NOVARTIS

Clinical Development

QGE031/Ligelizumab / NCT05024058

CQGE031E12301 / NCT05024058

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 patients inadequately controlled by H1-antihistamines

Statistical Analysis Plan (SAP)

Author:	Trial Statistician: [redacted]

Document type:	SAP Documentation
Document status:	Final 2.0
Release date:	20-Jul-2022
Number of pages:	62

Template Version 4.0, Effective from 23-Apr-2021

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
07-Nov-2021	Prior to FPFV	Creation of final version	N/A - First version	NA
5-May-2022	Prior to LPLV	Study early Termination	Changes to statistical analyses and summarization due to sample size limitations	2. Statistical Methods 4. Change to protocol specified analyses

List of abbreviations

AC	Adjudication Committee
[redacted]	
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
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
DMS	Document Management System
[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]	
IA	Interim Analysis
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
[redacted]	
IL	Interleukin
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
PCE	Pulse Controlled Ergometry
[redacted]	
PGA	Physician Global Assessment
[redacted]	
PRO	Patient Reported Outcomes
PSD	Premature Subject Discontinuation
PSDS	Post Study Drug Supply
PT	Prothrombin Time
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
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]	

Table of contents

List of abbreviations 3
Table of contents 6
1 Introduction 8
1.1 Study design 8
1.1.1 Screening 9
1.1.2 Double-blinded treatment period 9
1.2 Study objectives, endpoints and estimands 11
1.2.1 Primary estimand(s) 14
1.2.2 Secondary estimand(s) 15
2 Statistical methods 18
2.1 Data analysis general information 18
2.1.1 General definitions 18
2.2 Analysis sets 21
2.2.1 Subgroup of interest 22
2.3 Patient disposition, demographics and other baseline characteristics 22
2.3.1 Patient disposition 22
2.3.2 Demographics and other baseline characteristics 23
2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance) 24
2.4.1 Study treatment / compliance 24
2.4.2 Prior and concomitant therapies 24
2.5 Analysis supporting primary objective(s) 25
2.5.1 Primary endpoint(s) 25
2.5.2 Statistical hypothesis, model, and method of analysis 25
2.5.3 Handling of intercurrent events 26
2.5.4 Sensitivity analyses 27
2.5.5 Supplementary analyses 27
2.6 Analysis supporting secondary objectives 28
2.6.1 Secondary endpoint(s) 28
2.6.2 Statistical hypothesis, model, and method of analysis 28
2.6.3 Handling of intercurrent events 31
2.6.4 Handling of missing values not related to intercurrent event 33
2.6.5 Sensitivity analyses 33
2.6.6 Supplementary analyses 33
2.7 Safety analyses 34

2.7.1 Adverse events (AEs) 35
2.7.2 Deaths 37
2.7.3 Laboratory data 37
2.7.4 Other safety data 38
[redacted] 39
[redacted] 40
[redacted] 40
[redacted] 40
[redacted] 40
[redacted] 40
[redacted] 41
[redacted] 43
[redacted] 44
[redacted] 45
[redacted] 45
[redacted] 45
[redacted] 46
[redacted] 46
[redacted] 46
[redacted] 47
2.13 Interim analysis 48
3 Sample Size 48
4 Change to protocol specified analyses 52
5 Appendix 53
5.1 Classification of study regions by country 53
5.2 Derivation rules for Week 12 treatment period 53
5.3 Imputation rules 54
5.3.1 Study drug 54
5.3.2 AE date imputation 54
5.3.3 Concomitant medication date imputation 55
5.4 AEs coding/grading 58
5.5 Laboratory parameters derivations 58
5.6 Statistical models 60
5.7 Rule of exclusion criteria of analysis sets 60
6 Reference 60

1 Introduction

The purpose of Statistical Analysis Plan (SAP) is to describe the statistical analysis planned in the protocol for the clinical study report. The clinical study report will describe the results from this SAP.

This SAP is based on the original protocol version 0.0, dated 07-Jul-2021

:

Due to the early termination of the trial, screening was stopped and all subjects in treatment where discontinued, therefore the trial has a limited sample size. No statistical analyses will be performed on any dataset. Summarization of the data will be limited to data listings and summary tables where necessary Sections of the SAP are written as per protocol, language was added at the end of each section to address the termination of the study. Below are specific, high level changes to the SAP and subsequent output:

- Screening was stopped and all subjects in treatment where discontinued
- No statistical analyses will be performed on the primary endpoints
- No statistical analyses will be performed on the secondary endpoints
- [redacted]
- No interim analysis will be preformed
- No summary tables will be produced for efficacy
- [redacted]

1.1 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 adults and adolescents 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 7 visits during this period. Participants will receive treatment at 6 visits (Week 0, Week 4, Week 8, Week 12, Week 16 and Week 20). Week 24 is the End of Treatment visit; no treatment will be given at this 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.

On 06 April 2022, following extensive assessment of data from the Phase III studies of ligelizumab in CSU, Novartis communicated a strategic decision to discontinue further clinical development of ligelizumab in chronic urticaria (CSU and chronic inducible urticaria (CINDU)). The decision to not proceed was not based on any safety concerns with ligelizumab. As a result of this decision, this study CQGE031E12301 was terminated. At the time of study termination 39 participants were enrolled in the study.

1.1.1 Screening

Screening was stopped as of 6th April 2022.

As per protocol, the screening period was up to 4 weeks. 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.

Rescreening may be allowed for participants who failed initial screening. Only 1 rescreening will be allowed. 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.

1.1.2 Double-blinded treatment period

As a result of study termination, all subjects in the treatment phase were discontinued from treatment and moved into the follow-up phase. Only 3 subjects had completed Week 12 visit.

Below is a description of the treatment period as per protocol:

Symptomatic dermographism and cold urticaria cohorts: On Day 1, participants werel 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. 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. During the treatment period, doses are administered at 6 visits: Week 0, Week 4, Week, 8, Week 12, Week 16 and Week 20. 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) 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 3.

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

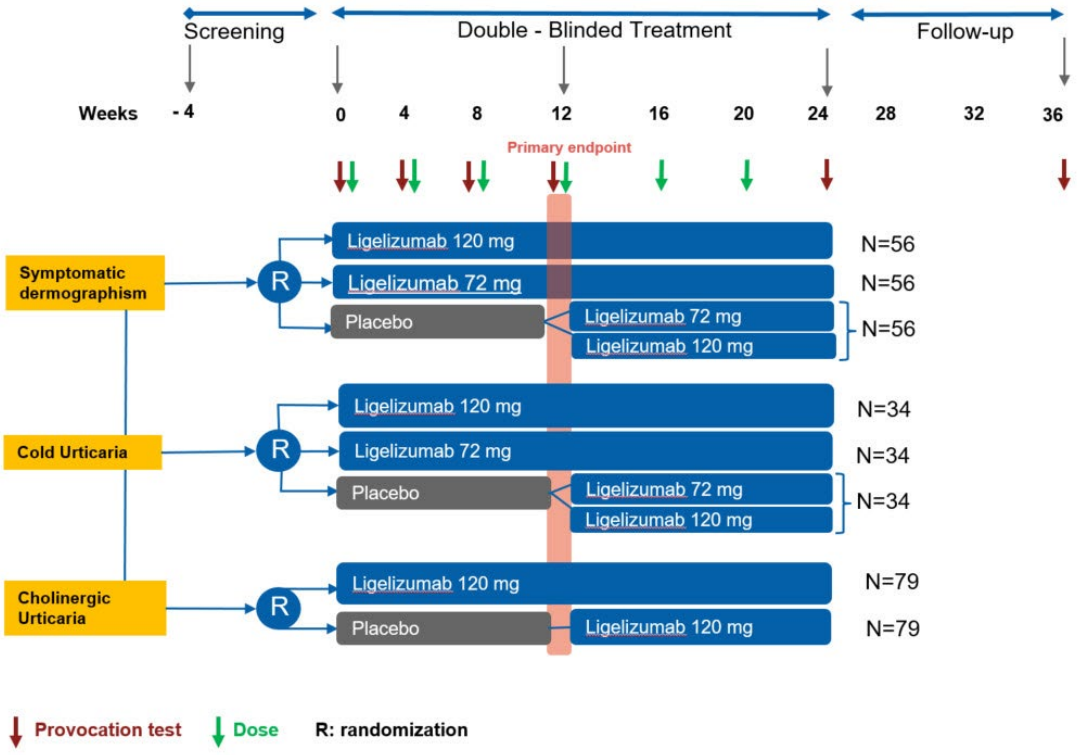
The follow-up period is 12 weeks with the last follow-up visit (Week 36) corresponding to 16 weeks after the last treatment dose. No study treatment will be given during the post-treatment follow-up period. Participants will continue with the background medication and will be allowed to take their rescue 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 of the study protocol, 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 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. The remote procedures will be offered in certain countries and sites as determined by Novartis based on national and local regulations. The off-site healthcare professionals whether provided by Novartis or by the site must be agreed with Novartis before use.

Figure 1-1 Study design



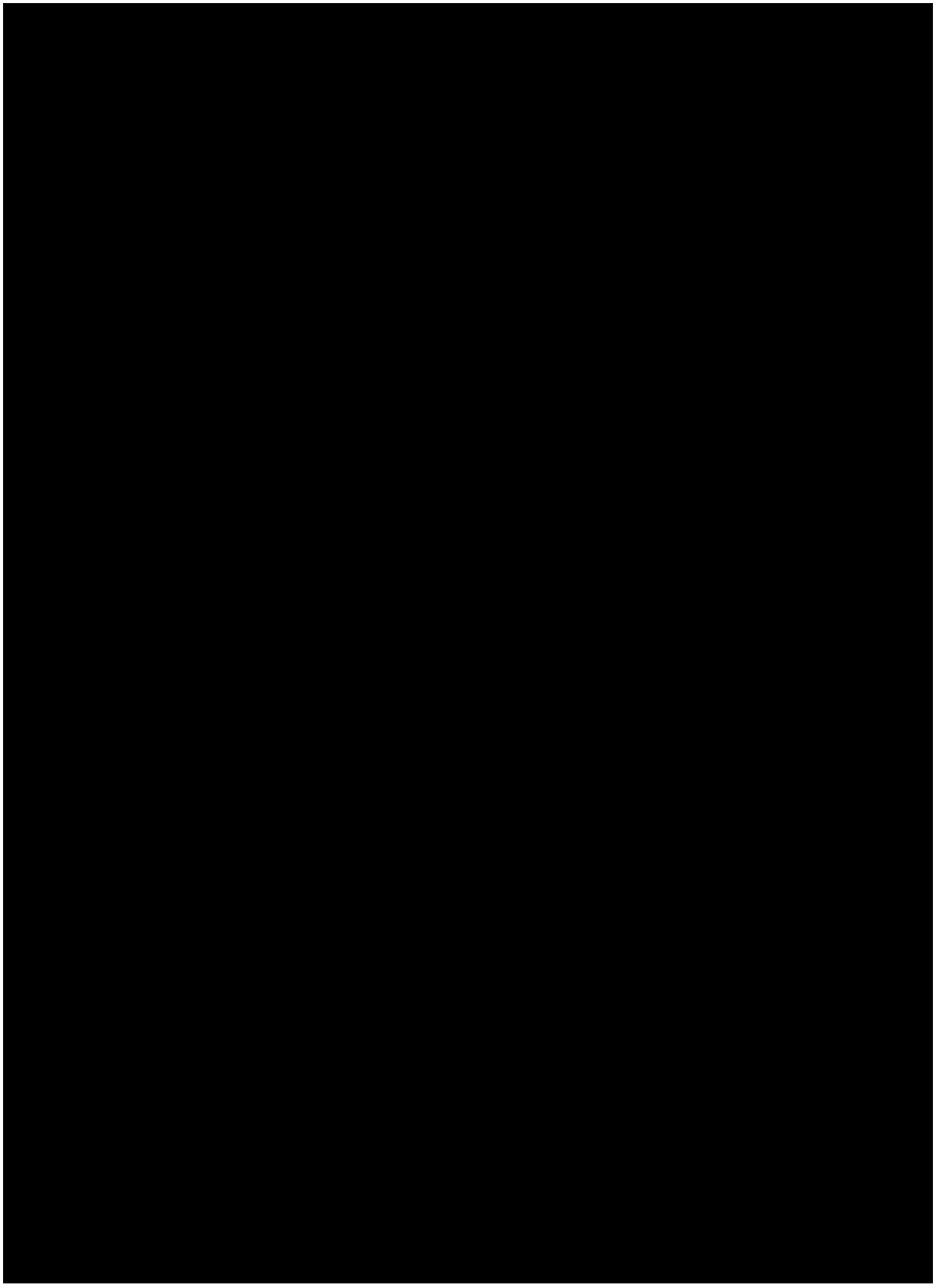
1.2 Study objectives, endpoints and estimands

Table 1-1 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.

