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QGE031

Clinical Trial Protocol CQGE031G12301 / NCT04984876

A 52 week, multi-center, randomized, double-blind placebo-controlled study to assess the clinical efficacy and safety of ligelizumab (QGE031) in decreasing the sensitivity to peanuts in patients with peanut allergy

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List of abbreviations

AC	Adjudication Committee
ACE	Angiotensin converting enzyme
ACR	Albumin-to-creatinine ratio
[redacted]	[redacted]
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of covariance
APTT	Activated partial thromboplastin time
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
ATS	American Thoracic Society
AUC	Area under Curve
AV	Atrioventricular
[redacted]	[redacted]
BM	Biomarker
bpm	Beats per minute
BUN	Blood Urea Nitrogen
CD23	IgE (low affinity) receptor
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	confidence intervals
CK	Creatine Kinase
cm	centimeter
CMO&PS	Chief Medical Office and Patient Safety
CO	Country Organization
COA	Clinical Outcome Assessment
COVID-19	Corona Virus Disease 2019
CRA	Clinical Research Associate
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSR	Clinical study report
CSU	Chronic Spontaneous Urticaria
CT	Computed Tomography
CV	coefficient of variation
DBL	Database Lock
DBPCFC	Double Blind Placebo Controlled Food Challenge
DDE	Direct Data Entry
DIN	Drug Inducted Nephrotoxicity
DMC	Data Monitoring Committee
[redacted]	[redacted]
EAACI	European Academy of Allergy and Clinical Immunology
ECG	Electrocardiogram
eCRF	Electronic case report form

EDC	Electronic Data Capture
eSource	Electronic Source
EMA	European Medicines Agency
EOS	End of study
ERS	European Respiratory Society
EU	European Union
FAIM	Food Allergy Independent Measure
Fab	Fragment antigen binding region
FAQLQ	Food Allergy Quality of Life Questionnaire
FAS	Full Analysis Set
FcεRI	IgE (high affinity) receptor
FDA	Food and Drug Administration
FEV1	Forced Expiratory Volume during the 1st second
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GCS	Global Clinical Supply
eGFR	Estimated Glomerular Filtration Rate
GGT	Gamma-glutamyl transferase
GINA	Global Initiative for Asthma
GLDH	Glutamate Dehydrogenase
gMCP	Graph Based Multiple Comparison Procedures
HLT	High Level Term
HRQoL	Health-Related Quality of Life
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IG	Immunoglobulin
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IMP	Investigational Medicinal Product
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IU	International unit
IUD	Intrauterine device
IUS	Intrauterine system
KDIGO	Kidney Disease: Improving Global Outcomes
L	liter
LDH	lactate dehydrogenase
LFT	Liver function test
LLOQ	lower limit of quantification
MAR	Missing at random

[redacted]	[redacted]
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
mm	millimeter
mmHg	Blood pressure unit millimeters of mercury
MMRM	Mixed model with repeated measures
MRI	Magnetic Resonance Imaging
ms	millisecond
MTD	Maximum Tolerated Dose
NIH	National Institutes of Health
NOAEL	No Observed Adverse Effect level
NSD	Needle Safety Device
NYHA	New York Heart Association
OCS	Oral corticosteroids
OFC	Oral Food Challenge
OIT	Oral immunotherapy
PB	Parental Burden
PCR	Protein-creatinine ratio
PD	Pharmacodynamic(s)
PF	Parental Form
PFS	Prefilled Syringe
PK	Pharmacokinetic(s)
PRO	Patient Reported Outcomes
PSD	Premature Subject Discontinuation
PT	prothrombin time
q2w	every two weeks
q4w	Every 4 weeks
QMS	Quality Management System
QTcF	QT interval corrected by Fridericia's formula
RAS	Randomized Analysis Set
RBC	red blood cell(s)
RR	Responder rate
SABA	short-acting ß-agonist
SAE	Serious Adverse Event
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SC/ s.c.	subcutaneous
SCRN	Screening
sCD23	Soluble (low affinity) IgE receptor
SCq4W	Subcutaneous injection every 4 weeks
SD	standard deviation
sIgE	specific IgE for the study allergen
SLIT	Sublingual immunotherapy
SMQ	Standardized MedDRA Query

SOP	Standard Operating Procedure
SPT	Skin Prick Test
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBIL	Total Bilurubin
TBL	Total bilirubin
TFQ	Trial Feedback Questionnaires
Total IgE	Drug-bound and free IgE
TSPT	Titration skin prick test
UK	United Kingdom
ULN	upper limit of normal
US	United States
WBC	white blood cell(s)
WHO	World Health Organization
WK	Week
WoC	Withdrawal of Consent
β-hCG	Beta-Human Chorionic Gonadotropin
µL	microliter

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
Clinical Trial Team	A group of people responsible for the planning, execution and reporting of all clinical trial activities. Examples of team members include the Study Lead, Medical Monitor, Trial Statistician etc.
Cohort	A group of individuals who share a common exposure, experience or characteristic, or a group of individuals followed-up or traced over time
Control drug	A study drug (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Discontinuation from study	Point/time when the participant permanently stops receiving the study treatment and further protocol required assessments or follow-up, for any reason. No specific request is made to stop the use of their samples or data.
Discontinuation from study treatment	Point/time when the participant permanently stops receiving the study treatment for any reason (prior to the planned completion of study drug administration, if any). Participant agrees to the other protocol required assessments including follow-up. No specific request is made to stop the use of their samples or data.
Dosage	Dose of the study treatment given to the participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from source data/documents used at the point of care
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant or at a later point in time as defined by the protocol
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained
eSource (DDE)	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource Platform/Applications combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate
Estimand	As defined in the ICH E9(R1) addendum, estimand is a precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same participants under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
Investigational drug/ treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits
Mis-randomized participants	Mis-randomized participants are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study or the participant allocated to an invalid stratification factor

Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
Part	A sub-division of a study used to evaluate specific objectives or contain different populations. For example, one study could contain a single dose part and a multiple dose part, or a part in participants with established disease and in those with newly-diagnosed disease
Participant	A trial participant (can be a healthy volunteer or a patient)
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Patient-Reported Outcome (PRO)	A measurement based on a report that comes directly from the patient about the status of a participant's health condition without amendment or interpretation of the patient's report by a clinician or anyone else
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Premature participant withdrawal	Point/time when the participant exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued and no further assessments are planned
Randomization	The process of assigning trial participants to investigational drug or control/comparator drug using an element of chance to determine the assignments in order to reduce bias.
Randomization number	A unique identifier assigned to each randomized participant
Re-screening	If a participant fails the initial screening and is considered as a Screen Failure, he/she can be invited once for a new Screening visit after medical judgment and as specified by the protocol
Remote	Describes any trial activities performed at a location that is not the investigative site where the investigator will conduct the trial, but is for example a home or another appropriate location
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant
Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Study treatment discontinuation	When the participant permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Treatment of interest	The treatment of interest and, as appropriate, the alternative treatment to which comparison will be made. These might be individual interventions, combinations of interventions administered concurrently, e.g. as add-on to standard of care, or might consist of an overall regimen involving a complex sequence of interventions. This is the treatment of interest used in describing the related

	clinical question of interest, which might or might not be the same as the study treatment.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of study consent (WoC)	Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data and/ or biological samples AND no longer wishes to receive study treatment, AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. This request should be distinguished from a request to discontinue the study. Other study participant's privacy rights are described in the corresponding informed consent form.

Amendment 1 (12-Apr-2022)

Amendment rationale

The main purpose of this amendment is to

- Change the data review mode for the DMC from semi-blinded to unblinded as per request of the DMC from 12-Oct-2021.
- Adjust inclusion criterion number 4: The amended cutoff for positive peanut-specific IgE (peanut sIgE) is set at ≥ 0.35 kUA/L at Screening Visit 1 in order to avoid excluding patients with otherwise strong evidence supporting the diagnosis of peanut allergy (based on medical history and SPT).
- Clarify and harmonize usage of prohibited medication and medication allowed under certain conditions
- [redacted]
- Reduce the number of stool samples required to determine participant eligibility at screening from three to one in asymptomatic participants.
- Define two entry timepoints for participants who wish to enter the Extension study: at week 68 (end of follow-up) for the first one third of participants or week 52 (end of treatment) for the remaining participants.

It also includes other clarifications, minor updates and corrections of typographical errors across the document.

Changes to protocol and rationale:

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

- **Cover page:** addition of approval date and PIP number
- **List of Abbreviations:** Removal of abbreviations that are not required, correction of typographical errors, additions of required abbreviations
- **Glossary of terms:** Rewording of withdrawal of consent, mis-randomized participants and cohort.
- **Protocol summary:** rewording of data analysis section, rewording of eligibility criteria: positive skin prick test (SPT) for peanut allergen at Screening Visit 1 defined as an average diameter (Longest diameter and mid-point orthogonal diameter) ≥ 4 mm wheal compared to negative control, positive peanut-specific immunoglobulin E (peanut sIgE), ≥ 0.35 kUA/L at Screening Visit 1, a positive peanut DBPCFC at baseline (Screening Visit 2, Part 1 and Part 2 DBPCFC) defined as the occurrence of dose-limiting symptoms at a single dose ≤ 100 mg of peanut protein.
- [redacted]
- **Section 2.1:** Combining two intercurrent events due to operational complications caused by public health emergency into one category for simplification, rewording for clarity
- **Section 2.2:** Rewording of secondary estimands for clarification and simplification

