (UAS7 change from baseline at Week 12) and the key secondary endpoint (UAS7=0 response rate at Week 12) through the recycled alpha based on the simulations. The detail simulation results are provided in the statistical analysis plan.

The analysis strategy has been adjusted to mitigate the potential COVID-19 impact on the study. The original proposed sample size will be still sufficient to maintain the statistical power of the overall multiple testing strategy (at least 90%) for the primary endpoint (UAS7 change from baseline at Week 12) based on individual study data. The power of the key secondary endpoint (UAS7=0 response rate at Week 12) will be maintained (at least 90%) through the pooled data set as well. Detailed simulation results of the statistical power for the updated testing strategy will be provided in a separate document (e.g., statistical analysis plan).

Sample size justification for adolescent subjects

The target sample size of 50 adolescent subjects receiving ligelizumab treatment and completing the treatment period is based upon the expected prevalence of adolescent CSU patients in a representative patient population (see Table 12-1 for details). The annual prevalence of CSU in the pediatric population is low and comparable with adults (< 1%).

Although the age-related prevalence of CSU for adolescent patients is similar to adults, the overall target for enrollment is impacted by the fact that 11 to 17 year old patients only comprise about 10% of the total population (9.5% of the population in the US Census Bureau).

Table 12-1 Summary of annual prevalence of CSU in pediatric population

		Annual prevalence (%)		
Region	**Source (year)**	**0-5[1] or 0-6[2] years**	**6-11 years**	**12-17 years**
UK	IMS LifeLink (2010)	0.01-0.03	0.07	0.07
UK	CPRD (2013)	0.003-0.092	0.006-0.098	0.006-0.081
USA	IMS LifeLink (2010)	0.25-0.33	0.18	0.16
USA	MarketScan (2014)	0.01-0.13	0.01-0.06	-

[1] Age category for IMS LifeLink and MarketScan analyses
[2] Age category for CPRD (UK) and Study CQGE031C5001 analyses

In order to satisfy Health Authority requirements to provide pediatric patients with new treatment options, a total of 100 adolescent subjects are planned to be enrolled equally across the CQGE031C2302 and CQGE031C2303 studies taking into consideration the prevalence of adolescent CSU patients and the uncertainty of completing their enrollment. Ninety adolescent subjects are planned to be randomized equally across the 2 ligelizumab and omalizumab treatment arms, and 10 adolescent subjects into the placebo arms. Assuming an approximately 20% drop out rate for the adolescent subjects, this is anticipated to provide approximately 25 adolescent subjects in each of the 2 ligelizumab and the omalizumab arms, and 8 adolescent subjects in the placebo arms at the end of the studies.

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 ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

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

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (eg, 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 (eg, 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 (QMS) 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 Standard Operating Procedures (SOPs), and are performed according to written Novartis processes.

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If, despite this interdiction prohibition, data, information, or observations are 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.

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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.

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

Notable values for vital signs and change from baseline will be summarized.

Notable values for adults are defined as follows:

- heart rate of < 60 and > 100 bpm
- systolic blood pressure of < 90 and ≥ 140 mmHg
- diastolic blood pressure of < 60 and ≥ 90 mmHg

For ECGs a notable QTc value is defined as a QTcF (Fridericia's) interval of greater than 450 ms for males or greater than 460 ms for females – all such ECGs will be flagged by the Central CRO's cardiologist and require assessment for clinical relevance by the investigator. For adolescent subjects, the Central CRO will use age-and gender-specific reference values.

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 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 SBP and DBP. 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 DBP, 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 mid-thigh and the stethoscope placed over the popliteal artery. The SBP in the legs is usually 10%–20% higher than the brachial artery pressure.

Adapted from Pickering et al 2005.

16.1.2 Appendix 1.1.2 : Notable values for adolescents' vital signs

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
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, Tschudy M. 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 total bilirubin normal at baseline:	• ALT or AST > 5 × ULN • ALP > 2 × ULN (in the absence of known bone pathology) • Total bilirubin > 3 × ULN (in the absence of known Gilbert syndrome) • ALT or AST > 3 × ULN and INR > 1.5 • Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and Total bilirubin > 2 × ULN [mainly conjugated fraction] without notable increase in 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 > 2x baseline or > 300 U/L (whichever occurs first)
*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; non-infectious hepatitis; benign, malignant and unspecified liver neoplasms ULN: upper limit of normal	