Objective(s)	Endpoint(s)
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 To demonstrate superiority of ligelizumab versus placebo in itch NRS following the provocation test.	**Symptomatic Dermographism** Proportion of participants with complete response in FricTest® at Week 12 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

[redacted]



1.2.1 Primary estimand(s)

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 study protocol 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 study protocol Section 5.1 and 5.2). Further details about the population are provided in study protocol section 5.
- **Endpoint**:
    1. Symptomatic Dermographism: change from baseline to Week 12 in Total Fric Score (TFS, i.e., score derived based on results from the Fric Test 4.0, see study protocol Section 8.3.1.1 for details)

2. Cold urticaria: change from baseline to Week 12 in critical temperature thresholds (CTT, i.e. the highest temperature hives are triggered, see study protocol 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 (itch NRS) in response to the pulse-controlled ergometry (see study protocol 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 study protocol Section 6.
- **Handling of remaining intercurrent events**:
  - Discontinuation of initial assigned study treatment prior to Week 12 due to either adverse events (AE), or 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 study protocol Section 9.1.1. Retrieved drop out (RDO) data collected after study treatment discontinuation will be used for analysis. (*treatment policy*).
  - 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*)
  - Use of prohibited medications prior to Week 12 and not result in treatment discontinuation: ignore (*treatment policy*)
  - 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 other non-human controlled emergency situations (*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)

1.2.2 Secondary estimand(s)

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 study protocol Section 5.1 and 5.2).
- **Endpoints:**

Symptomatic dermographism:

1. proportion of participants achieving complete response (i.e. TFS = 0) in the FricTest®4.0 at week 12.
2. change from baseline to Week 12 in itch numeric rating scale (NRS) following the FricTest ®4.0.

Cold urticaria:

1. proportion of participants achieving complete response (a negative provocation test result for the lowest temperature (4°C) in TempTest®4.0 at week 12.
2. change from baseline to Week 12 in itch numeric rating scale (NRS) following the TempTest®4.0.

Cholinergic urticaria:

1. proportion of participants achieving complete response in itch NRS (itch NRS =0) following the pulse-controlled ergometry test at Week 12.
2. 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.

- **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.
- **Handling of remaining intercurrent events**:
    1. Discontinuation of initial assigned study treatment prior to Week 12 due to either adverse events (AE), or use of prohibited medications, or lack of efficacy (LoE):
        a. For continous endpoints “change from baseline to Week 12 in itch NRS following provocation tests” (applicable to symptomatic dermographism and cold uriticaria cohorts): participants who discontinue from study treatment early will be encouraged to stay in the study as detailed in study protocol Section 9.1.1.

Retrieved drop out (RDO) data collected after study treatment discontinuation will be used for analysis (*treatment policy*).

b. For binary endpoints (see table below): 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. (*composite strategy*).

Cohort	Endpoints
• symptomatic dermographism • cold urticaria	proportion of participants achieving complete response at Week 12 in response to provocation tests
• cholinergic urticaria	proportion of participants achieving complete response in itch NRS (itch NRS =0) following the pulse-controlled ergometry test at Week 12
	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

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 other non-human controlled emergency situations (*hypothetical strategy*)

- **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 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)

2 Statistical methods

2.1 Data analysis general information

Given that the study is terminated, the sample size is limited. Hence, the statistical analyses are narrow in scope. Summarization of the data will be limited to data listings and summary tables where necessary.

Data will be analyzed by the Novartis team internally following the protocol section 12, using SAS version 9.4 or above.

All data will be analyzed separately for each cohort (symptomatic, cold urticaria, cholinergic urticaria).

All listings will be provided by cohort and treatment groups.

All analyses will be provided for adolescents and the adults combined, unless stated otherwise. [redacted] Adolescents (<18 years old) or adults (≥ 18 years old) will be determined based on the baseline age at the time of enrollment The general descriptive statistical rules for summarizing the categorical data and continuous data are provided below:

All categorical data will be summarized by frequencies and percentages. The frequencies and percentages will also be presented for missing observations.

Continuous data will be summarized with either standard descriptive statistics (i.e. the number of non-missing data points, arithmetic mean, standard deviation, minimum, 25% percentiles(Q1), median, 75% percentiles (Q3) and maximum), or will be collapsed into categorical data and be summarized as categorical data.

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 between the three cohorts. This 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. If triggered, the interim futility analyses will be performed by the independent statistician and programmers in the separate CRO. An independent DMC will review unblinded interim reports created by the independent analysis team. Statistical Analysis Plan for the interim futility analyses will be prepared separately.

Due to a limited sample size and early termination of the study a futility analysis will not be conducted. Based on this, a DMC will not be triggered.

2.1.1 General definitions

2.1.1.1 Study Treatment

For symptomatic dermographism and cold urticaria cohorts, study treatment groups used for analysis are defined as below:

- Ligelizumab 72 mg q4w
- Ligelizumab 120 mg q4w
- Placebo – Ligelizumab 72 mg q4w
- Placebo – Ligelizumab 120 mg q4w

For cholinergic urticaria cohort, study treatment groups used for analysis are defined as below:

- Ligelizumab 120 mg q4w
- Placebo – Ligelizumab 120 mg q4w

2.1.1.2 Study Day 1 and other study days

The first day of administration of randomized study treatment (first dose) is defined as *study Day1* or *Day 1*.

All other study days will be labeled relative to Day 1. For event dates on or after Day 1, study day for a particular event date will be calculated as [Date of event] - [Date of first dose] + 1. For the dates before Day 1, study day for an event date will be calculated as [Date of event] - [Date of first dose].

Duration of an event will be calculated as (Event end date – Event start date + 1).

The descriptor "Day 0" will not be used.

2.1.1.3 Study Week based on RaveX collected visit information

For efficacy and safety data collected by eCRF at scheduled visit (provocation test outcomes, lab results, ECGs, vital signs, PROs, [redacted] etc..), study week will be defined based on the visit name. For by visit summary tables, all the information collected at the scheduled visit will be included for the analyses. Unscheduled visit information will not be included in the by visit summary descriptive statistics. The unscheduled visit information will be only included in the maximum or minimum post treatment assessment summaries.

[redacted]

[redacted]

2.1.1.5 Screening, baseline, and post-baseline

Screening refers to any procedures (e.g., checking inclusion and exclusion criteria) performed prior to the first dose of study treatment. Per protocol, subject informed consent must be obtained prior to performing any study related activity. The date of signing informed consent is the start date of screening period. Any assessment obtained during the screening period will be labeled screening assessment. Assessments made on Day 1 may occur before or after the first dose.

For efficacy analyses based on the provocation tests, baseline is the last assessment (including unscheduled visits) obtained on the randomization day. [redacted] All assessments obtained after randomization are considered as post-baseline unless otherwise specified.

For safety analyses (e.g., lab, vital sign assessments etc), baseline is the last assessment (including unscheduled visits) obtained (on or) before the first dose (day) of study treatment. For a subject who receives partial dose for the first dose day of study treatment, the baseline will still be defined according to the first dosing date of the partial dose. For a subject without any administration of study dose, the baseline assessment will be his/her last assessment under the study. If multiple assessments are taken on the same date, then the pre-dosing assessment closest to the dosing time (i.e., the latest recorded time prior to the dosing time on that date) will be used for baseline. If the recorded time parts of duplicated assessments are the same or missing, then the averaged outcome of the duplicated assessment on that date will be used for baseline. All assessments obtained after the first dose (day) of study treatment are considered as post-baseline unless otherwise specified.

Handling of multiple assessment on the same date, on the last date on or before treatment start date:

- ECG measurements: the worst outcome of them will be used for baseline.
- [redacted]

2.2 Analysis sets

For each CINDU cohort, the following analysis sets will be used in this trial:
The **Enrolled set (ENR)** will include all patients who had signed an informed consent form and had a screening visit.

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. Mis-randomized patients (mis-randomized in IRT) will be excluded. Mis-randomized patients are defined as cases where IRT contacts were made by the site either prematurely or inappropriately prior to confirmation of the patient's final randomization eligibility and no study medication was administered to the patient. FAS will be used for all efficacy variables, unless otherwise stated.

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.

[redacted]

The summary statistics analyses in this study will be performed in each cohort separately, according to domains with respective specifications of analyses sets, analyses period and treatment groups as described in Table 2-2.

Table 2-2 Summary statistics specifications

Domains	Analyses sets	Analysis Period	Treatment group labels for each analysis period
• Patient disposition	ENR	• Treatment period • follow-up period Entire study	Ligelizumab 72 mg q4w† Ligelizumab 120 mg q4w Placebo- Ligelizumab 72 mg q4w† Placebo- Ligelizumab 120 mg q4w Total

Domains	Analyses sets	Analysis Period	Treatment group labels for each analysis period
• Protocol deviations • Demographics • Other baseline characteristics	RAS	Entire study	Ligelizumab 72 mg q4w† Ligelizumab 120 mg q4w Placebo- Ligelizumab 72 mg q4w† Placebo- Ligelizumab 120 mg q4w Total
Efficacy data	FAS	Up to Week 12*	Ligelizumab 72 mg q4w † Ligelizumab 120 mg q4w Placebo
		Entire study	Ligelizumab 72 mg q4w † Ligelizumab 120 mg q4w Placebo- Ligelizumab 72 mg q4w † Placebo- Ligelizumab 120 mg q4w
• Study treatment exposure and • Safety data	SAF	Up to Week 12*	Ligelizumab 72 mg q4w † Ligelizumab 120 mg q4w Placebo
	SAF	Entire Study	Ligelizumab 72 mg q4w † Ligelizumab 120 mg q4w Placebo- Ligelizumab 72 mg q4w † Placebo- Ligelizumab 120 mg q4w

*Week 12 is defined as described in Appendix.
†Not applicable to the cholinergic urticaria cohort.

2.2.1 Subgroup of interest

There will be no subgroup analyses.

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

Patient disposition will be summarized and listed for each cohort separately

The number of screened subjects who complete the screening period will be given and the reasons for not entering into the double-blind treatment period will be summarized based on the ENR set.

The number and percentage of subjects in the RAS who got mis-randomized, completed or discontinued the treatment period will be presented by treatment group and overall. Reasons for discontinuation will be listed.

The number and percentage of subjects in the RAS who completed or discontinued the follow-up period, and the reasons for discontinuation will also be presented by treatment group and overall. The number and percentage of subjects who completed the entire study (defined as completed both the treatment period and the follow-up period) will be presented by treatment group and overall as well.

2.3.2 Demographics and other baseline characteristics

For each CINDU cohort, demographics and other baseline data including disease characteristics will be listed and summarized descriptively by treatment group in the RAS. Relevant medical history will be listed.

Summary statistics will be presented for continuous demographics and baseline characteristic variables for each treatment group and for all subjects in the RAS. The number and percentage of subjects in each category will be presented for categorical variables for each treatment group and all subjects.

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.

2.3.2.1 Demographics (collected at Visit 1)

- Age
- Age group (adolescents (12-17 years), adults (18 - <65 years, ≥ 65 years))
- Sex
- Race
- Ethnicity
- Region
- Weight
- Height
- Body Mass Index (BMI) – calculated as weight (kg) / (height (m))^2
- BMI group (< 25, 25 - < 30, >= 30 kg/m^2)

2.3.2.2 Disease characteristics at baseline

[redacted]

- Baseline score in response to the provocation test (TFS for symptomatic dermographism, CTT for cold urticaria, itch NRS for all three cohort)
- Baseline itch NRS=0 status

[redacted]

- Duration of CINDU – calculated as (first study treatment date – first diagnosis date +1)/365.25 years)
- Duration of a typical angioedema episode
- Type of prior urticaria medication
- Experienced angioedema within the past 4 weeks
- Duration of a typical episode of angioedema

2.3.2.3 Medical History

Any conditions entered as medical history or current medical condition at baseline will be coded using the MedDRA dictionary. They will be listed and include system organ class and preferred term of the MedDRA dictionary for RAS. Listings for CINDU-specific medical history will be provided as well.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

The analysis of treatment will be performed by each treatment group based on the SAF in each cohort separately.
The number of participants and the duration of exposure to each study drug and dose will be summarized by treatment. Duration of exposure is defined as the date of the last treatment minus the date of first study drug administration plus 4 weeks (28 days).

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

For all protocol deviations (PDs) listings will be generated by PD category and treatment groups in each cohort separately.