- **Section 3:** Correction of visit timepoint (week 1), clarification of role of unblinded sponsor members in the interim analysis; clarification of timepoint: "baseline" replaced by "screening"; Definition of two timepoints for entering the Extension study, at week 52 or week 68.
- **Section 4.4:** Addition of wording on DMC for clarification
- **Section 4.5:** Summary of risk benefit section added; clarification that DMC review is unblinded; clarification that no contraception is required for male participants; explanation added why a double-blind placebo-controlled food challenge is required; addition of statement that most experience with OFC has been collected in children.
- **Section 4.6:** Public health emergency language updated.
- **Section 5:** typographical errors corrected
- **Section 5.1**: Peanut specific IgE cutoff changed to 0.35; symptoms on placebo challenge are allowed unless they are dose-limiting symptoms.
- **Section 5.2**: Reference for assessing renal values in children added – National Kidney Foundation 2002.
- **Section 6.2.1:** Addition of usage of stable regimen of controller treatment for asthma patients
- **Section 6.2.1.1:** Medications allowed under certain conditions: local corticosteroid and local anti-histamine usage adjusted; usage of long and short acting anti-histamines aligned.
- **Section 6.2.2:** Prohibited medication: Removal of short-term administration of prohibited medications; JAK inhibitors added; washout of systemic corticosteroids clarified.
- **Section 6.3.1.1:** Clarification added that the investigator must provide accountability for locally sourced material used for administration.
- **Section 6.4.2:** clarification of timepoint: "baseline" replaced by "screening"
- **Section 6.5:** Typographical errors corrected; Removal of sentence that participant needs to look away from injection site. Table 6-4: DMC removed from blinding table as they review unblinded data.
- **Section 7:** Addition of wording on ICF regarding risk/ benefit, voluntary study participation, source data documentation, optional consent for additional research and ICF copy for study participant
- **Section 8:** Emphasizing that original study schedule should be followed in case of a rescheduled visit; reconciliation of all dispensed investigational product for final visit needs to be done; delegation of investigator responsibility clarified; assessment schedule table 8-1: numbering of days corrected; PROs need to be done before physical exam at Randomization visit, physical exams need to be done at Day1, body height needs to be collected in the clinical database at Screening Visit 1, [redacted]; typographical errors corrected.
- **Section 8.1:** Assent added to Informed Consent.
- **Section 8.2:** Addition that collection of race and ethnicity data are depending on HA feedback.
- **Section 8.3.1:** Typographical errors corrected.

- **Section 8.4:** Spirometry added to safety evaluations
- **Section 8.4.1:** Clarification that if blood limits are exceeded, the guidance in the prioritization table in the flow chart should be followed.
- **Section 8.4.3:** FSH testing is suggested but not required.
- **Section 8.4.4:** Reduce the number of stool samples required to determine participant eligibility at screening from three to one in asymptomatic participants and three in symptomatic patients at screening and throughout the study.
- **Section 8.5.1**: References corrected
- [redacted]
- **Section 8.5.3.3:** Double coding of samples is not done anymore.
- **Section 9.1.1:** Redundant sentence on emergency code break removed.
- **Section 9.2:** Withdrawal of consent/ exercise of participants' data privacy rights are further specified in this section as well as the heading is updated to align with protocol template V5.0.
- **Section 9.3**: Definition of two entry timepoints for participants who wish to enter the Extension study: at week 68 (end of follow-up) for the first one third of participants or week 52 (end of treatment) for the remaining participants.
- **Section 10.1.3:** SAE reporting language updated; including reference to more stringent local regulations. Reporting of SAEs is described with reference to ligelizumab half-life.
- **Section 10.1.4:** Pregnancy reporting: clarification added on SAE reporting and timepoints
- **Section 10.1.5:** Table on study treatment errors removed; the text from deleted table is included in the text of Section 10.1.5.
- **Section 10.3.1**: Clarification that the DMC will review unblinded data.
- **Section 11.1:** Removal of redundant sentence
- **Section 12.1:** Editorial changes were made for clarification
- **Section 12.2**: Replacing FAS and Safety set with Randomized set and adding geometric mean for non-normal variables
- **Section 12.3 and Section 12.4.2:** Editorial changes were made for clarification
- **Section 12.4.3**: Combing two intercurrent events due to operational complications caused by public health emergency into one category for simplification
- **Section 12.4.7**: Clarifying total IgE at Screening Visit 1 for subgroup analysis, and removing the method of handling non-convergence issue for simplification
- **Section 12.5.1**: Adding the principle of handling intercurrent events and missing data for key secondary endpoints; Adding log-transformed total IgE at Screening Visit 1 into ANCOVA model for peanut specific IgE and IgG4 endpoints, correcting comparison time point for SPT (Week 16 instead of Week 12) and adding details of descriptive analysis for FAQLQ and SF-36v2.
- **Section 12.5.2**: Adding editorial changes and removing description of listings for simplicity as details of listings will be provided in SAP

[redacted]

- **Section 12.6.1**: Removing the description of listings for simplicity; Removing wording of handling values below LLOQ as details will be fully specified in SAP

[redacted]

- **Section 12.6.4:** Editorial changes were made for clarification
- **Section 12.6.5**: Removing the description of listings for simplicity
- **Section 12.7:** Adding DMC analysis for clarification; clarification that a dose-exposure-Response model to describe the responder rate and the factors impacting the response will be developed
- **Section 16:** References on CoFAR grading scale, ICF E2D Guideline, National Kidney Foundation added.
- **Section 16.4.2:** Reference to exceeding 7 day window removed.
- **Section 16.4.2.1:** Dry weight information for OFC challenge base material added.
- **Section 16.4.2.3:** Dry weight information added to dosing table
- **Section 16.4.3:** High and low dose composition corrected.
- **Section 16.4.4:** Information on allergen kit assignment added
- **Section 16.4.5**: CoFAR reference added
- **Section 16.4.6**: Causality assessment added to SAE reporting
- **Section 16.5.2**: Syringe added to material used for SPT
- **Section 16.5.3**: Prohibited medication for SPT aligned with section 6.2.2

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC and Health Authority approval according to local regulations prior to implementation.

The changes herein affect the trial specific model ICF.

Protocol summary

Protocol number	CQGE031G12301
Full Title	A 52 week, multi-center, randomized, double-blind placebo-controlled study to assess the clinical efficacy and safety of ligelizumab (QGE031) in decreasing the sensitivity to peanuts in patients with peanut allergy
Brief title	Efficacy and safety of QGE031 (ligelizumab) in patients with peanut allergy
Sponsor and Clinical Phase	Novartis Phase 3
Investigation type	Biological
Study type	Interventional
Purpose	The purpose of this study is to evaluate the clinical efficacy and safety of ligelizumab 240 mg and 120 mg compared to placebo in participants with peanut allergy
Primary Objective(s)	To evaluate the efficacy of ligelizumab 240 mg and 120 mg (SCq4w) compared to placebo, as measured by the proportion of participants who can tolerate a single dose of ≥ 600 mg (1044 mg cumulative tolerated dose) of peanut protein without dose-limiting symptoms during the DBPCFC at Week 12. The primary clinical question of interest is: What is the efficacy of ligelizumab compared to placebo as measured by the proportion of participants who can tolerate a single dose of ≥ 600 mg (1044 mg cumulative tolerated dose) of peanut protein without dose-limiting symptoms during the DBPCFC at Week 12, in the absence of operational complications caused by a public health emergency (e.g. the COVID-19 pandemic), regardless of intake of rescue medication prior to Week 12?
Secondary Objectives	**Key secondary objectives** • To evaluate the efficacy of ligelizumab 240 mg and 120 mg (SCq4w), compared to placebo, as measured by the proportion of participants who can tolerate a single dose of ≥ 1000 mg (2044 mg cumulative tolerated dose) of peanut protein without dose-limiting symptoms during the DBPCFC at Week 12 • To evaluate the efficacy of ligelizumab 240 mg and 120 mg (SCq4w), compared to placebo, as measured by the proportion of participants who can tolerate a single dose of 3000 mg (5044 mg cumulative tolerated dose) of peanut protein without dose-limiting symptoms during the DBPCFC at Week 12 • To evaluate the efficacy of ligelizumab 240 mg and 120 mg (SCq4w), compared to placebo, as measured by the maximum symptom severity at any single challenge dose up to and including 1000 mg of peanut protein during the DBPCFC at week 12 • To evaluate the efficacy of 8 weeks of placebo treatment followed by 4 weeks of ligelizumab 120 mg / 240 mg (SCq4w) treatment compared to 12 weeks of placebo treatment, as measured by the proportion of participants who can tolerate a single dose ≥1000 mg of peanut protein without dose-limiting symptoms during the DBPCFC at Week 12 **Other secondary objectives** • To evaluate the efficacy of ligelizumab 240 mg and 120 mg (SCq4w), as measured by the proportion of participants who can tolerate a single dose of ≥1000 mg (2044 mg cumulative tolerated dose) of peanut protein without dose-limiting symptoms during the DBPCFC at Week 52 compared to Week 12 • To evaluate the effects of ligelizumab 240 mg and 120 mg (SCq4w), compared to placebo (when applicable), as measured by multiple systemic biomarkers to inform on response to treatment or disease severity • To evaluate the safety and tolerability of ligelizumab 240 mg and 120 mg (SCq4w) • To assess the ability of IgE suppression to impact skin mast cells through the assessment of allergen-specific skin prick test (SPT). • To evaluate the impact of ligelizumab on the health-related quality of life (HRQoL) of patients with peanut allergy.

Study design	This is a 52-week, Phase 3 multi-center, randomized, double-blind and placebo-controlled study to assess the safety and clinical efficacy of two dosing regimens of ligelizumab (240 mg and 120 mg) SCq4w (subcutaneous injection every 4 weeks) in participants with a medically confirmed diagnosis of IgE-mediated peanut allergy.
Rationale	To demonstrate that ligelizumab 240 mg and 120 mg given subcutaneously (SC) every 4 weeks (q4w) ensures protection against food allergic reactions by decreasing the sensitivity to oral peanut allergen in participants aged 6 to 55 years with peanut allergy.
Study population	The study consists of approximately 486 participants (male and female) aged 6 - 55 years who have been diagnosed with IgE-mediated peanut allergy.
Key Inclusion criteria	• Male or female participants who are ≥ 6 and ≤ 55 years of age at the time of signing informed consent/assent. • Documented medical history of allergy to peanuts or peanut-containing foods. • Positive peanut-specific immunoglobulin E (peanut sIgE), ≥ 0.35 kUA/L at Screening Visit 1.Screening • Positive skin prick test (SPT) for peanut allergen at Screening Visit 1 defined as an average diameter (Longest diameter and mid-point orthogonal diameter) ≥ 4 mm wheal compared to negative control. • A positive peanut DBPCFC at baseline (Screening Visit 2, Part 1 and Part 2 DBPCFC) defined as the occurrence of dose-limiting symptoms at a single dose ≤ 100 mg of peanut protein. Eligibility to proceed with the DBPCFC requires fulfillment of all other eligibility criteria. • Participants must weigh ≥ 20 kg at Screening Visit 1.

