NOVARTIS

Novartis Research and Development

QGE031/Ligelizumab / NCT05024058

Clinical Trial Protocol

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

Document type:	Clinical Trial Protocol
EUDRACT number:	2020-003018-11
Version number:	00 (Original Protocol)
Clinical Trial Phase:	III
Release date:	07-Jul-2021 (content final)

Clinical Trial Protocol Template Version 3.0 dated 31-Jan-2020

Table of contents

List of tables

List of figures

List of abbreviations

AC	Adjudication Committee
ADA	Anti-Drug Antibody
AE	Adverse Event
AESI	Adverse Events of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
ATE	Arterial Thromboembolic Event
BP	Blood Pressure
BUN	Blood Urea Nitrogen
[redacted]	
CFR	Code of Federal Regulations
[redacted]	
CINDU	Chronic Inducible Urticaria
ClinRO	Clinician Reported Outcomes
CMO&PS	Chief Medical Office and Patient Safety
COA	Clinical Outcome Assessment
COVID-19	Corona Virus Disease of 2019
CRA	Clinical Research Associate
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CS	Corticosteroids
CSR	Clinical Study Report
CSU	Chronic Spontaneous Urticaria
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CTT	Critical Temperature Threshold
[redacted]	
DIN	Drug Inducted Nephrotoxicity
[redacted]	
DMC	Data Monitoring Committee
[redacted]	
EC	European Community
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medical Association
EOS	End of Study
EOT	End of Treatment
[redacted]	
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trial Database
FAS	Full Analysis Set

FcεRI	High Affinity Immunoglobulin E Receptor
FcεRII	Low Affinity Immunoglobulin E Receptor
FDA	Food and Drug Administration
Fric	Friction
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GGT	Gamma-glutamyl transferase
H1-AH	H1 antihistamines
HA	Health Authorities
HBV	Hepatitis B Virus
hCG	Human Chorionic Gonadotropin
HCV	Hepatitis C Virus
HIV	Human immunodeficiency virus
HLT	High Level Term
[redacted]	
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IG	Immunogenicity
[redacted]	
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISR	Injection Site Reaction
IUD	Intrauterine Device
IUS	Intrauterine System
LDH	lactate dehydrogenase
LFT	Liver function test
LLOQ	lower limit of quantification
LT	Life Threatening
MAR	Missing at Random
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
MRCT	Multi Regional Clinical Trial
MRI	Magnetic Resonance Imaging
NRS	Numeric Rating Scale
NYHA	New York Heart Association
PCE	Pulse Controlled Ergometry
PD	Pharmacodynamic(s)
PDCO	Pediatric Committee at the European Medicines Agency

PGA	Physician Global Assessment
[redacted]	
[redacted]	
PK	Pharmacokinetic(s)
POCT	Point Of Care Tests
[redacted]	
PSD	Premature Subject Discontinuation
PSDS	Post Study Drug Supply
PT	Prothrombin Time
PTA	Post Trial Access
QMS	Quality Management System
QoL	Quality of Life
QTcF	QT interval corrected by Fridericia's formula
RBC	red blood cell(s)
RDO	Retrieved Drop-out
s.c.	subcutaneous
SAE	Serious Adverse Event
SAF	Safety Set
SAP	Statistical Analysis Plan
SAR-CoV-2	Severe Acute Respiratory syndrome CoronaVirus 2
SAS	Statistical Analysis System
SC	Subcutaneous
SD	Standard Deviation
SMQ	Standardized MedDRA Query
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBL	Total Bilirubin
TEAE	Treatment Emergent Adverse Events
TFS	Total Fric Score
TNF	Tumor Necrosis Factor
[redacted]	
ULN	upper limit of normal
UPV	Unplanned Visit
US	United States
[redacted]	
VAS	Visual Analog Scale
WHO	World Health Organization
[redacted]	

Glossary of terms

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 participant.
Clinical Outcome Assessment (COA)	A measure that describes or reflects how a participant feels, functions, or survives.
Coded Data	Personal Data which has been de-identified by the investigative center team by replacing personal identifiers with a code.
Cohort	A group of individuals who share a common exposure, experience or characteristic, or a group of individuals followed up or traced over 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.
Discontinuation from study	Point/time when the participant permanently stops receiving the study treatment and further protocol required assessments or follow-up, for any reason. No specific request is made to stop the use of their samples or data.
Discontinuation from study treatment	Point/time when the participant permanently stops receiving the study treatment for any reason (prior to the planned completion of study drug administration, if any). Participant agrees to the other protocol required assessments including follow-up. No specific request is made to stop the use of their samples or data.
Dosage	Dose of the study treatment given to the participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day).
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from source data/documents used at the point of care.
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant or modify if different as defined by the protocol.
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained. The action of enrolling one or more participants.
Estimand	As defined in the ICH E9 (R1) addendum, estimand is a precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same participants under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant.
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
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 participants	Mis-randomized participants are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study or the participant allocated to an invalid stratification factor.
Off-site	Describes trial activities that are performed at remote location by an off-site healthcare professional, such as procedures performed at the participant's home.

Off-site healthcare Professional (OHP)	A qualified healthcare professional, such as include those used in the study e.g. Nurse, Phlebotomist, Physician, who performs certain protocol procedures for the participant in an off-site location such as a participant's home.
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy).
Participant	A trial participant (can be a healthy volunteer or a patient). "Participant" terminology is used in the protocol whereas term "Subject" is used in data collection.
Participant number	A unique number assigned to each participant upon signing the informed consent, the participant is assigned to the next sequential Participant No. available in the EDC system. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
[redacted]	[redacted]
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis.
Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Randomization	The process of assigning trial participants to investigational drug or control/comparator drug using an element of chance to determine the assignments in order to reduce bias.
Randomization number	A unique identifier assigned to each randomized participant.
Re-screening	Describes any trial activities performed at a location that is not the investigative site where the investigator will conduct the trial, but is for example a home or another appropriate location.
Remote	Describes any trial activities performed at a location that is not the investigative site where the investigator will conduct the trial, but is for example a home or another appropriate location.
Screen Failure	A participant who did not meet one or more eligibility criteria that were required for randomization in to 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.
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant.
Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s).
Tele-visit	Procedures or communications conducted using technology such as telephone or video-conference, whereby the participant is not at the investigative site where the investigator will conduct the trial.
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Treatment of interest	The treatment of interest and, as appropriate, the alternative treatment to which comparison will be made. These might be individual interventions, combinations of interventions administered concurrently, e.g. as add-on to standard of care, or might consist of an overall regimen involving a complex sequence of interventions. This is the treatment of interest used in describing the related clinical question of interest, which might or might not be the same as the study treatment.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.

Withdrawal of study consent (WoC) / Opposition to use of data /biological samples	Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data and biological samples (opposition to use data and biological samples) AND no longer wishes to receive study treatment, AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. Opposition to use data/biological samples occurs in the countries where collection and processing of personal data is justified by a different legal reason than consent.

Protocol summary

Protocol number	CQGE031E12301
Full Title	A multi-center, randomized, double-blind, placebo controlled study study to investigate the efficacy and safety of ligelizumab (QGE031) in the treatment of Chronic Inducible Urticaria (CINDU) in adolescents and adults inadequately controlled with H1-antihistamines
Brief title	Study of efficacy and safety of ligelizumab in adolescents and adults with chronic inducible urticaria who remain symptomatic despite treatment with H1- antihistamines
Sponsor and Clinical Phase	Novartis Phase III
Investigation type	Biological
Study type	Interventional
Purpose and rationale	The purpose of this study is to establish efficacy and safety of ligelizumab (QGE031) over placebo in participants with chronic inducible urticaria (CINDU) who remain symptomatic despite treatment with H1 antihistamine. There are currently no approved therapies for patients with CINDU who remain symptomatic despite treatment with H1-antihistamines.
Primary Objective(s)	The primary objective is to demonstrate superiority of ligelizumab versus placebo with regards to the change from baseline in response to a standardized provocation test at Week 12 for each CINDU subtype. For each subtype of CINDU, the primary clinical question of interest is: what is the treatment effect of the ligelizumab treatment versus placebo on the primary endpoint in participants with H1-AH as background medication, regardless of use of rescue medications and/or prohibited medications and treatment discontinuations due to either adverse events, or use of prohibited medications, or lack of efficacy, assuming that participants had never discontinued treatment due to other reasons or missed any treatment prior to Week 12 due to other non-human controlled emergency situations (e.g. COVID-19)?.
Secondary Objectives	To demonstrate superiority of ligelizumab versus placebo with regard to proportion of participants with a complete response after standardized provocation test at Week 12 for each CINDU. To demonstrate superiority of ligelizumab versus placebo in itch NRS (numerical rating scale) following the provocation test at week 12 for each CINDU. To assess the safety of ligelizumab during the study. For each subtype of CINDU the secondary clinical question of interest is: what is the treatment effect of the ligelizumab treatment versus placebo on the secondary endpoints in participants with H1-AH as background medication, regardless of use of rescue medications and/or prohibited medications, and considering treatment discontinuations due to either AE, or use of prohibited medications, or lack of efficacy as non-responders, assuming that participants had never discontinued treatment due to other reasons or missed any treatment prior to Week 12 due to other non-human controlled emergency situations (e.g. COVID-19)?.
Study design	This is a Phase III multicenter, randomized, double-blind, placebo-controlled, parallel-group study. There is a screening period of up to 28 days, a 24 week double-blind treatment period, and a 12 week post-treatment follow-up period.
Study population	The study population will consist of approximately 428 male and female participants aged ≥ 12 years who have been diagnosed with symptomatic dermographism, cold urticaria or cholinergic urticaria and who remain symptomatic despite the use of H1-AH at the approved dose level. Of these, approximately 168, 102 and 158 participants with symptomatic dermographism, cold urticaria and cholinergic urticaria, respectively, are planned for inclusion in the study.

Key Inclusion criteria	• Signed informed consent must be obtained before any assessment is performed.
	• Participant's parent's or legal guardian's signed informed consent and child's assent, if appropriate, must be obtained before any assessment is performed. Of note, if the participant 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 participants ≥ 12 years of age at the time of screening. (NOTE: Recruitment of adolescent participants, ≥ 12 to <18 years of age, will be in accordance with local regulatory/ethics committee requirements).
	• Confirmed CINDU diagnosis (as per guidelines) for symptomatic dermographism, cold urticaria or cholinergic urticaria for ≥ 4 months (defined as onset of CINDU with supporting documentation (e.g medical record, clinical history, photographs)).
	• Diagnosis of CINDU (symptomatic dermographism, cold urticaria or cholinergic urticaria) inadequately controlled with H1-AH at local label approved doses at the time of randomization, as defined by all of the following:
	  • Positive response (i.e development of symptoms) to triggers despite treatment with H1-AH
	  • Positive response (i.e. development of symptoms, see Section 8.3.1) to provocation test on day of randomization
	• Participants must be able to physically perform the protocol defined provocation test specific to the participant's CINDU.
	• Cholinergic urticaria participants must show sweating in performing the pulse-controlled ergometry test on day of randomization. Participants with anhidrosis must not be included.
	• Willing and able to complete a daily symptom eDiary as per protocol requirement and adhere to the study visit schedules.

Key Exclusion criteria	• History of hypersensitivity to any of the study drugs or its components or to drugs of similar classes (i.e. to murine, chimeric or human antibodies) or to the provocation test or items used in provocation tests • Participants who have concomitant CSU at screening • Participants who have a familial form (e.g familial cold autoinflammatory syndrome, familial cold urticaria) of the target CINDU that is being considered for the participant's inclusion in this study • Participants having a more defined other form of inducible urticaria than the target CINDU that is being considered for the participant's inclusion in this study • Diseases, other than chronic inducible urticaria, with urticaria or angioedema symptoms such as urticarial vasculitis, erythema multiforme, cutaneous mastocytosis (urticaria pigmentosa) and hereditary or acquired angioedema (eg, due to C1 inhibitor deficiency). • 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.) or skin diseases associated with only wheals and no itch e.g asymptomatic dermographism • Prior exposure to ligelizumab, omalizumab or other anti-IgE therapies.
Study treatment	• Ligelizumab 120 mg sc • Ligelizumab 72 mg sc • Placebo 0 mg sc
Treatment of interest	The randomized treatment which is ligelizumab or the placebo treatment (no further treatment for participants who discontinue treatment due to AE, lack of efficacy or intake of prohibited medications) with stable H1-antihistamines at local-approved doses as background medication + allowed rescue medication. The dose of the allowed background medication for CINDU must remain stable during the trial. Further details about the investigational treatment and control treatment are provided in Section 6.

Efficacy assessments	Total Fric Score (TFS) Critical Temperature Threshold (CTT) Itch [redacted] numeric rating scale (NRS) scores Physician global assessment of severity of hives
Key safety assessments	• Adverse event monitoring • Physical examination • Vital signs • Laboratory evaluation • ECG • Pregnancy and assessment of fertility • Parasitic infections • Immunogenicity • Liver safety monitoring • Renal safety monitoring
Other assessments	[redacted]
Data analysis	The primary endpoint is change from baseline to Week 12 in Total Fric Score, critical temperature thresholds, and itch NRS in response to pulse-controlled ergometry for symptomatic dermographism, cold urticaria, and cholinergic urticaria, respectively. Regardless of the use of rescue medication and/or prohibited medication and discontinuation of the study assigned treatment due to AE, lack of efficacy, or intake of prohibited medication up to the assessment time point, assuming that participants had never discontinued treatment due to other reasons. The primary analysis method for the primary endpoint is based on a two-sample t-test. The testing hierarchy test ligelizumab dose group(s) vs. placebo group in primary endpoint and the following secondary endpoints: **Symptomatic dermographism** 1. proportion of participants achieving complete response in response to the FricTest 4.0 (Total Fric Score=0) at Week 12 2. change from baseline to Week 12 on itch NRS following the FricTest 4.0. **Cold urticaria** 1. proportion of participants achieving complete response in response to the TempTest at Week 12 2. change from baseline to Week 12 on itch NRS following the TempTest. **Cholinergic urticaria** 1. proportion of participants achieving complete response in itch NRS following the pulse-controlled ergometry test, assessed as itch NRS=0 at Week 12. 2. proportion of participants achieving complete response in physician global assessment of severity of hives following the pulse-controlled ergometry test, assessed as PGA hive score=0 at Week 12. The proportion of participants with complete response at Week 12 will be compared by the Fisher's Exact test between each of the ligelizumab dose group(s) and the placebo group.
Key words	anti-IgE, CINDU, chronic inducible urticaria, symptomatic dermographism, cold urticaria, cholinergic urticaria, urticaria, itch, hives, adults, adolescents

1 Introduction

1.1 Background

Urticaria lasting for greater than 6 weeks is defined as chronic urticaria (Bernstein et al 2014). Chronic urticaria, characterized by the recurrence of itchy hives (also known as wheals) and/or angioedema, is further divided into two sub-types: chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CINDU) or physical urticaria. As the name suggests, symptoms of CINDU are induced by exposure to a particular non-physical stimuli or by physical triggers such as heat, cold, or pressure (Bernstein et al 2014, Zuberbier et al 2018). CINDUs triggered by external physical stimuli include symptomatic dermographism, cold contact urticaria, delayed pressure urticaria, solar urticaria, vibratory urticaria, while those induced by non-physical stimuli include cholinergic urticaria, aquagenic urticaria, and exercise induced anaphylaxis/urticaria (Maurer et al 2018). Among these various CINDUs, symptomatic dermographism, cold and cholinergic urticaria are reported to be the most prevalent forms globally (Maurer et al 2017, Maurer et al 2018).

There are no reliable population based estimates available on the prevalence and incidence of CINDU in the general population. Only treatment center-based or burden of disease studies have reported frequency of CINDU among patients with chronic urticaria or frequency of co-existing CINDU in patients with CSU. An observational study reported that 1 in every 4 patients with chronic urticaria had co-existing CINDU (Maurer et al 2017, Maurer et al 2018).

CINDU can be a debilitating disease with a severe impact on the quality of life. Management of CINDU typically involves threshold testing and avoidance of relevant triggers (Zuberbier et al 2018). Where this is not feasible or possible, symptomatic treatment follows a stepwise approach (Metz et al 2011, Dressler et al 2018), similar to that for CSU. The first line of treatment is with standard doses of non-sedating H1-anti-histamines (H1-AH) followed by updosing in case of non-responsiveness to standard doses (Maurer et al 2018). Higher than standard doses are usually required for symptom control, and up to half the participants do not achieve complete symptom control despite use of H1-antihistamines. Therefore, there is a considerable unmet medical need for treatment options for anti-histamine refractory CINDU.

Although the exact pathophysiology of CINDU is still under investigation, IgE mediated degranulation of tissue resident mast cells, and subsequent release of histamine has been postulated to play an important role Maurer et al 2018). In this context, there is a growing body of evidence demonstrating that omalizumab, a humanized anti-IgE monoclonal antibody, may be efficacious in anti-histamine refractory CINDU patients. A recent systematic literature review evaluated 43 studies, including case reports or case studies of omalizumab treatment across 9 CINDU subtypes, and reported substantial treatment benefits in CINDU patients with the strongest evidence of benefit in symptomatic dermographism, cold urticaria and solar urticaria (Maurer et al 2018). Two randomized, placebo controlled investigator initiated trials with omalizumab, one in symptomatic dermographism and another in cold urticaria, demonstrated clinically meaningful improvements in provocation threshold (FricTest®) and change in critical temperature, respectively (Maurer et al 2017, Metz et al 2017).

Ligelizumab is a humanized, IgG_1-subtype monoclonal antibody, which is a highly potent inhibitor of human IgE. Overall, the mode of action of ligelizumab is closely related to the one

of omalizumab. However, ligelizumab binds to a different epitope on IgE than omalizumab. This differential epitope recognition translates into a qualitatively different IgE inhibition profile with ligelizumab showing a significantly enhanced blockade of high-affinity IgE receptor FcεRI (predominantly found on the surface of mast cells and basophils) compared to omalizumab. Conversely, omalizumab more potently blocks IgE binding to FcεRII/CD23 (Gasser et al 2020). These data suggest that ligelizumab may have higher clinical efficacy than omalizumab in diseases in which engagement of the IgE/FcεRI axis on mast cells and basophils is the more prominent driver of disease pathology than FcεRII/CD23.

In completed human studies CQGE031A2102, CQGE031A2103, CQGE031A1101 and CQGE031B2203, ligelizumab showed higher potency compared to omalizumab, evidenced by enhanced suppression of free IgE, FcεRI and surface IgE expression of basophils, allergen skin prick test and bronchial allergen challenge responses. These studies consistently support the scientific rationale for the development of ligelizumab in IgE driven diseases.

Ligelizumab is currently being developed in the CSU indication. Data from CQGE031C2201, the first clinical study in CSU, demonstrated that ligelizumab (72 and 240 mg q4w SC) was efficacious i.e. achievement of complete hives response when added to standard of care treatment in patients with moderate to severe CSU (Maurer et al 2019). Data from the CQGE031C2201E1 study (an open-label extension study for participants who complete CQGE031C2201 study and present with active disease) showed that 1- year treatment with ligelizumab 240 mg q4w resulted in a high rate of early onset, sustained and complete control of hives and itch (UAS7=0), and angioedema. There were no newly identified or unexpected safety concerns.

Two pivotal Phase 3, randomized, placebo- and omalizumab-controlled studies (CQGE031C2302 and CQGE031C2303) are currently ongoing. The purpose of these studies is to establish the efficacy and safety of ligelizumab (72 mg and 120 mg q4w) in adult and adolescent participants with CSU, who remain symptomatic despite standard of care treatment. Dose selection for these studies was based on the observed efficacy, supported by a model based exposure response analysis, from the Phase 2b CQGE031C2201 study.

Based on pediatric plan agreements with the Pediatric Committee at the European Medicines Agency (PDCO) and with the US Food and Drug Administration (FDA), a randomized, double blind, placebo-controlled Phase 2b dose-finding study in adolescents has been completed (CQGE031C2202). The purpose of the study was to evaluate pharmacokinetics, safety and efficacy of ligelizumab (24 mg and 120 mg q4w) in children from 12 to <18 years of age with CSU. A descriptive analysis of efficacy results showed that ligelizumab was effective for treatment of CSU in adolescents. Dose dependent changes from baseline in weekly UAS were observed at Week 12. The proportion of subjects with complete UAS7 response (UAS7=0) was higher in the ligelizumab 120 mg q4w arm compared to the ligelizumab 24 mg q4w and placebo. Ligelizumab exposure was generally in line with data from the previous study in adult CSU patients considering PK variability. Ligelizumab was safe and well tolerated by the adolescent patients with no newly identified safety signals.

In summary, the available data on omalizumab use in CINDU (Maurer et al 2017, Metz et al 2017, Maurer et al 2018), its approved use for the treatment of CSU and the promising efficacy

data for ligelizumab in CSU, together support the potential for ligelizumab to be an effective therapy for the treatment of CINDU.

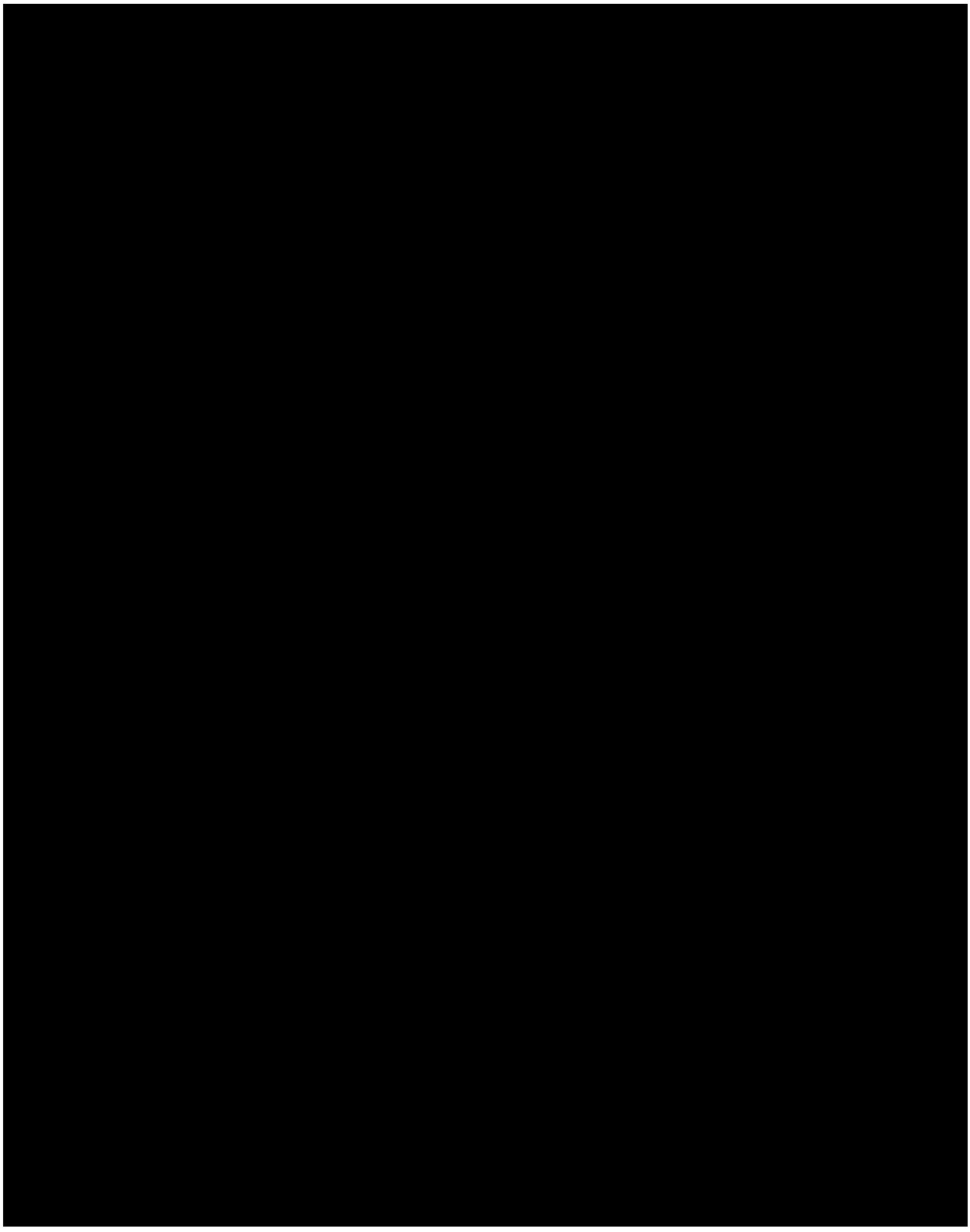
1.2 Purpose

The purpose of this study is to establish efficacy and safety of ligelizumab (QGE031) versus placebo in adolescents and adults with chronic inducible urticaria who remain symptomatic despite treatment with H1 antihistamine.