2.4.2 Prior and concomitant therapies

For each CINDU cohort, the Safety set will be used for the analyses below. Due to the limited sample size of the safety dataset only listing will be presented for prior, concomitant, and post therapies.

Prior medications are defined as medications taken by trial subject and the use was stopped prior to first dose of study treatment. Prior medications for CINDU and non-related to CINDU will be listed.

Concomitant medications are defined as any medication given at least once between the day of first dose of study treatment and the date of the last study visit. The medications started taking prior to the first dosing and still be used on or after the first dosing date will be also counted as concomitant medications. CINDU-related background medications, CINDU related concomitant medication and non-CINDU related medications listings will be provided.

Listings for rescue medication (H1-antihistamin) will be generated

Concomitant medication and rescue listings will be provided for:

- Up to Week 12 visit (Visit 130) in the treatment period: in all the treatment groups and will include data from the placebo arm prior to (and on) transition to active treatment (transitioned to ligelizumab 72mg or ligelizumab 120mg group). If the start date is before the 12 week treatment period cut off definition, it will be counted in the listing for the 12 weeks treatment period.

Entire study period: in all the treatment groups and will include data from the placebo arm after transition to active treatment (transitioned to ligelizumab 72mg or ligelizumab 120mg group).

2.5 Analysis supporting primary objective(s)

2.5.1 Primary endpoint(s)

For the three CINDU cohorts, the primary endpoint(s) is defined in the "endpoint" attribute of the primary estimand (Section 1.2).

2.5.2 Statistical hypothesis, model, 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 1.2.1.

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 TFS 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 TFS at week 12, negative value indicates improvement.

No formal statistical analysis will be performed due to limited sample size (see Section 4.). Listings will be presented for change from baseline at week 12 of Symptomatic Dermographsim.

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 1.2.1.

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.

No formal statistical analysis will be performed due to limited sample size (see Section 4.). Listings will be presented for change from baseline at week 12 of Cold Urticaria.

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 1.2.1.

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 2.6.2.

No formal statistical analysis will be performed due to limited sample size (see Section 4.). Listings will be presented for change from baseline at week 12 of Cholinergic Urticaria

2.5.3 Handling of intercurrent events

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

- **Discontinuation of assigned study treatment prior to Week 12 either for the reasons of 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 provocation tests are performed at the EOT and/or the EOS visit, and the provocation test date(s) is within the +/- 4 weeks window of the date of the planned Week 12 visit, then the outcomes yield from the EOT or EOS provocation test, whichever is closer to the planned Week 12 date, will be considered as the RDO data for the primary endpoint. If no RDO data was collected after study treatment permanent discontinuation, missing data for ligelizumab groups will be multiply imputed based on information borrowed from the placebo, and under the MAR assumption for the placebo group (*Treatment policy*).
- **Discontinuation of study treatment prior to Week 12 for the reasons other than AE or lack of efficacy or use of prohibited medications**: primary variable will be replaced by the multiply imputed values under the MAR assumption for all the groups (*hypothetical strategy*).
- **Use of prohibited medications prior to Week 12 and not result in treatment discontinuation**: handled by treatment policy, data collected after the intercurrent event will be used as it is (*Treatment policy*).

- **Missed treatment prior to Week 12 due to other non-human controlled emergency situations (e.g. COVID-19)**: primary variable will be replaced by the multiply imputed values under the MAR assumption for all the groups (*hypothetical strategy*).

2.5.3.1 Multiple intercurrent events occurring prior to Week 12

Multiple intercurrent events occurring prior to Week 12 will be handled by the hypothetical strategy only if all of them are classified as to be handled by the hypothetical strategy individually, in which case, data after the first intercurrent event will be replaced by multiply imputed values under the MAR assumption.

2.5.3.2 Handling of missing values not related to intercurrent event

For each of the CINDU cohort, the following will be considered as intermittent missing data, which are not related to intercurrent event:

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

The provocation test is not performed due to any reasons other than specified intercurrent events

Symptomatic dermographism

Handling of missing or incomplete results in the FricTest 4.0:

The missing TFS 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.

2.5.4 Sensitivity analyses

No sensitivity analyses will be performed.

2.5.5 Supplementary analyses

No supplementary analyses will be performed.

2.6 Analysis supporting secondary objectives

2.6.1 Secondary endpoint(s)

For the three CINDU cohorts, the secondary endpoint(s) is defined in the "endpoint" attribute of the secondary estimand (Section 1.2.2).

2.6.2 Statistical hypothesis, model, and method of analysis

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, missing responder status in corresponding provocation test (i.e. TFS, CTT, and itch NRS) will be multiply imputed in similar manner as described in Section 2.5.3 and Section 2.5.4, respectively.

Change from baseline to Week 12 on itch NRS in response to provocation tests will be analyzed 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 2.5.3 and Section 2.5.4, 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 endpoints

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 1.2.1.

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}: $\pi_{ligelizumab} > \pi_{Placebo}$

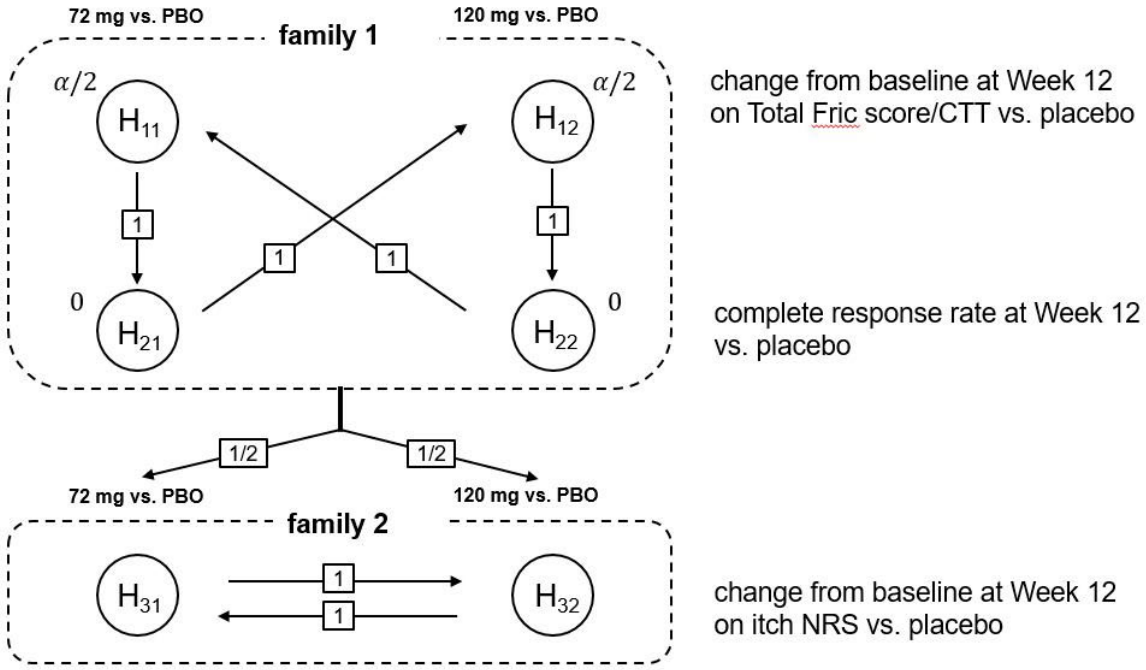
where π is the proportion of participants achieving complete response status at Week 12, as described in Section 1.2.2.

- 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 2-1 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

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

where μ is the mean change from baseline in itch NRS following the pulse-controlled ergometry test at Week 12, as described in Section 1.2.1.

Secondary endpoints

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

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

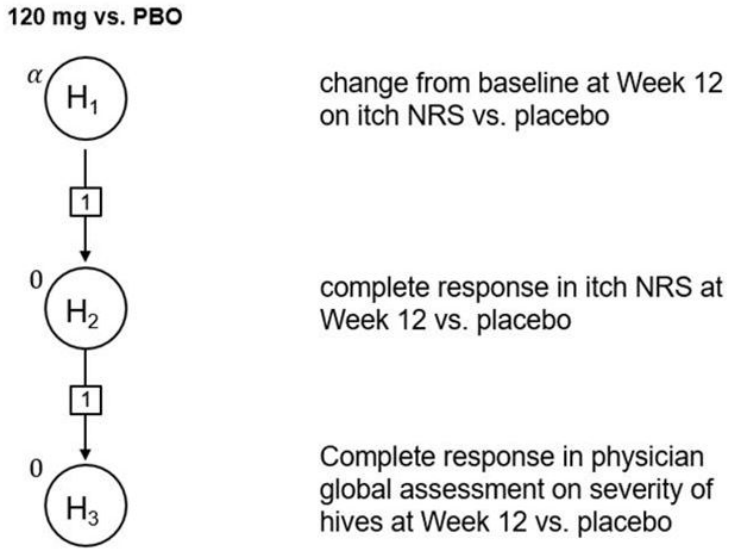
where π^{itch} is the proportion of participants achieving complete response in itch NRS at Week 12, as described in Section 1.2.2.

- 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

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

where π^{hive} is the proportion of participants achieving complete response in PGA hive score=0 at Week 12, as described in Section 1.2.2.

Figure 2-2 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.

There will be no statistical modeling, hypothesis testing, or methodology used for symptomics dermographism, cold urticaria, cholinergic urticaria due to limited sample size.

2.6.3 Handling of intercurrent events

Participants who discontinue from study treatment early will be encouraged to stay in the study following the procedure described in study protocol 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 for the secondary estimands will account for different intercurrent events as explained in the following:

- **Discontinuation of assigned study treatment prior to Week 12 either for the reasons of AE, or lack of efficacy, or use of prohibited medications**:
  a. For endpoints of "change from baseline to Week 12 in itch NRS following provocation tests" (applicable to symptomatic dermographism and cold uriticaria cohorts): participants who discontinue from study treatment early will be encouraged to stay in the study as detailed in study protocol Section 9.1.1.

Retrieved drop out (RDO) data collected after study treatment discontinuation will be used for analysis (*treatment policy*). If provocation tests are performed at the EOT and/or the EOS visit, and the provocation test date(s) is within the +/- 4 weeks window of the date of the planned Week 12 visit, then the outcomes yield from the EOT or EOS provocation test, whichever is closer to the planned Week 12 date, will be considered as the RDO data for the secondary endpoint. 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.

b. For binary endpoints (see table below): 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. (*composite strategy*).

Cohort	Endpoints
• symptomatic dermographism • cold uriticaria	proportion of participants achieving complete response at Week 12 in response to provocation tests
• cholinergic urticaria	proportion of participants achieving complete response in itch NRS (itch NRS =0) following the provocation test at Week 12
	proportion of participants achieving complete response in physician global assessment of severity of hives (i.e. PGA hive score=0) following the provocation test at week 12

- **Discontinuation of study treatment prior to Week 12 for the reasons other than AE or lack of efficacy or use of prohibited medications**: complete response status (Section 1.2.2) and itch NRS following the provocation tests will be treated as missing and multiply imputed under the MAR assumption for all the groups (*hypothetical strategy*).
- **Use of prohibited medications prior to Week 12 and not result in treatment discontinuation**: handled by treatment policy, data collected after the intercurrent event will be used as it is (*treatment policy*).
- **Missed treatment prior to Week 12 due to other non-human controlled emergency situations (e.g. COVID-19)**: complete response status (Section 1.2.2) and itch NRS following the provocation tests will be treated as missing and multiply imputed under the MAR assumption for all the groups (*hypothetical strategy*).

2.6.3.1 Multiple intercurrent events occurring prior to Week 12

For secondary estimands, multiple intercurrent events occurring prior to Week 12 will be handled by the following rules:

- If all of them are classified as to be handled by the hypothetical strategy individually: the hypothetical strategy will be used. Data after the first intercurrent event will be replaced by multiply imputed values under the MAR assumption.

- If one of them is classified as to be handled by the composite strategy: other intercurrent events will be ignored, complete response status after the composite-strategy intercurrent event will be regarded as non-responder.

2.6.4 Handling of missing values not related to intercurrent event

For each of the CINDU cohort, the following will be considered as intermittent missing data, which are not related to intercurrent event:

- The provocation test is stopped due to any reason e.g. participant discomfort, technical issues the data will be considered as missing.
- The provocation test is not performed due to any reasons other than specified intercurrent events

Symptomatic dermographism

Handling of missing or incomplete results in the FricTest 4.0:

- The missing TFS=0 complete response status will be multiply imputed under the MAR assumption for all the groups.
- The missing itch NRS following the provocation test 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 complete response status (a negative provocation test result for the lowest temperature (4°C) in TempTest®4.0) will be multiply imputed under the MAR assumption for all the groups.
- The missing itch NRS following the provocation test will be multiply imputed under the MAR assumption for all the groups.