Key Exclusion criteria	• Total IgE >2000 IU/mL at Screening Visit 1.
	• History of severe or life-threatening hypersensitivity event needing an ICU admission or intubation within 60 days prior to baseline DBPCFC (Screening Visit 2).
	• Participants with uncontrolled asthma (according to GINA guidelines, GINA 2020) who meet any of the following criteria:
	  • FEV1 <80% of subject's predicted normal value at Screening Visit 1
	  • One hospitalization for asthma within 12 months prior to Screening Visit 1

Study treatment	QGE031 120 mg/1ml QGE031 Placebo/1ml
Efficacy assessments	Double blind placebo controlled food challenge (DBPCFC)
Key safety assessments	Adverse event monitoring, physical examinations, monitoring of laboratory markers in blood and urine, ECGs, assessment of pregnancy and fertility, assessment of parasitic infection, assessment of anaphylactic events, cardiocerebrovascular and neoplastic events.
[redacted]	
Data analysis	The primary endpoint for this study is the proportion of participants tolerating a single dose of ≥ 600 mg (1044 mg cumulative tolerated dose) of peanut protein without dose-limiting symptoms during the DBPCFC conducted at the end of 12 weeks of treatment.

	Participants with treatment discontinuation or missing more than 1 dose of study drug prior to Week 12 due to non-operational public health emergency or reasons unrelated to public health emergency will be considered non-responders. The null hypotheses for the primary endpoint being tested is any of the ligelizumab groups (low or high dose) is not superior to placebo group with respect to the responder rate at a single dose of 600 mg peanut protein without dose-limiting symptoms at Week 12. The primary estimation method is based on a logistic regression model, including treatment, age subgroup (6– 11 years, 12–17 years, 18-55 years), region as fixed class effects and log-transformed total IgE at Screening Visit 1 as a covariate. The key secondary efficacy endpoints included in the testing strategy are: • Responder status defined as tolerating a single dose of ≥ 1000 mg (2044 mg cumulative tolerated dose) peanut protein without dose-limiting symptoms at Week 12. • Responder status defined as tolerating a single dose of 3000 mg (5044 mg cumulative tolerated dose) peanut protein without dose-limiting symptoms at Week 12. • Maximum severity of symptoms occurring at any challenge dose of peanut protein up to and including 1000 mg during the DBPCFC conducted at Week 12. Symptom severity will be categorized as 4 levels: None, Mild, Moderate, Severe. • Responder status defined as participants tolerating a single dose of ≥ 1000 mg (2044 mg cumulative tolerated dose) peanut protein without dose-limiting symptoms at Week 12 (8 weeks of placebo + 4 weeks of ligelizumab treatment vs. 12 weeks of placebo). The familywise type I error rate will be controlled at the one-sided 0.025 level across the primary and key secondary null hypotheses in a closed testing procedure (Bretz et al 2009). The estimands of interest are described in detail in the corresponding sections.
Key words	Food allergy, peanut allergy, oral food challenge, IgE, ligelizumab

1 Introduction

1.1 Background

Food allergy affects people of all ages and nations and, giving its prevalence and the costs associated to the disease, it represents an emerging population health priority (Warren et al 2020). An estimated 11% of US adults and approximately 8% of US children are affected by food allergies (Gupta et al 2019). The overall economic cost of food allergy is estimated at approximately $24.8 billion annually (Gupta et al 2013).

The National Institutes of Health (NIH) Food Allergy Expert Panel defines food allergy as a specific IgE-mediated adverse reaction to a given food (Boyce et al 2010). A slightly broader definition by the European Academy of Allergy and Clinical Immunology (EAACI) regards food allergy as an immune mediated adverse reaction to food involving specific IgE-mediated, cell-mediated, or combined IgE and cellular mechanisms (Muraro et al 2014). Peanut allergy is an IgE-mediated disease and, in peanut allergic individuals, ingestion of small quantities of the allergen may lead to severe and potentially life-threatening allergic reactions (Wood 2003).

The underlying pathogenesis of food allergy involves an immunologic mechanism in which IgE is synthesized in response to allergen exposure and binds to high affinity receptors for IgE (FcεRI receptors) via its Fc region on the surface membranes of mast cells and basophils (Sampson et al 2006). Cross-linking of receptor-bound IgE molecules occurs on re-exposure to the allergen and results in cell activation and mediator release (Peavy and Metcalfe 2008). IgE also contributes to the intensity of the reaction by enhancing the expression of FcεRI on mast cells and basophils. Mast cells and basophils play an important role in initiating and amplifying the acute allergic response through the release of preformed chemical mediators of inflammation, as well as newly generated mediators leading to the characteristic symptoms of allergic reaction and anaphylaxis (Vadas et al 2008).

Currently the standard of care for food allergy is limited to strict avoidance of the inciting food(s), rescue medication in case of unintentional exposure, and community wide interventions for schools (i.e., peanut free classrooms) and restaurants (i.e., ingredient alerts) (Jones and Burks 2017). Nevertheless, accidental exposures of food-sensitive individuals to the very antigen they are striving to avoid are frequent. For example, 58% of young children with clinical peanut hypersensitivity followed for up to 5 years experienced adverse reactions from accidental peanut exposure despite best efforts at allergen avoidance (Vander Leek et al 2000). Recently, a peanut oral immunotherapy (OIT) (Vickery et al 2018) was approved by FDA to mitigate allergic reactions during accidental exposure to peanuts (Jan-2020) and by EMA for the treatment of peanut allergy (Dec-2020). Yet this treatment is not fundamentally changing the unmet medical need in this space as it is only targeting one allergen; is indicated only for a subset of age groups and might not be suitable for all peanut allergic patients.

Due to rising prevalence (including allergy to multiple foods) (Sicherer and Sampson 2018), current limited therapeutic options and the lifelong disease burden in many, there is a recognized medical need to develop novel therapies for food allergy. Following the identification of IgE as a principal player in allergic diseases and the advent of monoclonal antibody (mAb) technology in the 1970s, mAbs to IgE were developed to the site on IgE that binds the FcεRI receptor (Baniyash et al 1988). These antibodies were identified based on their

ability to inhibit the IgE–FcεRI interaction and to block the activation of IgE sensitized cells. It was recognized that these antibodies would thereby prevent the initiation of the allergic cascade through both the FcεRI and FcεRII (CD23) pathways. Such antibodies are termed "non-triggering"; in contrast to conventional anti-IgE antibodies that cross-link cell bound IgE thus precipitating degranulation and even systemic anaphylaxis. Based on this strategy, the development of monoclonal anti-IgE treatment (TNX-901) was shown to be able to significantly increase the threshold of sensitivity to peanut antigen, as assessed by an oral food challenge (OFC), in a dose dependent manner, to levels that should translate into at least partial protection against most unintended ingestions of peanut (Leung et al 2003).

Ligelizumab (QGE031) is a humanized IgG-type mAb that binds to human IgE (Investigator Brochure, 17 Ed.). Upon binding to specific epitopes in the C3 region of IgE, ligelizumab is able to block the interaction of IgE with both the high and low affinity IgE receptors (FcεRI and CD23, respectively). Ligelizumab does not mediate IgE receptor cross-linking and consequent histamine release (i.e. is non-activating). The rationale for its development reflects the evidence that a more efficient suppression of IgE than that achieved by omalizumab may be associated with improved clinical outcomes in IgE mediated diseases (Lowe et al 2009, Ankerst et al 2010).

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

Consequently, it is hypothesized that the higher level of suppression elicited by ligelizumab [redacted] will result in a more efficient desensitization against the allergen therefore, ensuring protection against food allergic reactions by decreasing the sensitivity to oral peanut allergen.

1.2 Purpose

The purpose of this Phase 3 study is to evaluate the safety and clinical efficacy of ligelizumab 240 mg and 120 mg given subcutaneously (s.c.) every 4 weeks (q4w) to ensure protection against allergic reaction by decreasing the sensitivity to oral peanut allergen in participants aged 6 to 55 years with peanut allergy, compared to placebo.Data from this study, as well as data from an additional Phase 3 study assessing two other major food allergens (milk and egg), will support the registration of ligelizumab in food allergy to protect participants against allergic reactions due to an accidental exposure irrespective of the causative food allergen(s).

2 Objectives, endpoints and estimands

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To evaluate the efficacy of ligelizumab 240 mg and 120 mg (SCq4w) compared to placebo, as measured by the proportion of participants who can tolerate a single dose of ≥ 600 mg (1044 mg cumulative tolerated dose) of peanut protein without dose-limiting symptoms during the DBPCFC (Section 16.4, Table 16-7) at Week 12	• Responder status defined as tolerating a single dose of ≥ 600 mg (1044 mg cumulative tolerated dose) of peanut protein without dose-limiting symptoms during the DBPCFC conducted at Week 12 (Section 2.1 Primary Estimands).
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• **Key secondary objectives**	• **Key secondary endpoints**
• To evaluate the efficacy of ligelizumab 240mg and 120mg (SCq4w), compared to placebo, as measured by the proportion of participants who can tolerate a single dose of ≥ 1000 mg (2044 mg cumulative tolerated dose) of peanut protein without dose-limiting symptoms during the DBPCFC at Week 12	• Responder status defined as tolerating a single dose of ≥ 1000 mg (2044 mg cumulative tolerated dose) of peanut protein without dose-limiting symptoms during the DBPCFC conducted at Week 12 (Section 2.2 Secondary Estimands).
• To evaluate the efficacy of ligelizumab 240mg and 120mg (SCq4w), compared to placebo, as measured by the proportion of participants who can tolerate a single dose of 3000 mg (5044 mg cumulative tolerated dose) of peanut protein without dose-limiting symptoms during the DBPCFC at Week 12	• Responder status defined as tolerating a single dose of 3000 mg (5044 mg cumulative tolerated dose) of peanut protein without dose-limiting symptoms during the DBPCFC conducted at Week 12 (Section 2.2 Secondary Estimands).
• To evaluate the efficacy of ligelizumab 240mg and 120mg (SCq4w), compared to placebo, as measured by the maximum symptom severity at any single challenge dose up to and including 1000 mg of peanut protein during the DBPCFC at week 12	• Maximum severity of symptoms occurring at any challenge dose of peanut protein up to and including 1000 mg during the DBPCFC conducted at Week 12. Symptom severity will be categorized as 4 levels: None, Mild, Moderate, Severe (Section 2.2 Secondary Estimands).
• To evaluate the efficacy of 8 weeks of placebo treatment followed by 4 weeks of ligelizumab 120 mg and 240 mg (SCq4w) treatment compared to 12 weeks of placebo treatment, as measured by the proportion of participants who can tolerate a single dose ≥1000 mg of peanut protein without dose-limiting symptoms during the DBPCFC at Week 12	• Responder status defined as tolerating a single dose of ≥ 1000 mg (2044 mg cumulative tolerated dose) of peanut protein without dose-limiting symptoms during the DBPCFC conducted at Week 12 (8 weeks of placebo + 4 weeks of ligelizumab treatment vs. 12 weeks of placebo) (Section 2.2 Secondary Estimands).
• **Other secondary objectives**	• **Other secondary endpoints**
• To evaluate the efficacy of ligelizumab 240mg and 120mg (SCq4w), as measured by the proportion of participants who can tolerate a single dose of ≥1000 mg (2044 mg cumulative tolerated dose) of peanut protein without dose-limiting symptoms during the DBPCFC at Week 52 compared to Week 12	• Proportion of participants tolerating a single dose of ≥ 1000 mg (2044 mg cumulative tolerated dose) of peanut protein without dose-limiting symptoms during DBPCFC conducted at Week 52 • Change in maximum tolerated dose (MTD) of peanut protein without dose-limiting symptoms during the DBPCFC at Week 52 compared to Week 12
• To evaluate the effects of ligelizumab 240 mg and 120 mg (SCq4w), compared to placebo (when applicable), as measured by multiple	• Change from baseline at Week 12, 16 and Week 52 of • peanut-specific IgE