Table 16-4 Follow-up requirements for liver laboratory triggers with liver symptoms

	ALT	**TBL**	**Liver Symptoms**	**Action**
ALT increase without bilirubin increase:				
	If normal at baseline: ALT > 3 x ULN	Normal For patients with Gilbert's syndrome: No change in baseline TBL	None	• **No change to study treatment** • Measure ALT, AST, ALP, GGT, TBIL, INR, albumin, CK,
	If elevated at baseline: ALT > 2 x baseline			

	ALT	TBL	Liver Symptoms	Action
	or > 300 U/L (whichever occurs first)			and GLDH in 48-72 hours. • Follow-up for symptoms.
	If normal at baseline: ALT > 5 x ULN 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, TBIL, 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 elevated at baseline: ALT > 3 x baseline or > 300 U/L (whichever occurs first) for more than two weeks			
	If normal at baseline: ALT > 8 x ULN	Normal	None	
ALT increase with bilirubin increase:				
	If normal at baseline: ALT > 3 x ULN	TBL > 2 x ULN (or INR > 1.5) For patients with Gilbert's syndrome: Doubling of direct bilirubin	None	
	If elevated at baseline: ALT > 2 x baseline or > 300 U/L (whichever occurs first)			
	If normal at baseline: ALT > 3 x ULN	Normal or elevated	Severe fatigue, nausea, vomiting, right upper quadrant pain	
	If elevated at baseline: ALT > 2 x baseline or > 300 U/L (whichever occurs first)			

Table 16-5 Follow up requirements for liver laboratory triggers

Criteria	Actions required	Follow-up monitoring
Total Biliruin (isolated)		

Criteria	Actions required	Follow-up monitoring
>1.5 – 3.0 ULN	• Maintain treatment • Repeat LFTs within 48-72 hours	Monitor LFTs weekly until resolution[c] to ≤ Grade 1 or to 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 (e.g. conmeds, med hx, lab) in the appropriate CRF	Monitor LFTs weekly until resolution** to ≤ Grade 1 or to baseline (ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT) Test for hemolysis (e.g. reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 10 x ULN	• Discontinue the study treatment immediately • Hospitalize the participant • Establish causality • Record the AE and contributing factors(e.g. conmeds, med hx, lab)in the appropriate CRF	ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT until resolution** (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	• Consider study treatment interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality • Record the AE and contributing factors(e.g., conmeds, med hx, lab)in the appropriate CRF	Investigator discretion
**Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death. *These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage – related conditions; non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms.		

Based on investigator's discretion investigation(s) for contributing factors for the liver event can include: serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease.

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 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:

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

Table 16-7 Renal event follow-up

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

Patient Diary: Urticaria Patient Daily Diary (UPDD)

General Instructions

Please answer each question to the best of your ability.

There are no right or wrong answers.

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

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

Instructions for Counting the Number of Hives

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

Today's Date 

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

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

Itch (severity)

0 = none

1 = mild

2 = moderate

3 = severe

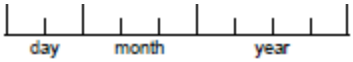
Hives (number)

0 = none

1 = between 1 and 6 hives

2 = between 7 and 12 hives

3 = greater than 12 hives

Today's Date 

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

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

Itch (severity)

0 = none

1 = mild

2 = moderate

3 = severe

Hives (number)

0 = none

1 = between 1 and 6 hives

2 = between 7 and 12 hives

3 = greater than 12 hives

Today's Date day month year

Please complete this section 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

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

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							

Dermatology Life Quality Index (DLQI):

DERMATOLOGY LIFE QUALITY INDEX

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

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

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

Please check you have answered EVERY question. Thank you.

Children Dermatology Life Quality Index (CDLQI):