Cholinergic urticaria

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

- The missing itch NRS=0 complete response status will be multiply imputed under the MAR assumption for both treatment groups.

The missing PGA hive score=0 complete response status will be multiply imputed under the MAR assumption for both treatment groups.

2.6.5 Sensitivity analyses

No sensitivity analyses will be performed.

2.6.6 Supplementary analyses

No Supplementary analyses will be performed.

2.7 Safety analyses

The following applies to each of the three cohorts (i.e., symptomatic dermographism, cold urticaria, and cholinergic urticaria) separately, and in the overall CINDU population.

For all safety analyses (i.e. AEs, laboratory data, vital signs, and ECG), the SAF 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.

Treatment groups for evaluation of treatment period

The summaries for evaluation of the treatment periods will allow for comparisons of treatment groups with placebo, before treatment switch is initiated. Therefore, the safety data for the Placebo-Ligelizumab 72mg/120mg q4w group will be provided in two separate periods.

As adverse event tables will be provided for the treatment period up to Week 12 separately, the Week 12 treatment period definition is the treatment period up to Week 12 dosing date (excluding the Week 12 dosing date). For the Placebo-Ligelizumab 72mg/120mg q4w group, if the first dosing date transitioning to ligelizumab happened earlier or later than the Week 12 dosing date (e.g. Week 4 or Week 8) due to a dosing error, the placebo treatment period will be cut-off by all the information prior to the first ligelizumab dosing date. The detailed description of the Week 12 cutoff date definition is provided in the statistical analysis plan appendix.

Treatment groups for evaluation of entire study

The summaries for evaluation of entire study will include all the information following the study design treatment groups. In addition, the following combined groups may be used for safety analysis.

Table 2-3 Treatment groups for safety analysis

	Ligelizumab 72mg q4w	**Ligelizumab 120mg q4w**	**Placebo**	**Transitioned to Ligelizumab 72mg/120mg q4w**
Treatment Period up to Week 12 visit	Yes[a]	Yes[a]	Yes[1]	No
Entire Study	Yes	Yes	No	Yes[2]

[1] The information before the treatment switching is initiated will be included. It means only the safety information from the period when participants receive placebo will be included in the analysis.

[2] The information after the treatment transitioned is initiated will be included. It means only the safety information from the period when participants receive ligelizumab 72mg/120mg q4w will be included in the analysis.

[a] The treatment groups will be included in the summary tables include information up to Week 12 visit.

2.7.1 Adverse events (AEs)

Treatment emergent adverse events (TEAEs) are events which started on or after the first dose of study treatment and within 16 weeks after the last study treatment, or events present prior to the first dose of study treatment but increased in severity based on preferred term within 16 weeks after the last study treatment.

TEAEs will be summarized in each cohort separately by the actually received treatment group:

- The number and exposure-adjusted incidence of subjects having any TEAE by system organ class (SOC) and preferred term (PT): For the participants in the placebo arm, adverse events after switching to ligelizumab (on or after Week 12) will be summarized separately for the treatment phase. The summary of the TEAEs up to Week 12 will include all the TEAEs up to Week 12 for all the treatment groups, including the placebo only group. The summary of the TEAEs for the entire study will be provided for all the treatment groups listed in Table 2-3.
- The number and exposure-adjusted incidence of subjects having any TEAE by severity: if a subject reported more than one adverse event with the same preferred term, the adverse event with the greatest severity will be presented. If a subject reported more than one adverse event within the same primary system organ class, the subject will be counted only once with the greatest severity at the system organ class level, where applicable.
- The number and exposure-adjusted incidence of subjects having any related TEAEs.: if a subject reported more than one adverse event with the same preferred term, the adverse event with the greatest severity will be presented. If a subject reported more than one adverse event within the same primary system organ class, the subject will be counted only once with the greatest severity at the system organ class level, where applicable.
- The number exposure-adjusted incidence of subjects having any serious treatment emergent adverse events (TESAEs), related TESAEs. The following significant adverse event will be listed - TEAEs leading to discontinuation and dose interruption, and TEAE adverse events of special interest (AESIs). For AESIs with adjudication (anaphylaxis, malignancy, CCV), separate listings will be provided based on the adjudicated results.
- A listing will be provided for safety topics of immunogenicity, COVID-19 infection, Liver Toxicity.

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables with treatment emergent adverse events which are not serious adverse events with an incidence greater than 5% and with treatment emergent serious adverse events and SAEs suspected to be related to study treatment, will be provided by system organ class and preferred term on the safety set population. These tables will not be included in the CSR.

If for the same participant, several consecutive TEAEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding TEAE and the start date of the consecutive TEAE.
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding TEAE and the start date of the consecutive TEAE.

For occurrence, the presence of at least one TESAE / TESAE suspected to be related to study treatment / non TESAE has to be checked in a block e.g., among TEAE's in a ≤ 1 day gap block. If at least one SAE is occurring, then one occurrence is calculated for that TESAE.

The number of deaths resulting from TESAEs suspected to be related to study treatment and TESAEs irrespective of study treatment relationship will be provided by SOC and PT.

2.7.1.1 Exposure-Adjusted Incidence Rate

Due to expected differences in exposure and follow-up due to varied duration of study participation between participants, adverse event incidence rates will be provided as "exposure adjusted AE incidence rates".

The EAIR is defined as the number of subjects with a specific event divided by the total exposure-time among the subjects in the study group. That is, the EAIR is calculated as:

$EAIR = n / \Sigma\, t_i$, where n is the number of subjects having the i^{th} type event, and t_i is a subject's exposure time and defined as the shortest of the following:

1) time to the first episode of the i^{th} type event (if the event occurs),
2) duration of study treatment plus the 16-week washout period (approximately corresponding to five half-lives) after last treatment dose, or
3) end of the analysis period (Week 12 for the placebo period, week 36 for all safety follow-up).

The total exposure time of all subjects in a treatment group is $\Sigma\, t_i$. The EAIR is interpreted as the number of events occurring in a population per unit time. The exact Poisson 95% confidence interval for the EAIR will be provided as well, where an exact 100*(1-α)% confidence interval will be derived as follows (Garwood 1936, Sahai and Khurshid 1993):

- Lower confidence limit $L = \frac{0.5C_{\alpha/2,2n}}{\Sigma\, t_i}$ for n>0, 0 otherwise,
- Upper confidence limit $U = \frac{0.5C_{1-\alpha/2,2n+2}}{\Sigma\, t_i}$,

where $C_{\alpha,k}$ is the αth quantile of the Chi-square distribution with k degrees of freedom.

Whenever applicable, exposure adjusted incidence rates will be provided for the type as below:

1. TEAE and TESAE: Primary SOC level, PT level
2. Most frequent (at least 5% in any treatment group) TEAE: Primary SOC level, PT level

Treatment emergent AE of special interest.

2.7.1.2 Adverse events of special interest / grouping of AEs

Treatment emergent adverse events of special interest (TEAESIs) for ligelizumab treatment will be summarized in each cohort separately.

AEs of special interest for QGE031 treatment include the following, specified as compound-level risk factors defined in the Case Retrieval Strategy (eCRS). The search criteria in the latest eCRS corresponding the MedDRA version at the database lock will be used and reported in the CSR:

- Hypersensitivity reactions (including anaphylaxis)
- Cardiovascular and Cerebrovascular (CCV) events
- Neoplastic conditions
- Injection site reactions
- Serum Sickness
- Churg-Strauss syndrome-Hypereosinophilic syndrome (HES)
- Parasitic (Helminthic) infections
- Thrombocytopenia

Adjudicated AEs

From the AESIs listed above, the following AEs will be adjudicated by the independent committee. The adjudicated events will be listed and a summary table will be provided following the adjudication.

- Anaphylaxis
- Cardiovascular and Cerebrovascular (CCV) events
- Neoplastic conditions

COVID-19 infection related analyses

Listings of all TEAE COVID infections will be presented. All suspected and confirmed infection will be provided. The COVID-19 infection will be filtered based on eCRS.

2.7.2 Deaths

Death will be reported as part of TESAE with a fatal outcome and will be listed in separate listings.

2.7.3 Laboratory data

The listings for laboratory evaluations will be presented for 3 groups of laboratory tests (hematology, serum chemistry, urinalysis) in each cohort separately.

Listings for the change from baseline to each study visit and maximum/minimum value will be generated. These listings will be presented by test group, laboratory test and treatment group. Change from baseline will only be summarized for subjects with both baseline and post baseline values for quantitative parameters, and the maximum/minimum value could come from post-baseline scheduled, unscheduled or premature discontinuation visits. Data from local laboratories will be presented in the listings together. 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, these results will be flagged in the listings.

The numerical part of the reported result will be treated as the actual LLOQ or ULOQ. These laboratory values will be displayed in listings using the standard unit with the reported sign ("<" or ">").

The number of participants with newly occurring or worsening abnormalities during the study will be listed by treatment based on the range of the observed data . A case is considered as a newly occurring abnormality if the value is not notable or missing at baseline but is notable thereafter during the study. A case is considered as a worsening abnormality if the value is notable at baseline and at least one post-baseline value during the study is worse than baseline.

If an adolescent subject turned to be an adult subject during the study, the normal range, notable criteria for analysis will be based on the age by the visit assessment.

2.7.4 Other safety data

2.7.4.1 ECG and cardiac imaging data

All listings will be provided for each CINDU cohort separately. A listing of all newly occurring or worsening abnormalities will be provided, as well as a by-subject listing of all quantitative ECG parameters.

The following will be considered as notable values for adults: QT > 500 msec; QTcF > 450 msec (males), QTcF > 460 msec (females); QTcF change from baseline > 30 msec, >60 msec; PR > 250 msec. The following were considered as notable ECG values for adolesents: QTcF >450 msec (males), QTcF >460 msec (females); QTcF change from baseline >30 msec, >60 msec; PR >250 msec.