Objective(s)	Endpoint(s)
systemic biomarkers to inform on response to treatment or disease severity	• peanut-specific IgG4
• To evaluate the safety and tolerability of ligelizumab 240 mg and 120 mg (SCq4w)	• Summaries of treatment-emergent adverse events, vital signs, ECG, and laboratory values
• To assess the ability of IgE suppression to impact skin mast cells through the assessment of allergen-specific skin prick test (SPT).	• Change from baseline (screening) in SPT mean wheal diameters at Week 16, Week 56 and Week 68.
• To evaluate the impact of ligelizumab on the health-related quality of life (HRQoL) of patients with peanut allergy.	• Change from baseline in total and domain scores in the FAQLQ, FAIM, and SF-36v2 by age and responder (subject and/or caregiver) at various points in time.
[redacted]	

2.1 Primary estimands

The estimand is the precise description of the treatment effect and reflects strategies to address events occurring during trial conduct which could impact the interpretation of the trial results (e.g. premature discontinuation of treatment). The primary clinical question of interest is, 'What are the effects of ligelizumab 120mg SCq4w vs. placebo, and ligelizumab 240mg SCq4w vs. placebo on the proportion of responders at Week 12 in the absence of operational complications caused by a public health emergency (e.g. the COVID-19 pandemic), regardless of intake of rescue medication prior to Week 12?' Responder status is defined as tolerating a single dose of ≥ 600 mg (1044 mg cumulative tolerated dose*) of peanut protein without dose-limiting symptoms** during the DBPCFC conducted at Week 12.

The primary estimand will account for two categories of intercurrent events which will be treated in different ways. We will distinguish between intercurrent events unrelated to public health emergency and intercurrent events that happen due to operational complications caused by public health emergency; e.g., participants missed their dose as they are not able to receive their study medication due to regional lockdowns. Intercurrent events due to non-operational public health emergency related reasons will be classified as intercurrent events unrelated to public health emergency.

The primary estimand is described by the following attributes:

- **Population**: participants aged 6 - 55 years who have been diagnosed with IgE-mediated peanut allergy and met study inclusion/exclusion criteria. Further details about the population are provided in Section 5.
- **Variable**: Responder status defined as tolerating a single dose of ≥ 600 mg (1044 mg cumulative tolerated dose) of peanut protein without dose-limiting symptoms during the DBPCFC conducted at Week 12.
- **Treatment**: the randomized treatment^ (ligelizumab 120mg SCq4w, ligelizumab 240mg SCq4w, and placebo) plus rescue medication (e.g., epinephrine, SABA, anti-histamines), if needed. Further details about the randomized treatment and rescue medication are provided in Section 6.
- **Handling of intercurrent events**:

Category 1 - Intercurrent events unrelated to public health emergency (e.g. COVID-19 pandemic):

- Discontinuation of treatment prior to Week 12: participants who discontinue treatment prior to Week 12 and therefore do not undergo DBPCFC at Week 12 will be considered non-responders (composite variable strategy).
- Missing more than one dose prior to Week 12: participants who miss more than one dose and therefore do not undergo DBPCFC at Week 12 will be considered non-responders (composite variable strategy).Intake of rescue medication prior to DBPCFC conducted at Week 12: ignorable (treatment policy strategy, reflected in the Treatment attribute)

Category 2 - Intercurrent events related to operational complications caused by public health emergency (e.g., regional lockdowns):

- Discontinuation of treatment or missing more than one dose of study drug prior to Week 12: the interest lies in the responder status at Week 12 that would be observed if participants had not had intercurrent events due to operational complications caused by public health emergency prior to Week 12 (hypothetical strategy)

Intercurrent events due to non-operational public health emergency related reasons (e.g., COVID-19 infection) are classified as intercurrent events unrelated to public health emergency.

- **Summary measure**: odds ratio comparing the proportion of responders between each ligelizumab dose group and placebo group

**The cumulative tolerated dose is the sum of the tolerated doses, not including the reactive dose (*Casale et al 2019*)*

*** Dose-limiting symptoms indicate a true allergic reaction occurring during administration of a single dose of peanut protein at the DBPCFC* that should preclude the administration of any further doses in the view of the investigator.

^ *The randomized treatment indicates three arms specified in Section 6.1.2 , i.e.,* ligelizumab 120 mg arm, *ligelizumab 240 mg arm, and* placebo 16wk/ligelizumab 120/240 mg arm

Supplementary estimands to the primary estimand are defined in Section 12.

2.2 Secondary estimands

Only key secondary objectives are considered for estimands below.

2.2.1 Proportion of responders who can tolerate a single dose of ≥1000 mg of peanut protein at Week 12

The secondary estimand is the same as the primary estimands except that "a single dose of ≥ 600 mg (1044 mg cumulative tolerated dose)" is replaced by "a single dose of ≥ 1000 mg (2044 mg cumulative tolerated dose)".

2.2.2 Proportion of responders who can tolerate a single dose of 3000 mg of peanut protein at Week 12

The secondary estimand is the same as the primary estimands except that "a single dose of ≥ 600 mg (1044 mg cumulative tolerated dose)" is replaced by "a single dose of 3000 mg (5044 mg cumulative tolerated dose)".

2.2.3 Maximum severity of symptoms at any single challenge dose up to and including 1000 mg of peanut protein at Week 12

This secondary estimand is described by the following attributes:

Population: same as for the primary estimand

Variable: maximum severity of symptoms occurring at any challenge dose of peanut protein up to and including 1000 mg during the DBPCFC conducted at Week 12. According to the CoFAR grading scale of dose-limiting symptoms (Section 16.4.5), symptom severity will be categorized as Mild, Moderate, and Severe. In addition, symptom severity for participants who completed DBPCFC without any symptom will be categorized as "None".

Treatment: same as for the primary estimand

Handling of intercurrent events:

- Category 1 - Intercurrent events unrelated to public health emergency (e.g. COVID-19 pandemic):
  - Discontinuation of treatment prior to Week 12: participants who discontinue study treatment will no longer undergo any DBPCFC. The interest lies in efficacy at week 12 regardless of study drug compliance (treatment policy strategy)
  - Missing more than one dose prior to Week 12: participants who miss more than one dose of study treatment will not undergo the DBPCFC at Week 12. The interest lies in efficacy at week 12 regardless of study drug compliance (treatment policy strategy).

  - Intake of rescue medication prior to DBPCFC conducted at Week 12: ignorable (treatment policy strategy, reflected in the 'Treatment' attribute)
- Category 2 - Intercurrent events related to operational complications caused by public health emergency:
  - Discontinuation of treatment or missing more than one dose of study drug prior to Week 12: the interest lies in the efficacy at Week 12 that would be observed if participants had not had intercurrent events due to operational complications caused by public health emergency prior to Week 12 (hypothetical strategy)

Intercurrent events due to non-operational public health emergency related reasons are classified as intercurrent events unrelated to public health emergency.

Summary measure: odds ratio comparing the odds of developing less severe symptoms between each ligelizumab dose group and placebo group

2.2.4 Proportion of responders who can tolerate a single dose of ≥1000 mg of peanut protein at Week 12 with 8 weeks of placebo followed by 4 weeks of ligelizumab

The secondary estimand provides insight into the magnitude of efficacy that might be achieved if all participants were able to take one dose of study treatment. The attributes of the secondary estimand are described as follows:

Population: same as for the primary estimand.**Variables**: Responder status defined as tolerating a single dose of ≥ 1000 mg (2044 mg cumulative tolerated dose) of peanut protein without dose-limiting symptoms during the DBPCFC conducted at Week 12

Treatment: the randomized treatment (placebo 8wk/ligelizumab 120 mg SCq4w, placebo 8wk/ligelizumab 240 mg SCq4w, and placebo 16wk/ligelizumab 120/240 mg SCq4w) plus rescue medication, if needed.

Handling of intercurrent events:

- Discontinuation of treatment prior to Week 12: the interest lies in the responder status at Week 12 that would be observed if participants had not discontinued treatment prior to Week 12 (hypothetical strategy).
- Missing the dose of study treatment at Week 8: the interest lies in the responder status at Week 12 that would be observed if participants had not missed the dose of study treatment at Week 8 (hypothetical strategy).
- Intake of rescue medication prior to DBPCFC conducted at Week 12: ignorable (treatment policy strategy, reflected in the 'Treatment' attribute).

The same approach of handling intercurrent events will be used for events related and unrelated to public health emergency.

Summary measure: odds ratio comparing the proportion of responders between each ligelizumab dose group and placebo group.