2 Objectives, endpoints and estimands

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
To demonstrate superiority of ligelizumab versus placebo with regards to the change from baseline in response to a standardized provocation test for each CINDU subtype	**Symptomatic Dermographism** Change from baseline in Total Fric Score (TFS) at Week 12 in response to FricTest® 4.0 **Cold Urticaria** Change from baseline in critical temperature threshold (CTT) at Week 12 in response to the TempTest® 4.0 **Cholinergic Urticaria** Change from baseline in itch numerical rating scale (NRS) at Week 12 in response to the pulse-controlled ergometry test.
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
To demonstrate superiority of ligelizumab versus placebo with regard to proportion of participants with a complete response after standardized provocation test	**Symptomatic Dermographism** Proportion of participants with complete response in FricTest® at Week 12
To demonstrate superiority of ligelizumab versus placebo in itch NRS following the provocation test.	Change from baseline in itch NRS following provocation test at Week 12, in participants with itch NRS > 0 at baseline **Cold Urticaria** Proportion of participants with complete response in TempTest® at Week 12 Change from baseline in itch NRS following provocation test at Week 12, in participants with itch NRS > 0 at baseline **Cholinergic Urticaria** Proportion of participants with itch NRS=0 following the pulse-controlled ergometry test at Week 12 Proportion of participants with physician global assessment of severity of hives=0 following the pulse-controlled ergometry test at Week 12
To assess the safety of ligelizumab	Safety endpoints will include but not be limited to: • Occurrence of treatment emergent adverse events (serious and non-serious) during the study • Occurrence of treatment emergent adverse events during the study leading to discontinuation of study treatment • Occurrence of treatment emergent adverse events of interest listed as either identified or potential risks, during the study • Changes in safety parameters



2.1 Primary estimands

The estimand is the precise description of the treatment effect and reflects strategies to address events occurring during trial conduct which could impact the interpretation of the trial results (e.g premature discontinuation of treatment).

For each subtype of CINDU, the primary clinical question of interest is: what is the treatment effect of the ligelizumab treatment versus placebo on the primary endpoint in participants with H1-AH as background medication, regardless of use of rescue medications and/or prohibited medications and treatment discontinuations due to either AE, or use of prohibited medications, or lack of efficacy, assuming that participants had never discontinued treatment due to other reasons or missed any treatment prior to Week 12 due to other non-human controlled emergency situations (e.g. COVID-19)?

The justification for the primary estimand is that it will capture both the effect of the study drug and the effect of additional background and rescue medications, mirroring the conditions in clinical practice. This will also enable an estimation of the effect of study drug for the full duration of the study. Further details can be found in Section 5.

The primary estimand for each of the CINDU cohort is described by the following attributes:

- **Population**: participants receiving H1-antihistamines therapy at local-approved dose level as background medication suffering from symptomatic dermographism, cold urticaria, or cholinergic 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**:
  1. Symptomatic Dermographism: change from baseline to Week 12 in Total Fric Score (score derived based on results from the Fric Test 4.0, see Section 8.3.1.1 for detail)
  2. Cold urticaria: change from baseline to Week 12 in critical temperature thresholds (CTT, i.e. the highest temperature hives are triggered, see Section 8.3.1.2 for details) in response to the TempTest®
  3. Cholinergic urticaria: change from baseline to Week 12 in itch numerical rating scale (NRS) in response to the pulse-controlled ergometry (see Section 8.3.1.3 for details).
- **Treatment of interest**: ligelizumab or the placebo treatment (no further treatment for patients who discontinue treatment due to AE, lack of efficacy or intake of prohibited medications) with stable H1-antihistamines at local-approved doses as background medication + allowed rescue medication. The dose of the allowed background medication for CINDU must remain stable during the trial. Further details about the investigational treatment and control treatment are provided in Section 6.
- **Handling of remaining intercurrent events**:
  1. Discontinuation of initial assigned study treatment prior to Week 12 due to adverse events (AE), use of prohibited medications or lack of efficacy (LoE): 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).
  2. Discontinuation of initial assigned study treatment prior to Week 12 due to reasons other than adverse events (AE), use of prohibited medications, or lack of efficacy

(LoE): had participants taken the assigned treatment up to Week 12 (hypothetical strategy).

3. Use of prohibited medications prior to Week 12 and not result in treatment discontinuation: ignore (treatment policy).
4. Missed treatment prior to Week 12 due to other non-human controlled emergency situations (e.g. COVID-19): had participants not missed treatment prior to Week 12 (hypothetical strategy).

- **The summary measure**:
  1. Symptomatic Dermographism: difference in mean change from baseline in Total Fric Score at Week 12 between treatments (ligelizumab 72 mg q4w vs placebo and ligelizumab 120 mg q4w vs placebo)
  2. Cold urticaria: difference in mean change from baseline of CTT at Week 12 between treatments (ligelizumab 72 mg q4w vs placebo and ligelizumab 120 mg q4w vs placebo)
  3. Cholinergic urticaria: difference in mean change from baseline in itch NRS in response to the pulse-controlled ergometry test at Week 12 between treatments (ligelizumab 120 mg q4w vs placebo)

2.2 Secondary estimands

For each subtype of CINDU, the secondary clinical questions of interest are similar as the primary clinical questions of interest and are based on the secondary endpoints. The only difference is that, for the endpoint of complete responder status, participants with discontinuation of initially assigned study treatment prior to Week 12 due to either AEs, or use of prohibited medications or lack of efficacy (LoE) will be considered as non-responders (i.e. composite strategy).

The secondary estimand for each of the CINDU cohort is described by the following attributes:

- **Population:** participants receiving H1-antihistamines therapy at local-approved dose level as background medication suffering from symptomatic dermographism, cold urticaria, or cholinergic urticaria and meeting study inclusion/exclusion criteria (as listed in Section 5.1and Section 5.2).
- **Endpoints:**
  - Symptomatic dermographism:
    proportion of participants achieving complete response (i.e. Total Fric score = 0) in the FricTest®4.0 at week 12. Participants with discontinuation of initially assigned study treatment prior to Week 12 due to AEs, use of prohibited medications or lack of efficacy (LoE) will be considered as non-responders.
    change from baseline to Week 12 in itch numeric rating scale (NRS) following the FricTest ®4.0.
  - Cold urticaria:
    proportion of participants achieving complete response (a negative provocation test result for the lowest temperature (4°C) in TempTest®4.0 at week 12. Participants with discontinuation of initially assigned study treatment prior to

Week 12 due to AEs, use of prohibited medications or lack of efficacy (LoE) will be considered as non-responders.

change from baseline to Week 12 in itch numeric rating scale (NRS) following the TempTest®4.0

- Cholinergic urticaria:

proportion of participants achieving complete response in itch NRS (itch NRS =0) following the pulse-controlled ergometry test at Week 12. Participants with discontinuation of initially assigned study treatment prior to Week 12 due to AEs, use of prohibited medications or lack of efficacy (LoE) will be considered as non-responders.

proportion of participants achieving complete response in physician global assessment of severity of hives (i.e. PGA hive score=0) following the pulse-controlled ergometry test at week 12.

Participants with discontinuation of initially assigned study treatment prior to Week 12 due to AEs, use of prohibited medications or lack of efficacy (LoE) will be considered as non-responders.

- **The summary measure:**

Symptomatic dermographism and cold urticaria:

1. difference in complete response rates at Week 12 between treatments (ligelizumab 72 mg q4w vs placebo and ligelizumab 120 mg q4w vs placebo)
2. difference in mean change from baseline of itch NRS following provocation tests (i.e. FricTest® 4.0 and TempTest®4.0 for symptomatic dermographism and cold urticaria) at Week 12 between treatments (ligelizumab 72 mg q4w vs placebo and ligelizumab 120 mg q4w vs placebo)

Cholinergic urticaria:

1. difference in proportion of participants achieving itch NRS=0 at week 12 between treatments (ligelizumab 120 mg q4w vs placebo)
2. difference in proportion of participants achieving PGA hive score=0 at week 12 between treatments (ligelizumab 120 mg q4w vs placebo)

3 Study design

3.1 Study design

This is a Phase III multicenter, randomized, double-blind, placebo-controlled study to demonstrate superiority of ligelizumab 72 mg and/or 120 mg sc q4w over placebo as an add-on therapy to H1-antihistamines at local-approved doses in adolescents and adults for the treatment of Chronic Inducible Urticaria (CINDU). The study will be approximately 40 weeks in duration with the primary endpoint assessed at Week 12. There are 3 subtypes of CINDU populations being assessed in three parallel cohorts; symptomatic dermographism, cold urticaria and cholinergic urticaria. The study consists of 3 distinct periods:

Screening period (Day - 28 to Day 0): Duration of up to 4 weeks in which participants who have given informed consent are assessed for eligibility.

Treatment period (24 weeks): There are 8 visits during this period. Participants will receive treatment at 6 visits (Week 0, Week 4, Week 8, Week 12, Week 16 and Week 20). No treatment will be given at Week 1 and Week 24 (End of Treatment visit). Provocation testing will be done at Week 0, Week 4, Week 8, Week 12 and Week 24.

Follow-up period (12 weeks): The participants should be seen in the clinic every 4 weeks until Week 36. There will be no study treatment administered at these visits; provocation testing will be done at Week 36 only.

Screening

Participants will have up to 4 weeks for screening to establish eligibility for the study. The screening period can be shortened depending on the availability of the laboratory results and adherence to wash-outs related to non-allowed medication. Only in exceptional circumstances, when information concerning eligibility is outstanding (e.g pending laboratory data), will an extended period be permitted. Along with the participant's background medication, participants will also be allowed to take rescue medication (non sedating H1-AH) on an as needed basis for unbearable symptoms from screening up to the end of the study (Section 6.2.3).

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

Double-blinded treatment period

Symptomatic dermographism and cold urticaria cohorts: On Day 1, participants will be randomized equally into ligelizumab 120mg vs ligelizumab 72 mg vs placebo, with participants in the placebo arm being randomly re-allocated to ligelizumab 120 mg and ligelizumab 72 mg at week 12. Randomization will only be performed once at Day 1, in a 2:2:1:1 fashion into 4 arms: ligelizumab 120 mg, ligelizumab 72 mg, placebo to ligelizumab 120 mg and placebo to ligelizumab 72 mg.

During the treatment period, doses are administered at 6 visits; Week 0, Week 4, Week, 8, Week 12, Week 16 and Week 20. No dose is administered at Week 1 (Day 8) visit. Participants randomized to the placebo arm will receive placebo for the first three treatment visits; Week 0, Week 4 and Week 8 and will then switch to ligelizumab 120 mg q4w or ligelizumab 72 mg q4w (1:1 ratio) for the remaining 3 treatment visits; Week 12, Week 16 and Week 20. Participants will continue to use their stable background therapy (H1-AH) at stable doses during the study.

Cholinergic urticaria cohort: On Day 1, participants will be randomized into a 1:1 fashion to ligelizumab 120 mg q4w vs. placebo. Participants of the placebo arm will be allocated to ligelizumab 120 mg at Week 12. Participants of the cholinergic urticaria cohort will not receive the ligelizumab 72 mg dose (see rationale in Table 4.1). During the treatment period, doses are administered at 6 visits; Week 0, Week 4, Week, 8, Week 12, Week 16 and Week 20. No dose is administered at Week 1 (Day 8) visit. Participants randomized to the placebo arm will receive placebo for the first three treatment visits; Week 0, Week 4 and Week 8 and will then switch to

ligelizumab 120 mg q4w for the remaining 3 treatment visits; Week 12, Week 16 and Week 20. Participants will continue to use their stable background therapy (H1-AH) at stable doses during the study.

At weeks 0, 4, 8, 12, 24 and 36 participants from all cohorts will be subjected to provocation tests in order to elicit symptoms. A positive response at Week 0 (Day 1) (see Section 8.3.1) to the FricTest®4.0, TempTest®4.0 or Pulse Controlled Ergometry is required to be randomized to the symptomatic dermographism, cold urticaria or cholinergic urticaria cohorts, respectively. Based on medical history, if a participant has more than one form of inducible urticaria (example: symptomatic dermographism and cold urticaria) then the participant must be considered for randomization into the group that is most bothersome to the participant. Since thresholds are not defined in CINDU, it is left to the investigator's judgement to enroll only those participants with moderate or severe disease burden.

For the symptomatic dermographism cohort, it is planned to allocate approximately 168 participants so that each treatment arm has 56 participants. For the cold urticaria cohort, it is planned to allocate approximately 102 participants so that each treatment arm has 34 patients. For the cholinergic urticaria, it is planned to allocate approximately 158 participants so that each treatment arm has 79 participants. For details on the calculation of the sample size for each of the three cohorts, see Section 12.8.

Due to the low prevalence of this indication among the three cohorts, it is plausible that not all cohorts will be able reach their planned sample size, requiring modification of the sample size and modification to the statistical analysis with different data cut-offs for the different cohorts.

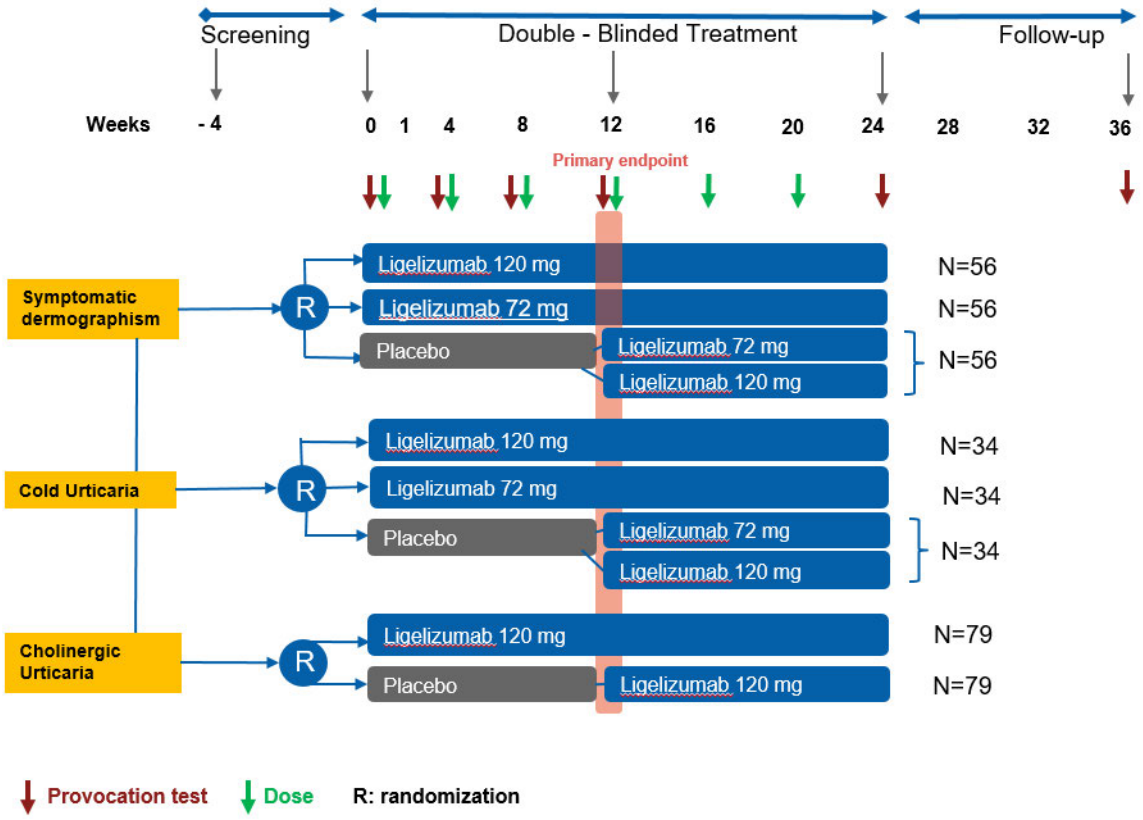
Follow-up period

The follow-up period is 12 weeks with the last follow-up visit (Week 36) corresponding to 16 weeks after the last treatment dose. No study treatment will be given during the post-treatment follow-up period. Participants will continue with the background medication and will be allowed to take their rescue medication on an as needed basis, [redacted] Participants will be required to visit the study center every 4 weeks during post-treatment / follow-up period.

Remote procedures

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 ensure participant safety and trial integrity, the option of conducting the entire visit 105, 170 and visit 180 remotely may be offered to participants. For any other visit it may also be possible to conduct certain assessments for safety and efficacy remotely as described within Section 8. Any assessment performed remotely will be performed under the oversight of the Investigator, who retains accountability for the oversight and all efficacy and safety decisions with delegation of tasks to an off-site healthcare professional (OHP). The remote procedures will be offered in certain countries and sites as determined by Novartis based on national and local regulations. The OHPs whether provided by Novartis or by the site must be agreed with Novartis before use.

Figure 3-1 Study design



3.2 Provocation tests

Important: Study treatment must NOT be administered before any provocation test.

The procedure to perform the provocation tests are outlined in detail in the provocation test manual and should be followed.

Participants from the three subtypes should avoid exposure to triggers 24 hours before their provocation test.

For symptomatic dermographism and cold urticaria, participants must not have any CINDU related symptoms at the **provocation test site** for at least 24 hours prior to the provocation test. For cholinergic urticaria, participants with cholinergic urticaria are required to be symptom free before the start of the provocation test.

All participants must avoid taking any rescue medication in the 24 hours prior to the provocation test. It is recommended to keep at least 30 minutes between provocation test and drug administration.

For both cold urticaria and symptomatic dermographism participants, the provocation test will be applied to specific areas on the body e.g left volar forearm, upper back. The body area will be recorded in the eCRF (Electronic case report form). The body area must be free from inflammation, injuries, broken or infected skin and it is recommended that the same body part be used throughout the study. For cholinergic urticaria as the whole body is involved in the

provocation test, the different body areas where the hives appear will also be recorded in the eCRF.

In certain situations, the provocation test may be repeated as long as the participant has refrained from taking rescue medication in the 24 hours preceding the repeat provocation test.

For all three subtypes, if the provocation test was not performed correctly as per user instructions or if there were technical issues encountered during the provocation test or if the investigator suspects a false negative and the participant did not experience any symptoms, the test may be repeated. In this case, a minimum of 30 minutes is required between tests.

For symptomatic dermographism and cold urticaria, if the participant did experience symptoms from the provocation test that was incorrectly performed, the test can be repeated at a different area on the skin that has been 24 hours symptom free. There has to be a minimum of 30 minutes between provocation tests. For cholinergic urticaria, if the participant did experience symptoms from the provocation test that was incorrectly performed, the test can be repeated after all symptoms have subsided.

The results of the last repeat test are to be recorded in the eCRF.

The number of times the test is repeated is left to the discretion of the investigator, taking the participant's safety and well-being into consideration.

It should be noted, the provocation tests are considered to be completed correctly even if the test is stopped early due to participants reaching their maximum symptoms, results of which are to be recorded in the eCRF.

4 Rationale

4.1 Rationale for study design

Table 4-1 Rationale for study design

Overall	This is a Phase 3, parallel group, placebo-controlled, confirmatory study to evaluate efficacy of ligelizumab over placebo in chronic inducible urticaria. There are currently no approved therapies for patients with CINDU who remain symptomatic despite treatment with H1-antihistamines. Hence, even though the signs and symptoms of the disease can be burdensome, this study is designed as a placebo-controlled study, with a background therapy of H1-antihistamines. Additionally, comparison to placebo will provide an estimate of background incidence of possible safety findings in this rarely studied population. Among the various CINDUs, symptomatic dermographism, cold and cholinergic urticaria are reported to be the most prevalent forms globally (Maurer et al 2017, Maurer et al 2018). Further, specific tools have been developed for these CINDUs to elicit disease symptoms in a reproducible manner. Based on these considerations, symptomatic dermographism, cold and cholinergic urticaria were selected for this proposed study.
Randomization (strata, allocation ratio)	On Day 1, using Interactive Response Technology (IRT), all eligible participants from the symptomatic dermographism and cold urticaria cohort will be randomized in a 2:2:1:1 ratio to ligelizumab 120 mg q4w, ligelizumab 72 mg q4w or placebo to ligelizumab 120 mg and placebo to ligelizumab 72 mg while all eligible participants from the cholinergic urticaria cohort will be randomized in a 1:1 ratio to ligelizumab 120 mg q4w or placebo to ligelizumab 120 mg. The data from the completed Phase 2 dose range finding study - CQGE031C2201 suggest that the 72 mg q4w dose can achieve 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 coupled with the overall low prevalence for cholinergic urticaria compared to symptomatic dermographism and cold urticaria are reasons for evaluating only the higher dose of 120 mg q4w in the cholinergic urticaria subtype. Since both adults and adolescent participants will be enrolled into this study, randomization will be stratified by age group (adolescent 12-17 years old and adult ≥ 18 years old). Randomization of adults will be further stratified by region to ensure a balanced assignment to each treatment group.
Blinding	Blinding participants to the treatment they have received in a controlled trial is particularly important when the response criteria are subjective such as assessing severity of itch. Double-blinding is used in this study up to week 12 to minimize bias in the evaluation of safety and efficacy assessments. It will allow for unbiased assessment of the improvement in terms of CINDU control for participants with disease not controlled by background medication who are treated with ligelizumab, in comparison to those continuing solely on background medication.
Duration of study periods	Data from the completed CQGE031C2201 and CQGE031C2201E1 studies shows a rapid onset and sustained efficacy beyond 12 weeks of treatment. A treatment period of 24 weeks is more than the 12- week treatment period in the omalizumab studies (Maurer et al 2018) in symptomatic dermographism and cold urticaria and is considered sufficient to demonstrate the efficacy of ligelizumab in the three subtypes of CINDU. The ongoing pivotal Phase 3 studies with ligelizumab in CSU consist of 1-year treatment with 72 and 120 mg s.c. q4w doses of ligelizumab with a primary endpoint at week 12. The similarities between CSU and CINDU allow for further inference of sustained efficacy and safety following longer ligelizumab treatment duration from the Phase 3 studies in CSU. The 12 week follow-up period is consistent with the ongoing Phase 3 CSU trials and was selected based on the half-life of ligelizumab.
Study population	The symptoms and natural course of disease, burden of disease and unmet medical need for CINDU appear to be similar in both adult and pediatric populations.therefore, adolescents are also being included in this study. This is similar to the approach taken for the pivotal Phase 3 CSU studies. To prevent any confounding effect of CSU symptoms, the study population will consist of participants with only CINDU and no concomitant CSU. Only ligelizumab- and omalizumab-naïve participants will be enrolled. This is done to avoid any potential influence of prior treatment with an anti-IgE antibody on the disease outcome, and avoids potential selection bias based on results of prior exposure in the study population.