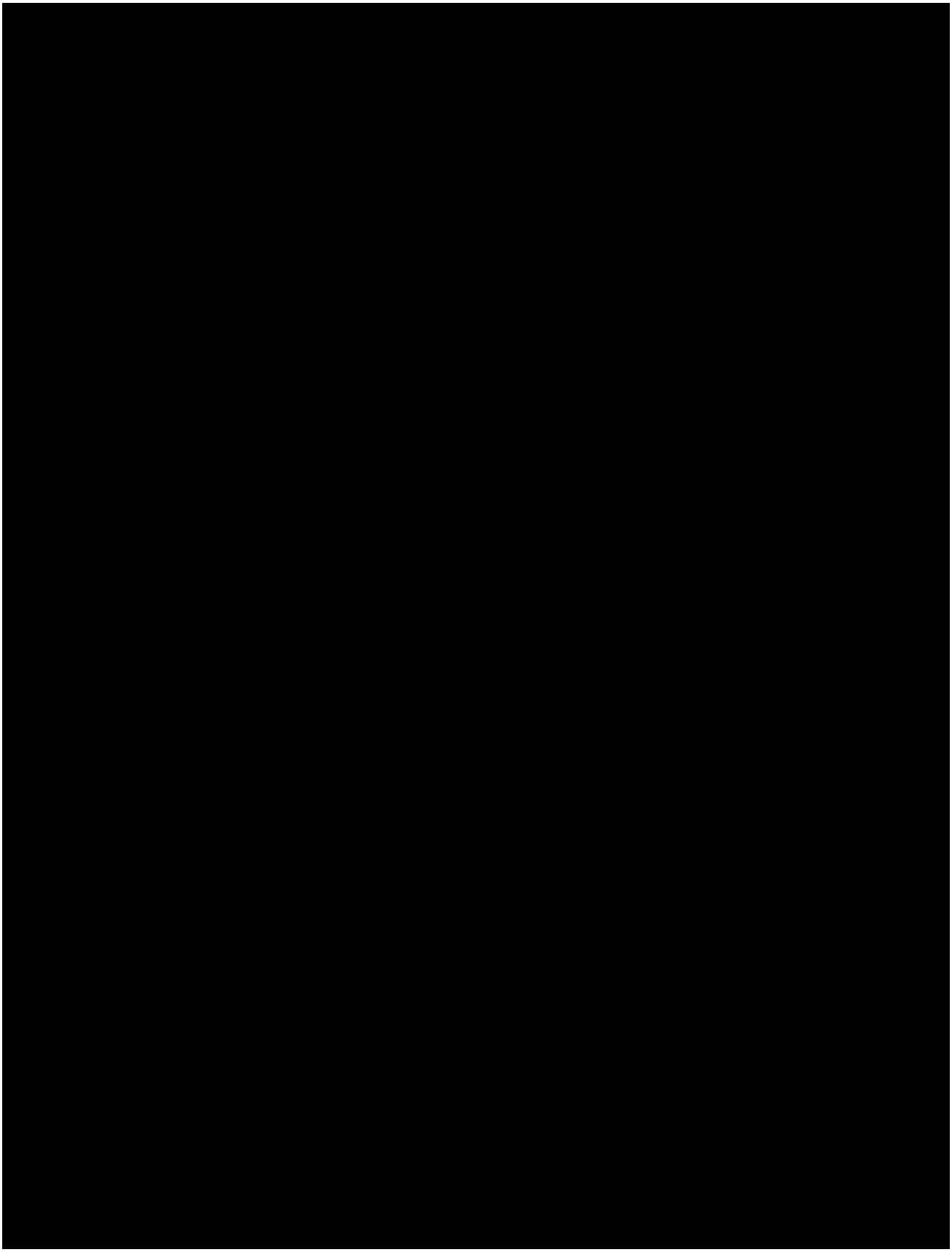
2.7.4.2 Vital signs

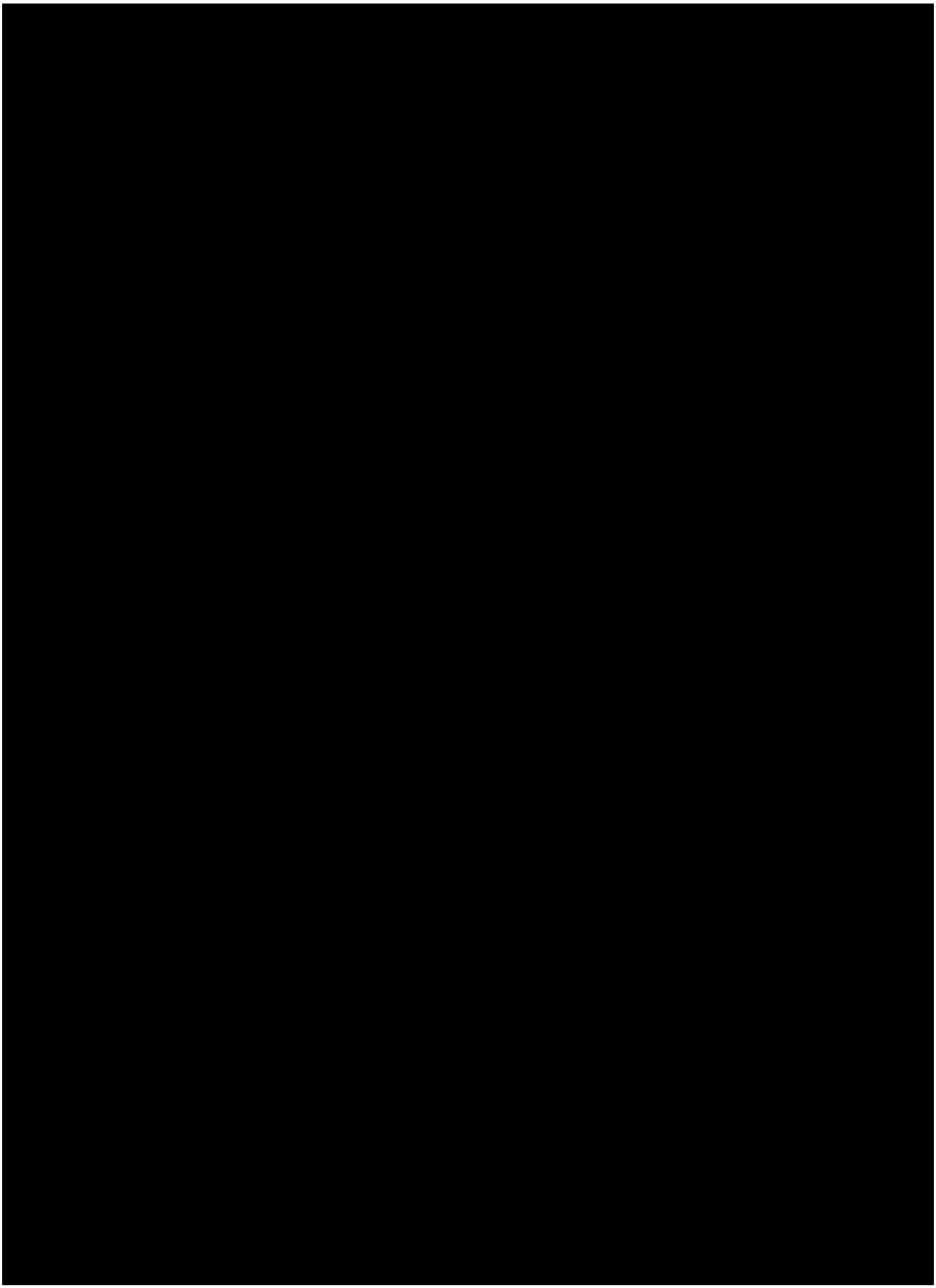
Subjects with notable vital signs as defined below will be listed.

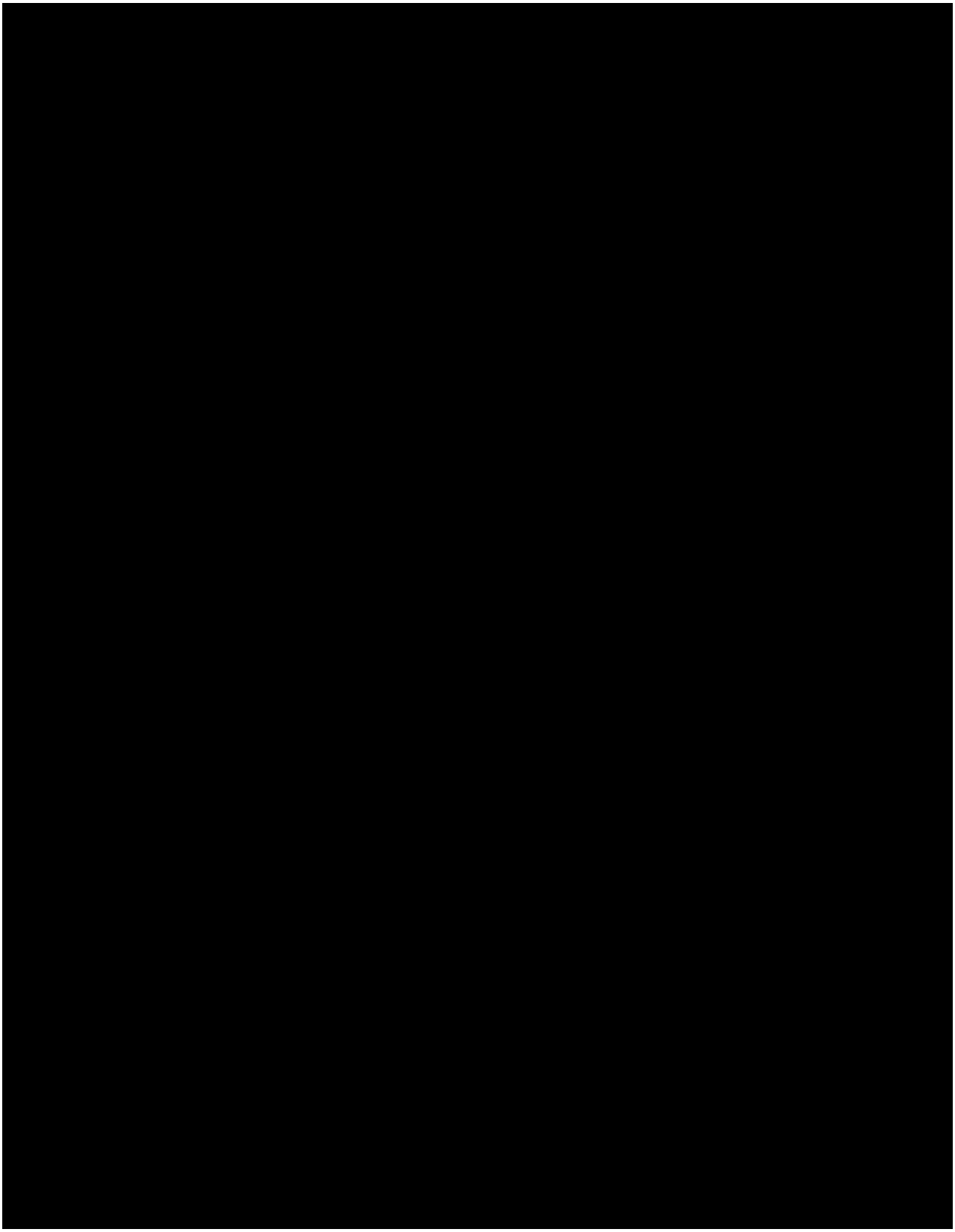
For adults:

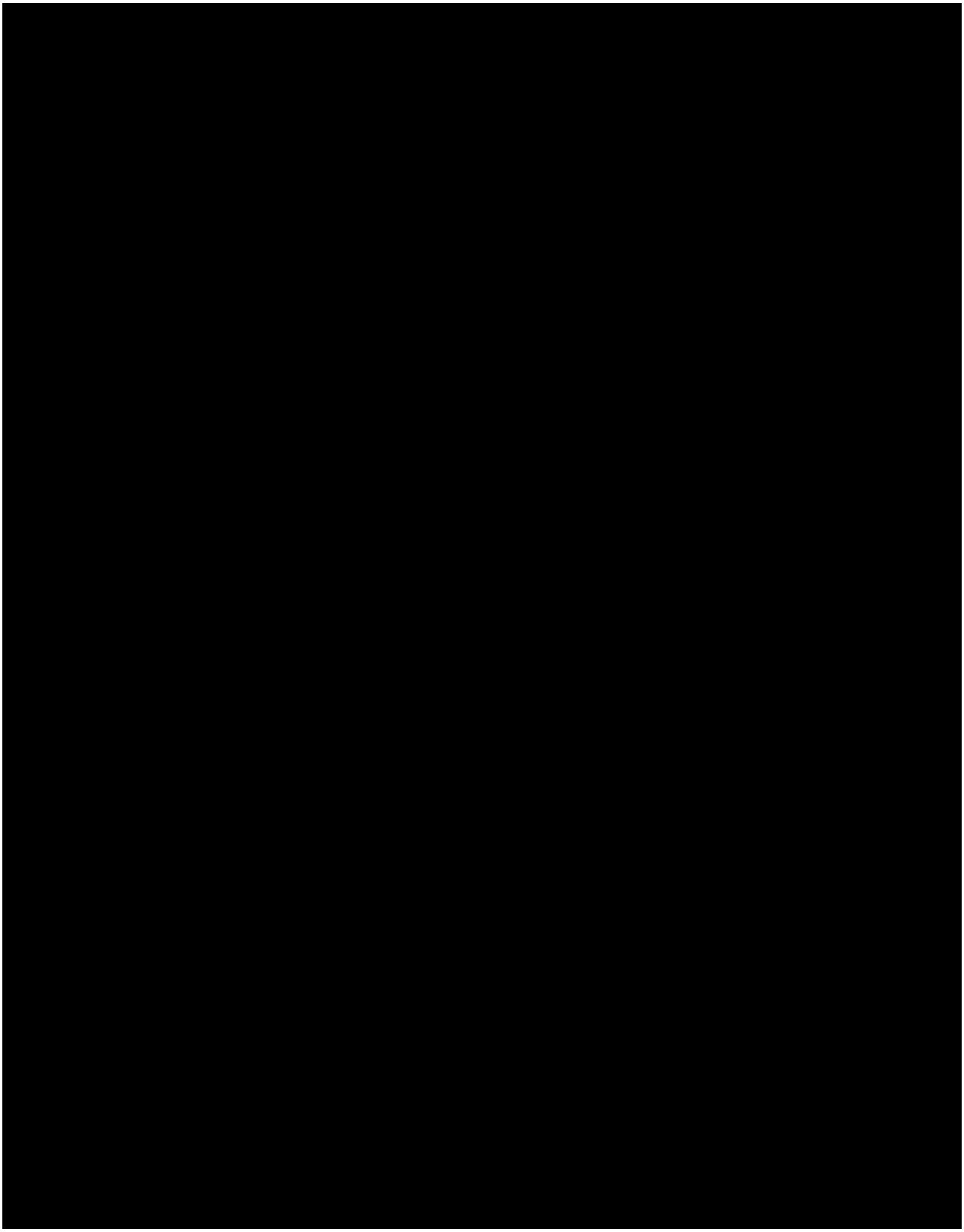
- Hypertension (systolic blood pressure of ≥ 140 mmHg and/or diastolic blood pressure of ≥ 90 mmHg) or hypotension (systolic blood pressure of < 90 mmHg and/or diastolic blood pressure of < 60 mmHg).
- Pulse rate below 60 bpm (bradycardia) or above 100 bpm (tachycardia).