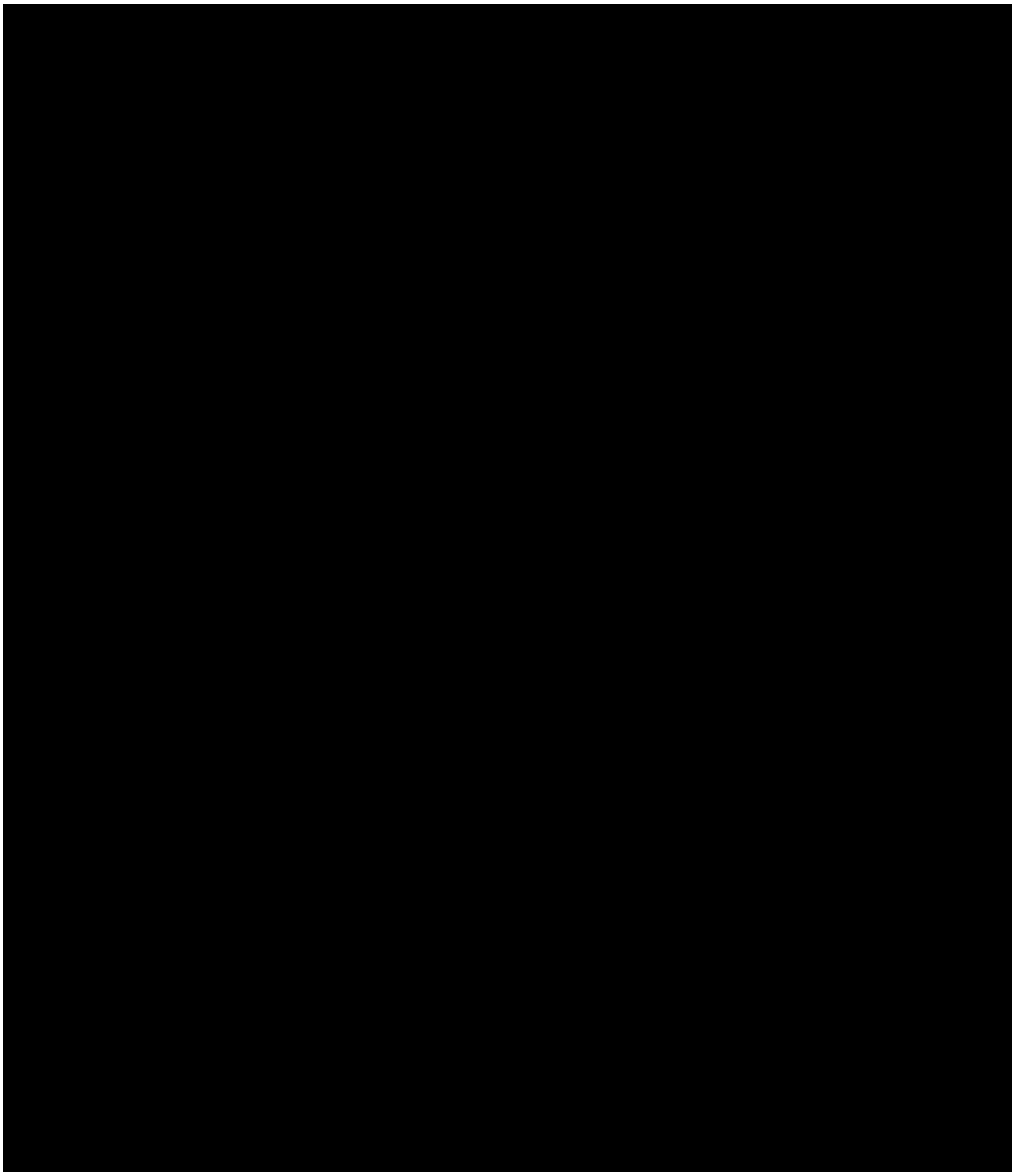
CHILDREN'S DERMATOLOGY LIFE QUALITY INDEX