4.1.1 Rationale for choice of background therapy

The choice for background medication in this study is based on the current standard of care for treatment of CINDU. The study requires that all participants, regardless of the treatment arm they get randomized to, must use one second generation-H1-AH at local-approved doses (approved by the local Health Authority) as background medication. Participants must remain on a stable treatment regimen (type and dose of H1-AH) throughout the study. If a participant must switch to another background H1-AH (at approved dose) as a result of an AE or due to unavailability of medication in the country, the participant will be considered to have remained on stable treatment.

4.1.2 Rationale for use of provocation testing to elicit urticaria

Since the symptoms can occur upon exposure to commonly used items such as clothing, belts, etc. or common daily activities, self-reporting by patients can be high in CINDU. In a recent study by Sánchez et al, the authors reported that 76% of patients with CSU reported a physical trigger to their symptoms although only 36.3% had a positive response to a challenge test

(Sánchez et al 2017). The outcome of a challenge test i.e., eliciting urticaria in a clinical setting substantiates the diagnosis and also allows quantification of the symptoms. The results from the test also serve as a guide to both the patient and physician to help inform appropriate avoidance measures and potential treatment options. Methods and specific devices that have been developed to elicit urticaria allow for a systematic approach to study CINDU thus circumventing the uncertainty created by a patient's avoidance of triggers, and allowing for a true estimation of treatment effect. Hence, in the proposed clinical study, FricTest®4.0, the TempTest®4.0 and pulse-controlled ergometry will be used to elicit symptoms caused by symptomatic dermographism, cold urticaria and cholinergic urticaria, respectively. In order to keep participant burden at a minimum, provocation testing will be done only at randomization, Week 4, 8, 12, 24 and 36.

4.2 Rationale for dose/regimen and duration of treatment

Ligelizumab 72 and 120 mg s.c. q4w will be evaluated in symptomatic dermographism and cold urticaria cohorts for treatment of CINDU. Given the overall low prevalence of cholinergic urticaria and the modeling and simulation data from CSU suggesting sustained efficacy throughout the dosing interval with the 120 mg dose, only the 120 mg dose is being evaluated in cholinergic urticaria. There is no evidence to suggest that ligelizumab will have a different mode of action or cleared differently in adolescents versus adults. Hence, the same doses of ligelizumab are being evaluated in both adolescents and adults.

The rationale for selection of ligelizumab doses is as follows:

- A robust phase 2b dose range finding study with ligelizumab in CSU which led to the choice of 72 and 120 mg s.c. q4w for the ongoing Phase 3 pivotal CSU studies.
- Approximately 2100 patients enrolled in the ongoing Phase 3 pivotal CSU studies, with no overt safety events observed so far.
- Clinical and pathophysiological similarities between CSU and CINDU resulting in similar manifestation of the disease i.e. hives and/or angioedema (Maurer et al 2018).
- An efficacy signal for omalizumab, another anti-IgE in CINDU at the same doses as those approved for CSU (Maurer et al 2018, Dressler et al 2018).
- A similar safety profile between CSU and CINDU is anticipated.

Rationale for route of administration

In the ongoing and completed CSU studies, ligelizumab has been administered subcutaneously. The subcutaneous (s.c.) route of administration will continue to be used in this study, based on the favorable bioavailability and tolerability demonstrated with s.c. administration of ligelizumab in previous studies and the ease of administration via this route.

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

Placebo is used as a comparator in this study for the following reasons:

- to allow blinding of investigators and participants to treatment and thereby minimizing bias in the evaluation of safety and efficacy assessments,

- to allow assessment of the improvement of disease in participants with CINDU 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.

To minimize exposure to placebo, all participants in the placebo arm will receive either ligelizumab 72 or 120 mg s.c. q4w, at Week 12 of study participation.

4.4 Purpose and timing of interim futility analyses

Due to the low prevalence of cholinergic urticaria, an interim analysis may be conducted in case there is an obvious difference in recruitment speed between the three cohorts. The interim futility analysis may be triggered when approximately 50% of randomized participants in the cholinergic urticaria cohort have completed the Week 12 visit and all randomized participants in the symptomatic dermographism and cold urticaria cohorts have completed the Week 12 visit. Depending on the outcome of the futility analysis, further recruitment in cholinergic urticaria subtype may be stopped or continued as planned. Participants who have already been enrolled in the study prior to the futility analysis will continue to remain the study.

4.5 Risks and benefits

This study investigates the efficacy and safety of ligelizumab in participants with CINDU inadequately controlled with H1-AH, and seeks to address a significant unmet treatment need in this patient population. In all the clinical studies thus far, the highest single dose of ligelizumab administered to participants intravenously (iv) was 10 mg/kg (CQGE031A2102 study) and subcutaneously (s.c) was 420 mg (CQGE031B2101 study). The highest multiple dose of ligelizumab administered to participants was up to six s.c administrations of 280 mg once every 2 weeks (CQGE031X2201 study). The longest exposure to ligelizumab is approximately 17 months (across studies CQGE031B2201, CQGE031B2201E1, CQGE031C2201 and CQGE031C2201E1).

Potential risks related to study treatment for study participants

The most common AEs reported at a greater frequency after s.c. administration of ligelizumab as compared to placebo were upper respiratory tract infections (including nasopharyngitis), injection site reactions and headache. A brief summary of identified and potential risks with ligelizumab that require close monitoring during the study is listed below. Please refer to the Ligelizumab Investigator Brochure for more details on each of these risks.

Injection site reactions

Majority of the injection site reactions (ISR) events reported in ligelizumab clinical studies were mild (94%) in severity. No ISRs were reported as severe or serious adverse events (SAEs) in the CQGE031C2201 and CQGE031C2201E1. Majority of ISRs resolved spontaneously without treatment either on the same day or next day of study drug administration and did not require discontinuation of study drug.

Hypersensitivity reactions (including anaphylaxis)

Hypersensitivity reactions are anticipated AEs to biologics class of drugs. For all the completed and prematurely terminated studies (non-CSU), hypersensitivity events were comparable amongst the ligelizumab and the placebo groups (7.6% on ligelizumab treatment and 6.1% on placebo treatment). In the completed CSU studies, hypersensitivity events were noted in 30.2% on ligelizumab treatment and 20.9% on placebo treatment.

An adjudication committee (AC) was put in place after the start of CQGE031B2201 study (Phase IIa in asthma) to assess events that could potentially represent anaphylactic reactions. In the completed studies, in asthma and CSU indications, four patients in ligelizumab arm experienced anaphylaxis, positively adjudicated. Three cases have been positively adjudicated as anaphylaxis in the ongoing blinded studies.

Investigators should be alert to the occurrence of hypersensitivity events. Investigators should be familiar with the diagnosis and treatment of allergic and anaphylactic reactions and have on hand injectable epinephrine, antihistamine, corticosteroids, IV supplies, oxygen, an oral airway, Ambu bag, etc. when administering the study treatment. Appendix 4 includes the diagnostic criteria for anaphylaxis (Sampson et al 2014) and Appendix 7 includes the grading guidance for allergic reactions. In the clinical studies with ligelizumab, patients are required to be monitored on site for two hours during the first three administrations and for a 30-minute observation period for the remaining treatment visits. In this trial as there is a switch from placebo to ligelizumab, to maintain blinding, all participants will be required to be monitored onsite for two hours during all six treatment visits. Participants who experience severe hypersensitivity reactions should be immediately discontinued and not allowed to participate in future ligelizumab studies. Please note additional discontinuation criteria related to anaphylaxis or severe hypersensitivity reactions in Section 9.1.1

Participants with conditions or medications that would complicate the diagnosis and treatment of anaphylaxis should not be enrolled in this trial.

Treatment should be immediately employed for any signs or symptoms suggesting anaphylaxis (e.g. decrease in systolic or diastolic blood pressure and/or bronchospasm requiring emergency treatment). Prior to discharge, participants should be counseled by site personnel to watch for symptoms of anaphylaxis such as bronchospasm, urticaria, angioedema or hypotension. As an additional safety precaution, participants will be instructed on the management of suspected anaphylactic events (e.g. the use of epinephrine, seeking urgent medical care) should they suspect they are having such an event.

Further, the ligelizumab program has an AC that independently assesses events that could potentially represent anaphylactic events.

Immunogenicity (anti-drug antibodies)

All biologics have the potential to induce anti-drug antibodies (ADAs). Across all studies and in all different populations (including but not limited to patients with bullous pemphigoid, atopic dermatitis, asthma and CSU) so far, ADAs against ligelizumab were formed in approximately 15% of subjects. The occurrence of ADAs was only noted after prolonged treatment (i.e. after 3rd or 4th monthly dose of ligelizumab. For majority of the ADAs the titres were low and transient in nature. In only a few ADA positive subjects the occurrence of ADAs

appeared to correlate with loss of exposure. The variability in the data set on total IgE did not allow to draw conclusions on the impact of ADA formation on target engagement in the absence of a neutralizing Ab assay. When correlating the timing and incidence of occurrence of ADAs with AEs, there was no clear correlation between ADA formation and AEs, because the AEs were either equally distributed between ADA positive and ADA negative subjects or the occurrence of ADAs was separated in time from the AEs. Given the trend for similar rates across different populations, and similar pathophysiology between CSU and CINDU, we can anticipate that the rate of ADA formation to be similar to that noted in the completed CSU studies.

Serum sickness: While to date no such events have been reported in the ligelizumab database, immune complex formation triggering serum sickness or vasculitis is a potential risk of monoclonal antibody administration.

Thrombocytopenia

No effects on platelets or signs of thrombocytopenia have been observed with ligelizumab in the nonclinical safety studies in adult and juvenile cynomologous monkeys. Severe thromobocytopenia was reported in preclinical studies in cynomolgous monkeys with high doses of omalizumab but has not been seen in humans. The current ligelizumab protocols include monitoring of platelets as part of the hematology assessment and participants with counts below 75,000 /µL should be discontinued.

Parasitic infections

IgE is an antibody that may have role in adaptive immune response 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 participants at high risk of geohelminth infection who receive ligelizumab.

Potential risks due to study procedures to study participants:

- **Provocation tests**

The provocation tests used in the study (FricTest®4.0, TempTest®4.0 and pulse-controlled ergometry) are commonly used, are highly sensitive and specific for diagnosing and inducing symptoms associated with CINDU. Specific to cholinergic urticaria, the provocation test involves physical exercise to induce symptoms of CINDU. Since the ergometry is pulse-controlled, the provocation is gentle (Altrichter et al 2014). Mild increases in body temperature following physical exercise are likely. In the study by Altrichter et al, the maximum increase in body temperature from baseline noted in cholinergic urticaria patients was 2.52 °C versus 2.31° C in healthy volunteers. The provocation test allows for recording of time to occurrence of hives. In the same study by Altrichter et al, the authors noted that while the median time to hives was 27 minutes, 19 minutes was the earliest time to occurrence of hives. The investigator will be instructed to keep patient safety as a priority and if participants experience uncontrolled hives or any discomfort within a short timeframe of initiation of provocation, the test may be stopped. Management of the reactions should be first considered, following with the administration of study treatment once the participants recover.

Risk management

A Data Monitoring Committee (DMC) was established in 2018 to review the data from all ongoing Chronic Urticaria studies (CQGE031C2202, CQGE031C2302E1, CQGE031C2302 and CQGE031C2303). To date, after review of all the data the DMC has recommended no change to the conduct of these ongoing studies.

The non-clinical safety evaluation for ligelizumab supports the development of ligelizumab in the pediatric population. There is no evidence to suggest that ligelizumab will have a different mode of action or will be cleared differently in pediatric versus adult participants.

No new or unexpected safety signals have been identified in the completed or ongoing studies thus far, including the recently completed Phase 2b study (CQGE031C2202) in adolescent patients with CSU as well two ongoing Phase 3 studies (CQGE031C2302 and CQGE031C2303) in adult and adolescent patients with CSU. The inclusion and exclusion criteria are selected to enroll participants with CINDU who are likely to benefit from participating in the study. The overall risk will be minimized by compliance with the inclusion/exclusion criteria, protocol guidance on managing side effects, discontinuation criteria, close clinical monitoring, the use of an electronic diary at home to monitor symptoms [redacted].

Investigators will be instructed on acceptable treatments for managing worsening of disease with rescue medication during the course of this study (see Section 6.2.3), thereby allowing participants to continue in the study as long as possible.

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.

Women of child-bearing potential

Women of child-bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the participant will not reliably comply, they should not be entered or continue in the study.

Potential benefits to study participants

There is evidence that CINDU is an IgE-mediated disease similar to CSU. Literature evidence shows that omalizumab, an anti-IgE antibody, is effective in the treatment of refractory CINDUs, further substantiates the role of IgE in CINDU. The data from CQGE031C2201 demonstrated significant improvement of CSU symptoms including itch, hives, angioedema and quality of life (QoL), with ligelizumab treatment. In the same study, at Week 12, a statistically significantly higher proportion of ligelizumab treated patients (72 and 240 mg q4w) achieved complete hives response (Hive Severity Score7=0) compared to omalizumab 300 mg q4w. Considering the evidence of treatment benefit with IgE suppression in CINDU, and a superior suppression of IgE with ligelizumab compared to omalizumab, it is anticipated that ligelizumab treatment in patients participating in the current study could result in significant improvement in their disease symptoms and overall quality of life.

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 Study Population

The study population will consist of both adolescents and adults. Approximately 428 male and female participants aged ≥ 12 years who have been diagnosed with symptomatic dermographism, cold urticaria or cholinergic urticaria and who remain symptomatic despite the use of H1-AH at the approved dose level. Of these, approximately 168, 102 and 158 adolescent and adult participants with symptomatic dermographism, cold urticaria and cholinergic urticaria, respectively, are planned for inclusion in the study. An approximate 10% study drop-out rate is included in estimating the sample size. As recruitment of adolescents is expected to be low due to the very low prevalence of CINDU in the pediatric population, no minimum number of adolescents is defined as required neither for any of the CINDU subtypes nor for the overall study population.

It is anticipated that approximately 612 participants will need to be screened in order to randomize approximately 428 participants into the 24 week treatment period due to an estimated screening failure rate of approximately 30%. Participants that drop out of the trial will not be replaced.

5.1 Inclusion criteria

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

1. Signed informed consent must be obtained before any assessment is performed.
2. Participant's parent's or legal guardian's signed informed consent and child's assent, if appropriate, must be obtained before any assessment is performed. Of note, if the participant 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 participants ≥ 12 years of age at the time of screening (NOTE: Recruitment of adolescent participants, ≥ 12 to <18 years of age, will be in accordance with local regulatory/ethics committee requirements).
4. Confirmed CINDU diagnosis (as per guidelines) for symptomatic dermographism, cold urticaria or cholinergic urticaria for ≥ 4 months (defined as onset of CINDU with supporting documentation (e.g medical record, clinical history, photographs)).
5. Diagnosis of CINDU (symptomatic dermographism, cold urticaria or cholinergic urticaria) inadequately controlled with H1-AH at local label approved doses at the time of randomization, as defined by all of the following:
    a. Positive response (i.e., development of symptoms) to triggers despite treatment with H1-AH

b. Positive response (i.e., development of symptoms, see Section 8.3.1) to provocation test on day of randomization

6. Participants must be able to physically perform the protocol defined provocation test specific to the participant's CINDU.
7. Cholinergic urticaria participants must show sweating in performing the pulse-controlled ergometry test on day of randomization. Participants with anhidrosis must not be included.
8. Willing and able to complete a daily symptom eDiary as per protocol requirement and adhere to the study visit schedules.

5.2 Exclusion criteria

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

1. Use of other investigational drugs within 5 half-lives of enrollment, or within 30 days for small molecules prior to the screening visit 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 its components or to drugs of similar classes (i.e. to murine, chimeric or human antibodies) or to the provocation test or items used in provocation tests
3. Participants who have concomitant CSU at screening
4. Participants who have a familial form (e.g familial cold autoinflammatory syndrome, familial cold urticaria) of the target CINDU that is being considered for the participant's inclusion in this study
5. Participants having a more defined other form of inducible urticaria than the target CINDU that is being considered for the participant's inclusion in this study
6. Diseases, other than chronic inducible 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).
7. 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.) or skin diseases associated with only wheals and no itch e.g asymptomatic dermographism
8. Participants with evidence of helminthic parasitic infection as evidenced by stools being positive for a pathogenic organism according to local guidelines. All participants will be screened at Visit 1 (see Section 8.4). If stool testing is positive for pathogenic organisms, the participant will not be randomized and will not be allowed to rescreen.
9. Prior exposure to ligelizumab, omalizumab or other anti-IgE therapies.
10. Any H1-AH used as stable background medication at greater than local label approved doses after screening visit (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 drugs used in the study including but not limited to fexofenadine, loratadine, desloratadine, cetirizine, levocetirizine, rupatadine, epinephrine or any of their ingredients.
15. Documented history of anaphylaxis including exercise induced anaphylaxis (not related to anaphylactoid-like reaction associated with CINDU).
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 screening visit (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 participants, 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. Participants with history of HIV (Human immunodeficiency virus) infection.
20. Participants with evidence of or history of chronic hepatitis B virus (HBV) infection and/or hepatitis C virus (HCV) infection.
21. History of, or current treatment for, hepatic disease including but not limited to cirrhosis or hepatic failure or AST (aspartate aminotransferase)/ALT (alanine aminotransferase)/albumin/TBL (total bilirubin)/ levels of more than 1.5x upper limit of normal (ULN) at screening visit (Visit 1).
22. History of renal disease or creatinine level above 1.5x ULN at screening visit (Visit 1).
23. Platelets < 100 000/µL at screening visit (Visit 1).
24. History of long QT syndrome or whose QTcF (Fridericia) measured at screening visit (Visit 1) is prolonged (> 450 ms for males or > 460 ms for females).
25. Pregnant or nursing (lactating) women.
26. Female participants, 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 effective methods of contraception during dosing of study treatment. Effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the participant. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable effective methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least six weeks before

taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment

- Male sterilization (at least 6 months prior to screening). For female participants on the study, the vasectomized male partner should be the sole partner for that participant
- Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps). For UK: with spermicidal foam/gel/film/cream/ vaginal suppository
- Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS)

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

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

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

Study treatment includes investigational drug and placebo. Novartis Global Clinical Supply (GCS) will provide these investigational products in an open-label fashion. Unblinded pharmacists are responsible at sites towards IMP accountability.

6.1.1 Investigational and control drugs

Table 6-1 Investigational and control drug

Investigational/ Control Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Presentation	Sponsor (global or local)
Ligelizumab 120 mg per 1 mL	Liquid in vial (solution for injection)	s.c	Open label kits; vials	Novartis Pharma AG
Ligelizumab Placebo 0 mg per 1 mL	Liquid in vial (solution for injection)	s.c	Open label kits; vials	Novartis Pharma AG
For 72 mg arm, 0.6 mL of 1mg/mL solution will be administered				

6.1.2 Additional study treatments

No other treatment beyond investigational drug (ligelizumab) and control drug (placebo to ligelizumab) are included in this trial. Participants will continue to use their background medication H1-AH (at local-approved doses) with a stable regimen during the study. For rescue medication, see Section 6.2.3.

6.1.3 Supply of study treatment

Novartis Global Clinical Supply (GCS) will supply the investigational drug and the placebo. GCS will not supply other treatment that are listed in Section 6.2.

6.1.4 Treatment arms/group

Participants in the symptomatic dermographism and cold urticaria cohorts will be assigned at Week 0 to one of the following 4 treatment arms in a ratio of 2:2:1:1. Each participant will receive 1 injection every 4 weeks at the clinic:

- Ligelizumab 120 mg arm: 1 injection of 1.0 mL ligelizumab
- Ligelizumab 72 mg arm: 1 injection of 0.6 mL ligelizumab
- Placebo / ligelizumab 120 mg arm: 1 injection of 1.0 mL ligelizumab placebo from Week 0 through Week 8; 1 injection of 1.0 mL ligelizumab from Week 12 through Week 20
- Placebo / ligelizumab 72 mg arm: 1 injection of 0.6 mL ligelizumab placebo from Week 0 through Week 8; 1 injection of 0.6 mL ligelizumab from Week 12 through Week 20

Participants in the cholinergic urticaria cohort will be assigned at Week 0 to one of the following 2 treatment arms in a ratio of 1:1. Each participant will receive 1 injection every 4 weeks:

- Ligelizumab 120 mg arm: 1 injection of 1.0 mL ligelizumab
- Placebo / ligelizumab arm: 1 injection of 1.0 mL ligelizumab placebo from Week 0 through Week 8; 1 injection of 1.0 mL ligelizumab from Week 12 through Week 20

During the double-blind treatment period, study drug will be administered at 6 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. All study treatment dispensing visits will occur at the clinic.

6.1.5 Treatment duration

The planned duration of treatment is 24 weeks, with the last planned dispensing visit for every participant at week 20. Discontinuation of the study drug treatment can be initiated by either the participant or the investigator (Section 9.1.1).

Participants who complete participation in this trial prior to the investigational treatment becoming available in the country of the participant and continues to derive clinical benefit from the treatment based on the investigator's evaluation may receive post-trial access. Post Trial Access (PTA) means the provision of treatment to trial participants following their completion of trial participation. PTA will be provided until one of the following is met: participant no longer derives clinical benefit, investigator discontinues treatment, launch or

reimbursement (where applicable), treatment fails to achieve registration in the trial participant's country, or the clinical program is discontinued for any other reason.

Mechanisms for provision of PTA may include an extension phase to this study, a separate extension protocol, a rollover protocol, a registry trial, provision of the Novartis investigational product in a non-trial setting (known as post-study drug supply (PSDS)) when no further safety or efficacy data are required, or any other mechanism appropriate for the country.