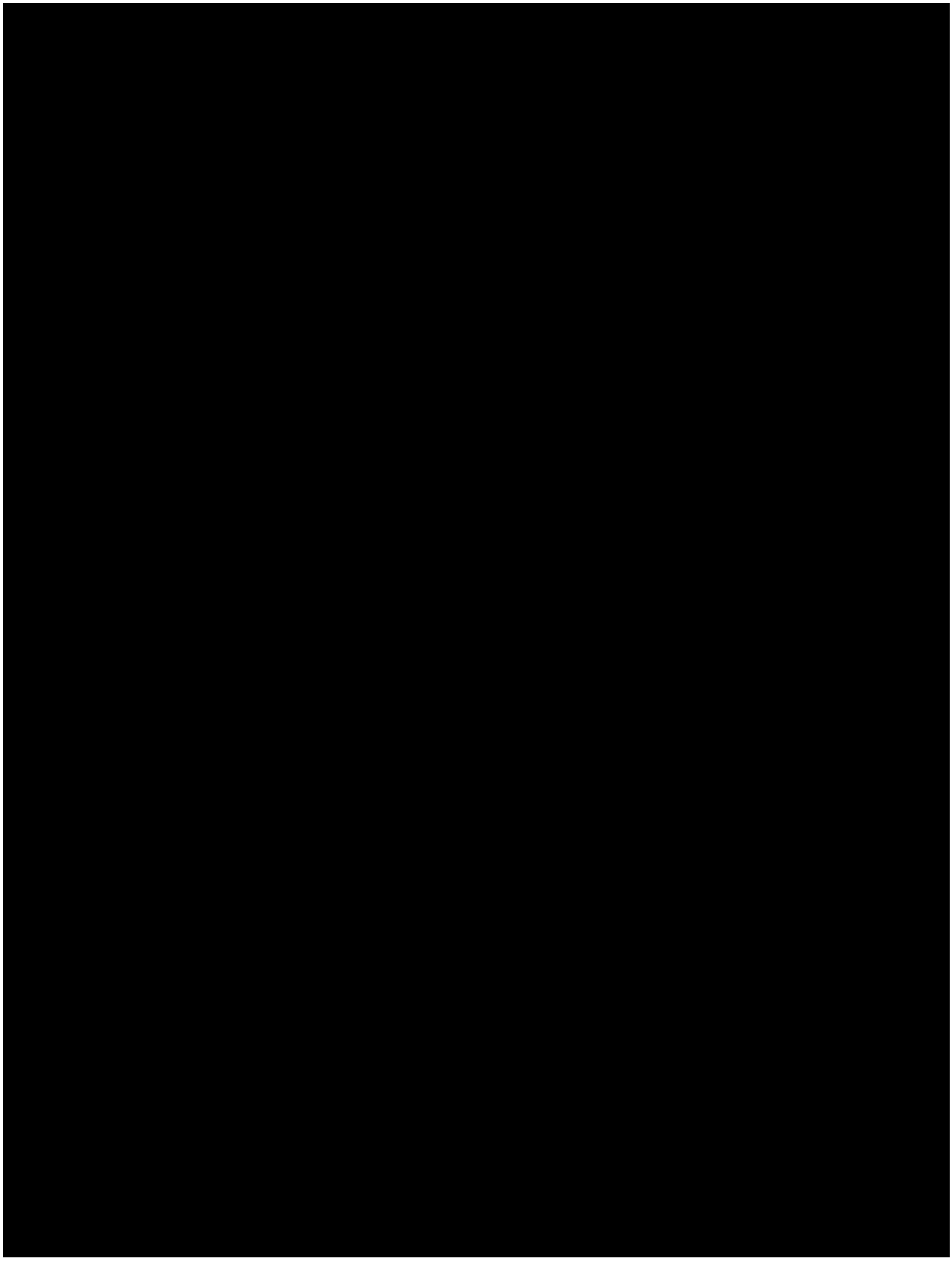
For adolescents: same normal range for adult will be used for adolescents.