3 Study design

This is a 52-week, Phase 3 multi-center, randomized, double-blind and placebo-controlled study to assess the safety and clinical efficacy of two dosing regimens of ligelizumab (240 mg and 120 mg) SCq4w (subcutaneous injection every 4 weeks) in participants with a medically confirmed diagnosis of IgE-mediated peanut allergy. Approximately 486 participants will be randomized to ligelizumab 240 mg, ligelizumab 120 mg, or placebo (5 treatment arms, randomization ratio of 2:2:2:2:1; Figure 3-1) for the double-blind placebo-controlled treatment period (up to Week 12). Participants initially assigned to the 8-week placebo arms will receive the first dose of blinded ligelizumab treatment at the Week 8 visit. Participants initially assigned to the 16-week placebo arm will receive the last dose of placebo before the DBPCFC at week 12 and the first dose of blinded ligelizumab treatment at the Week 16 visit.

Participants will be stratified based on region, total IgE at screening (<350 IU/ mL; ≥350 IU/ mL at Screening Visit 1) and age (6-11y, 12-17y, and 18-55y). Approximately the same number of participants will be randomized into each age group.

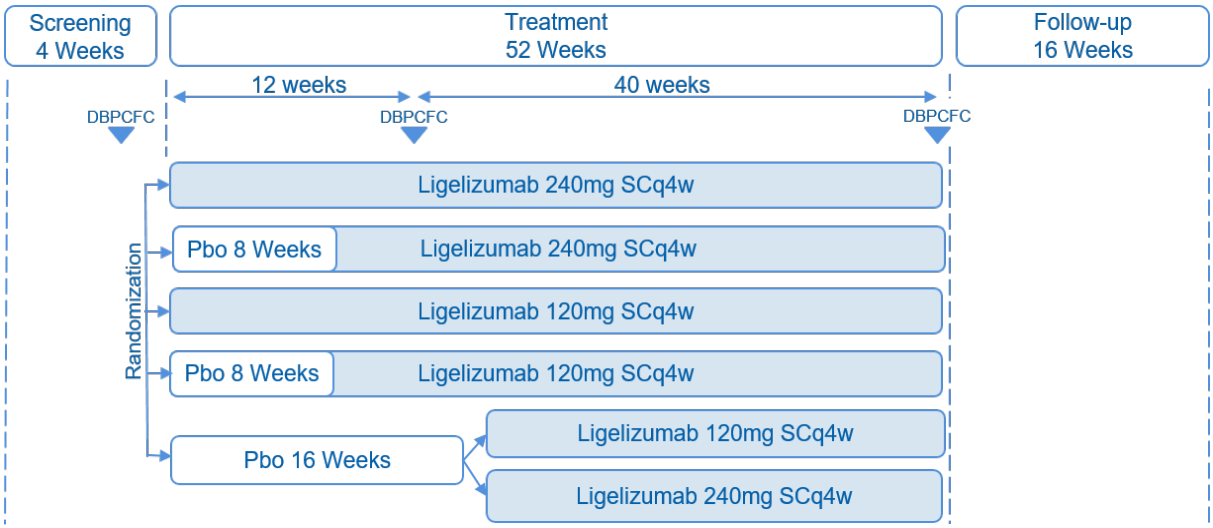
Age groups are defined as follows:

6-11y corresponds to ≥ 6 to < 12 years of age

12-17y corresponds to ≥ 12 to < 18 years of age

18-55y corresponds to ≥ 18 to ≤ 55 years of age

Figure 3-1 Study design



The study will include the following:

1. **Screening period (Duration of 4 weeks)**: Written informed consent and assent (as applicable) will be obtained before any study related assessments or procedures are performed. Consented participants will be assessed for study eligibility during the Screening period which includes the initial qualifying DBPCFC.

2. **Treatment period (Duration of 52 weeks):** The study treatment will be administered in the clinic every 4 weeks.

- **Double-blind placebo controlled** treatment period **(Duration of 12 weeks):** Study participants will be seen in the clinic at Day 1, Week 1, Week 4, Week 8 and Week 12. The DBPCFC will be performed at Week 12. Participants assigned to the 16 week placebo arm will receive the first dose of blinded ligelizumab treatment at the Week 16 visit.
- **Long-term active blinded (no placebo control)** treatment period **(Duration of 40 weeks/ 36 weeks for participants on the 16-week placebo arm):** Starting at Week 16, all study participants will receive blinded ligelizumab study treatment in the clinic every 4 weeks until Week 52. A final DBPCFC will be performed at Week 52.

3. **Post-treatment follow-up period (Duration of 16 weeks):** There are 4 planned clinic visits (every 4 weeks). Study evaluations include safety, [redacted], [redacted]. Study treatment is not given and there is no DBPCFC.

An Extension Study will be made available for participants to enter at the completion of the treatment period (week 52) or the completion of the follow-up period (week 68)(Section 9.3).

At the start of the study, recruitment will be restricted to 12 - 55 year old participants. When approximately 60 adolescent participants (defined as 12 -17 years of age) have completed all Week 12 assessments, [redacted] (safety will be reviewed by a Data Monitoring Committee - DMC). Independent sponsor members who are responsible for [redacted] and [redacted]

[redacted]

4 Rationale

4.1 Rationale for study design

The randomized, parallel group, double blind, placebo controlled design has been used in the past to assess the ability of an anti-IgE treatment to shift the level of reactivity against the peanut allergen during a DBPCFC (Leung et al 2003, Sampson et al 2011). Details of the DBPCFC are provided in Section 8.3.1. The randomized, double-blind, parallel-group, and placebo-controlled design supports the assessment of efficacy as well as safety by minimizing bias.

The choice of peanut as the main food allergen in this study relates to the following key factors:

- It represents an important unmet medical need as food allergic reactions are most often severe with this allergen (Gupta et al 2011), and is a leading cause of fatal and near-fatal anaphylaxis in the US (Jones and Burks 2017)
- Most patients (> 80%) retain their phenotype into adulthood (Byrne et al 2010) which enables a study across multiple age groups

The DBPCFC has demonstrated regulatory significance and will support the main efficacy outcome of the study. [redacted]

The recruitment of an approximately equal amount of participants across the three age groups [redacted]

The long-term blinded treatment period will assess the sustainability of the effect of the clinical response achieved in the first 12 weeks of treatment through a final DBPCFC. In this study all participants assigned to the 16-week placebo arm will receive their last placebo dose before the week 12 DBPCFC and the first dose of blinded ligelizumab treatment at the week 16 visit. This change to active treatment (120 mg or 240 mg SC4qW pre-assigned at randomization) avoids longer-term placebo exposure, which is no longer necessary to support the primary objective. At randomization, participants in the 16-week placebo group will be pre-assigned 1:1 to 120 mg and to 240 mg SC4qW which they will receive after week 12.

The Follow-up period will ensure that investigational drug has been completely cleared from the body before the final visit (EOS). Sixteen weeks of follow-up correspond to five half –lives after the last dose of ligelizumab.

[redacted]

4.1.1 Rationale for choice of background therapy

Strict avoidance of the inciting food(s) and symptomatic treatment of allergic symptoms with epinephrine, antihistamines and corticosteroids represent the current standard of care. No other anti-IgE medication is currently indicated for the prevention of allergic events in participants with peanut allergy. Therefore, the active treatment will be compared to placebo on top of standard of care for acute allergic reactions.

4.2 Rationale for dose/regimen and duration of treatment

The two selected dosing regimens (120 mg SCq4w and 240 mg SCq4W) reflect the clinical goal to maximize the protection against potentially life-threatening allergic reactions triggered by accidental exposure to food allergens. In fact the cascade of events leading to full blown anaphylaxis is mediated by the cross-linking of the high affinity IgE receptor (FcεRI) on effector cells (basophils and mast cells) that triggers the release of the inflammatory mediators. In this pathophysiologic context, a profound blockade of IgE binding to the FcεRI receptors with the consequent maximal downregulation of these FcεRIs is required because data suggests that basophils can respond maximally to stimulation with only 5000 antigen-specific IgE molecules per cell (MacGlashan 1993). Maximal suppression is also desirable considering that the IgE system is exposed to external factors like infections that may further increase its reactivity as described by Xepapadaki et al 2019.

The proposed two doses have been selected based on simulations with a model build on atopic healthy volunteers and asthmatic participants then adapted in another version with CSU data for a sensitivity analysis (QGE031 simulations food allergy, Novartis). The activity of the FcεRI (wheal diameter of a skin prick test and PC15 = the dose of allergen required to trigger an acute 15% decrease of FEV1) and selected critical biomarkers required for its activation (density of basophil-bound FcεRI and its occupancy with IgE) Figure 4-1 provides the output from this model.

[redacted]

Time (days)

[redacted] of bronchially administered allergen required to induce a 15% change in FEV1) were simulated.

[redacted]

The decision to include the 120 mg on top of the 240 mg regimen is based on two main considerations:

- The study population will be characterized by a range of [redacted] These parameters are well known to impact [redacted] ligelizumab and some participants with [redacted] might sufficiently benefit of the 120 mg SC4qW regimen.
- A lower dosing regimen of 120 mg SCq4w is also important to generate a broad range of data (exposure/response), supporting robust modeling at the end of the Phase 3 program to support the final posology for registration purposes.

Finally, the two selected dosing regimens are also supported by several key safety aspects, which are very important considering the inclusion of participants ≥6y:

- The maximal dose expected with the proposed 240 mg SCq4w posology in the phase 3 program in food allergy based on the eligibility criteria is 12 mg/kg body weight/month.
- [redacted]
- In the CSU program (currently in Phase 3 studies with 72 and 120 mg SCq4w for up to 12 months, the completed Phase 2b study evaluated doses up to 240 mg SCq4w), no dose related adverse events were identified (with the exception of injection site reactions due to the two times higher number of injections required for the 240 mg dose compared with lower doses).

[redacted]

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

Placebo is used in this study for the following reasons:

- to minimize bias in the evaluation of safety and efficacy assessments and
- to allow assessment of the change in sensitivity from DBPCFC when comparing participants taking ligelizumab 240 mg and ligelizumab 120 mg SCq4W with those continuing solely on food avoidance.