The PTA mechanism must comply with local laws and regulations in the participating trial countries. If Novartis discontinues the PTA for this trial, Novartis will work with investigators to transition patients onto locally available alternative treatment, or standard of care.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

This study requires concurrent use of one second generation H1-AH at local approved doses as background medication. Participants must remain on a stable treatment regimen (type and dose of H1-AH) throughout the study. If a participant must switch to another background H1-AH (at approved dose) as a result of an AE or it being no longer available in the country, the participant will be considered to have remained on stable treatment.

All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the participant 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 participant or allowing a new medication to be started. If the participant is already enrolled, contact Novartis to determine if the participant should continue participation in the study.

6.2.2 Prohibited medication

Use of the class of treatments displayed in Table 6-2 is NOT allowed after start of screening (Visit 1) and up until after the end of the follow-up period. The minimum required period without prohibited treatment before screening visit (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 participant or allowing a new medication to be started.

Table 6-2 Prohibited medication

Medication	Prohibition period prior to Screening visit (Visit 1)	Action taken if prohibited medication is administered
Omalizumab	No prior use allowed	Discontinue from study
Ligelizumab	No prior use allowed	Discontinue from study
Routine (daily or every other day during more than one consecutive day /month) doses of systemic corticosteroids*	30 days prior to Visit 1	Stop prohibited treatment

Medication	Prohibition period prior to Screening visit (Visit 1)	Action taken if prohibited medication is administered
IV/IM/IA corticosteroids	30 days prior to Visit 1	Stop prohibited treatment or discontinue from study treatment
Beta-blocker therapy	7 days prior to Visit 1	Stop prohibited treatment or discontinue from study treatment
Leukotriene antagonists	Stop at Visit 1	Stop prohibited treatment or discontinue from study treatment
H2-antihistamines	Stop at Visit 1	Stop prohibited treatment or discontinue from study treatment
First generation H1-antihistamines	Stop at Visit 1	Stop prohibited treatment or discontinue from study treatment
Hydroxychloroquine or chloroquine	30 days prior to Visit 1	Stop prohibited treatment or discontinue from study treatment
Other immunosuppressive and immunomodulatory medication with or without known effect on CINDU including but not limited to Methotrexate, cyclosporine A, cyclophosphamide, tacrolimus and mycophenolate mofetil, anti-IL-1, anti-TNF-alpha	30 days prior to Visit 1	Stop prohibited treatment or discontinue from study treatment
Intravenous immunoglobulin G	30 days prior to Visit 1	Discontinue study treatment
Plasmapheresis	30 days prior to Visit 1	Discontinue study treatment
Regular (daily or every other day) doxepin (oral)	14 days prior to Visit 1	Stop prohibited treatment or discontinue from study treatment
Vaccination with inactivated viruses	48 hours prior to each dosing visit (i.e. Week 0 to Week 20)	Stop prohibited treatment
Live attenuated vaccine	30 days prior to Visit 1	Discontinue study treatment

*Corticosteroids (CS) with limited systemic exposure for non-CINDU indications can be used (e.g. Intra nasal or any topical CS) on an as-needed basis.

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

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

6.2.3 Rescue medication

If unbearable symptoms occur during the study, investigators must instruct participants on the acceptable treatment for managing their disease with the use of rescue medication, thereby allowing participants to continue in the study as long as possible. Investigators must instruct participants to assess the need for rescue medication on a day-by-day basis, following the limitations for H1-AH rescue medications and adhering to local regulations. It is only during the 24 hours prior to the provocation visit, participants must avoid taking any rescue medication (see Section 3.2).

In addition to being used as background medication (see Section 6.2.1), 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 participants 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 participant. For each individual participant, the H1-AH rescue medication used must differ from the H1-AH used for background medication (see Section 6.2.1), in order to avoid the potential use of H1-AHs at non-approved doses. A switch of the H1-AH rescue medication for an individual participant is not permitted except due to an AE or if the medication is no longer available in the country.

Rescue medication will be sourced locally. [redacted] Participants will be asked to return all unused rescue medication at the end of the study or at the time of discontinuation from the study.

6.3 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under Section 6.1.

Please refer to the Pharmacy Manual for drug preparation and administration.

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

Unblinded investigator staff will identify the study medication kits to dispense to the participant by contacting the IRT and obtaining the medication number(s). The study medication has a 2-part label (base plus tear-off label), immediately before administering the medication to the participant, the unblinded pharmacist (or authorized delegate) site personnel will detach the outer part of the label from the packaging and affix it to the source document.

6.3.1 Handling of study treatment and other treatment

6.3.1.1 Handling of study treatment

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

Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CO Quality Assurance.

The study treatment will be prepared by an independent pharmacist or qualified site personnel in order to ensure treatment masking. Details are provided in the Pharmacy Manual.

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

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

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

6.3.1.2 Handling of additional treatment

Not applicable.

6.3.2 Instruction for prescribing and taking study treatment

Table 6-3 Dose and Treatment schedule

Investigational / Control Drug (Name and Strength)	Dose	Frequency and/or Regimen
QGE031 120 mg per 1 mL	1 mL	Every 4 weeks
QGE031 120 mg per 1 mL	0.6 mL	Every 4 weeks
Ligelizumab Placebo 0 mg per 1 mL	1 mL	Every 4 weeks
Ligelizumab Placebo 0 mg per 1 mL	0.6 mL	Every 4 weeks

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

The injection 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 participant and/or site. The injection is 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. The injections should not be administered on damaged skin and the injections sites should be rotated.

The guidelines for the preparation and administration of study medication are described in the Pharmacist Manual.

Participants will remain on-site for observation for a period of 2 h post-dose for all visits where study drug treatment is administered. 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 2011) 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 participant rapidly to an emergency department/hospital). Prior to discharge, participants should be counseled by site personnel to watch for symptoms of anaphylaxis such as bronchospasm, urticaria, angioedema or hypotension. As an additional safety precaution, participants will be instructed on the management of suspected anaphylactic events should they suspect they are having such an event.

Except for participants on placebo, the participant will receive the same dose at all treatment administration visits. Participants on placebo will be switched at week 12 to ligelizumab and will receive the same dose at subsequent treatment visits.

All study drug dosages prescribed and dispensed to the participant 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 participant 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 participant's safety and the validity of the study. The participant must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed.

6.4 Participant numbering, treatment assignment, randomization

6.4.1 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned when the participant is enrolled for screening and is retained for the participant throughout his/her participation in the trial. A new Participant No. will be assigned at every subsequent enrollment. The Participant No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential participant number suffixed to it, so that each participant's participation is numbered uniquely across the entire database. Upon signing the informed consent form, the participant is assigned to the next sequential Participant No. available in the EDC system.

A new ICF will need to be signed if the investigator chooses to re-screen the participant after a participant has screen failed, and the participant will be assigned a new Participant No. Only one rescreening will be allowed per participant.

6.4.2 Treatment assignment, randomization

At Week 0 (Day 1/Visit 100), all eligible participants in the symptomatic dermographism and cold urticaria cohorts will be randomized into 4 arms via IRT in a 2:2:1:1 ratio to ligelizumab 120 mg, ligelizumab 72 mg, placebo to ligelizumab 120 mg or placebo to ligelizumab 72 mg while all eligible participants in the cholinergic urticaria cohort will be randomized in a 1:1 ratio to ligelizumab 120 mg or placebo to ligelizumab 120 mg. The investigator or his/her delegate will contact the IRT system after confirming that the participant fulfills all the inclusion/exclusion criteria. The IRT call must be made only after provocation test results are available.

The IRT system will assign a randomization number to the participant, which will be used to link the participant to a treatment arm and will specify a unique medication number for the package of study drug treatment to be dispensed to the participant. This information will not be provided to the blinded site user. Only the unblinded pharmacist or delegate can access the participant treatment details and is provided with the kit details. All kits of study treatment assigned by the IRT will be recorded in the IRT system.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from participants and investigator staff. A participant randomization list will be produced by the IRT provider using a validated system that automates the random assignment of participant 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 Novartis Global Clinical Supply (GCS) using a validated system that automates the random assignment of medication numbers to packs containing the study treatment.

Since both adults and adolescent participants will be enrolled into this study, randomization will be stratified by age group (adolescent 12-17 years old and adult ≥ 18 years old). In addition, randomization for adults will be stratified by region to ensure a balanced assignment to each treatment group.

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

6.5 Treatment blinding

Participants, investigator staff and persons 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). Unblinding a single participant at site for safety reasons (necessary for participant management) will occur via an emergency system in place at the site. As a result the participant should be discontinued from the study treatment. [redacted]

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:
   - [redacted]
   - Independent personnel (external to Novartis) involved in monitoring anaphylaxis, neoplastic and cerebro-cardiovascular events (Adjudication Committee members), if needed; and
   - An independent DMC (see Section 10.3.1) and an independent analysis team involved in preparing the interim analysis reports for the DMC (Table 6-4).
   - An independent committee used for assessing interim results, if required
2. The following measures will be applied to keep the participant and study personnel blinded despite differences of the study drug 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 study drug must be done in a separate space/room where participants and study personnel have no access during time of preparation.
- The liquid volume in the syringe must be blinded to the participant and caregiver, see Pharmacist Manual. One method is to cover the syringe with 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. The prepared syringe must be placed on a tray which is covered by an opaque towel to ensure the syringe is not visible to the participant and caregiver 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 study drug. The participant and care giver will be instructed to look away, from the tray with prepared syringe (whenever the tray is uncovered) and from the injection site. Other methods for blinding the participant and caregiver to the liquid volume in the syringe may also be used such as participants and caregivers wearing sleeping masks, covering syringes etc.

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, participants receive 1 injection at every treatment visit (Table 6-1) during the treatment period. Participants in the placebo arm will have placebo administered at Week 0, Week, 4 and Week 8, then will be switched to ligelizumab 72 mg or to ligelizumab 120 mg for the three remaining treatment visits. All participants 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 2011) for the anti-IgE therapy currently available (omalizumab). All participants will need to remain at the site for a 2 hour observation at all study drug administration visits. This approach will help maintain the blind for participants and site staff.

Unblinding of the site staff will occur in the case of participant emergencies and at the conclusion of the study. Health authorities will be granted access to unblinded data if needed.

[redacted]

At the time of interim futility analysis, the DMC will review unblinded interim reports created by an independent analysis team. More details will be provided in the DMC charter.

Table 6-4 Blinding and unblinding plan

	Time or Event			
Role	**Randomization list generated**	**Treatment allocation & dosing**	**Safety event (single participant unblinded)**	**DMC Interim Futility Analysis**
Participants	B	B	B	B
Site staff	B	B	UI	B
Novartis CTT	B	B	B	B
Global Clinical Supply	B	UI	UI	UI
Randomization office	UI	UI	UI	UI
Unblinded site staff e.g. pharmacy staff and study drug administrator Unblinded sponsor staff e.g. for study treatment re-supply, unblinded monitor(s), sample analyst(s)	B	UI	B	B
Unblinded Pharmacovigilance sponsor staff	B	B	UI	B
{Independent}Statistician/ statistical programmer/data analysts [redacted]	B	UI	B	UI
Independent committees used for assessing interim results, if required (e.g. DMC)	B	UI	UI	UI
Adjudication committee	B	B	B	B
Steering committee	B	B	B	B
All other Sponsor staff not identified above(i.e project team, support functions)	B	B	B	B

UI: Allowed to be unblinded on individual participant level
B: Complete blinded

6.6 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 participant's eligibility to continue study treatment.

The decision to interrupt or defer study treatment in case of a suspected and symptomatic COVID-19 or similar type of disease should be based on investigator judgment and should take into account factors such as severity of symptoms, comorbidities, and the course of the infection. E.g., very mild symptoms in an otherwise healthy participant or resolving symptoms at the time of notification to the investigator may not necessarily require treatment interruption.

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

6.7 Additional treatment guidance

6.7.1 Treatment compliance

Participants will receive 1 subcutaneous injection every 4 weeks at 6 visits during the double-blind treatment period. Compliance of the study drug 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.

The investigator must promote compliance by instructing the participant to take the background and rescue medication exactly as prescribed and by stating that compliance is necessary for the participant's safety and the validity of the study. The participant must also be instructed to contact the investigator if he/she is unable for any reason to take the background and rescue medication as prescribed.

6.7.2 Emergency breaking of assigned treatment code

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

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

Study treatment must be discontinued after emergency unblinding. After an emergency break, the participants may not be eligible for post-trial access.

7 Informed consent procedures

Eligible participants may only be included in the study after providing (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

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

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the participant source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH E6 GCP (good clinical practice) guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the Institutional Review Board/Independent Ethics Committee IRB/IEC.

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.).

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 participant informed consent and should be discussed with the participant 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 participant.

The following informed consents are included in this study:

- [redacted]
  - A subsection that requires a separate signature for the 'Optional exit interview'
  - A subsection that requires a separate signature for additional research
- [redacted]
- Adult Pregnancy Follow-up Consent for pregnant participants
- Parent/legal guardian informed consent for adolescent participants which includes:
  - A subsection that requires a separate signature for additional research
- Adolescent assent form
- Parent/legal guardian informed consent for pregnancy follow up for adolescent participants
- [redacted]

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

Declining to participate in the optional assessments ([redacted] exit interviews, [redacted] pregnancy outcomes reporting and additional research) will in no way affect the participant's ability to participate in the main research study.

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

8 Visit schedule and assessments

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

Participants should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1) or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Participants who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed study treatment products should be reconciled, and the AE and concomitant medications recorded on the eCRF.

The "X" in the table denotes the assessments to be recorded in the clinical database or received electronically from a vendor. The "S" in the table denotes the assessments that are only in the participant's source documentation and do not need to be recorded in the clinical database.

At Day 1, IRT contact must be made only after the provocation test is completed and results are available.

When the following assessments are scheduled to be performed at the same visit, the suggested order of conduct follows:

- [redacted]
- Vital signs measurement, weight, physical exam, urine pregnancy test
- 12-Lead ECG (electrocardiogram)
- Hematology, Chemistry, Urinalysis, [redacted]
- AEs, liver and renal safety monitoring, concomitant medications, rescue and background medication usage and dispensing
- Provocation test
- Assessment of symptoms
- [redacted]
- Drug administration
- AE check
- 2 hour observation period (when applicable)

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, virtual contacts (e.g. tele consult) or visits by site staff/ home nursing staff to the participant´s home, 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**	**Treatment**								**Follow-Up**			**USV**
Visit Name	**Screening**	**Randomization**	**Treatment**						**EOT/TD**	**Follow-Up**		**EOS/PSD**	**UPV**
Visit Numbers[1]	**1**	**100**	**105**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**	**190**	**200**
Days	**-28 to -1**	**1**	**8**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**-**
Weeks	**-4 to -1**	**0**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**-**
Informed consent[2]	X												
[redacted]													
Informed consent for optional exit interview for adults only (at selected sites/countries)[3]	X												
[redacted]													
Inclusion / Exclusion criteria	X	X											
Demography	X												
Relevant medical history (including CINDU history)	X												
Evidence of urticaria	X												
Prior urticaria treatment	X												
Family malignancy history (eCRF to be completed if participant develops malignancy during the study)							X						
Prior and Concomitant medication usage							X						
Surgery and Procedures							X						

Period	**Screening**	**Treatment**							**Follow-Up**			**USV**
Visit Name	**Screening**	**Randomization**	**Treatment**					**EOT/TD**	**Follow-Up**		**EOS/PSD**	**UPV**
Visit Numbers[1]	**1**	**100**	**105**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**	**190**	**200**
Days	**-28 to -1**	**1**	**8**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**-**
Weeks	**-4 to -1**	**0**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**-**
Rescreening (rescreening eCRF should be recorded if the participant is rescreened)	X												
Randomization		X											
IRT registration	X	X		X	X	X	X	X	X	X	X	X	
Dispense Participants' eDiary	S												
Collect Participants' eDiary												S	

[redacted]

Period	**Screening**	**Treatment**							**Follow-Up**			**USV**
Visit Name	**Screening**	**Randomization**	**Treatment**					**EOT/TD**	**Follow-Up**		**EOS/PSD**	**UPV**
Visit Numbers[1]	**1**	**100**	**105**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**	**190**	**200**
Days	**-28 to -1**	**1**	**8**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**-**
Weeks	**-4 to -1**	**0**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**-**
[redacted]													
Hematology	X	X		X	X	X	X	X	X	X	X	X	X
Clinical Chemistry (FSH to be done only if required as per Section 8.4.3)	X	X		X	X	X	X	X	X	X	X	X	X
Serum β-hCG (for all pre-menopausal women who are not surgically sterile)	X												X
Urine Pregnancy Test (local) (If positive, confirmation by serum β-hCG test should be done by central lab)[5]		S		S	S	S	S	S	S	S	S	S	S
[redacted]													

Period	**Screening**	**Treatment**							**Follow-Up**			**USV**
Visit Name	**Screening**	**Randomization**	**Treatment**					**EOT/TD**	**Follow-Up**		**EOS/PSD**	**UPV**
Visit Numbers[1]	**1**	**100**	**105**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**	**190**	**200**
Days	**-28 to -1**	**1**	**8**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**-**
Weeks	**-4 to -1**	**0**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**-**
[redacted]													
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)[5]	X					X			X			X	X
Stool ova and parasite evaluation if clinical signs or symptoms of parasitosis develop at any time prior to the last study drug administration, additional assessments for parasitic conditions will be performed[7]	X											X	X
[redacted]													
Background Medication Usage	X												
Dispense H1-AH rescue medication	S	S	S	S	S	S	S	S	S	S	S		S
Physical Exam (physical exam at screening visit (Visit 1) is comprehensive but subsequent physical	S												

Period	**Screening**	**Treatment**							**Follow-Up**			**USV**
Visit Name	**Screening**	**Randomization**	**Treatment**					**EOT/TD**	**Follow-Up**		**EOS/PSD**	**UPV**
Visit Numbers[1]	**1**	**100**	**105**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**	**190**	**200**
Days	**-28 to -1**	**1**	**8**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**-**
Weeks	**-4 to -1**	**0**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**-**
exams can be limited to a short exam)													
Body Weight	X					X			X			X	X
Body Height (for adult participants body height will be collected only at screening visit)	X					X			X			X	X
Vital Signs	X												
ECG (single ECG to be taken at Visits 1 and 160/EoT/TD)	X								X				X
Adverse Events	X												
Liver Safety Monitoring	S												
Renal Safety Monitoring[5]	S												
Sweat detection test (cholinergic urticaria only)		X		X	X	X			X			X	X
Provocation Test (FricTest for symptomatic dermographism, TempTest for cold urticaria or Pulse-Controlled Ergometry test for cholinergic urticaria)		X		X	X	X			X			X	X
Itch (NRS) post-provocation test for symptomatic dermographism, cold urticaria and cholinergic urticaria		X		X	X	X			X			X	X

Period	**Screening**	**Treatment**							**Follow-Up**			**USV**
Visit Name	**Screening**	**Randomization**	**Treatment**					**EOT/TD**	**Follow-Up**		**EOS/PSD**	**UPV**
Visit Numbers[1]	**1**	**100**	**105**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**	**190**	**200**
Days	**-28 to -1**	**1**	**8**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**-**
Weeks	**-4 to -1**	**0**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**-**
[redacted]													
Total Fric Score (symptomatic dermographism), Critical Temperature Threshold (cold urticaria), Physician global assessment of severity of hives (cholinergic urticaria)		X		X	X	X			X			X	X
[redacted]													
Study drug/placebo administration[8]		X		X	X	X	X	X					
Treatment completion or Discontinuation Form		X											
Provide participant contact details for exit interview (if applicable)[3] Interview is to be performed after end of									S				S

Period	Screening	Treatment							Follow-Up			USV
Visit Name	Screening	Randomization	Treatment					EOT/TD	Follow-Up		EOS/PSD	UPV
Visit Numbers[1]	1	100	105	110	120	130	140	150	160	170	180	190	200
Days	-28 to -1	1	8	29	57	85	113	141	169	197	225	253	-
Weeks	-4 to -1	0	1	4	8	12	16	20	24	28	32	36	-
treatment visit by a Novartis designated CRO													
Study Completion or Discontinuation Form	X												

EOT/TD = End of Treatment / Study treatment discontinuation
EOS/PSD = End of Study / Premature subject discontinuation
USV = Unscheduled visit
UPV = Unplanned visit
[1] Visit structure given for internal mapping and programming purpose only
[2] IC obtained prior to all study specific screening procedures during or as close to the start of the screening period as possible
[redacted] 1
[5] For point of care tests (POCT), the clinical sites in China will be allowed to analyze parameters such as urine/serum for pregnancy test and urinalysis as per clinical site practice (refer to China laboratory manual for further details)
[redacted]
[7] At Week 32 (Visit 180), 3 stool collection kits should be dispensed, in order for participants to collect stool samples prior to Week 36 (Visit 1990/EOS/PSD)
[8] Study drug must not be administered prior to provocation testing. 2 hours observation period required after study drug administration

8.1 Screening

Screening

Participants will have up to 4 week screening period to establish eligibility for the study. 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 participants who failed initial screening. Only 1 rescreening will be allowed. If a participant rescreens for the study, the participant must sign a new informed consent and will be issued a new participant number. Informed consent for a rescreened participant must be obtained prior to performing any study-related assessments or collecting any data for the screening visit (Visit 1).

8.1.1 Information to be collected on screening failures

Participants who sign an informed consent form and are 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 Case Report Form. The demographic information, informed consent, and inclusion/exclusion pages must also be completed for screen failure participants. No other data should be entered into the clinical database for participants who are screen failures, unless the participant experienced an SAE during the screening phase (see SAE Section 10.1.2 for reporting details). If the participant fails to be randomized, the IRT must be notified within 2 days of the screen fail that the participant was not randomized.

Participants who are randomized and fail to start treatment, e.g. participants randomized in error, will be considered an early terminator. The reason for early termination should be recorded on the appropriate Case Report Form.

8.2 Participant demographics/other baseline characteristics

Participant demographic and baseline characteristic data to be collected on all participants include age, sex, race and ethnicity. As this trial is conducted in more than one region, this trial is considered to be a multi-regional clinical trial (MRCT) and in line with ICH guideline E17, participant race and ethnicity are collected and analyzed to identify variations in safety or efficacy due to these factors as well as to assess the diversity of the study population as required by Health Authorities.

Relevant medical history (including CINDU history, cardio-vascular history)/current medical condition present before signing the informed consent will be captured. Where possible, diagnoses, and not symptoms, will be recorded. Data on participants' family history of malignancies will be collected on the respective eCRF page, only when a participant has a malignancy event, to assess possible risk factors related to any malignancies.