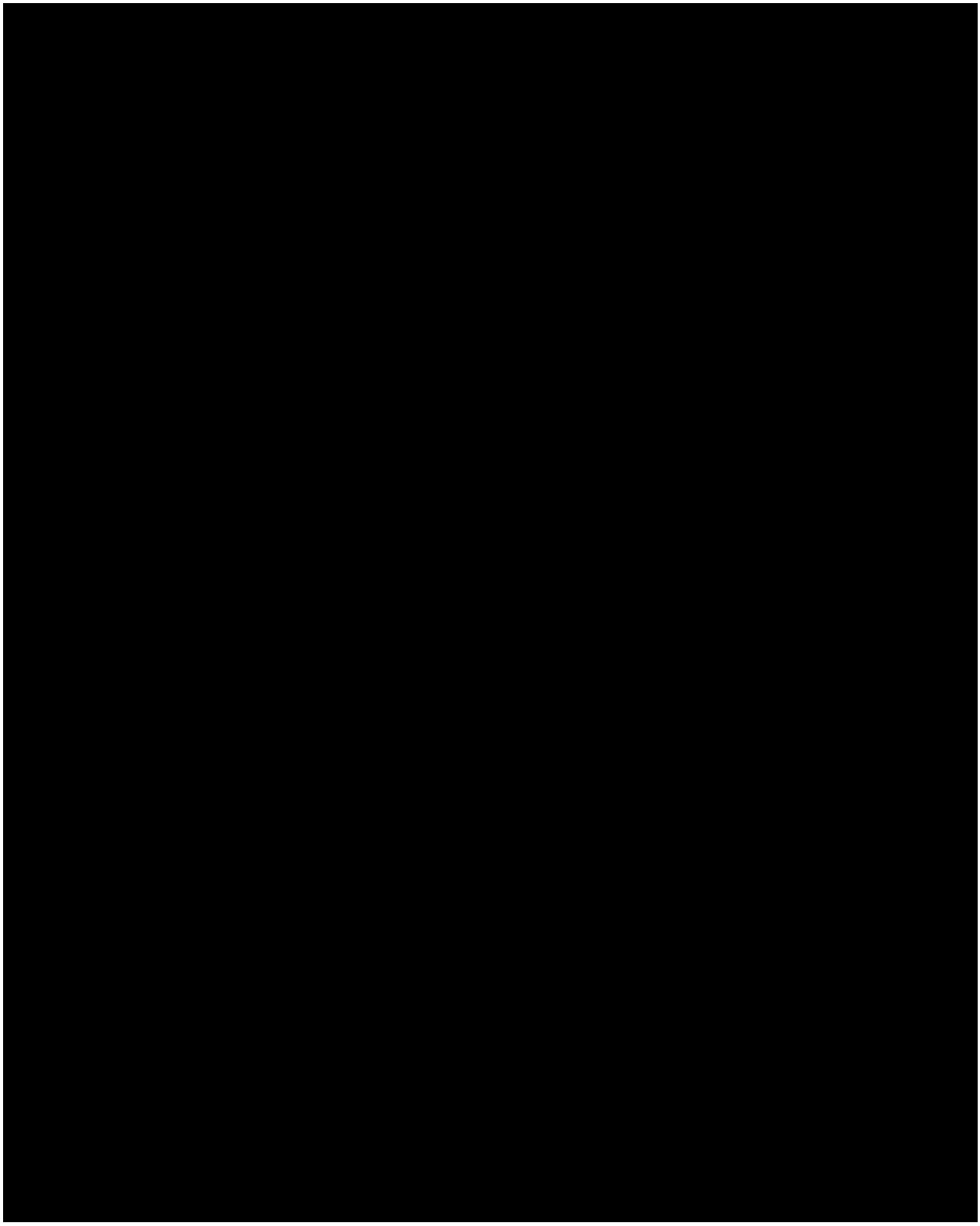


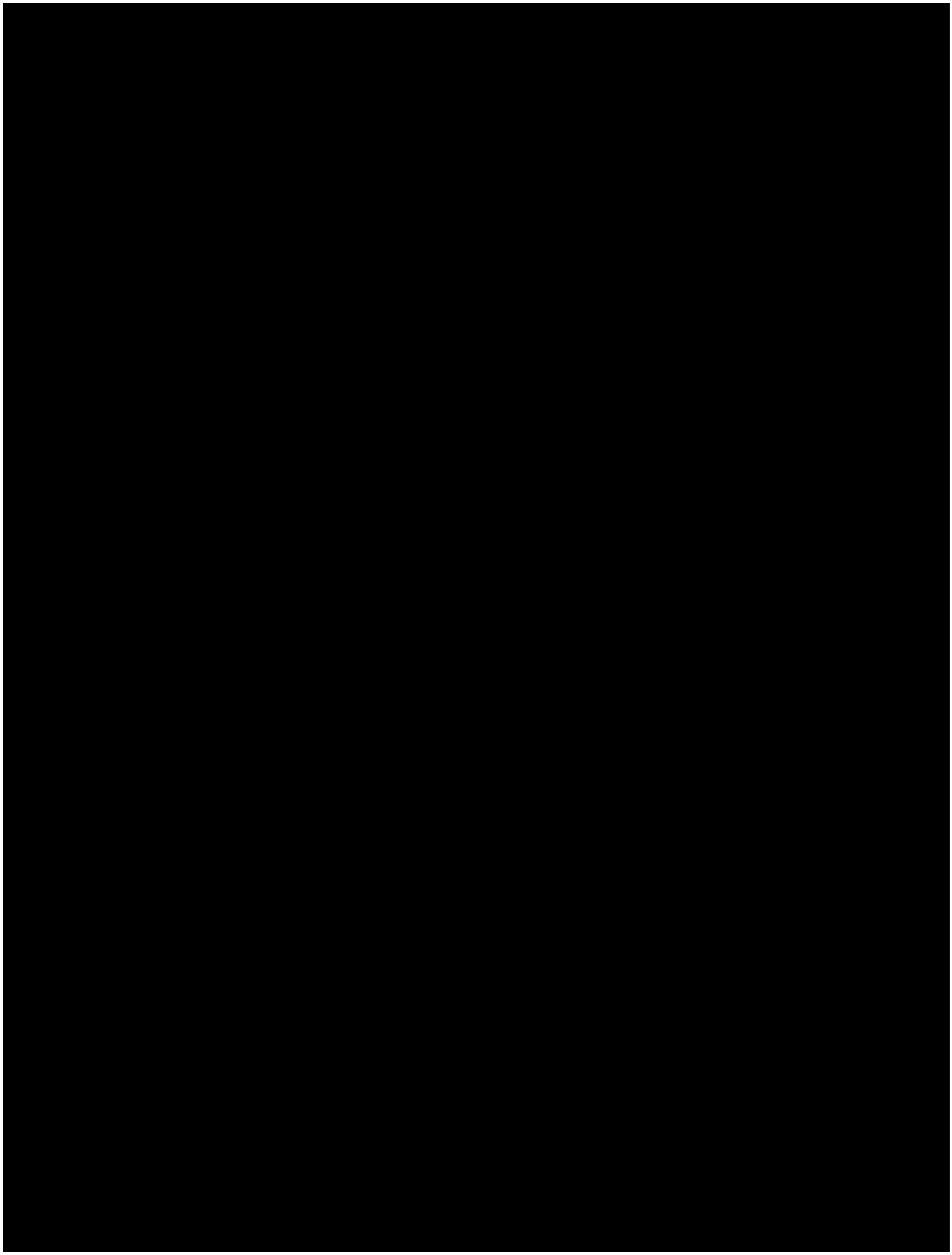


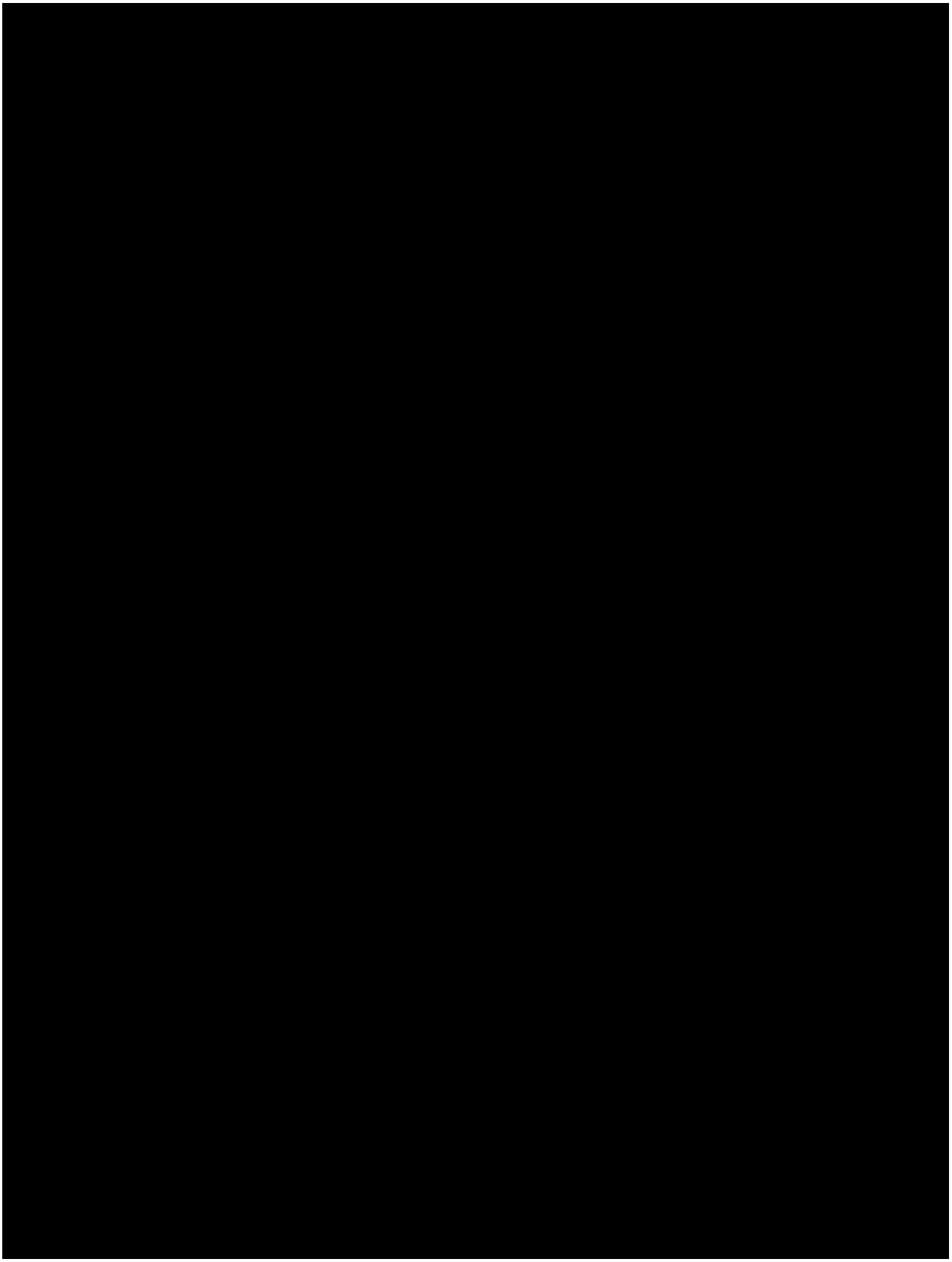


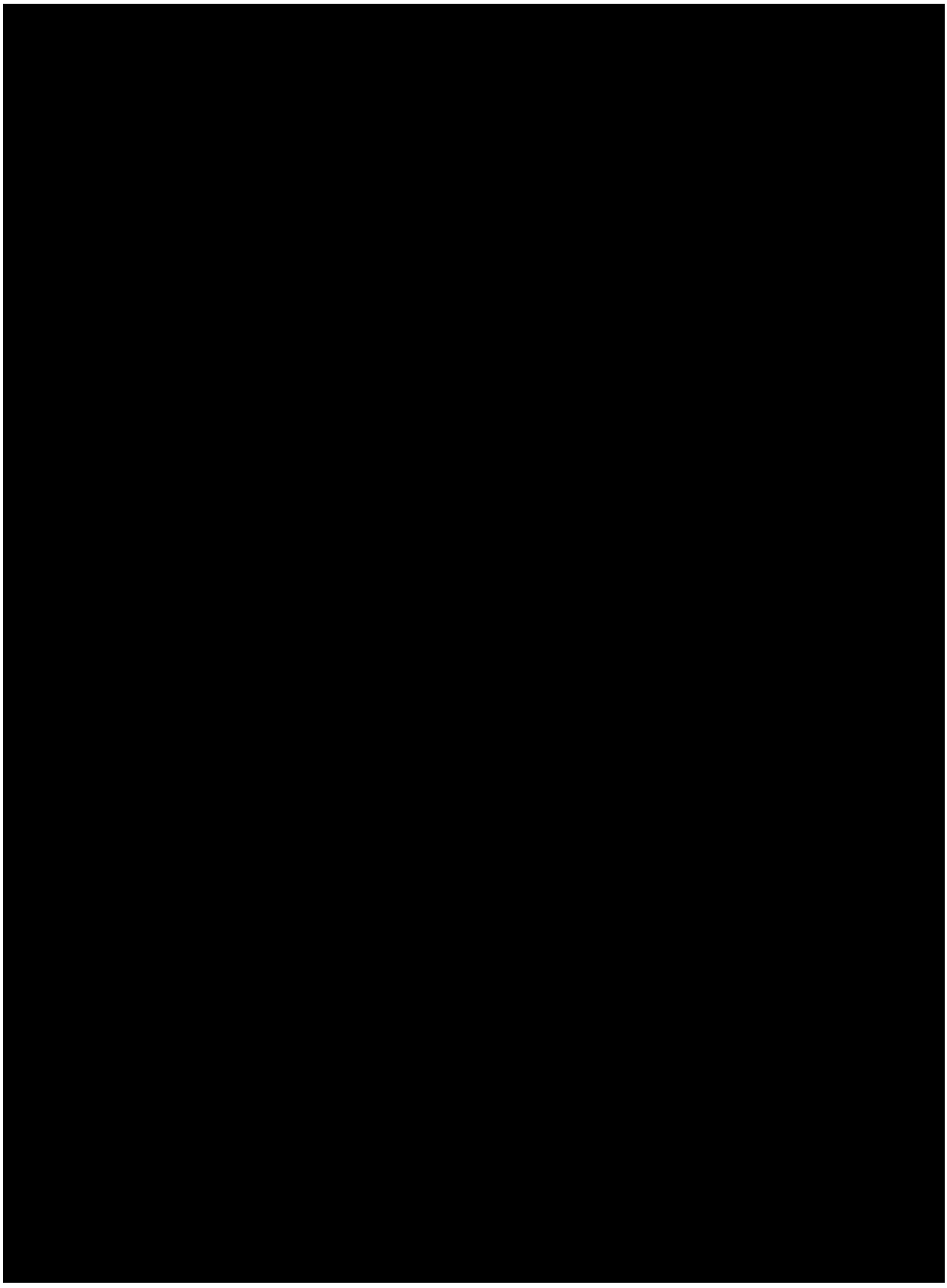












[redacted]

2.13 Interim analysis

The early termination of the trial was due to limited enrollment and hence a limited sample size. Therefore, a futility analysis will not be conducted.

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.

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.

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

3 Sample Size

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.

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.

3.1.1 Primary endpoint(s)

3.1.1.1 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 3-1 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				

3.1.1.2 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 3-2 Sensitivity of power to changes in assumptions (cold urticaria)

True treatment difference ligelizumab vs placebo (°C)	SD (°C)	Power for primary endpoint (one-sided α =1.25%, for N=34 per arm)		
		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				

3.1.1.3 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 3-3 Sensitivity of power to changes in assumptions (cholinergic urticaria)

True treatment difference ligelizumab vs placebo (itch NRS)	SD (itch NRS)	Power for primary endpoint (one-sided α =2.5%, N=79 per arm)		
		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 3-4 Required sample size for different targeted statistical power (cholinergic urticaria)

True treatment difference ligelizumab vs placebo (itch NRS)	SD (itch NRS)	Targeted statistical power for primary endpoint (one-sided α=2.5%)	Sample size required (%), from N=79 per arm		
			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					

3.1.2 Secondary endpoint(s)

3.1.2.1 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.

3.1.2.2 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

4 Change to protocol specified analyses

Due to the early termination of the trial and limited sample size no statistical analyses will be performed on any dataset. Summarization of the data will be limited to data listings and summary tables where necessary Below are specific changes to the SAP and subsequent output:

- No statistical analyses will be performed on the primary endpoints
- No statistical analyses will be performed on the secondary endpoints
- [redacted]
- No interim analysis will be preformed
- No summary tables will be produced for efficacy
- [redacted]

5 Appendix

5.1 Classification of study regions by country

Table 5-1 Region stratification defined by country enrollment:

Name	Study Countries
Asia	China; Korea; Malaysia; Thailand; Singapore;Vietnam; Philippines;Taiwan
Non-Asia	Other

5.2 Derivation rules for Week 12 treatment period

Week 12 treatment period cut-off date

The cutoff date for Week 12 treatment period is defined as below.

For the Placebo-Ligelizumab 72mg/120mg q4w group,

1. The first ligelizumab dosing date will be used if available;
2. Otherwise, if no ligelizumab dosing happened, then the cutoff date = min(end of study date, withdrawal of ICF date, date of death, IA cutoff date(if applicable)).

For other groups,

1. If participants complete treatment period or are still ongoing, the cutoff date is the first non-missing date of the following dates: Week 12 dosing date, Week 12 visit date, PD date of missing visit at Week 12, first dosing date + 12 weeks.
2. If participants early discontinue treatment,
    a. If last dosing visit is less than Week 12, then the cutoff date = min(end of study date, withdrawal of ICF date, date of death, IA cutoff date(if applicable)).
    b. If last dosing visit is great than or equal to Week 12, then the cutoff date is the first non-missing date of the following dates: Week 12 dosing date, Week 12 visit date, PD date of missing visit at Week 12, first dosing date + 12 weeks.

Adverse events summary tables:

The summary table is will be generated based on the cut-off date following the definition of “treatment period up to Week 12” in Table 2-5:

Adverse events happened at the same day with this cut-off date NOT included in “treatment period up to Week 12” tables.

5.3 Imputation rules

5.3.1 Study drug

No imputation of missing/partial start or study end date drug. If missing, the time of study end date will be imputed to 00:00:00.

5.3.2 AE date imputation

Rules for imputing the AE end date:

- If the AE end date month is missing, then the imputed end date should be set to the earliest of the study end date, 31DECYYYY or date of death.
- If the AE end date day is missing, then the imputed end date should be set to the earliest of the study end date, last day of the month or date of death.
- If AE year is missing or AE is ongoing, then the end date will not be imputed.

Rules for imputing the AE start date:

- If imputing end dates, then this should be done prior to calculating imputed start dates.

The following table explains the notation used in the logic matrix. Please note that **missing start dates** will not be imputed.

	Day	Month	Year
Partial Adverse Event Start Date	Not used	MON	YYYY
Treatment Start Date	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
YYYY MISSING	**(1)** No convention	**(1)** No convention	**(1)** No convention	**(1)** No convention
YYYY < TRTY	**(2.a)** Before Treatment Start	**(2.b)** Before Treatment Start	**(2.b)** Before Treatment Start	**(2.b)** Before Treatment Start
YYYY = TRTY	**(4.a)** Uncertain	**(4.b)** Before Treatment Start	**(4.c4.c)** Uncertain	**(4.c)** After Treatment Start
YYYY > TRTY	**(3.a)** After Treatment Start	**(3.b)** After Treatment Start	**(3.b)** After Treatment Start	**(3.b)** After Treatment Start

Before imputing AE start date, find the AE start reference date.

1. If the (imputed) AE end date is complete and the (imputed) AE end date < treatment start date, then AE start reference date = min(informed consent date, earliest visit date).
2. Otherwise, AE start reference date = treatment start date.

Impute AE start date:

1. If the AE start date year value is missing, then the date uncertainty is too high to impute a rational date. Therefore, if the AE year value is missing, then the imputed AE start date is set to NULL.
2. If the AE start date year value is less than the treatment start date year value, then the AE started before treatment. Therefore:
    a. If AE month is missing, then the imputed AE start date is set to the mid-year point (01JulYYYY).
    b. Otherwise, if AE month is not missing, then the imputed AE start date is set to the mid-month point (15MONYYYY).
3. If the AE start date year value is greater than the treatment start date year value, then the AE started after treatment. Therefore:
    a. If the AE month is missing, then the imputed AE start date is set to the year start point (01JanYYYY).
    b. Otherwise, if the AE month is not missing, then the imputed AE start date is set to the later of month start point (01MONYYYY) or AE start reference date + 1 day.
4. If the AE start date year value is equal to the treatment start date year value:
    a. If the AE month is missing, then the imputed AE start date is set to the AE reference start date + 1 day.
    b. If the AE month is less than the treatment start month, then the imputed AE start date is set to the mid-month point (15MONYYYY).
    c. Otherwise, if the AE month is equal to the treatment start date month or greater than the treatment start date month, then the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).