4.4 Purpose and timing of interim analyses/design adaptations

An independent DMC (see Section 10.3.1) will conduct periodic monitoring of safety data and emerging risk/benefit. Interim reports to the DMC will be generated by an independent statistical group not involved in the conduct of the trial.

There are three planned analyses before the final DBL, in addition to the DMC analyses. In order to maintain the integrity of the study data, a limited number of pre-specified sponsor team members will be unblinded to the study data for these analyses, and separate blinded sponsor team members will continue working on the study until its completion:

Interim Analysis:

At the start of the study recruitment will be restricted to 12 - 55 year old participants. When approximately 60 adolescent participants (defined as 12 - 17 years of age) have completed all week 12 assessments, an interim analysis on [redacted] safety [redacted] data [redacted]) will be performed. The intent of this analysis is to confirm the dosing strategy for the youngest age cohort. Once confirmed, recruitment will open to participants aged 6 - 11 years. Dosing of ligelizumab would be either 120 mg only or 120 and 240 mg for this age group.

Primary Analysis at Week 12:

Once all participants have completed 12 weeks of treatment (or prematurely withdrawn from the study), an interim database lock will be conducted to perform the Primary Analysis. The Primary Analysis includes primary, key secondary and pre-specified other secondary [redacted] endpoints.

Analysis at Week 52:

The study will continue in a blinded manner until EOS (week 68). The analysis at Week 52 will be performed on all participants who have either completed Week 52 or prematurely withdrawn from the study.

In terms of reporting, two separate CSRs will be written:

CSR1 will include the analyses of data after all participants have completed Week 52 or prematurely withdrawn from the study prior to Week 52.

CSR2 will include the final analyses of all data after follow-up, once all participants have completed their EOS visit or prematurely withdrawn from the study.

4.5 Risks and benefits

The risks to participants in this trial will be minimized by compliance with all of the eligibility criteria and by close clinical monitoring including periodic review of data by an independent Data Monitoring Committee (DMC).

As of the cut-off date of 22-Jan-2021, more than 2000 participants have been or are anticipated to have been exposed to ligelizumab across completed, prematurely terminated and ongoing studies, covering the indications of CSU, asthma, atopic dermatitis, and bullous pemphigoid. The longest exposure to ligelizumab is approximately 17 months (across studies CQGE031B2201, CQGE031B2201E1, CQGE031C2201 and CQGE031C2201E1). The following doses have been tested in the clinical programs: 12 mg, 24 mg, 36 mg, 72 mg, 180 mg and 240 mg SC q4w, 280 mg SCq2w and 120 mg SC single dose. To date in the CSU program alone, 254 participants have been exposed to ligelizumab at doses up to 240 mg SC q4w. [Investigator Brochure, 17 Ed.]

Overall, no apparent dose-dependent safety signals (except for a trend in injection site reactions, which can be easily managed clinically) have been observed to date, although the number of participants studied is relatively small, in line with the development phase of the CSU program.

In the asthma clinical study CQGE031B2201, there appeared to be a dose dependency of injection site reactions between ligelizumab high dose group (28.6% of 199 participants, pooled from ligelizumab 240 mg q2w, 240 mg q4w, 180 mg q2w, and 120 mg q2w treatment arms) and ligelizumab low dose group (12.5% of 40 participants, pooled from ligelizumab 36 mg q2w, and 12 mg q2w treatment arms), which was comparable to omalizumab (14.5% of 131 participants). The incidence of injection site reactions was higher among all the active treatment groups compared to that of placebo (5.2% of 96 participants). Similarly, in the CSU dose-finding study (CQGE031C2201), the overall safety profile was comparable between different doses of ligelizumab (24 mg, 72 mg and 240 mg q4w or 120 mg single dose), omalizumab and placebo. The exceptions were AEs related to injection site reactions, where a possible trend of dose dependency for ligelizumab was observed. All cases of injection site reactions (except 1 case of medical significance), regardless of treatment group or doses, were non-serious, mild to moderate in severity, reversible, and did not lead to discontinuation of study treatment.

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

Biologics can cause hypersensitivity reactions. Ligelizumab is in the same drug class as omalizumab, for which the risk and characteristics of anaphylaxis are well-characterized, and theoretically are applicable to the study drug. Investigators should therefore be alert to the occurrence of hypersensitivity events, including anaphylaxis, following the administration of ligelizumab and be familiar with the information and guidance provided in this protocol and in the Investigator Brochure.

IgE is an antibody that may have an adaptive role in immunity to parasitosis, particularly helminthic infections. Thus, blocking the interaction of IgE and its receptors with ligelizumab may alter immunologic responsiveness to parasites. Bearing this in mind, monitoring for the occurrence of infection and response to therapy is recommended for participants at high risk of geohelminth infection who receive ligelizumab. Insufficient data are available to determine the length of monitoring required for geohelminth infections after stopping ligelizumab. However, it is expected that ligelizumab will not interfere with a polyclonal reaction triggered by exposure to parasites. The resulting increase of IgE production would decrease, through target-mediated disposition, the half-life of ligelizumab hence restoring normal IgE levels more rapidly.

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

The non-clinical safety evaluation for ligelizumab supports a clinical treatment of children down to the age of 2 years: [redacted] No new or unexpected safety signals were identified in the CQGE031C2201 (CSU dose-ranging) study in adults.

This study is placebo-controlled design and approximately one-third of participants will receive placebo by randomization (Section 4.3), however, the participants who are initially allocated to placebo will be switched to the active treatment (ligelizumab 120 or 240 mg SCq4w) at Week

8 or Week 16, depending on the treatment arm. (Figure 4-1), therefore these participants are also able to receive the benefit of ligelizumab. Throughout the study including the placebo period, measures like strict avoidance of the inciting food(s) and symptomatic treatment of allergic symptoms with epinephrine, anti-histamines and corticosteroids will be taken to reduce the risk for the participant. The inclusion and exclusion criteria are selected to enroll participants with IgE-mediated peanut allergy likely to benefit from participating in the study, and to limit the presence of concomitant morbidities and medications that might increase the risks associated with the oral food challenge. The oral food challenge is the gold standard investigation for the objective diagnosis of IgE-mediated food allergy and the use of a double-blind placebo-controlled food challenge is recommended in research settings (Muraro et al 2014).

Oral food challenges have inherent risks including acute allergic reactions with potentially life-threatening anaphylaxis, exacerbation of atopic dermatitis, and emotional distress, particularly in older children, teenagers, and adults who may become more anxious about their food allergy (Feng and Kim 2019). In participants with cardiovascular disease, anaphylaxis or its treatment (e.g., with epinephrine) could result in morbidity due to a cardiovascular event. Also, participants with uncontrolled asthma are at higher risk of a dying from anaphylactic event. A prior history of a severe allergic event may increase the risk of a severe reaction during the OFC. These participants are excluded from participating in the study. To further limit the risks associated with this procedure the following measures have been applied:

- The OFC is based upon the Practall Consensus Meeting Report (Sampson et al 2012) and the current CoFAR definition of dose-limiting symptoms.
- Only highly trained experts representing facilities that are equipped and have the expertise to handle potentially life-threatening hypersensitivity events can participate in this study.
- Three adjudication committees will review all the suspected anaphylactic events, cardiovascular events and neoplastic events identified during the study (Section 8.4.4).
- A Data Monitoring Committee (DMC) will monitor the safety of this study. The DMC will review the data generated externally and independently of Novartis in an unblinded fashion, according to the charter at predetermined intervals. Based on the safety implications of the data, the DMC may recommend modification or termination of the study.

The lower limit of body weight (20 kg) set in the eligibility criteria covers at least 50% of the population in the 6-11 year age group according to the CDC growth curves for boys and girls.

[redacted] In addition, it has been shown that exposure to viral infections, to which children are very prone, might increase the specific IgE levels and consequently the reactivity to food allergens (Xepapadaki et al 2019). A high exposure might provide an “efficacy margin” against a potentially dangerous external factor of variable reactivity against food allergens.

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

With respect to the ongoing COVID-19 pandemic, IgE suppression is not expected to increase the risk of infection (Teach et al 2015). In case of the introduction of a vaccine against COVID-19, the guidance relative to immunizations summarized in Table 6-2 and Table 6-3 remains applicable.

The key mechanism underlying IgE mediated food allergy is the cross-linking of allergen specific IgE molecules bound to the high affinity receptor (FcεRI) on effector cells like basophils and mast cells, which triggers the release of inflammatory mediators responsible for the final clinical presentation. Therefore, IgE suppression is expected to decrease the probability of food allergens to initiate such an acute inflammatory response. Indeed multiple studies have supported this therapeutic approach (Leung et al 2003, Savage et al 2012, Schneider et al 2013). Recent mechanistic data has shown that ligelizumab is very effective at inhibiting the signaling cascade associated with the FcεRI (Gasser et al 2020) hence supporting its use in food allergy and anticipating a therapeutic benefit (basophil/ mast cell desensitization).

Risk and benefit evaluation for adolescents (12-17 yrs) and children (6-11 yrs)

IgE mediated food allergy affects all ages and upon exposure to the allergen(s) it can result in considerable morbidity and life-threatening anaphylaxis.

The standard of care consists of allergen avoidance and epinephrine administration upon accidental exposure. The unmet need, in particular for therapeutic solutions not requiring regular allergen administration, is significant in children and adolescents.

The evaluations specified in this study (including SPT and OFC) are clinically accepted and widely used in clinical research that investigates food allergy in adults, adolescents and children. With respect to the OFC most of the clinical experience has been collected in children but the procedure is also applicable to older patients (Nowak et al 2009). The limited use of placebo reflects a consideration for the need to treat this vulnerable population while preserving the study's primary objective. The staggered recruitment approach will allow for the determination of a suitable dose for children aged 6-11 years. Blood volume for laboratory evaluations for children 6-11 years is in line with the “The Hospital for Sick Children (SickKids) Research Ethics Board Blood Sampling Guidelines” (Howie 2011)(Section 8.4.1).