All prescription medications, over-the-counter drugs and significant non-drug therapies prior to the start of the study must be documented. See the Section 6.2.1 Concomitant Therapy for further details on what information must be recorded on the appropriate page of the eCRF

8.3 Efficacy

The efficacy assessments consist of CINDU specific patient provocation tests reported in the eCRF [redacted]. The following efficacy variables will be assessed during the study:

Table 8-2 Efficacy variables

Efficacy variable	Test/PRO used
Total Fric Score (TFS)	FricTest
Critical Temperature Threshold (CTT), time to critical temperature	TempTest
Itch score	Itch Numerical Rating Scale (NRS) following each provocation test
[redacted]	[redacted]
Severity of hives for cholinergic urticaria	Physician Global Assessment (PGA) of Severity of Hives
[redacted]	[redacted]

8.3.1 Provocation tests

Depending on the CINDU subtype, each participant will undergo provocation testing at the visits outlined in the Schedule of assessments (Table 8-1). Details on how to perform the provocation tests are outlined in the provocation test manual and must be followed. All provocation tests must be performed prior to administration of any study treatment. It is recommended to leave at least 30 minutes between the provocation test and drug administration. Each provocation test is evaluated 10 minutes after completion of provocation test where hives, itch, pain and burning are assessed.

The provocation test results will be reported in the eCRF.

8.3.1.1 FricTest 4.0

To elicit symptoms of symptomatic dermographism in a clinical setting, the FricTest® 4.0 will be used. This is a simple instrument producing objective responses to diagnose symptomatic dermographism (Mlynek et al 2013). It has a simplified design and consists of a flat plastic comb, 85 × 55 mm in size, with four round-ended plastic pins 3 mm in diameter, numbered 1–4, with lengths of 3.0, 3.5, 4.0 and 4.5 mm, respectively. For the provocation test, the FricTest® 4.0 is held perpendicular to the skin of the volar forearm or other areas such as the participant's back, and constant sufficient pressure is applied so that all pins make complete contact with the skin and are almost, but not completely, invisible. The instrument is then stroked across the skin

for a distance of approximately 60 mm (Magerl et al 2016). Each pin is responsible for producing a linear hive depending on the severity of the participant's symptomatic dermographism. An itchy palpable clearly visible hive with a width of ≥ 3mm is considered as a positive response. 10 minutes after the test, the participant is asked to evaluate the severity of their itch, pain and burning where the FricTest® 4.0 was applied using a 11 point numerical rating scale ranging from no symptom (scored 0) to worst possible symptom (scored 10). The higher the number of linear hives, the more severe the disease is. The total number of linear hives with a width of ≥ 3mm is the Total Fric Score (TFS) and is recorded in the eCRF.

The following scoring method for Total Fric Score is used:

0= no linear hive ≥ 3mm in width, 1= one linear hive ≥ 3mm in width, 2= two linear hives ≥ 3mm in width, 3= three linear hives ≥ 3mm in width and 4 = four linear hives ≥ 3mm in width

8.3.1.2 TempTest 4.0

To elicit symptoms of cold urticaria, the TempTest® will be used. The TempTest® 4.0 has a single 2 mm wide 350 mm U-shaped Peltier element generating a temperature gradient from 4 °C to 44 °C along its length. The device is applied to the participant's skin. The test skin area chosen must be an area where it is comfortable for the participant to remain immobile for at least 5 minutes. Usually the test skin area chosen is the participant's volar forearm. The participant places the inner forearm or other test skin area on the aluminum stencil on the device for up to approximately 5 minutes. The stencil produces the temperature range continuously. With this procedure it is determined at which threshold temperature (highest temperature for cold urticaria) hives are triggered. A palpable clearly visible itchy hive is considered a positive response.

10 minutes after the provocation time is up, the hives on the skin are compared to the foil stencil and the threshold temperature is determined. The hives can be marked on the foil and it can be saved in the participant's file for medical documentation of the therapy. The threshold temperature at which hives are triggered will be recorded in the eCRF. The participant is asked to evaluate the severity of their itch, pain and burning where the TempTest 4.0 was applied using a 11 point numerical rating scale ranging from no symptom (scored 0) to worst possible symptom (scored 10) and is to be recorded in the eCRF.

8.3.1.3 Pulse-controlled ergometry test

To elicit symptoms of cholinergic urticaria in a clinical setting, pulse-controlled ergometry will be used. If a participant has risk factors for coronary artery disease, it is up to the discretion of the investigator to decide whether the patient needs cardiac clearance prior to undergoing the pulse controlled ergometry provocation test. In general, participants must be feeling well to perform this test. In this procedure, participants undergo pulse-controlled incremental ergometry for 30 min (stationary bicycle ride) increasing their pulse rate by 15 beats every 5 min to a final maximum increase of 90 beats per minute above the starting level at 30 min (Altrichter et al 2014). A pulse oximeter is fitted to the participant to monitor pulse rate. Only participants that are able to sweat should be included in the cholinergic urticaria cohort, hence, to detect sweating on day of randomization, starch-iodine powder or similar is applied to the lower back or other area that shows sweating. This sweat detection test must be performed on all provocation test days and is described in the provocation test manual for cholinergic urticaria.

The start time of sweating and the start time that hives appear are recorded on the eCRF. Time to appearance of hives correlates with disease activity; in other words, the sooner the hives appear, the more active the disease (Altrichter et al 2014). Observations are continued during a 10 min recovery period at the end of the 30 min of exercise.

Itchy hives are considered a positive response. Ten minutes after the end of the provocation test, the participant is asked to evaluate the severity of their itch, pain and burning using a 11 point numerical rating scale ranging from no symptom (scored 0) to worst possible symptom (scored 10). The investigator will also assess the severity of hives using the physician global assessment of severity of hives.

8.3.2 Clinical Outcome Assessments (COAs)

The Clinical Outcomes Assessment for this trial consists of [redacted] and Clinician reported Outcomes (ClinROs). See Appendix 5.

[redacted]

8.3.2.1 Clinician Reported Outcomes (ClinRO)

For the cholinergic urticaria cohort, the participant's hives will be assessed by the investigator using the physician global assessment of severity of hives ten minutes after the provocation test is finished. This is a 5 item measure intended to assess the severity of the participant's hives. This assessment is scored 0 to 4 with 0=no hives, 1=mild hives, 2=moderate hives, 3=severe hives and 4=very severe hives and is recorded on the eCRF.

For all cohorts, the participant's itch, pain and burning will be assessed by the participant ten minutes after the provocation test is finished and reported to the investigator using a numerical rating scales (NRS) and recorded on the eCRF. The scale used is an 11 point scale ranging from no symptom [scored 0] to worst possible symptom [scored 10])

[redacted]

[redacted]

[redacted]

8.3.3 Appropriateness of efficacy assessments

Provocation tests are being used in this study to assess therapeutic efficacy and dosage. These provocation tests are exposing participants to natural conditions for example, cold temperature, increase in body temperature and friction against the skin. To determine drug efficacy, all provocation tests have clear positive and negative responses (Section 8.3.1).

[redacted]

[redacted]

8.4 Safety

Safety assessments are specified below with the assessment schedule detailing at which visits the assessment is to be performed. All safety assessments should be performed prior to provocation testing and administration of study drug. 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, virtual calls or remote procedures 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.

For details on AE collection and reporting, refer to AE Section 10.1.

Main safety and tolerability assessments include:

- AEs and SAEs, including AEs leading to treatment discontinuation and events of interest such as injection site reactions, hypersensitivity reactions including anaphylaxis, malignancy, cardio-cerebrovascular events, parasitic infections, serum sickness, hypereosinophilic conditions/ churg-strauss syndrome.
- Physical examination
- Vital signs
- Laboratory evaluations
- ECG

Table 8-4 Safety assessments

Assessment	Specification
Physical examination	A comprehensive physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, and extremities and vascular and neurological systems. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. A short physical exam will include the examination of general appearance, vital signs and symptom-directed exams A short physical exam will be conducted at all visits except where a comprehensive 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 participant 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 participant's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used. Clinically notable vital signs are defined in Appendix 1.

Height and weight	Height in cm and Body weight (to the nearest 0.1 kg in indoor clothing, but without shoes) will be measured as specified in Table 8-1.

8.4.1 Laboratory evaluations

A central laboratory will be used for analysis of all specimens detailed in this section unless noted otherwise. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the Laboratory Manual.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, if participants cannot visit the site for protocol specified safety lab assessments, or if the central lab cannot be used, an alternative lab (local) collection site may be used. Safety samples that can be collected remotely will be collected and analyzed in line with the study laboratory manual. Where samples are collected and analyzed at a local laboratory instead of the central laboratory, the local laboratory reports need to be reviewed by the investigator, collected and filed in the medical record or chart. The local laboratory report should be available for review at request of Novartis.

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 eCRFs capturing medical history/Current medical conditions/AEs.

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

Table 8-5 Laboratory assessments

Test Category	Test Name
Hematology	Hemoglobin, Platelets count, Leukocytes, , Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils,),
Chemistry	Albumin, Alkaline phosphatase (ALP), Alanine aminotransferase (ALT), Aminotransferase (AST), Lactate dehydrogenase (LDH), Calcium, Magnesium, Phosphate, Sodium, Potassium, Creatinine, total bilirublin, Urea Nitrogen or Urea, Uric acid, Glucose (non-fasting)
Urinalysis*	Semi-quantitative “dipstick” evaluation for specific gravity, pH, glucose, protein, bilirubin, ketones, leukocytes and blood will be performed at site. When a dipstick evaluation is abnormal, e.g., positive for White blood cells (WBC) and/or blood, a urine sample must be sent to the Central Lab for microscopic examination including Red blood cells (RBC) and WBC. (Details on collection of urine for analysis by central laboratory are provided to investigators in the Laboratory Manual.)
Coagulation	At screening visit (Visit 1) and Day 1 (Visit 100), coagulation will be assessed by International Normalized Ratio (INR), Activated partial thromboplastin time (APTT)
Parasite screening	Local laboratory assessment of stool samples for parasitic infections (Section 8.4.4)
Pregnancy Test*	Serum / Urine pregnancy test (Section 8.4.3)

* For point of care tests (POCT), the clinical sites in China will be allowed to analyze several parameters such as urine/serum for pregnancy test and urinalysis as per clinical site practice (refer to China laboratory manual for further details)

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 local 12 lead ECGs will be collected at Screening (Visit 1), Week 24 (Visit 160) and unscheduled as required.

The Fridericia QT correction formula (QTcF) must be used for clinical decisions, e.g., at the Screening (as applicable) to assess eligibility. The investigator must calculate QTcF if it is not auto-calculated by the ECG machine.

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, participant initials, participant number, date and time, and signed and archived in the study site source documents.

Clinically significant ECG findings prior to dosing with study drug treatment must be discussed with the sponsor. Additional, unscheduled, safety ECGs may be repeated at the discretion of the investigator at any time during the study as clinically indicated. For any ECGs with participant safety concerns or clinically significant abnormalities, two additional ECGs must be performed to confirm the safety finding. ECG safety monitoring, or a review process, should be in place for clinically significant ECG findings at baseline before administration of study treatment and during the study.

Clinically significant abnormalities must be recorded on the eCRF as either medical history/current medical conditions or AEs as appropriate.

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

8.4.3 Pregnancy and assessments of fertility

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 eCRF.

All pre-menopausal women who are not surgically sterile will have urine pregnancy testing during the treatment and follow-up period. Urine pregnancy tests must be performed before study drug administration. A positive urine pregnancy test needs to be confirmed with a central lab serum pregnancy test during all study periods. If positive, the participant must be discontinued from study treatment.

If participants cannot visit the site to perform the urine pregnancy tests, urine pregnancy test kits may be used to perform the urine pregnancy test at home and report the result to the site. It is important that participants be instructed to perform the urine pregnancy test first and only if the test result is negative proceed with the administration of the study treatment, if applicable.

A communication process should be established with the participant so that the Site is informed and can verify the pregnancy test results (e.g. following country specific measures).

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 (Visit 1) or Day 1 (Visit 100).

8.4.4 Assessment of parasitic infections

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

All participants will be given three stool sample collection kits at screening visit (Visit 1) and Week 32 by the site or site's local laboratory. Participants will take the stool sample kits home and collect stool samples from three different bowel movements, ideally on three different days, within seven days after Visit 1 and in the week prior to Week 36(EOS/PSD). Participants will return the three stool samples to the site or local laboratory as soon as possible after the screening visit (in order to allow processing within the screening period) and at Week 36(EOS/PSD).

Stool samples for parasitic disease will be examined by microscopy 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 helminthic parasites (pathogenic as defined by the local laboratory), the result must be recorded in the source document and the participant will not be randomized and will not be allowed to rescreen. Stool samples negative for pathogenic parasites must be recorded in the source document before Day 1 (Visit 100).

Participants 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.

8.4.5 Anaphylaxis assessment

An Adjudication Committee (AC) will be put in place to determine whether cases of hypersensitivity reactions identified through a search algorithm based on the Standardized

MedDRA (Medical dictionary for regulatory activities) Queries. Further details regarding the AC will be documented in the AC charter.

8.4.6 Assessment of cardio-cerebrovascular events

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

8.4.7 Assessment of neoplastic events

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

8.4.8 Appropriateness of safety measurements

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

8.5 Additional assessments

8.5.1 Resource utilization

Healthcare utilization (contacting a doctor, nurse, or nurse practitioner) will be reported by the participant in the daily diary.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8.5.6 Exit interviews (optional at selected sites)

Exit interviews are optional in this study. Only for selected countries, adult participants will be asked if they want to participate in the exit interview. The participant must indicate in the ICF if he/she consents to do the exit interview. A Novartis designated CRO will conduct the exit interview. The interview will be conducted via telephone, web conference or similar. The CRO will collect information such as patient experiences of chronic inducible urticaria prior to and during their participation in the clinical trial as well as to elicit feedback on key patient-reported outcomes collected during the study. To minimize recall bias, interviews should be conducted shortly, e.g. within 3 weeks, following end of treatment visit (Week 24) or after treatment discontinuation. The results will be independently reported.

9 Discontinuation and completion

9.1 Discontinuation from study treatment and from study

9.1.1 Discontinuation from study treatment

Discontinuation of study treatment for a participant occurs when study treatment is permanently stopped for any reason (prior to the planned completion of study drug administration, if any) and can be initiated by either the participant or the investigator.

The investigator must discontinue study treatment for a given participant if the investigator believes that continuation would negatively impact the participant's well-being.

Discontinuation from study treatment is required under the following circumstances:

- Participant/guardian decision
- AEs for which continued exposure to the study drug would be detrimental
- Abnormal renal laboratory results requiring discontinuation (see Appendix 3)
- Abnormal liver laboratory results requiring discontinuation (see Appendix 2)
- Platelets < 75000/µL
- Pregnancy (see Section 8.4.3 and Section 10.1.4)
- Unblinding of study treatment other than to authorized personnel (see Section 6.5) for any reason
- Participant develops a medical condition that requires use of prohibited treatment as per Section 6.2.2, or if participant exhibits a behavior of non-compliance regarding prohibited medications
- Participant received a live virus vaccination during the study
- Participant experiences an unexpected hypersensitivity reaction of grade 5, as defined by the World Allergy Organization Grading System (Cox et al 2017), see Appendix 7:
- Emergency use of epinephrine due to anaphylactic or anaphylactoid reaction.
- Any other protocol deviation that results in a significant risk to the participant's safety
- Any situation in which study participation might result in a safety risk to the participant
- Following emergency unblinding

If 3 consecutive doses are missed (i.e a 12 week gap from last dose) a significant drop in drug exposure may be expected which can lead to aggravation of disease symptoms. Hence for the benefit of the participant, it is recommended that the participant be discontinued from the study treatment and avail of other alternative treatment options either in the follow up period or outside the study, as appropriate with participant condition.

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

Participants who discontinue from study treatment will be expected to perform the Week 24/EoT/TD assessments 4 weeks after their last dose and will be expected to perform all follow-up assessments (Week 28 to 36).

If the participant cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the participant, or with a person pre-designated by the participant. This telephone contact should preferably be done according to the study visit schedule.

For participants who wish to prematurely discontinue treatment prior to the primary endpoint (Week 12) for any reason, every effort should be made to have them continue study visits as per the assessment schedule, at least until Week 12.

After discontinuation from study treatment, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- New / concomitant treatments
- Adverse Events / Serious Adverse Events

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

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

9.1.2 Discontinuation from study

Discontinuation from study is when the participant permanently stops receiving the study treatment, and further protocol-required assessments or follow-up, for any reason.

If the participant agrees, a final evaluation at the time of the participant's study discontinuation should be made as detailed in the assessment table (refer to Section 8).

9.1.3 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits without stating an intention to discontinue from study treatment or discontinue from study or withdraw consent/oppose to the use of their data/biological samples, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the participant, e.g. dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.2 Withdrawal of informed consent/Opposition to data/biological samples

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

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

and

- No longer wishes to receive study treatment

and

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

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

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the participant's decision to withdraw their consent/opposition to use data/biological samples and record this information.

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

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

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

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

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

9.3 Study completion and post-study treatment

Study completion is defined as when the last participant 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. Participants may be eligible for post-trial access after completion of the study.

9.4 Early study termination by the sponsor

The study or any of the subtypes can be terminated by Novartis at any time for any reason. This may include reasons related to

- Benefit/risk assessment of participating in the study
- Practical reasons (including slow enrollment)
- Regulatory or medical reasons
- Decision based on recommendations following interim futility analysis
- Discontinuation of study drug development

In taking the decision to terminate, Novartis will always consider the participant's welfare and safety. Should early termination be necessary, participants must be seen as soon as possible and treated as a prematurely withdrawn participant. 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 participant'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.

10 Safety monitoring, reporting and committees

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a clinical investigation participant 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 (study treatment) product.

For medical devices, an adverse event (AE) is any untoward medical, unintended disease or injury or untoward clinical signs, including an abnormal laboratory finding, in participants, users or other persons, in the context of a clinical investigation, whether or not related to the device.

The investigator has the responsibility for managing the safety of individual participant 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 participant at each visit during the study. AEs also may be detected when they are volunteered by the participant during or between visits or through physical examination findings, laboratory test findings, or other assessments.

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

1. The Common Toxicity Criteria (CTC) AE grade (version 5 or higher)
2. Its relationship to the investigational study treatment and other study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single participant.

   More specific, worsening of urticaria (progression of the underlying condition) or reactions to the provocation tests or reactions following accidental exposure to CINDU triggering factors, such as exposure to cold, physical exercise should be considered "not suspected".
3. Its duration (start and end dates) and the outcome 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 with regard to study treatment.

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

- Dose not changed
- Drug interrupted/permanently discontinued

6. Its outcome (i.e. 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 participant.

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

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

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

Information about adverse drug reactions for the investigational drug can be found in the Investigator's 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 participant with the underlying disease. Alert ranges for laboratory and other test abnormalities are included in Appendix 1.

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 AE [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 participant 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 participant’s general condition

- treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission

- is medically significant, e.g. defined as an event that jeopardizes the participant 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 participant 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.

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 as a serious adverse event irrespective if a clinical event has occurred (see Section 10.1.5).

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until 30 days after last study visit must be reported to Novartis Safety immediately, without undue delay, under no circumstances later than within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site. 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.

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 unless otherwise specified by local law/regulations. Any SAEs reported up to the participant's last visit will be reported in the eCRF and the Novartis Safety database. SAEs beyond that date will only be recorded in the Novartis Safety database.

All follow-up information for the SAE including recurrent episodes, information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode immediately, without undue delay, and under no circumstances later than within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the 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 participant 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

If a female trial participant becomes pregnant, the study treatment should be stopped, and the pregnancy consent form should be presented to the trial participant. The participant must be given adequate time to read, review and sign the pregnancy consent form. This consent form is necessary to allow the investigator to collect and report information regarding the pregnancy. To ensure participant 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 for any pregnancy outcome. Any SAE experienced during pregnancy must be reported. After consent is provided, the pregnancy reporting will occur up to one year after the estimated date of delivery.

10.1.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, participant 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 eCRF 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 eCRF (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 participant safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

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

Once a participant is exposed to study treatment, every liver event defined in Table 16-3 should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 16.4 and Table 16.5. Repeat liver chemistry tests (i.e. ALT, AST, TBL, PT/INR, ALP and G-GT) 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 participant. 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 eCRF.
- If the initial elevation is confirmed, close observation of the participant will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the study treatment (Section 9.1.1), if appropriate
- Hospitalization of the participant if appropriate
- Causality assessment of the liver event

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

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

10.2.2 Renal safety monitoring

The following base monitoring for renal laboratory values, as per the Novartis Drug-Induced Nephrotoxicity (DIN) Guidelines (Table 10-2 below) of abnormal renal laboratory values, will be carried out as part of the assessment schedule (Table 8-1) during the course of the study for those participants who have received study drug:

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

*For point of care tests (POCT), the clinical sites in China will be allowed to analyze these tests as per clinical site practice (refer to China laboratory manual for further details)

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.

10.3 Committees

10.3.1 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 evaluate the results of the futility analysis.

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

10.3.2 Steering Committee

The Steering Committee (SC) consists of a limited number of investigators drawn from the pool of investigators participating in the trial, i.e., not being members of the DMC, AC or Novartis representatives from the Clinical Trial Team.

The SC will help to conduct the study with highest scientific and ethical standards by providing input to the study protocol and/or potential amendments as required. Together with the clinical trial team, the SC will also develop recommendations for publications of study results including authorship rules. The details of the role of the steering committee will be defined in the steering committee charter.

10.3.3 Adjudication committee

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

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

11 Data Collection and Database management

11.1 Data collection

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

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

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

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

11.2 Database management and quality control

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

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and AEs will be coded using the MedDRA terminology.

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

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

[redacted] The remaining PROs will be completed by participants on site on the day of applicable visits. [redacted] The source data collected by the vendor will be sent electronically to Novartis.

At selected sites digital photos will be taken as per Section 8.5.5. These photographs will be sent electronically by the site to the central dermatology-imaging vendor and from there electronically to Novartis.

Dates of screenings, randomizations and screen failures, as well as randomization codes and data about all study treatment (s) dispensed to the participant and all dosage changes will be tracked using IRT. The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis (or a designated CRO) at specific timelines.

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.

Once all the necessary 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/moved to restricted area to be accessed by independent programmer and statistician. 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/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 participant records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis/delegated CRO/CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

The investigator must maintain source documents for each participant 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 eCRFs must be traceable to these source documents in the participant's file. Data not requiring a separate written record will be defined before the study start and will be recorded directly on the CRFs. The investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant).

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 eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the participants will be disclosed.

12 Data analysis and statistical methods

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

Inferential efficacy comparisons with placebo will be focus on the placebo-controlled period (i.e. up to Week 12).

Data analyses will be presented by treatment group. For symptomatic dermographism and cold urticaria, efficacy and safety data for the placebo-controlled period will be presented by the 3 treatment groups of ligelizumab 120 mg q4w, ligelizumab 72 mg q4w, and placebo. For cholinergic urticaria, efficacy and safety data for the placebo-controlled period will be presented by the 2 treatment groups of ligelizumab 120 mg q4w and placebo.

These treatment groups represent the treatment participants will be assigned to during the placebo-controlled period.

For the entire treatment period or study period, data will be presented by a combination of the "original" and "after switch" treatment groups (e.g. placebo - ligelizumab 120 mg q4w), as appropriate.

12.1 Analysis sets

For each CINDU cohort, the following analysis sets will be used in this trial:

The Randomized Analysis Set (RAS) consists of all randomized participants, regardless of whether or not they receive a dose of study drug. Participants will be analyzed according to the treatment they are assigned.