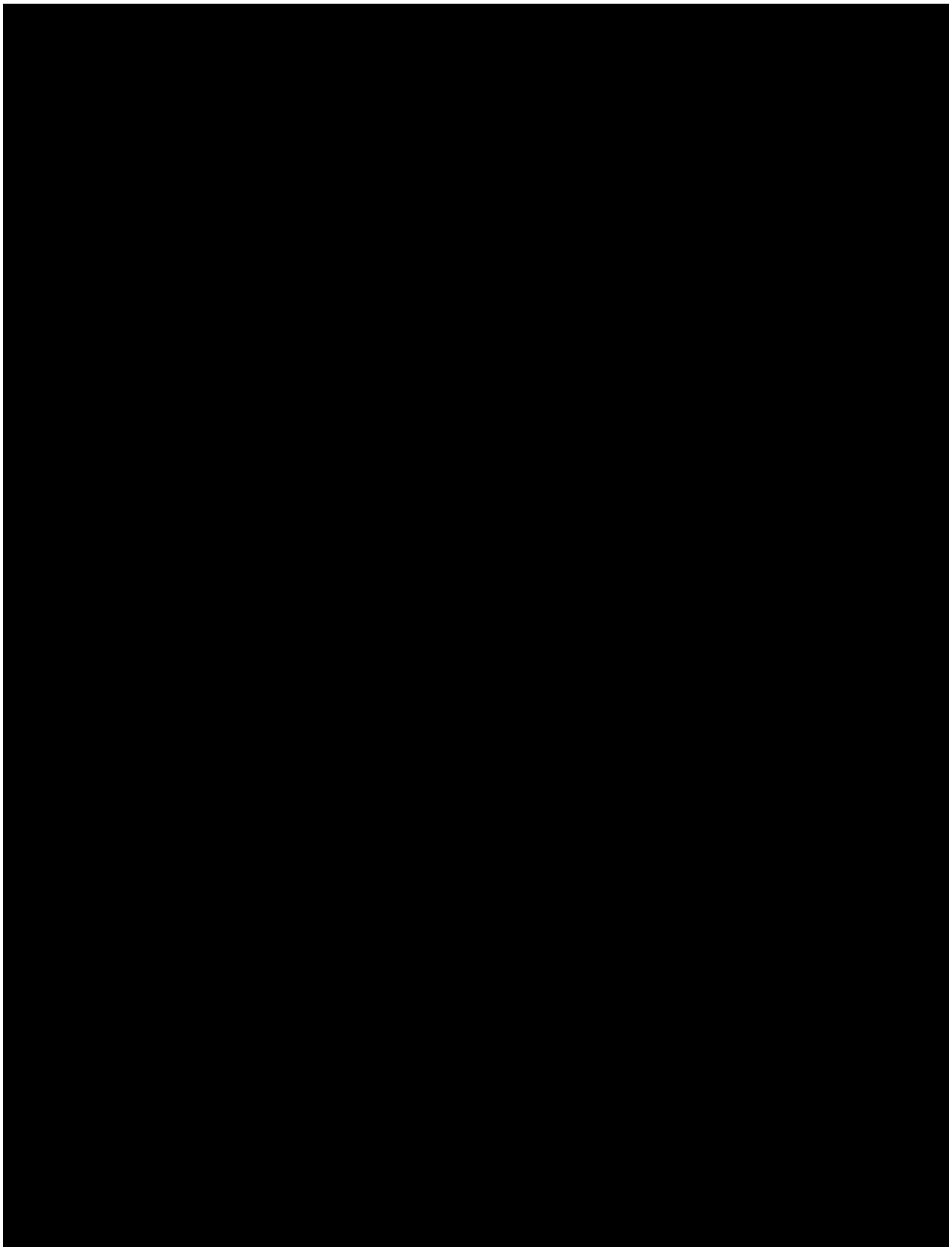
Hospital No
Name: Diagnosis: CDLQI SCORE:
Age:
Address: Date:

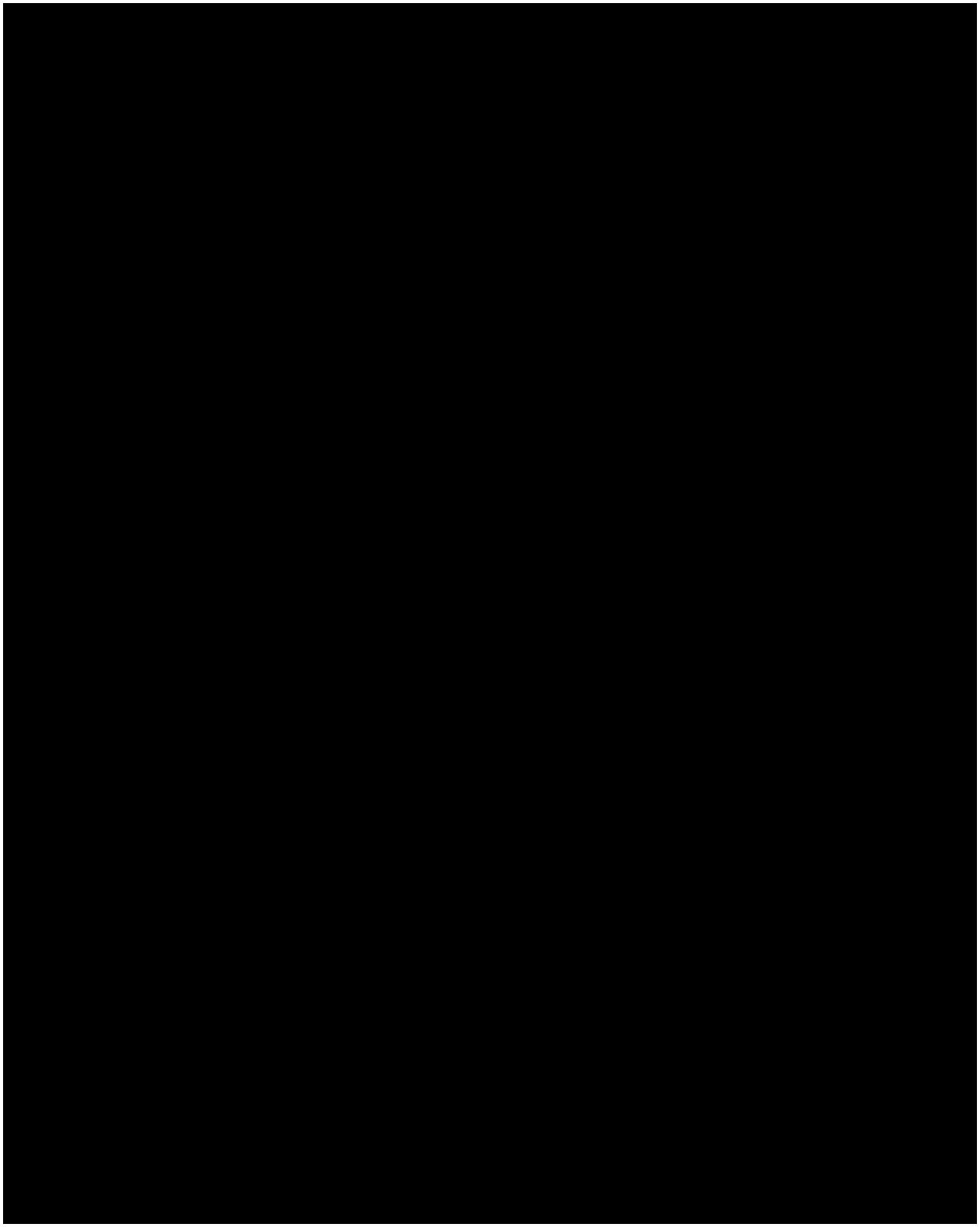
The aim of this questionnaire is to measure how much your skin problem has affected you OVER THE LAST WEEK. Please tick ✓ one box for each question.