In conclusion, IgE mediated food allergy is a potentially life-threatening condition affecting all age groups for which current standard of care still mainly consists of allergen avoidance and epinephrine use upon accidental exposure. IgE suppression directly addresses the underlying pathophysiology and data from other anti-IgE monoclonal antibodies support this mechanism. The proposed ligelizumab regimens aim at an efficient suppression of the FcεRI receptor while generating exposures that have been well characterized clinically and that accordingly have not been associated with dose-related safety concerns. Residual risks due to hypersensitivity reactions related to the investigational drug or to the oral food challenge have been addressed by a series of measures that include (but are not limited to) clear eligibility criteria, study drug

discontinuation rules, limitations of key risk factors (uncontrolled asthma, selected medications), a highly standardized food challenge protocol (and material), adjudication committees for event of special interests, and the implementation of a DMC.

4.6 Rationale for Public Health Emergency mitigation procedures

In the event of a Public Health emergency as declared by Local or Regional authorities (i.e. pandemic, epidemic or natural disaster), mitigation procedures may be required to ensure participant safety and trial integrity and are listed in relevant sections of the study protocol. Notification of the Public health emergency should be discussed with Novartis prior to implementation of mitigation procedures, and permitted/approved by local or regional health authorities and ethics committees as appropriate.

5 Study Population

The study population consists of approximately 486 male and female participants aged 6 - 55 years who have been diagnosed with IgE-mediated peanut allergy. Participants with multiple food allergies will be allowed to enroll as long as an allergy to peanuts exists. A screen failure rate of approximately 40% is expected.

Participants will receive one of three treatments (ligelizumab 240 mg SCq4w, ligelizumab 120 mg SCq4w, or placebo SCq4w) and will be randomized into five treatment arms with a ratio 2:2:2:2:1. Participants will be also stratified based on region, total IgE at screening (<350 IU/ mL; ≥350 IU/ mL at Screening Visit 1) and age (6 -11 y, 12 - 17 y, and 18 - 55 y). Approximately the same number of randomized participants will be recruited into each age group.

If after the interim analysis it is determined that dosing will be limited to 120 mg for the youngest age group, the 240 mg treatment arms will be removed for this age group and participants aged 6-11 years will be randomized into the 3 remaining treatment arms (randomization ratio of 4:4:1, 1 being the 16 week placebo arm).

5.1 Inclusion criteria

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

1. Signed informed consent and/or assent (where applicable) must be obtained prior to study participation. Participant (and parent/legal guardian) must be able to understand and provide informed consent and assent, as applicable. If a minor participant providing assent reaches the age of legal majority (as defined by local law), he/she must be re-consented (ICF) at the next study visit.
2. Male or female participants who are 6 to 55 years of age at the time of signing informed consent/assent.
3. Documented medical history of allergy to peanuts or peanut-containing foods.
4. Positive peanut-specific IgE (peanut sIgE), ≥ 0.35 kUA/L at Screening Visit 1.
5. Positive skin prick test (SPT) for peanut allergen at Screening Visit 1. This is defined as the average diameter (longest diameter and mid-point orthogonal diameter) ≥ 4 mm wheal compared to the negative control.

6. A positive peanut DBPCFC at baseline (Screening Visit 2, Part 1 and Part 2 DBPCFC) defined as the occurrence of dose-limiting symptoms at a single dose ≤ 100 mg of peanut protein . Eligibility to proceed with the DBPCFC requires presence of all inclusion and absence of all exclusion criteria.
7. Participants must weigh ≥ 20 kg at Screening Visit 1.
8. Participants must be able to receive injections (study treatment), participate in the DBPCFC, and must be willing to continue avoiding exposure to peanuts and any other foods that they are allergic to throughout this study.

5.2 Exclusion criteria

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

1. Use of other investigational drugs within 5 half-lives or within 30 days prior to Screening Visit 1, whichever is longer.
2. History of hypersensitivity to ligelizumab or its excipients, or to other biologics (i.e. to murine, chimeric or human antibodies).
3. Hypersensitivity or intolerance to any of the matrix components used within the material for the oral food challenge. (Please refer to the QGE031G12301 Pharmacy Manual for the preparation of the DBPCFC and for details on the material components).
4. Any occurrence of dose-limiting symptoms to placebo allergen at baseline DBPCFC (Screening Visit 2).
5. Inability to comply with study and follow-up procedures.
6. Total IgE >2000 IU/mL at Screening Visit 1.
7. History of severe or life-threatening hypersensitivity event needing an ICU (intensive care unit) admission or intubation within 60 days prior to baseline DBPCFC (Screening Visit 2).
8. Participants with uncontrolled asthma (according to GINA guidelines, GINA 2020) who meet any of the following criteria:
   - FEV1 <80% of participant's predicted normal value at Screening Visit 1
   - One hospitalization for asthma within 12 months prior to Screening Visit 1
9. Current or previous history of a mast cell disorder, including mastocytosis.
10. Use of prohibited medication (Table 6-3) or medication that is not allowed under certain conditions (Table 6-2).
11. Participants with evidence of helminthic parasitic infection as evidenced by stools being positive for a pathogenic organism according to local guidelines at Screening Visit 1 (before start of Screening Visit 2) (Section 8.1). If stool testing is positive for pathogenic organisms, the subject should not be randomized and should not be allowed to be rescreened.
12. History of malignancy of any organ system within the past 5 years (except for basal cell carcinoma; actinic keratoses; Bowen disease (carcinoma in situ) that have been treated, with no evidence of recurrence in the past 12 weeks; carcinoma in situ of the cervix or non-invasive malignant colon polyps that have been removed).
13. Presence of clinically significant cardiovascular conditions such as but not limited to myocardial infarction, unstable ischemic heart disease, NYHA Class III/IV left ventricular

failure, arrhythmia and uncontrolled hypertension within 12 months prior to Screening Visit 1.

14. History or current diagnosis of ECG abnormalities indicating significant risk of safety for participants participating in the study such as:
    - Concomitant clinically significant cardiac arrhythmias, e.g. sustained ventricular tachycardia, and clinically significant second or third degree AV block without a pacemaker
    - History of familial long QT syndrome or known family history of Torsades de Pointe
15. Neurological, psychiatric, metabolic or other pathological conditions (such as but not limited to cerebrovascular disease, neurodegenerative or other neurological diseases, uncontrolled hypo- and hyperthyroidism and other autoimmune diseases, hypokalemia, hyperadrenergic state or ophthalmologic disorder) that could interfere with or compromise the safety of the participants, interfere with evaluation or interpretation of the study results, or preclude completion of the study.
16. History or evidence of ongoing alcohol or drug abuse, within the last 6 months prior to Screening Visit 1.
17. History of, or current treatment for, hepatic disease including but not limited to acute or chronic hepatitis, cirrhosis or hepatic failure or Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) levels of more than 1.5 x upper limit of normal (ULN) or International Normalized Ratio (INR) of more than 1.5 at Screening Visit 1.
19. History of renal disease or creatinine level above 1.5x ULN at Screening Visit 1. For children (<12y) this criterion is replaced by an eGFR <60cc/min/1.73m2 according to the Schwartz formula (National Kidney Foundation 2002) (Schwartz et al 2009). Platelets < 100'000/µL at Screening Visit 1.
20. Pregnant or nursing (lactating) females
21. Female subjects, including adolescent females of 12 to less than 18 years of age, of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using basic (acceptable effective) methods of contraception for the duration of the study (approx. 4 months, i.e. 5 half-lives, after last dose of ligelizumab). Basic (acceptable effective) contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the participant). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable effective methods of contraception
    - Female sterilization (surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment
    - Male sterilization (at least 6 months prior to screening). For female participants, the vasectomized male partner should be confirmed as their sole partner.
    - Barrier methods of contraception: Condom or Occlusive cap (e.g. diaphragm or cervical/vault caps). For UK: with spermicidal foam/gel/film/cream/ vaginal suppository

- Use of oral (estrogen and progesterone) injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS)

Female participants using oral contraception should be on a stable dose for a minimum of 3 months prior to taking study treatment.

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

If local regulations are more stringent the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the ICF/assent.

22. Sexually active children below the age of 12 years.

6 Treatment

6.1 Study treatment

Study treatment includes investigational drug QGE031 (120 mg/ml) and placebo. Study treatment must be administered by an independent drug administrator or unblinded pharmacist who is not involved in any of the study assessments. The procedure related to DBPCFC is provided in Section 16.4. Information on the food challenge materials and preparation instructions are provided separately in the pharmacy manual.

6.1.1 Investigational and control drugs

Novartis will supply ligelizumab (QGE031) 120 mg per 1 mL as prefilled syringe (PFS) with a needle safety device (NSD) and placebo.

Table 6-1 Investigational and control drug

Investigational/ Control Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Presentation	Sponsor (global or local)
QGE031 120 mg/1ml	Solution for injection	s.c.	Double-blind	global
QGE031 Placebo/1ml	Solution for injection	s.c.	Double-blind	global

6.1.2 Treatment arms/group

Participants will be assigned at randomization (Day1) to one of the following five treatment arms in a ratio of 2:2:2:2:1. Each participant will receive two (2) s.c. injections every four weeks starting at Day1:

1. ligelizumab 240 mg arm: 2 injections of 1.0 mL ligelizumab from Day1 through Week 52

2. placebo 8wk/ligelizumab 240 mg arm: 2 injections of 1.0 mL placebo at Day 1 and Week 4; 2 injections of 1.0 mL ligelizumab from Week 8 through Week 52

3. ligelizumab 120 mg arm: 1 injection of 1.0 mL ligelizumab and 1 injection of 1.0 mL placebo from Day1 through Week 52

4. placebo 8wk/ligelizumab 120 mg arm: 2 injections of 1.0 mL placebo at Day1 and Week 4; 1 injection of 1.0 mL ligelizumab and 1 injection of 1.0 mL placebo from Week 8 through Week 52

5. placebo 16wk/ligelizumab 120/240 mg arm: 2 injections of 1.0 mL placebo from Day1 through Week 12; as of week 16 participants will receive either 120 mg or 240 mg ligelizumab for the remaining of the treatment phase:

a. 120 mg: 1 injection of 1.0 mL ligelizumab and 1 injection of 1.0 mL placebo from Week 16 through Week 52

b. 240 mg: 2 injections of 1.0 mL ligelizumab from Week 16 through Week 52

The assignment to receive 120 mg or 240 mg ligelizumab from Week 16 through Week 52 will be determined at randomization.