The Full Analysis Set (FAS) comprises all participants to whom study treatment has been assigned and who received at least one dose of study treatment. Participants will be analyzed according to the treatment they have been assigned to.

The Safety Set (SAF) includes all participants who received any study treatment. Participants will be analyzed according to the study treatment(s) received. 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 Participant demographics and other baseline characteristics

For each CINDU cohort, demographic and other baseline data including disease characteristics will be listed and summarized descriptively by treatment group for the Safety set.

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

Relevant medical histories and 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, by treatment group.

Summaries for cardiovascular and urticaria specific medical history will also be provided.

12.3 Treatments

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

Number of participants and the duration of exposure (in weeks) to each treatment and dose will be summarized by means of descriptive statistics using the safety set. In addition, the number of doses, total cumulative dose, and number of missed doses will be presented.

Prior medications are defined as medications taken and stopped prior to first dose of study treatment. Prior medications will be summarized based on Safety set. Prior medications for CINDU will be summarized by type of therapy, preferred term and treatment group. Prior medications non-related to CINDU will be summarized by Anatomical Therapeutic Chemical (ATC) code and preferred term.

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

12.4 Analysis of the primary endpoint(s)/estimand(s)

This section will detail the statistical analysis of the primary estimand. Details of the hypothesis testing strategy including primary and secondary endpoints to handle multiplicity are provided in Section 12.5.

12.4.1 Definition of primary endpoint(s)/estimand(s)

The primary estimand for the three CINDU cohorts are provided in Section 2.1.

12.4.2 Statistical model, hypothesis, and method of analysis

Symptomatic Dermographism:

The aim is to estimate the treatment effect of ligelizumab compared to placebo, for the target population on the primary endpoint (i.e. change from baseline to week 12 in Total Fric Score). The justification of the corresponding primary estimand is detailed in Section 2.1.

The primary analysis method is based on a two-sample t-test.

The null hypothesis test (H_0) for the primary endpoint is that the change from baseline at Week 12 in Total Fric Score in any of the ligelizumab groups (low or high dose) is not superior to the placebo group:

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

where μ is the mean change from baseline of Total Fric Score at week 12, negative value indicates improvement.

Cold Urticaria:

The aim is to estimate the treatment effect of ligelizumab compared to placebo, for the target population on the primary endpoint (i.e. change from baseline to week 12 in CTT). The justification of the corresponding primary estimand is detailed in Section 2.1.

The primary analysis method is based on a two-sample t-test.

The null hypothesis (H_0) for the primary endpoint is that the change from baseline at Week 12 in CTT in any of the ligelizumab groups (low or high dose) is not superior to the placebo group:

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

where μ is the mean change from baseline of CTT at week 12, negative value indicates improvement.

Cholinergic Urticaria:

The aim is to estimate the treatment effect of ligelizumab compared to placebo, for the target population on the primary endpoint (i.e. change from baseline to week 12 in itch NRS following the pulse-controlled ergometry test). The justification of the corresponding primary estimand is detailed in Section 2.1.

The primary analysis method is based on a two-sampe t-test.

The null hypothesis (H_0) for the primary endpoint is that the change from baseline at Week 12 in itch NRS in the ligelizumab 120 mg q4w group is not superior to the placebo group:

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

where μ is the mean change from baseline in itch NRS following the pulse controlled ergometry test at week 12, negative value indicates improvement.

All primary and secondary endpoints will be tested against the respective alternative hypotheses in a closed testing procedure (Bretz et al 2009), so that the family-wise type I error will be controlled at 0.025 (one-sided) for each sub-type. The detailed testing strategy is provided in Section 12.5.

12.4.3 Handling of remaining intercurrent events of primary estimand

Participants who discontinue from study treatment early will be encouraged to stay in the study following the procedure described in Section 9.1.1. These are considered as retrieved drop-out (RDO) participants.

For all three CINDU subtypes, symptomatic dermographism, cold urticaria, and cholinergic urticaria, the primary analysis will account for different intercurrent events as explained in the following:

- **Discontinuation of assigned study treatment either due to AE or lack of efficacy or use of prohibited medications**: Retrieved drop out (RDO) data collected after study treatment discontinuation will be used for analysis. If no RDO data was collected after study treatment permanent discontinuation, missing data for ligelizumab groups will be

multiply imputed based on information from the placebo, and under the MAR assumption for the placebo group.

- **Discontinuation of study treatment for the reasons other than AE or lack of efficacy or use of prohibited medications**: primary variable will be treated as missing and multiply imputed under the MAR assumption for all the groups.
- **Use of prohibited medications prior to Week 12 and not resulting in treatment discontinuation**: handled by treatment policy, data collected after the intercurrent event will be used as it is.
- **Missed treatment prior to Week 12 due to other non-human controlled emergency situations (e.g. COVID-19)**: primary variable will be treated as missing and multiply imputed under the MAR assumption for all the groups.

12.4.4 Handling of missing values not related to intercurrent event

If the provocation testing is stopped due to any reason e.g participant discomfort, technical issues the data will be considered as missing.

Symptomatic dermographism

Handling of missing or incomplete results in the FricTest 4.0:

· The missing Total Fric Scores will be multiply imputed under the MAR assumption for all the groups.

Cold urticaria

Handling of missing or incomplete results in response to the TempTest®:

· The missing CTT will be multiply imputed under the MAR assumption for all the groups.

Cholinergic urticaria

Handling of missing or incomplete itch NRS results following the pulse-controlled ergometry test:

· The missing itch NRS will be multiply imputed under the MAR assumption for both treatment groups.

12.4.5 Sensitivity analyses for primary endpoint/estimand

For all three CINDU cohorts, the following sensitivity analysis will be performed for the primary estimand, to assess the robustness of the estimation in the presence of deviations from the assumptions specified in the primary analysis.

- The ANCOVA (Analysis of covariance) model with treatment group, baseline scores, region/country as covariates will be performed. Intercurrent events will be handled in the same way as in the primary analysis.
- To account for uncertainty in the imputations, the tipping point analyses will be considered, if needed.

12.4.6 Supplementary analysis

In addition to the primary analysis, change from baseline at week 12 on Total Fric Score/CTT/itch NRS will be tested using Wilcoxon rank sum test for symptomatic dermographism, cold urticaria, and cholinergic urticaria respectively.

For each CINDU cohort, if the primary analysis is statistically significant, subgroup analyses to assess the homogeneity of the treatment effect across demographic and baseline disease characteristics may be performed.

Other supplementary analysis will be described in the SAP (Statistical Analysis Plan) as needed.

12.5 Analysis supporting secondary objectives

For detailed definitions of secondary estimands, please refer to Section 2.2 The following secondary endpoints will be assessed and included into the testing strategy for the three CINDU cohorts:

- **Symptomatic dermographism**
  1. proportion of participants achieving complete response in response to the FricTest 4.0 (Total Fric Score=0) at Week 12
  2. absolute change from baseline to Week 12 on itch NRS following the FricTest 4.0.
- **Cold urticaria**
  1. proportion of participants achieving complete response in response to the TempTest at Week 12
  2. change from baseline to Week 12 on itch NRS following the TempTest.
- **Cholinergic urticaria**
  1. proportion of participants achieving complete response in itch NRS following the pulse-controlled ergometry test, assessed as itch NRS=0 at Week 12.
  2. proportion of participants achieving complete response in physician global assessment (PGA) of severity of hives following the pulse-controlled ergometry test, assessed as PGA hive score=0 at Week 12.

The proportion of participants with complete response at Week 12 will be compared by the Fisher's Exact test between each of the ligelizumab dose group and the placebo group. In case of missing data caused by discontinuation due to reasons other than AE, lack of efficacy, or intake of prohibited medication, or missing data not related to intercurrent events, raw scores in corresponding provocation test (i.e. Total Fric Score, CTT, and itch NRS) will be first imputed as described in Section 12.4.3 and Section 12.4.4, respectively, then the missing responder status will be derived based on the imputed raw score. As sensitivity analysis, proportion of complete responders will be analyzed using a logistic regression model including treatment group, region/country and baseline score.

Change from baseline to Week 12 on itch NRS in response to provocation tests will be analyzed based on participants who have baseline scores greater than zero by two-sample t-test. In case of missing data caused by discontinuation due to reasons other than AE, lack of efficacy, or intake of prohibited medication, or missing data not related to intercurrent events, itch NRS will be imputed in a same manner as described in Section 12.4.3 and Section 12.4.4, respectively.

Testing strategy for symptomatic dermographism and cold urticaria

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) for each CINDU cohort.

Primary endpoint

Total Fric Score/CTT change from baseline at Week 12

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

where μ is the mean change from baseline in Total Fric Score/CTT at Week 12, as described in Section 2.1.

Secondary endpoints

- proportion of participants achieving complete response in response to FricTest 4.0 and TempTest at Week 12

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

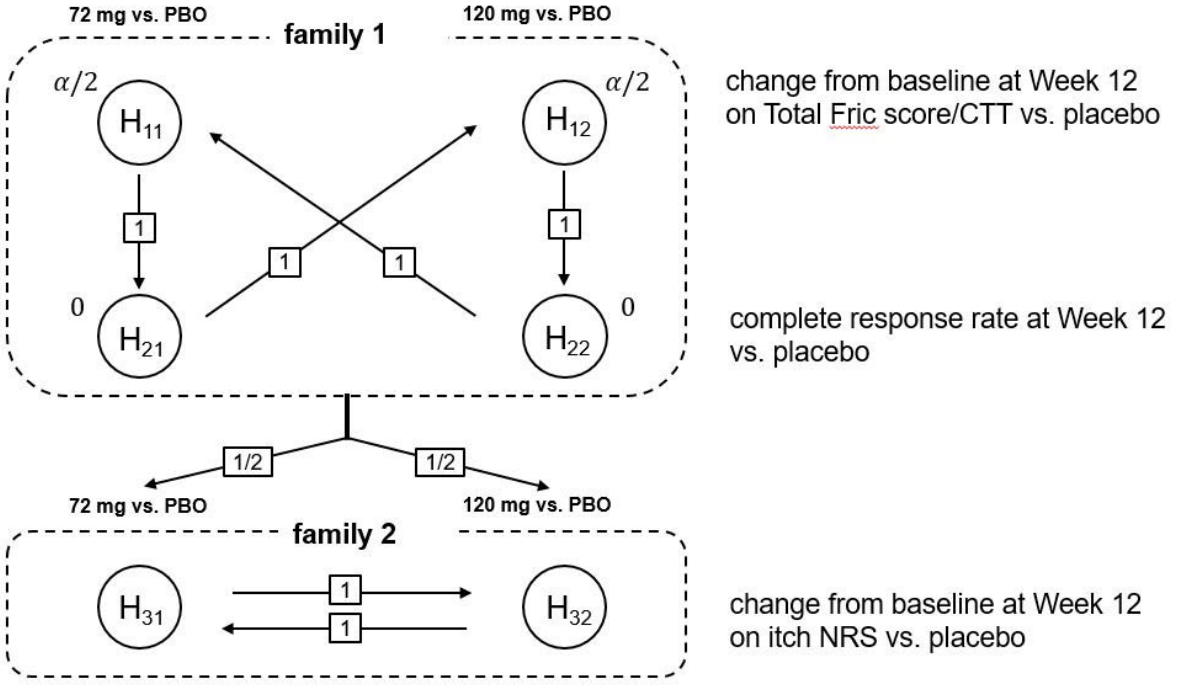
where π is the proportion of participants achieving complete response status at Week 12, as described in Section 2.2.

- itch NRS following provocation tests change from baseline at Week 12

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

where μ is the mean change from baseline in itch NRS following the FricTest 4.0 and TempTest at Week 12, as described in Section 2.2.

Figure 12-1 Testing strategy for symptomatic dermographism and cold urticaria



For symptomatic dermographism and cold urticaria CINDU cohort, the hypotheses are mapped into two families.

The first family consists of four hypotheses: H_{11}, H_{12}, H_{21}, and H_{22}. These four hypotheses form two branches such that hypotheses within a same branch correspond to the same ligelizumab dose regimen (72 mg q4w or 120 mg q4w). In essence, the type-I-error probability will be equally split for both branches of hypotheses and within each branch the hypotheses are tested sequentially as follows:

The initial alpha level for each branch is set to $\alpha/2=0.0125$ (one-sided). The first hypothesis (H_{11} and H_{12}) 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 hypotheses (H_{21} and/or H_{22}) of high/low dose ligelizumab versus placebo regarding the secondary endpoint on complete response is tested with $\alpha/2$.

In the first family, the testing within each dose is strictly hierarchical: the secondary endpoint on complete response will only be assessed if efficacy was shown previously for the primary endpoint. If efficacy is shown for both the primary and the secondary endpoint for one of the doses, the associated weight is passed on to the other dose.

The second family consists of H_{31} and H_{32}, will only be tested if all four hypotheses in the first family are rejected. The initial alpha level will be equally split (i.e. is set to $\alpha/2=0.0125$, one-sided) for each hypothesis. If either of the hypotheses is rejected, the associated weight is passed on to the other dose, so that other hypothesis is tested with α.

Testing strategy for cholinergic urticaria

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) for cholinergic urticaria.

Primary endpoint

Itch NRS change from baseline at Week 12

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

where μ is the mean change from baseline in itch NRS following the pulse-controlled ergometry test at Week 12, as described in Section 2.1.

Secondary endpoints

- proportion of participants achieving complete response in itch NRS (itch NRS=0) following the pulse-controlled ergometry test at Week 12

$H_{02}: \pi^{itch}_{ligelizumab} \leq \pi^{itch}_{Placebo}$ versus $H_{A2}: \pi^{itch}_{ligelizumab} > \pi^{itch}_{Placebo}$

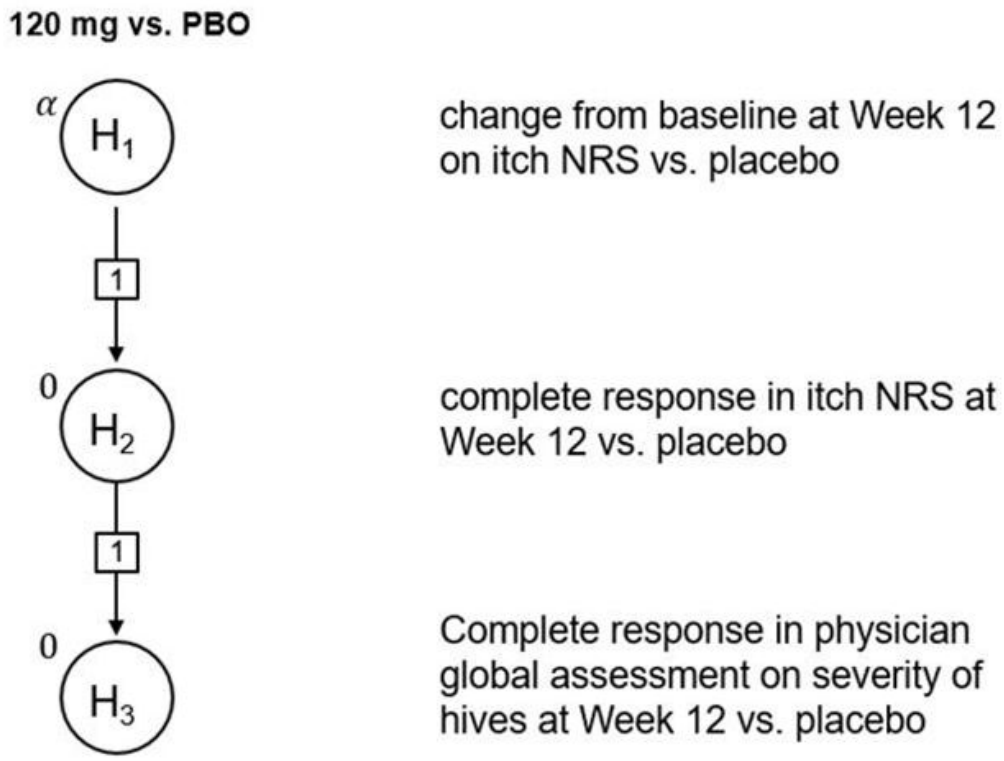
where π^{itch} is the proportion of participants achieving complete response in itch NRS at Week 12, as described in Section 2.2.

- proportion of participants achieving complete response in physician global assessment of severity of hives (PGA hive score =0) following the pulse-controlled ergometry test at Week 12

$H_{03}: \pi^{hive}_{ligelizumab} \leq \pi^{hive}_{Placebo}$ versus $H_{A3}: \pi^{hive}_{ligelizumab} > \pi^{hive}_{Placebo}$

where π^{hive} is the proportion of participants achieving complete response in PGA hive score=0 at Week 12, as described in Section 2.2.

Figure 12-2 Testing strategy for cholinergic urticaria



For cholinergic urticaria, the hypotheses are tested sequentially in a fix order as follows:

The initial alpha level is set to α=0.025 (one-sided) for the first hypothesis (H_1) of ligelizumab 120 mg q4w versus placebo regarding the primary endpoint. If H_1 is rejected, the second hypothesis (H_2) of ligelizumab versus placebo regarding the secondary endpoint on complete response in itch NRS is tested with α. If H_2 is rejected, the third hypothesis (H_3) of ligelizumab versus placebo regarding the secondary endpoint on complete response in physician global assessment of severity of hives is tested with α.

12.5.1 Efficacy [redacted] endpoint(s)

Efficacy endpoints other than the primary and secondary endpoints are detailed in Section 12.6.

12.5.2 Safety endpoints

The following applies to all three subtypes of CINDU (i.e. symptomatic dermographism, cold urticaria, and cholinergic urticaria).

For all safety analyses (i.e. AEs, laboratory data, vital signs, and ECG), the safety set will be used. All data will be included in the analysis regardless of rescue medication use. All listings and tables will be presented by treatment group.

Adverse events

All information obtained on AEs will be displayed by treatment group (or sequence) and participant.

Treatment emergent AEs will be summarized by actually received treatment.

Treatment emergent AEs (TEAE) are defined as:

- Events started after the first dose of study treatment (ligelizumab) in this study and within 16 weeks of last dose of study treatment
- Events present prior to the first dose of study treatment (ligelizumab) in this study but:
  1. increased in severity based on preferred term (e.g. worsening of headache),
  2. same PT but increased severity (e.g. from mild to moderate),
  3. same PT but increase in seriousness (from non-serious AE to SAE; if already a SAE from medical significant to LT/fatal)

  and within 16 weeks after the last dose of the study treatment.

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

- by treatment, primary system organ class and preferred term.
- by treatment, primary system organ class, preferred term and maximum severity.
- by treatment, Standardized MedDRA Query (SMQ) and preferred term.

Separate summaries will be provided for study medication related AEs, death, SAEs, other significant adverse events leading to treatment discontinuation.

The number (and proportion) of participants with treatment emergent AEs of special interest (AESI) will be summarized by treatment.

The number (and proportion) of participants with treatment emergent AEs related to other safety topics such as events related to “liver toxicity” will be summarized by treatment.

A participant with multiple AEs within a primary system organ class is only counted once towards the total of the primary system organ class.

For the placebo-ligelizumab treatment group, treatment-emergent AEs will be counted separately for the placebo treatment and ligelizumab treatment.

Vital signs

All vital signs data will be listed by treatment group, participant, and visit/time and if ranges are available, abnormalities will be flagged. Summary statistics will be provided by treatment, and visit/time and separately in adults and adolescents.

12-lead ECG

All ECG data will be listed by treatment group, participant and visit/time. Newly occurring or worsening abnormalities will be flagged.

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

Clinical laboratory evaluations

All laboratory data will be listed by treatment group, participant, and visit/time and if normal ranges are available abnormalities will be flagged.

Descriptive summary statistics for the change from baseline to each study visit will be presented. These descriptive summaries will be presented by laboratory test and treatment group. Change from baseline will only be summarized for participants with both baseline and post baseline values. For categorical parameters, frequencies by categories at each visit will be summarized.

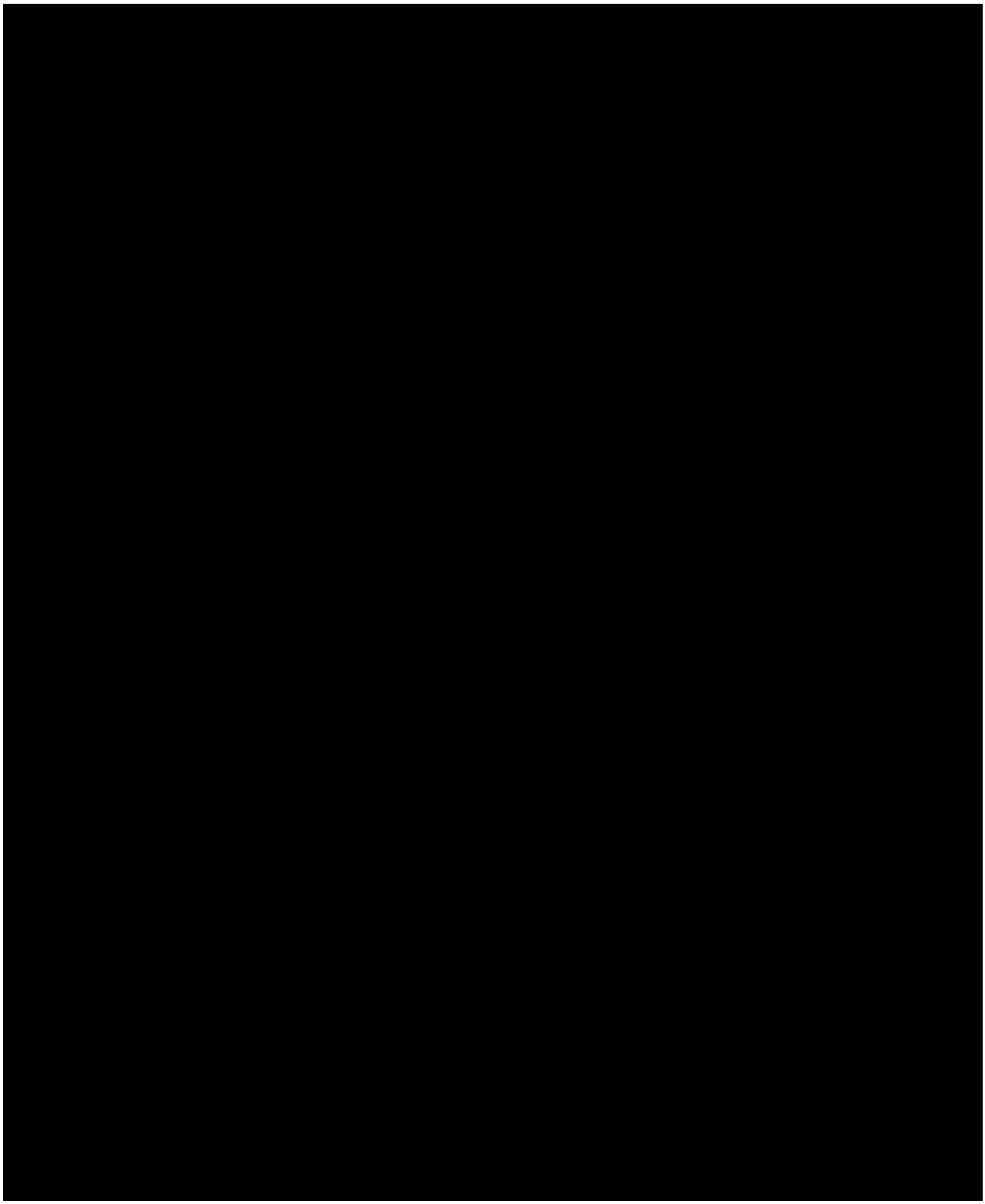
Shift tables using the low/normal/high/ (low and high) classification will be used to compare baseline to the worst on-treatment value.