If complete (imputed) AE end date is available and the imputed AE start date is greater than the (imputed) AE end date, then imputed AE start date should be set to the (imputed) AE end date.

5.3.3 Concomitant medication date imputation

Rules for imputing the CM end date (including on-going records):

- When the medication is ongoing at the end of the study, no numeric end date is derived.
- If the end date is completely missing no numeric end date is derived.

a) If CM end day is missing and CM month/year are non-missing, then impute CM date as the minimum of study end date and the last day of the month.

b) If CM end day/month are missing and CM year is non-missing, then impute CM date as the minimum of study end date and the end of the year (31DECYYYY).

c) If imputed CM end date is less than the complete CM start date, use the complete CM start date as the imputed CM end date.

Rules for imputing the CM start date:

- If imputing end dates, then this should be done prior to calculating imputed start dates.

The following table explains the notation used in the logic matrix.

	Day	Month	Year
Partial CM Start Date	Not used	MON	YYYY
Treatment Start Date	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
YYYY MISSING	**(2.a)** Uncertain	**(2.a)** Uncertain	**(2.a)** Uncertain	**(2.a)** Uncertain
YYYY < TRTY	**(2.a)** Before Treatment Start	**(2.b)** Before Treatment Start	**(2.b)** Before Treatment Start	**(2.b)** Before Treatment Start
YYYY = TRTY	**(4.a)** Uncertain	**(4.b)** Before Treatment Start	**(4.a)** Uncertain	**(4.c)** After Treatment Start
YYYY > TRTY	**(3.a)** After Treatment Start	**(3.b)** After Treatment Start	**(3.b)** After Treatment Start	**(3.b3.b)** After Treatment Start

1. If the CM start date year value is missing, then the imputed CM start date is set to one day prior to *Treatment start date (TR01SDT)*.
2. If the CM start date year value is less than the *Treatment start date (TR01SDT)* year value, then the CM started before treatment. Therefore;
    a) If the CM month is missing, then the imputed CM start date is set to the mid-year point (01JulYYYY).
    b) Else if the CM month is not missing, then the imputed CM start date is set to the mid-month point (15MONYYYY).
3. If the CM start date year value is greater than the *Treatment start date (TR01SDT)* year value, the CM started after treatment. Therefore;
    a) If the CM month is missing, then the imputed CM start date is set to the year start point (01JanYYYY).
    b) Else if the CM month is not missing, then the imputed CM start date is set to the month start point (01MONYYYY).
4. If the CM start date year value is equal to the *Treatment start date (TR01SDT)* year value;

a) And the CM month is missing or the CM month is equal to the *Treatment start date (TR01SDT)* month, then the imputed CM start date is set to one day prior *Treatment start date (TR01SDT).*

b) Else if the CM month is less than the *Treatment start date (TR01SDT)* month, then the imputed CM start date is set to the mid-month point (15MONYYYY).

c) Else if the CM month is greater than the *Treatment start date (TR01SDT)* month, then the imputed CM start date is set to the month start point (01MONYYYY).

If complete (imputed) CM end date is available and the imputed CM start date is greater than the complete (imputed) CM end date, then imputed CM start date should be set to the complete (imputed) CM end date.

If there is no end date and ongoing check is not ticked, the CM will be considered as ongoing and included in the summary table.

5.3.3.1 Prior therapies date imputation

All therapies on the Prior urticaria therapy CRF page will be considered as prior. No additional imputation will be performed.

5.3.3.2 Post therapies date imputation

Not applicable.

5.3.3.3 Other imputations

Surgical and medical procedures date imputation
Missing data for surgical and medical procedures will be imputed following the same rule for CM date.

Medication history date imputation
Only missing medication history date for CSU diagnosis will be imputed to calculate the duration of CSU. No additional imputation will be performed for other medical history information.

Rules for imputing the MH start date**:**

1. If the MH start date year value is missing, the imputed MH start date is set to one day prior to *Treatment start date (TR01SDT);*
2. If the MH start date year value is less than the *Treatment start date (TR01SDT)* year value, the MH started before treatment; Therefore:
    a) If the MH month is missing, the imputed MH start date is set to the mid-year point (01JulYYYY).
    b) Else if the MH month is not missing, the imputed MH start date is set to the mid-month point (15MONYYYY).
3. If the MH start date year value is equal to the *Treatment start date (TR01SDT)* year value;

a) And the MH month is missing or the MH month is equal to the *Treatment start date (TR01SDT)* month, then the imputed MH start date is set to one day prior *Treatment start date (TR01SDT).*

b) Else if the MH month is less than the *Treatment start date (TR01SDT)* month, the imputed MH start date is set to the mid-month point (15MONYYYY).

c) Else if the MH month is greater than the *Treatment start date (TR01SDT)* month, the imputed MH start date is set to the month start point (01MONYYYY).

5.4 AEs coding/grading

Not applicable.

5.5 Laboratory parameters derivations

Type Clinically notable criteria

The following notable criteria will be used in the study:

Table 5-2 Clinically notable criteria

Variable	Notable criterion	
Creatinine (umol/L), Plasma/Serum Platelets (10E9/L), Blood	>= 50% increase compared to baseline < 75 x10E9/L	
Creatinine (umol/L), Plasma/Serum	>ULN – 1.5 x ULN >1.5 - 3.0 x ULN; >1.5 - 3.0 x baseline >3.0 - 6.0 x ULN; >3.0 x baseline	
Blood urea nitrogen* (mmol/L)	1.25 – 2.5 x ULN >2.5 – 5.0 x ULN >5.0 – 10.0 x ULN >10.0 x ULN	
Albumin (g/L)	<LLN - 30 g/L <30 - 20 g/L <20 g/L	
Alanine aminotransferase, ALT (U/L)	Normal baseline >ULN - 3.0 x ULN >3.0 – 5.0 x ULN >5.0 – 20.0 x ULN >20.0 x ULN	Baseline abnormal 1.5 – 3.0 x baseline >3.0 – 5.0 x baseline >5.0 – 20.0 x baseline >20.0 x baseline
Aspartate aminotransferase, AST (U/L)	Normal baseline >ULN - 3.0 x ULN >3.0 – 5.0 x ULN >5.0 – 20.0 x ULN >20.0 x ULN	Baseline abnormal 1.5 – 3.0 x baseline >3.0 – 5.0 x baseline >5.0 – 20.0 x baseline >20.0 x baseline

Variable	Notable criterion	
Alkaline phosphatase, ALP (U/L)	Normal baseline >ULN – 2.5 x ULN >2.5 – 5.0 x ULN >5.0 – 20.0 x ULN >20.0 x ULN	Baseline abnormal 2.0 – 2.5 x baseline >2.5 – 5.0 x baseline >5.0 – 20.0 x baseline >20.0 x baseline
Gamma glutamyl transferase, GGT (U/L)	Normal baseline >ULN – 2.5 x ULN >2.5 – 5.0 x ULN >5.0 – 20.0 x ULN >20.0 x ULN	Baseline abnormal 2.0 – 2.5 x baseline >2.5 – 5.0 x baseline >5.0 – 20.0 x baseline >20.0 x baseline
Bilirubin (umol/L)	Normal baseline >ULN – 1.5 x ULN >1.5 – 3.0 x ULN >3.0 – 10.0 x ULN >10.0 x ULN	Baseline abnormal >1.0 – 1.5 x baseline >1.5 – 3.0 x baseline >3.0 – 10.0 x baseline >10.0 x baseline
Platelets (10E9/L), Blood	<LLN # to 75 x10E9/L <75 - 50 x10E9/L < 50- 25 x10E9/L < 25 x10E9/L	
Leukocytes, WBC (10E9/L)	<LLN - 3.0 x 10E9/L <3.0 - 2.0 x 10E9/L <2.0 - 1.0 x 10E9/L <1.0 x 10E3 /mL	
	>100 x 10E9/L (leukocytosis, grade 3)	
Hemoglobin (g/L)	<LLN - 100 g/L <100 - 80g/L <80 g/L	
Lymphocytes (10E9/L)	<LLN - 0.8 x 10E9/L <0.8 - 0.5 x 10E9/L <0.5 - 0.2 x 10E9/L <0.2 x 10E9/L	
	>4.0 - 20 x 10E9/L (grade 2 lymphocytosis) >20 x 10E9/L (grade 3 lymphocytosis)	
Neutrophils (10E9/L)	<LLN - 1.5 x 10E9/L <1.5 - 1.0 x 10E9/L <1.0 - 0.5 x 10E9/L <0.5 x 10E9/L	

LLN = 140 x10E9/L

* No CTCAE grades provided for BUN. Values derived from Division of Microbiology and Infectious Diseases (DMID) grading system

When the parameters have different criteria for different baseline status (e.g., ATL, AST), the patients with normal baseline will follow the criteria on the left side, and the patients with abnormal baseline will follow the criteria on the right side.

Liver-enzyme abnormalities

Table 5-3 Liver- enzyme abnormalities

Parameter	Notable criterion
ALT	>3xULN; >5xULN; >10xULN; >20xULN

Parameter	Notable criterion
ALT or AST	>3xULN; >5xULN; >8 xULN;>10xULN; >20xULN
(ALT or AST) & TBL	>3xULN & (TBL >1.5xULN; >2xULN)
(ALT or AST) & INR	>3xULN & INR>1.5
TBL	1 xULN; 1.5xULN ; >2xULN
ALP	1.5xULN ; >2xULN; >5xULN
ALP & TBL	> 3xULN; > 5xULN; & (TBL 2xULN;)
(ALT or AST) & TBL & ALP	ALT or AST>3xULN & (TBL)>2xULN & ALP<2xULN (potential Hy's Law case)

AST = Aspartate aminotransferase; also known as SGOT, ALT = Alanine aminotransferase; also known as SGPT, ALP = Alkaline phosphatase, TBL = Total bilirubin

5.6 Statistical models

Not applicable

5.7 Rule of exclusion criteria of analysis sets

No PD will be used for excluding from any analysis set.

Table 5-4 Subject Classification

Analysis Set	PD ID that cause subjects to be excluded	Non-PD criteria that cause subjects to be excluded
RAS	NA	Not randomized
FAS	NA	Not in RAS; Mistakenly randomized and no double-blind study drug taken
SAF	NA	No double-blind study drug taken
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

6 Reference

Bretz F, Maurer W, Brannath W, Posch M (2009) A graphical approach to sequentially rejective multiple test procedures. Statistics in Medicine; 28: 586-604.

Carpenter JR, Roger JH, Kenward MG (2013) Analysis of longitudinal trials with protocol deviation: a framework for relevant, accessible assumptions, and inference via multiple imputation. J Biopharm Stat; 23(6):1352-71.

Garwood F (1936). Fiducial limits for the Poisson distribution. Biometrica 28:437-442.

ICH E9(R1) Harmonized Guideline: addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials. Final version on 20 November 2019.

Little, R.J.A and Rubin, D.B. (2002). Statistical Analysis with Missing Data. Wiley Series in Probabiliy and Statistics.

Permutt T (2015) Sensitivity analysis for missing data in regulatory submissions. Statistics in Medicine; 35: 2876-9.

Rubin, D.B. (1987). Multiple Imputation for Nonresponse in Surveys. New York: Wiley.Bretz, F, & Xi, D. (2019). Commentary on "Statistics at FDA: Reflections on the Past Six Years". Statistics in Biopharmaceutical Research, 11(1), 20-25.

Rup et al. (2015) Standardizing terms, definitions and concepts for describing and interpreting unwanted immunogenicity of biopharmaceuticals: recommendations of the Innovative Medicines Initiative ABIRISK consortium. Clinical and Experimental Immunology, 181: 385–400

Sahai H, Khurshid A (1993). Confidence intervals for the mean of a Poisson distribution: a review. Biometrical Journal; 7:857-867.

Shankar et al. (2014) Assessment and Reporting of the Clinical Immunogenicity of Therapeutic Proteins and Peptides - Harmonized Terminology and Tactical Recommendations. AAPS Journal, 16(4): 658-673

Yan X, et al. (2009) Missing data handling methods in medical device clinical trials. Journal of Biopharmaceutical Statistics; 19:6, 1085-1098.

[redacted]