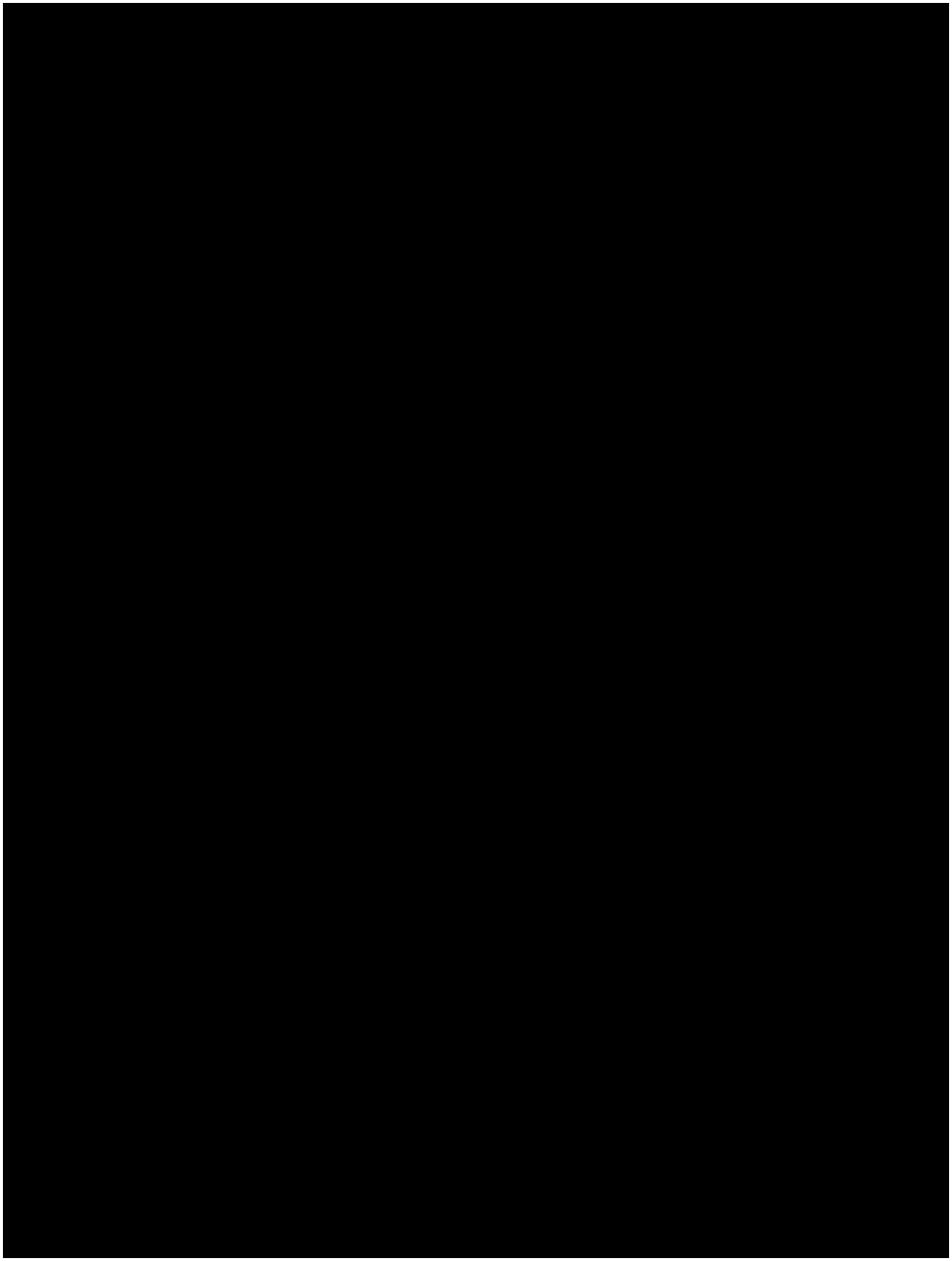
1.	Over the last week, how **itchy**, "**scratchy**", sore or **painful** has your skin been?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
2.	Over the last week, how **embarrassed** or **self conscious**, **upset** or **sad** have you been because of your skin?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
3.	Over the last week, how much has your skin affected your **friendships**?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
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	☐ ☐ ☐ ☐
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	☐ ☐ ☐ ☐
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	☐ ☐ ☐ ☐
7.	Last week, was it **school time**?	**If school time**: Over the last week, how much did your skin problem affect your **school work**?	Prevented school Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐ ☐
	OR		
	was it **holiday time**?	**If holiday time**: How much over the last week, has your skin problem interfered with your enjoyment of the **holiday**?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
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	☐ ☐ ☐ ☐
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	☐ ☐ ☐ ☐
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	☐ ☐ ☐ ☐