Other safety evaluations

[redacted]

Resource utilization

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



12.7 Interim analyses (Futility analysis)

A final analysis will be performed after all participants have completed Week 36 (or discontinued prior to Week 36). Formal testing of the primary endpoint with full level alpha will be performed at the primary analysis time point.

Due to the low prevalence of cholinergic urticaria, an interim futility analysis may be conducted in case there is an obvious difference in recruitment speed in the three cohorts. In other words, this interim futility analysis would be triggered when approximately 50% of randomized participants in the cholinergic urticaria cohort have completed the Week 12 visit while 100% of randomized participants in the symptomatic dermographism and cold urticaria cohorts have completed the Week 12 visit. During this analysis, there will be no decision rules applied for the symptomatic dermographism and cold urticaria cohort. This analysis will be conducted to assess whether efficacy met a pre-specified level only for the cholinergic urticaria cohort.

Depending on the outcome of the futility analysis, further recruitment in cholinergic urticaria subtype may be stopped or continued as planned. Participants who have already been enrolled in the study prior to the futility analysis will continue to remain in the study.

Futility analysis results will be evaluated by the DMC based on calculated predictive probabilities of the primary estimand (see Section 2) for cholinergic urticaria. Details of the calculations and the associated thresholds will be described in the DMC Charter and its associated analysis plan. Additional analyses on the secondary estimand (see section 2) and safety will also be performed to assist in the futility evaluation, as planned in the DMC charter.

12.8 Sample size calculation

Symptomatic dermographism

The sample size justification is based on change from baseline in Total Fric Score and achievement of complete response in FricTest®4.0 at Week 12.

Cold urticaria

The sample size justification is based on change from baseline in CTT (in response to TempTest®4.0) and achievement of complete response in TempTest®4.0 at Week 12.

Cholinergic Urticaria

The sample size justification is based on change from baseline in itch NRS in response to the pulse-controlled ergometry test and achievement of complete response in itch NRS (itch NRS=0) at Week 12.

For symptomatic dermographism and cold urticaria, participants will be randomized in a 2:2:1:1 ratio to ligelizumab 72 mg q4w, ligelizumab 120 mg q4w, placebo - ligelizumab 120 mg q4w, and placebo - ligelizumab 72 mg q4w, respectively. In other words, participants are randomly assigned to ligelizumab 72 mg q4w, ligelizumab 120 mg q4w, and placebo group with a 1:1:1 ratio in the placebo-controlled period (i.e. up to Week 12). For cholinergic urticaria, participants will be randomized in a 1:1 ratio to ligelizumab 120 mg q4w and placebo - ligelizumab 120 mg q4w.

All sample size calculations were performed with SAS 9.4 PROC POWER.

Based on simulation studies, the sample sizes calculated below for each of the three CINDU cohorts are sufficient to maintain the power of overall multiple testing strategy (at least 90%) for the primary endpoint (see Section 2.1) and the first secondary endpoint (i.e. complete response rate following the FricTest®4.0 for symptomatic dermographism, complete response rate following the TempTest®4.0 for cold urticaria, and complete response rate in itch NRS following the pulse-controlled ergometry test for cholinergic urticaria) through the recycled alpha. Detailed simulation results on power with all endpoints in the testing strategy (see Section 12.5) are provided in the statistical analysis plan.

Data from each subtype is analyzed separately. Hence if sample size is not achieved for one of the subtypes, this will not impact the analysis for the other subtypes. The overall population (adolescent and adult participants) will be considered for the primary and secondary analyses.

12.8.1 Primary endpoint(s)

Symptomatic Dermographism

Since two ligelizumab dose regimens will be tested versus placebo with respect to the primary endpoints (change from baseline in Total Fric Score at Week 12), the type-I-error will be split to 1.25% one-sided for each comparison.

Assuming the treatment difference in change from baseline to Week 12 in Total Fric Score is at least 1.3 in favor of the ligelizumab group, and a standard deviation of approximately 1.7, a sample size of approximate 56 participants per group and a drop-out rate of 10% provides 93.7% power to show that the primary analysis based on a two-sample t-test will be statistically significant at the one-sided 1.25% significance level (SAS 9.4, PROC POWER, difference in two sample means).

Mean changes from baseline in Total Fric Score of -0.6 (standard deviation: 1.4) in placebo group, -1.78 (standard deviation: 1.66) in omalizumab 150 mg group, and - 2.0 (standard deviation: 1.67) in omalizumab 300 mg group have been reported in Maurer et al 2017.

Table 12-1 Sensitivity of power to changes in assumptions (Symptomatic Dermographism)

True treatment difference ligelizumab vs placebo (Total Fric Score)	SD (Total Fric Score)	Power for primary endpoint (one-sided α =1.25%), for N= 56 per arm		
		With 5% drop-out rate	With 10% drop-out rate	With 15% drop-out rate
1.5	2	94.2%	92.8%	91.1%
1.3	2	85.6%	83.3%	80.7%
1.3	1.7	95.0%	93.7%	92.1%
1	1.3	95.3%	94.0%	92.5%

SD=Standard Deviations

Cold Urticaria

Since two ligelizumab dose regimens will be tested versus placebo with respect to the primary endpoints (change from baseline in critical temperature thresholds (CTT) at Week 12), the type-I-error will be split to 1.25% one-sided for each comparison.

Assuming the treatment difference in change from baseline to Week 12 in CTTs is at least 10°C in favor of the ligelizumab group, and a standard deviation of approximately 8°C, a sample size of approximate 34 participants per group a drop-out rate of 10% provides >99% power to show that the primary analysis based on a t-test will be statistically significant at the one-sided 1.25% significance level (SAS 9.4, PROC POWER, difference in two sample means).

Mean changes from baseline in CTT of -0.3°C (standard deviation: 3.9°C) in placebo group, CTT of -10.6°C (standard deviation: 7.6°C) in omalizumab 150 mg group, and CTT of -10.4°C (standard deviation: 9.4°C) in omalizumab 300 mg group have been reported in Metz et al 2017.

Table 12-2 Sensitivity of power to changes in assumptions (cold urticaria)

		Power for primary endpoint (one-sided α =1.25%) for N= 34 per arm		
True treatment difference ligelizumab vs placebo (°C)	**SD (°C)**	**With 5% drop-out rate**	**With 10% drop-out rate**	**With 15% drop-out rate**
11	10	98.1%	97.3%	96.2%
10	10	95.3%	93.9%	92.1%
10	9	98.3%	97.5%	96.5%
8	8	95.3%	93.9%	92.1%

SD=Standard Deviation

Cholinergic Urticaria

Assuming the treatment difference in change from baseline to Week 12 in itch NRS following the pulse-controlled ergometry test is at least 1.65 in favor of the ligelizumab 120 mg q4w group, and a standard deviation of approximately 3.0, a sample size of approximate 79 participants per group and a drop-out rate of 10% provides 90.2% power to show that the primary analysis based on a two-sample t-test will be statistically significant at the one-sided 2.5% significance level (SAS 9.4, PROC POWER, difference in two sample means).

Median pre-treatment itch VAS of 60 (25th percentile=40, 75th percentile=80) and median post-treatment itch VAS of 30 (25th percentile=20, 75th percentile=70) in the overall population after 4 doses of omalizumab 300 mg have been reported in Gastaminza et al.

Table 12-3 Sensitivity of power to changes in assumptions (cholinergic urticaria)

		Power for primary endpoint (one-sided α =2.5%) for N= 79 per arm		
True treatment difference ligelizumab vs placebo (itch NRS)	**SD (itch NRS)**	**With 5% drop-out rate**	**With 10% drop-out rate**	**With 15% drop-out rate**
1.5	2.5	95.5%	94.4%	93.2%
1.5	3.0	86.0%	84.1%	81.9%
1.65	3	91.7%	90.2%	88.5%
1.8	2.5	99.2%	98.9%	98.5%

SD= Standard Deviation

Table 12-4 Sensitivity of required sample size (per arm) to changes in assumptions for different targeted statistical power (cholinergic urticaria)

				Sample size required

True treatment difference ligelizumab vs placebo (itch NRS)	SD (itch NRS)	Targeted statistical power for primary endpoint (one-sided α=2.5%)	with 5% drop-out rate	with 10% drop-out rate	with 15% drop-out rate
1.65	3.0	90%	75%	79%	84%
1.65	3.0	80%	56%	59%	63%

SD=Standard Deviation

12.8.2 Secondary endpoint(s)

Symptomatic dermographism

- Complete response rate

Assuming a type-I-error of 2.5% two-sided and a complete response (negative outcome in the FricTest®4.0) rate of 11% in the placebo group. With approximate 56 participants per group and a drop-out rate of 10%, the power to show a complete response rate of 44% in the ligelizumab groups based on Fisher's exact test (SAS 9.4, two group Fisher's-exact test of equal proportions) is 91.5%.

Placebo-response rates of 11% (2 out of 18) have been reported in Maurer et al 2017.

The power of the all the endpoints included in the testing strategy is confirmed based on the simulation through the recycled alpha as planned. The detail simulation results will be provided in the statistical analysis plan.

Cold urticaria

- Complete response rate

Assuming a type-I-error of 2.5% two-sided and a complete response (negative outcome in the TempTest®4.0) rate of 5% in the placebo group. With approximate 34 participants per group and a drop-out rate of 8%, the power to show a complete response rate of 40% in the ligelizumab groups based on Fisher's exact test (SAS 9.4, two group Fisher's-exact test of equal proportions) is 81.8%.

Placebo-response rates of 0% (0 out of 12) and 5% (1 out of 20) have been reported in Metz et al 2017 and Krause et al 2013, respectively.

The power of the all the endpoints included in the testing strategy is confirmed based on the simulation through the recycled alpha as planned. The detail simulation results will be provided in the statistical analysis plan.

Cholinergic urticaria

- Complete response rate in itch NRS

For complete response in itch NRS, assuming a type-I-error of 5% two-sided and a complete response (see Section 2.2) rate of 13% in the placebo group. With approximate 79 participants per group and a drop-out rate of 10%, the power to show a complete response rate of 38% in the ligelizumab groups based on Fisher's exact test (SAS 9.4, two group Fisher's-exact test of equal proportions) is 91.1%.

In Gastaminza et al, complete response rates of 22% (2 out of 9) and 8% (1 out of 13) have been reported for placebo and omalizumab 300 mg group during the blinded treatment period, and 37.5% (6 out of 16) in the overall population in the open label treatment period.

The power of the all the endpoints included in the testing strategy is confirmed based on the simulation. The detail simulation results will be provided in the statistical analysis plan.

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

13.3 Publication of study protocol and results

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

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

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

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

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

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 participants 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 study treatment drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

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

14.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

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

15 References

References are available upon request

Altrichter S, Salow J, Ardelean E, et al (2014) Development of a standardized pulse-controlled ergometry test for diagnosing and investigating cholinergic urticaria. J Dermatol Sci; 88-93.

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

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

Bretz F, Maurer W, Brannath W, et al (2009) A graphical approach to sequentially rejective multiple test procedures. Stat Med; 586-604.

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

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

Cox L, Sanchez-Borges M, Lockey R (2017) World Allergy Organization Systemic Allergic Reaction Grading System: Is a Modification Needed? J allergy Clin Immunol Pract; 58-62.

Dressler C, Werner RN, Eisert L, et al (2018) Chronic inducible urticaria: A systematic review of treatment options. J Allergy Clin Immunol; 1726-34.

Finlay AY (2005) Current severe psoriasis and the rule of tens. Br J Dermatol; 861-7.

[redacted]

Fleming S, Thompson M, Stevens R, et al. Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. Lancet 2011; published online March 15. DOI:10.1016/S0140-6736(10)62226-X

Flynn JT, Kaelber DC, Baker-Smith CM, et al. Clinical practice guideline for screening and management of high blood pressure in children and adolescents

Gasser P, Tarchevskaya SS, Guntern P, et al (2020) The mechanistic and functional profile of the therapeutic anti-IgE antibody ligelizumab differs from omalizumab. Nat Commun; //doi.org/10.2210/pdb2Y7Q/pdb

Gastaminza G, Azofra J, Nunez-Cordoba JM, et al (2019) Efficacy and Safety of Omalizumab (Xolair) for Cholinergic Urticaria in Patients Unresponsive to a Double Dose of Antihistamines: A Randomized Mixed Double-Blind and Open-Label Placebo-Controlled Clinical Trial. J Allergy Clin Immunol Pract; 1599-1609.

[redacted]

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

Kind P, Dolan P, Gudex C, et al (1998) Variations in population health status: results from a United Kingdom national questionnaire survey. BMJ; 736-41.

Krause K, Spohr A, Zuberbier T (2013) Up-dosing with bilastine results in improved effectiveness in cold contact urticaria. Allergy; 921-8.

[redacted]

Magerl M, Altrichter S, Borzova E et al (2016) The definition, diagnostic testing, and management of chronic inducible urticarias. J. Allergy Clin Immunol; 780-802.

Maurer M, Abuzakouk M, Bérard F, et al (2017) The burden of chronic spontaneous urticaria is substantial: Real-world evidence from ASSURE-CSU. Allergy; 10.1111/all.13209.

Maurer M, Fluhr JW, Khan DA: (2018a), How to Approach Chronic Inducible Urticaria. J Allergy Clin Immunol Pract; 1119-30.

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

Maurer M, Metz M, Brehler R, et al (2018b) Omalizumab treatment in patients with chronic inducible urticaria: A systematic review of published evidence. J. Allergy Clin Immunol; 638-49.

Maurer M, Schütz A, Weller K, et al (2017) Omalizumab is effective in symptomatic dermographism-results of a randomized placebo-controlled trial. J Allergy Clin Immunol; 870-72.e5.

Metz M, Altrichter S, Ardelean E, et al (2011) Anti-immunoglobulin E treatment of patients with recalcitrant physical urticaria. Int Arch Allergy Immunol; 177-80.

Metz M, Schütz A, Weller K, et al (2017) Omalizumab is effective in cold urticaria-results of a randomized placebo-controlled trial. J Allergy Clin Immunol; 864-7

Mlynek A, Vieira dos Santos R, Ardelean E, et al (2013) A novel, simple, validated and reproducible instrument for assessing provocation threshold levels in patients with symptomatic dermographism. Clin Exp Dermatol; 360-6; quiz 366.

Ohanyan T, Schoepke N, Bolukbasi B, et al (2017) Responsiveness and minimal important difference of the urticaria control test. J Allergy Clin Immunol; 1710-3.

Permutt T (2016) Sensitivity analysis for missing data in regulatory submissions. Stat Med; 2876-9.

Pickering TG, Hall JE, Appel LJ, Falkner BE, et al (2005) Recommendations for blood pressure measurement in humans and experimental animals: part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional

and Public Education of the American Heart Association Council on High Blood Pressure Research; 111(5):697-716.

[redacted]

Sampson HA, Muñoz-Furlong A, Campbell RL, et al (2006) Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol; 391-7.

Simons FE, Ardusso LR, Bilò MB, et al (2011) World allergy organization guidelines for the assessment and management of anaphylaxis. World Allergy Organ J; 13-37.

Simons FE, Ebisawa M, Sanchez-Borges M, et al (2015) 2015 update of the evidence base: World Allergy Organization anaphylaxis guidelines. World Allergy Organ J 1-16.

Sánchez J, Amaya E, Acevedo A, et al (2017): Prevalence of Inducible Urticaria in Patients with Chronic Spontaneous Urticaria: Associated Risk Factors. J Allergy Clin Immunol Pract; 464-470.

[redacted]

Viswanathan RK, Biagtan MJ, Mathur SK (2012) The role of autoimmune testing in chronic idiopathic urticaria. Ann Allergy Asthma Immunol; 337-341;e1.

[redacted]

[redacted]

Yu Madamda RC, Ferre M, Matute OV, et al (2017) Sustained Effect and Clinical Outcomes in Chronic Spontaneous Urticaria in Patients receiving Omalizumab for several years [abstract]. J Allergy Clin Immunology; 139 (2):AB245

Zuberbier T, Aberer W, Asero R, et al (2018) The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. Allergy; 1393-1414.

16 Appendices

16.1 Appendix 1: Clinically notable laboratory values and vital signs

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 eCRF.

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

Notable values for adults are defined as follows:

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

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

Appendix 1.1: Clinically notable vital signs - adolescent participants

Guideline for pediatric blood pressure measurements:

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

1. The child should be seated in a quiet room for 3-5 min before measurement, with the back supported and feet uncrossed on the floor. 2. BP should be measured in the right arm for consistency, for comparison with standard tables, and to avoid a falsely low reading from the left arm in the case of coarctation of the aorta. The arm should be at heart level, supported, and uncovered above the cuff. The patient and observer should not speak while the measurement is being taken. 3. The correct cuff size should be used. The bladder length should be 80%-100% of the circumference of the arm, and the width should be at least 40%. 4. For an auscultatory BP, the bell of the stethoscope should be placed over the brachial artery in the antecubital fossa, and the lower end of the cuff should be 2-3 cm above the antecubital fossa. The cuff should be inflated to 20-30 mm Hg above the point at which the radial pulse disappears. Overinflation should be avoided. The cuff should be deflated at a rate of 2-3 mm Hg per second. The first (phase I Korotkoff) and last (phase V Korotkoff) audible sounds should be taken as systolic blood pressure and diastolic blood pressure. If the Korotkoff sounds are heard to 0 mm Hg, the point at which the sound is muffled (phase IV Korotkoff) should be taken as the diastolic BP, or the measurement repeated with less pressure applied over the brachial artery. The measurement should be read to the nearest 2 mm Hg. 5. To measure BP in the legs, the patient should be in the prone position, if possible. An appropriately sized cuff should be placed midthigh and the stethoscope placed over the popliteal artery. The systolic BP in the legs is usually 10%-20% higher than the brachial artery pressure.
Adapted from Pickering TG et al 2005

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

	Boys[1]		Girls[1]		
Age (Years)	**SBP (mm Hg)**	**DBP (mm Hg)**	**SBP (mm Hg)**	**DBP (mm Hg)**	**Heart Rate[2]**
12	>117	<75	>118	<75	62-96
13	>121	<75	>121	<76	
14	>126	<77	>122	<76	
15	>128	<79	>122	<77	60-92
16	>129	<80	>123	<77	
17	>131	<81	>124	<77	

The blood pressure values in the table above were adapted from Flynn et al 2017 by modifying 5% of height (in table 6 of the publication) with 50% height to represent 'average' child height per age/sex. The normal values for vital signs in children vary greatly with age, growth and development. Selected BP threshold values serve as a representative guide of 'elevated BP' for a child of 'average' size.
The purpose of the values listed in this table is to guide investigators to identify or screen for values of concern in pediatric participants by age. The significance of these findings must be considered in view of the participant's disease, time course and overall clinical condition.
[1] Flynn JT, Kaelber DC, Baker-Smith CM, et al. Clinical practice guideline for screening and management of high blood pressure in children and adolescents
[2] Fleming S, Thompson M, Stevens R, et al. Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. Lancet 2011; published online March 15. DOI:10.1016/S0140-6736(10)62226-X.

16.2 Appendix 2: Liver event and laboratory trigger definitions & 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 > 3x 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 – ALT, AST, TBL

	ALT	**TBL**	**Liver Symptoms**	**Action**
ALT increase without bilirubin increase:				
	If normal at baseline: ALT > 3 x ULN	Normal For participants with Gilbert's syndrome: No change in baseline TBL	None	• **No change to study treatment** • Measure ALT, AST, ALP, GGT, TBIL, INR, albumin, CK, and GLDH in 48-72 hours. • Follow-up for symptoms.
	If elevated at baseline: ALT > 2 x baseline or > 300 U/L (whichever occurs first)			

	ALT	TBL	Liver Symptoms	Action
	If normal at baseline: ALT > 5 x ULN for more than two weeks	Normal For participants 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 participants 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 events and laboratory triggers – Isolated Hyperbilirubinemia

Criteria	Actions required	Follow-up monitoring
Total Bilirubin (isolated)		
>1.5 – 3.0 ULN	• Maintain treatment • Repeat LFTs within 48-72 hours	Monitor LFTs weekly until resolution 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, TBL, 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

*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

Table 16-6 Specific renal alert criteria and actions

Renal Event	Actions
Confirmed serum creatinine increase 25% - 49%	· Consider causes and possible interventions · Follow up within 2-5 days
Serum creatinine increase ≥ 50% [+] **OR** **if <18 years old,** eGFR < 35mL/min/1.73 m2	· Consider causes and possible interventions · Repeat assessment within 24-48h if possible · Consider drug interruption or discontinuation unless other causes are diagnosed and corrected · Consider patient hospitalization and specialized treatment
New onset dipstick* proteinuria ≥ 3+ **OR** Protein-creatinine **ratio** (PCR) ≥ 1g/g Cr (or mg/mmol equivalent as converted by the measuring laboratory)	· Consider causes and possible interventions · Assess serum albumin & serum protein · Repeat assessment to confirm · Consider drug interruption or discontinuation unless other causes are diagnosed and corrected
New onset hematuria ≥ 3+ on urine dipstick*	· Assess & document · Repeat assessment to confirm · Distinguish hemoglobinuria from hematuria · Urine sediment microscopy · Assess SCR · Exclude infection, trauma, bleeding from the distal urinary tract/bladder, menstruation · Consider bleeding disorder
[+] Corresponds to KDIGO (Kidney Disease Improving Global Outcomes) criteria for Acute Kidney Injury * For point of care tests (POCT), the clinical sites in China will be allowed to analyze these tests as per clinical site practice (refer to China laboratory manual for further details)	

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
1. Assess, document and record in CRF • Urine dipstick* and sediment microscopy evidence of drug induced nephrotoxicity: crystals, red blood cells (dysmorphic/glomerular vs. non-dysmorphic/non-glomerular), white blood cells, tubular epithelial cells • Blood pressure and body weight

Follow-up of renal events
• Serum creatinine, BUN, electrolytes (sodium, potassium, phosphate, calcium), bicarbonate and uric acid • Urine output 2. Review and record possible contributing factors to the renal event (co-medications, other co-morbid conditions) and additional diagnostic procedures (Magnetic Resonance Imaging etc.) in the CRF 3. Monitor patient regularly (frequency at investigator's discretion) until - • Event resolution: (SCR within 10% of baseline or protein-creatinine ratio < 1 g/g Cr, or ACR <300 mg/g Cr of baseline) or • Event stabilization: SCR level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months 4. Analysis of urine markers in samples collected over the course of the drug induced nephrotoxicity event
*For point of care tests (POCT), the clinical sites in China will be allowed to analyze these tests as per clinical site practice (refer to China laboratory manual for further details)

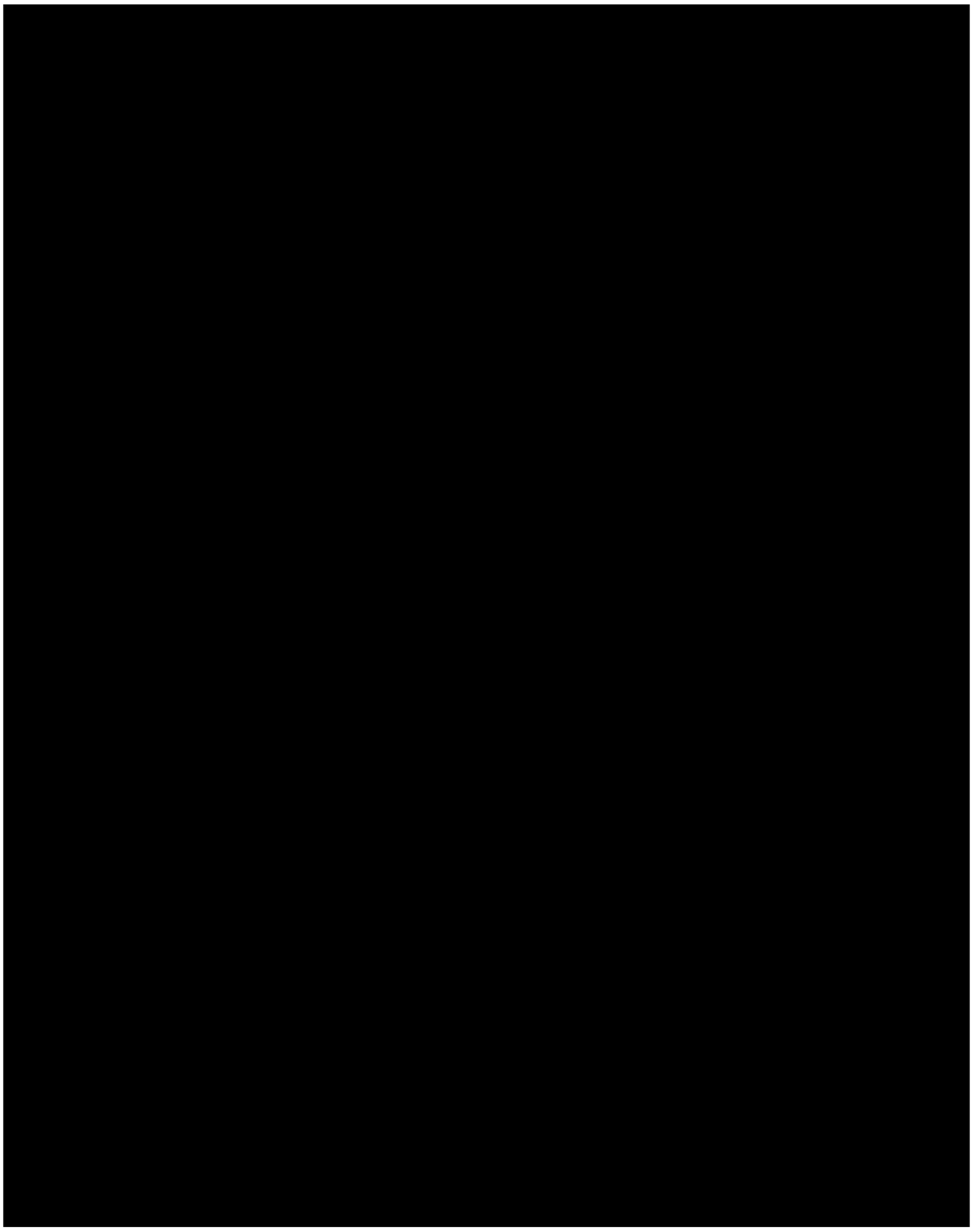
16.4 Appendix 4 Sampson Criteria for anaphylaxis

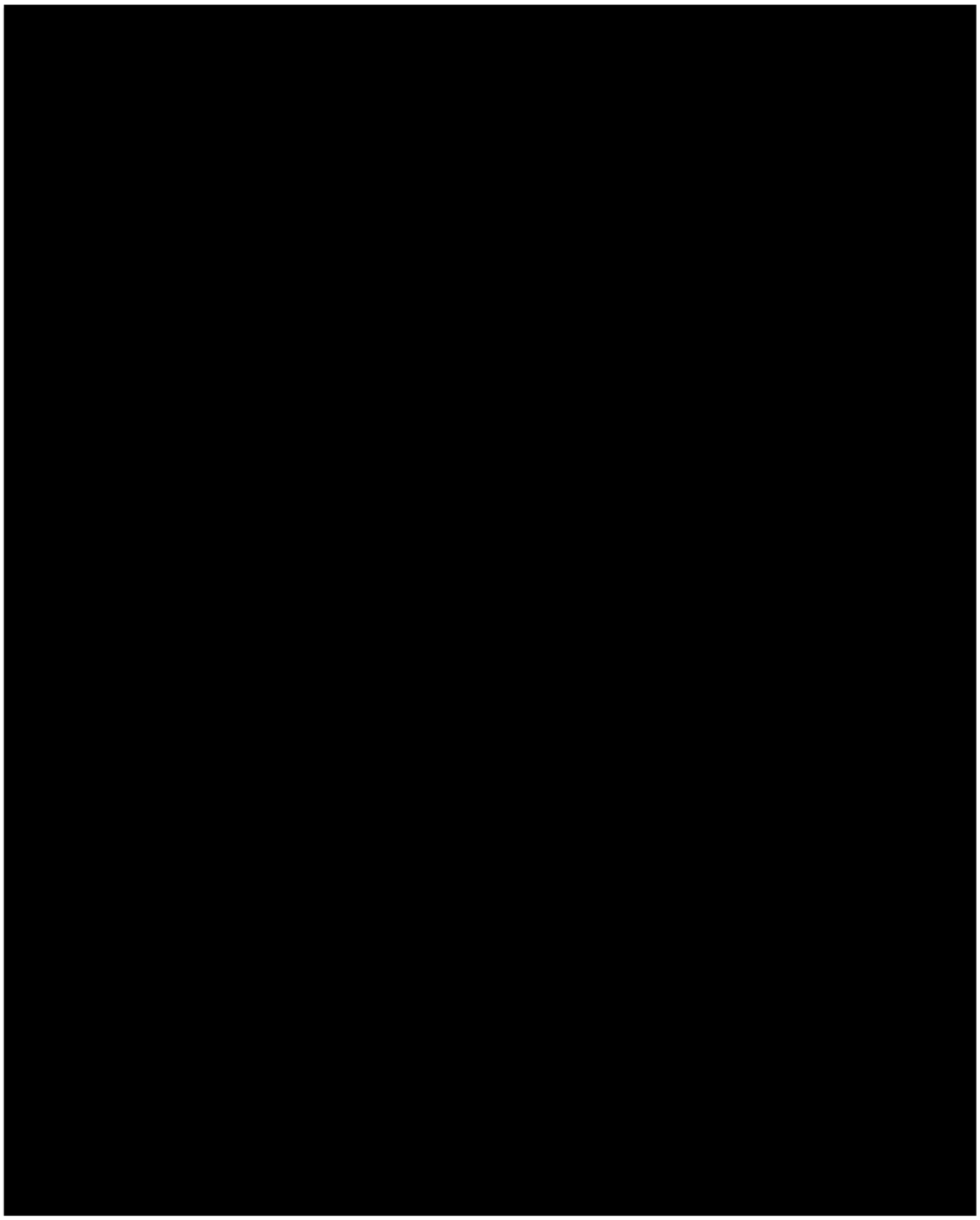
Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

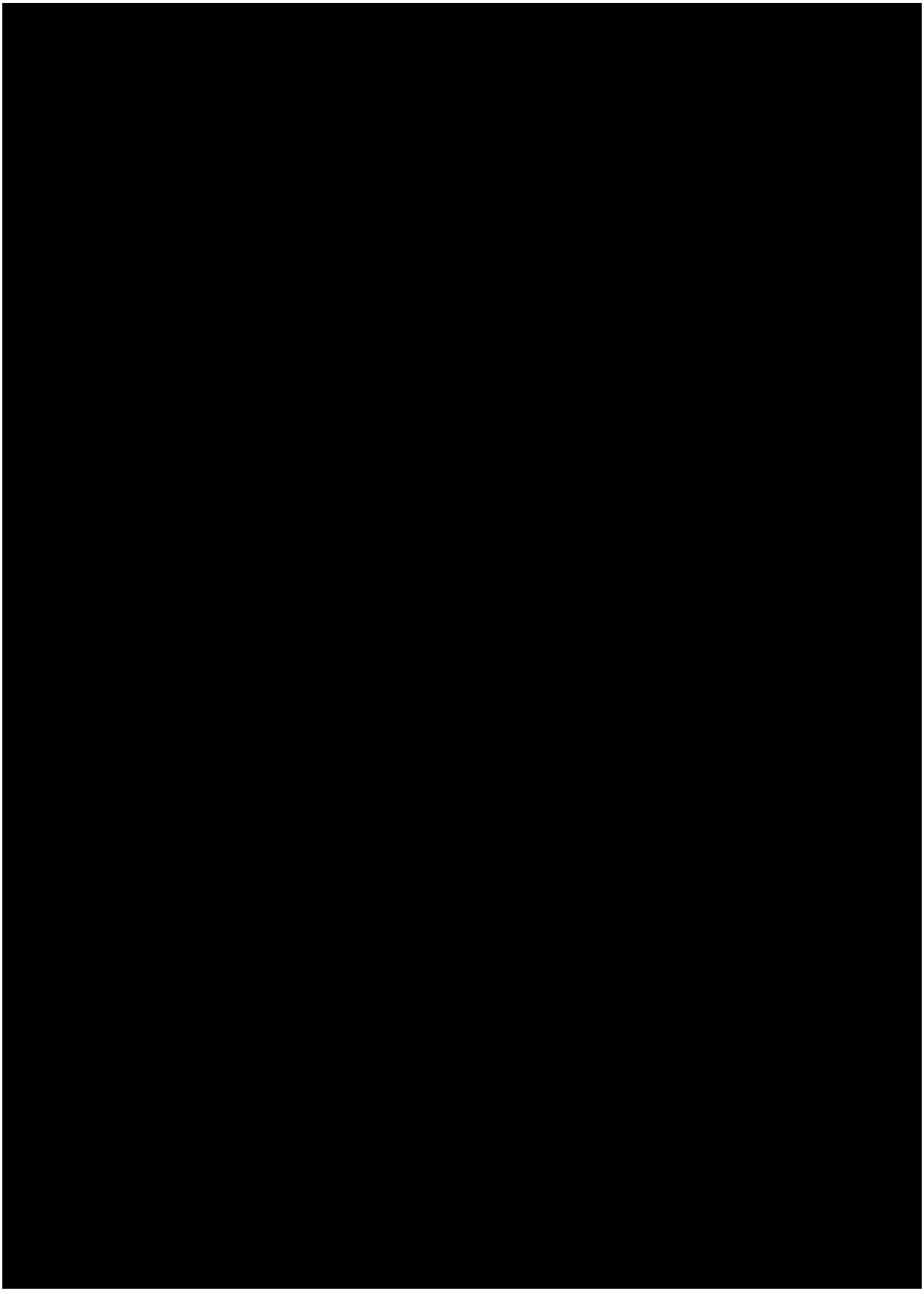
1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
   AND AT LEAST ONE OF THE FOLLOWING
   a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure *to a likely allergen for that patient* (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to *known allergen for that patient* (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

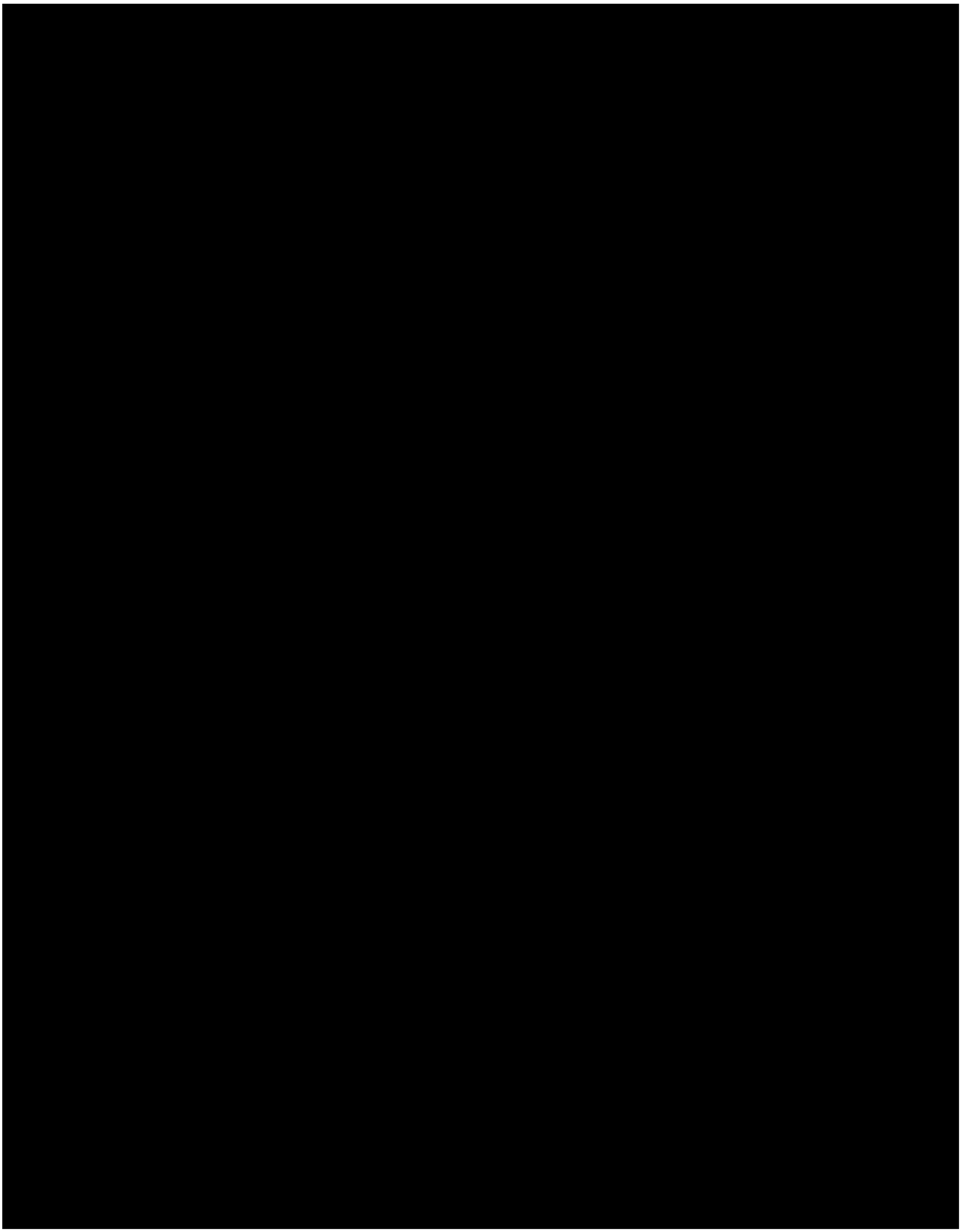
PEF, Peak expiratory flow; *BP*, blood pressure.
*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

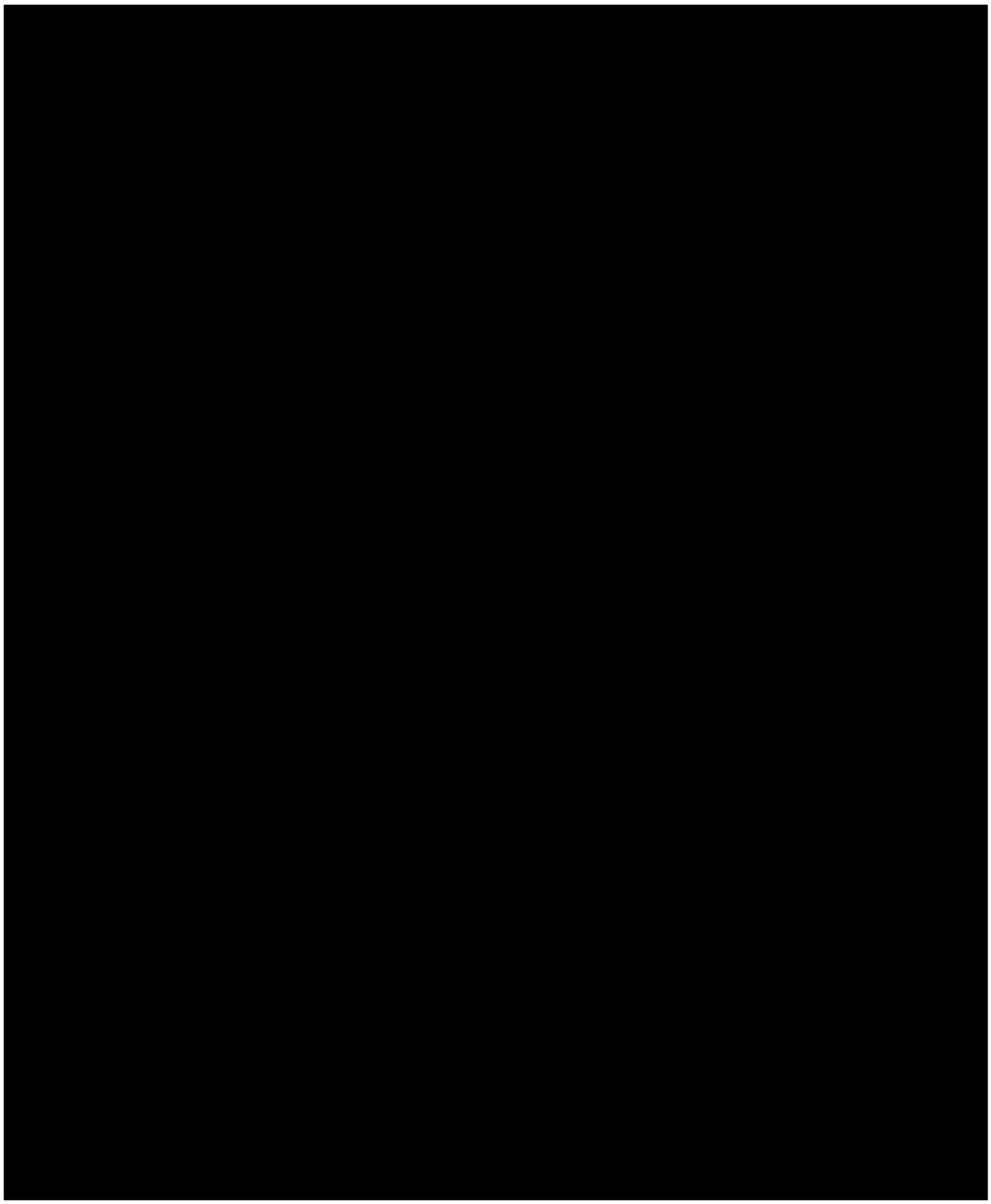
[redacted]

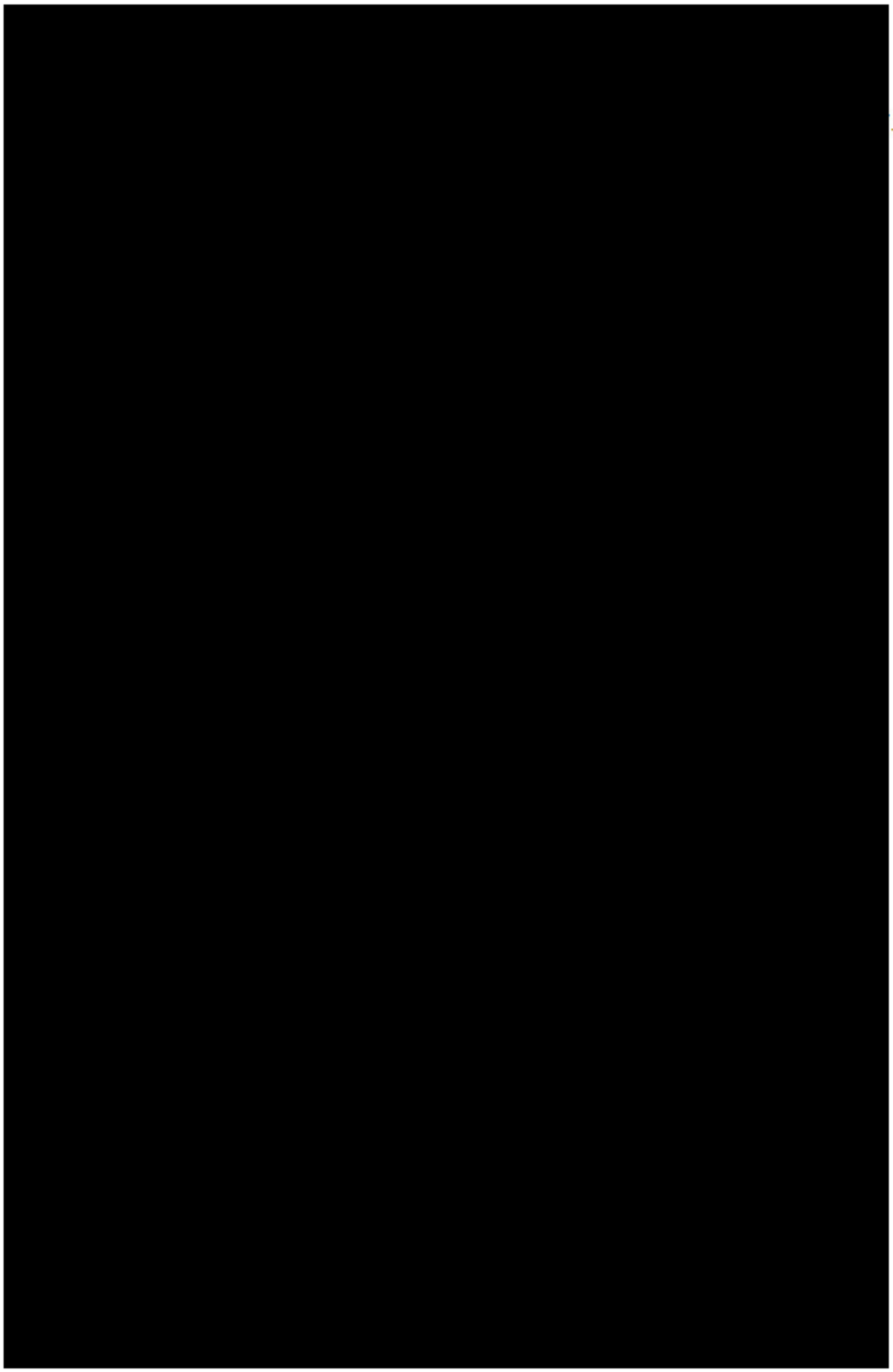












16.7 Appendix 7: World allergy organization grading system

Figure 16-1 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