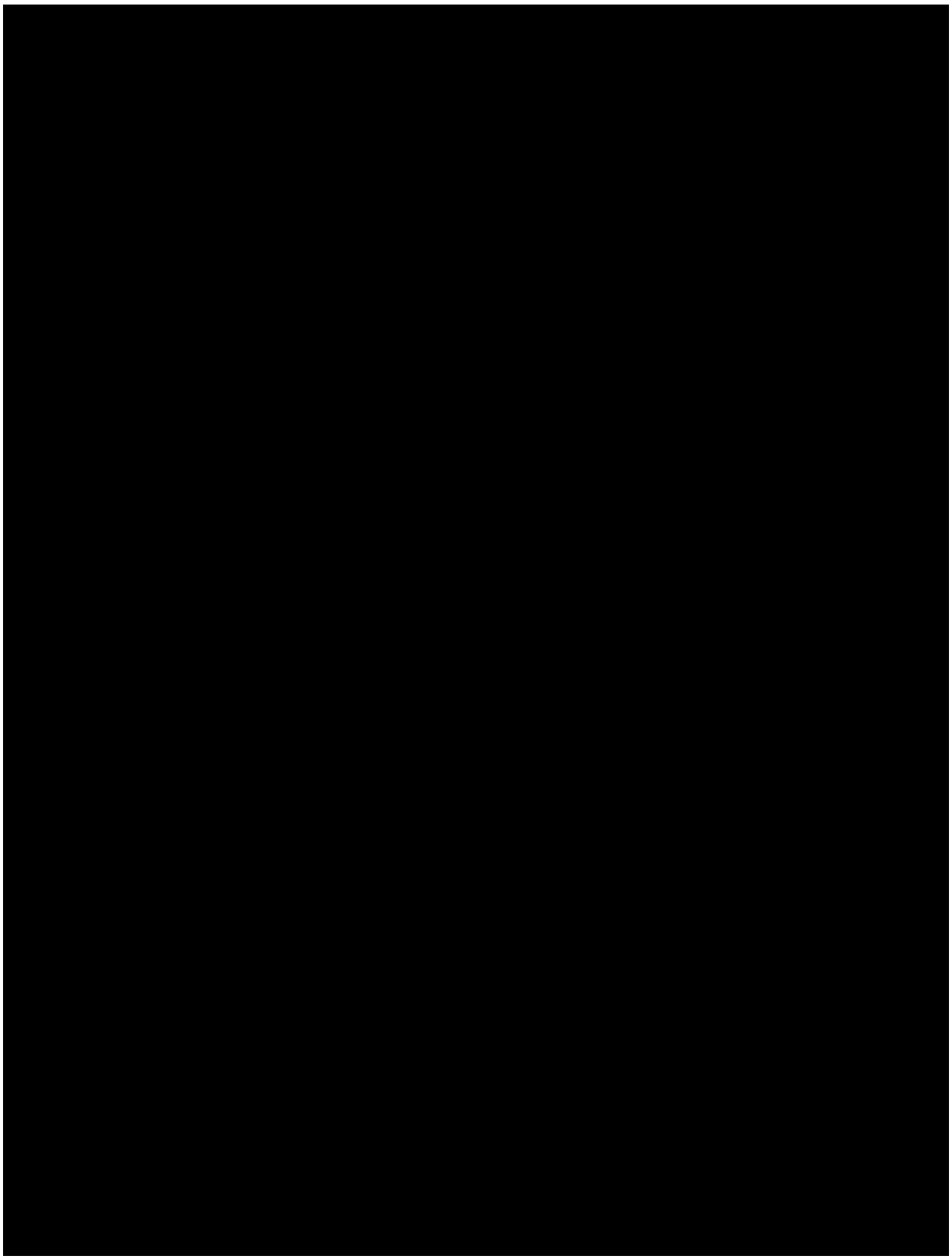
Please check that you have answered EVERY question. Thank you.











[redacted]

16.6 Appendix 6: 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

The final grade of the reaction is not determined until the event is over, regardless of the medication administered to treat the reaction. The final report should include the first symptom(s)/sign(s) and the time of onset after the causative agent exposure and a suffix reflecting if and when epinephrine was or was not administered: a, ≤5 min; b, >5 min to ≤10 min; c, >10 to ≤20 min; d, >20 min; z, epinephrine not administered.
Final report: Grade 1-5; a-d, or z; First symptom(s)/sign(s); Time of onset of first symptom(s)/signs(s).
Case example. Within 10 min of receiving an AIT injection, a patient develops generalized urticaria followed by a tickling sensation in the posterior pharynx. Intramuscular epinephrine is administered within 5 min of symptoms(s)/sign(s) resulting in complete resolution of the reaction. The final report would be: Grade 2; a; Urticaria; 10 min.
*Application-site reactions would be considered local reactions. Oral mucosa symptoms, such as pruritus, after SLIT administration, or warmth and/or pruritus at a subcutaneous immunotherapy injection site would be considered a local reaction. However, tingling or itching of the lips or mouth could be interpreted as a SAR if the known allergen, eg, peanut, is inadvertently placed into the mouth or ingested in a subject with a history of a peanut-induced SAR. Gastrointestinal tract reactions after SLIT or oral immunotherapy (OIT) would also be considered local reactions, unless they occur with other systemic manifestations. SLIT or OIT reactions associated with gastrointestinal tract and other systemic manifestations would be classified as SARs. SLIT local reactions would be classified according to the WAO grading system for SLIT local reactions.[6] A fatal reaction would not be classified in this grading system but rather reported as a serious adverse event.
†Hypotension is defined per the National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Expert Panel criteria[3]:"Reduced blood pressure after exposure to known allergen for that subject (minutes to several hours)

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

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