6.1.3 Treatment duration

Treatment duration is 52 weeks. Participants will receive two subcutaneous injections every 4 weeks (SCq4w) at 14 visits during the double-blind treatment period. Administration of study drug must be recorded in the source documents and the corresponding eCRF for each administration. The Follow-up period is a non-treatment period of 16 weeks where neither study treatment will be administered nor a DBPCFC will be performed.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the participant was enrolled into the study must be recorded on the appropriate Case Report Forms.

Each concomitant drug must be individually assessed against all exclusion criteria, medication allowed under certain conditions (listed in Table 6-2) and prohibited medication (listed in Table 6-3). If in doubt, the investigator should contact Novartis before randomizing a participant or allowing a new medication to be started. If a participant is already enrolled and taking a prohibited medication, contact Novartis to determine if the participant should continue to participate in the study.

It is recommended that participants with asthma who are eligible for study participation maintain a stable regimen of controller treatment throughout the study.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

The following medications are allowed if taken as per below conditions:

Table 6-2 Medications allowed under certain conditions

Medication	Condition under which medication is permitted
Topical Corticosteroids and other topical immunosuppressants	In recommended doses and dosage regimens
Immunotherapy for treatment of allergies in maintenance phase (except food allergies)	In maintenance phase for at least 3 months prior to Screening Visit 1 s.c. (subcutaneous) immunotherapy: time window of 1 week between DBPCFC/study drug administration and immunotherapy shot. SLIT (sublingual immunotherapy): Hold SLIT dose on the day of DBPCFC
Inactivated, non-live vaccines	Not administered within 48 hours prior to a study visit
Intra-nasal corticosteroids	in recommended doses and dosage regimens
Short acting and long acting anti-histamines (e.g., chlorpheniramine, promethazine, diphenhydramine, loratidine, cetirizine)	Not administered within 5 half-lives prior to SPT (skin prick test) and DBPCFC
Short Acting beta agonist (SABA)	Not used within 6h of all spirometry assessments for asthma participants and within 6h prior to start of DBPCFC
Anti-Histamine nose spray	in recommended doses and dosage regimens
Oral H2 receptor antagonists: e.g., cimetidine, ranitidine, famotidine, nizatidine	Not administered within 24 hours prior to SPT and DBPCFC

6.2.2 Prohibited medication

Use of the treatments displayed below (_Table 6-3) is not allowed after screening (Screening Visit 1) to the end of study. The minimum required period without prohibited treatment before Screening Visit 1 is also shown.

If a participant develops a medical condition that requires use of prohibited treatment or if participant exhibits a behavior of non-compliance regarding prohibited medications at any timepoint from Screening Visit 1 to the end of the study, investigational treatment and DBPCFC must be discontinued (see also Section 9.1.1).

Table 6-3 Prohibited medication

Medication	Minimum required period without medications	Action taken if medication is taken during study
Any monoclonal antibody treatment (including any Fab fragments); e.g. omalizumab (Xolair®), dupilumab (Dupixent®), benralizumab (Fasenra™),	6 months before Screening Visit 1	Discontinue investigational treatment

mepolizumab (Nucala®), reslizumab (Cinqair®),		
Immunotherapy for treatment of food allergies	6 months before Screening Visit 1	Discontinue investigational treatment
Other systemic immunosuppressive medication including but not limited to methotrexate, cyclosporine A, cyclophosphamide, tacrolimus and mycophenolate mofetil, Janus Kinase inhibitors	30 days prior to Screening Visit 1	Discontinue investigational treatment
Systemic corticosteroids (for short-term burst see footnote*)	≥5 half-lives prior to Screening Visit 1	Discontinue investigational treatment
Beta blockers	Depending on the compound, to be ≥ 5 half-lives prior to Screening Visit 1	Discontinue investigational treatment
ACE inhibitors	Depending on the compound, to be ≥ 5 half-lives prior to Screening Visit 1	Discontinue investigational treatment
Tricyclic antidepressants	Depending on the compound, to be ≥ 5 half-lives prior to Screening Visit 1	Discontinue investigational treatment
Other investigational drugs	30 days or 5 half-lives, whichever is longer prior to Screening Visit 1	Discontinue investigational treatment
Live attenuated vaccines	30 days prior to Screening Visit 1	Discontinue investigational treatment
* Short-term burst of corticosteroids is allowed (e.g. in case of an allergic reaction); a wash-out period of 5 half-lives is then required prior to DBPCFC and skin prick testing. The use of long-acting corticosteroids to treat allergic reactions during DBPCFC e.g. dexamethasone is not recommended to avoid long wash-out periods between two DBPCFCs.		

6.2.3 Rescue medication

Any treatment deemed necessary by the investigator can be used to treat adverse events, including allergic reactions. Typically, this includes epinephrine, SABA, anti-histamines and saline bolus. Any use of rescue medication must be captured on the designated CRF.

Epinephrine:

In alignment with treatment guidelines for food allergy, all study participants will be provided with rescue medication epinephrine (e.g. EpiPen®) to be used to treat any allergic reactions and potential anaphylactic events that occur throughout the study as needed. If the participant is treated with epinephrine (e.g. EpiPen®) outside of a study visit, the participant or parents/caregiver should contact the study site staff.

SABA (salbutamol/albuterol):

Participants with a documented diagnosis of asthma will additionally be provided with SABA rescue medication. As listed on Table 6-2, the participant should not use SABA rescue medication within 6 hours of a spirometry assessment and/or DBPCFC.

These two rescue medications are to be provided to the participant locally before the start of the DBPCFC (Screening Visit 2). Participants should be instructed to bring them to each visit.

The counseling of participants/caregivers on the identification of allergic reactions and symptoms of anaphylaxis, as well as proper instruction for the use of rescue medication must be documented in source.

Repeat counseling should be provided as needed to ensure complete understanding. Additional supplies of rescue medication should be provided as needed throughout the study.

Rescue medication can either be provided directly at the study center or prescribed to the participant. Please refer to Section 6.3.2 for further information.

6.3 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under investigational and control drugs section (Section 6.1.1).

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

Please refer to the QGE031G12301 Pharmacy Manual for study drug handling and administration.

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

6.3.1 Handling of study treatment and other treatment

6.3.1.1 Handling of study treatment

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

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

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

The designated site personnel must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. The investigator must also provide accountability for locally sourced materials used for administration.

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

6.3.1.2 Handling of additional treatment

All rescue medication regardless of dispensation method, must be documented in source and closely monitored. Participants should be reminded to bring rescue medication to all study visits. This applies to the following:

- SABA (for participants with a documented diagnosis of asthma)
- Epinephrine (e.g., EpiPen)

If rescue medication is provided at the study site it must be handled and stored according to the package label, kept in a secured location and dispensed only in accordance with the protocol.

The investigator must maintain an accurate record of dispensing of the above-mentioned treatment in a drug accountability log/inventory log, and source documents. Monitoring of drug accountability will be performed by monitors during site visits and at the completion of the study. Participants will be asked to return all unused SABA and epinephrine treatments and packaging at the end of the study or at the time of discontinuation from the study.

Any unused epinephrine and SABA stored at the site will be disposed of according to local regulation.

6.3.2 Instruction for prescribing and taking study treatment

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

The s.c. injections can be administered in the deltoid region on the upper right and/or left arm, the lower stomach area (but not the area 5 cm around the belly button) and/or into the front of the right and/or left thigh, or the abdomen as preferred by the participant and/or site. The injections are administered subcutaneously. Do not inject into skin that is tender, bruised, red, scaly, hard or into areas with scars or stretch marks. Each injection must be administered at a different site (e.g., right arm and left thigh). The guidelines for the preparation and administration of study treatment are described in the pharmacy manual (provided separately).

Participants will remain on-site for observation for a period of **2 h post-dose** for the drug administrations at the Randomization, Week 4, Week 8, Week 16, Week 20 and Week 24 visits.

At Week 12 and Week 52 there must be **a minimum of 1 hour between administration of study drug and performing the DBPCFC.** (Section 8.3.1). Study drug must be given **before the DBPCFC**.

For all remaining drug administrations participants will remain on-site for observation for a period of **30 min post-dose.**

These observation periods follow the recommendation suggested by the National Heart, Lung, and Blood Institute and by the American Academy of Allergy, Asthma & Immunology and the American College of Allergy, Asthma and Immunology Executive Committees Joint Task Force (Cox et al 2007) for the anti-IgE therapy currently available (omalizumab). As described in the Investigator Brochure, the site needs to ensure readiness to react to anaphylactic events (e.g., immediate availability of qualified staff, available injectable epinephrine, antihistamine,

corticosteroids, intravenous supplies, oxygen, an oral airway, Ambu bag and the ability to transport a participant rapidly to an emergency department/hospital).

The dose for individual participants will be the same within a treatment arm and will be assigned at randomization.

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

All kits of study treatment assigned by the IRT will be recorded in the IRT.

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

6.4 Participant numbering, treatment assignment, randomization

6.4.1 Participant numbering

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

A new ICF will need to be signed if the investigator chooses to re-screen the participant after a participant has screen failed.

6.4.2 Treatment assignment, randomization

At the Randomization Visit (Day 1), all eligible participants will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The designated site personnel will contact the IRT after confirming that the participant fulfills all the inclusion/exclusion and screening criteria. The IRT will assign a randomization number to the participant, which will be used to link the participant to a treatment arm and will specify a unique medication number for the first study treatment to be dispensed to the participant.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from participants and investigator staff. A participant randomization list will be produced by the IRT provider using a validated system that automates the random assignment of participant numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Global Clinical Supply (GCS) using a validated system that automates the random assignment of medication numbers to packs containing the study treatment.

In general, randomization will be stratified by region, total IgE at screening (<350 IU/ mL; ≥350 IU/ mL at Screening Visit 1) and age (6 - 11y, 12 - 17y, and 18 - 55y). The trial will aim to randomize approximately one third of total participants from each defined age cohort.

Treatment assignment as well as participant stratification is determined by the IRT at randomization.

Randomization will be stratified by patient age at Screening visit 1.

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

6.4.2.1 Replacement policy

Refer to Section 12.8.2.

6.5 Treatment blinding

This is a double-blind study. Participants, investigator study staff and the Novartis Clinical Trial Team will remain blinded to the identity of the treatment assignment from the time of randomization until clinical database lock. Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study with the following exceptions:

- Bioanalyst [redacted]): to enable identification of samples from the ligelizumab treatment arms of the study to facilitate bioanalysis;
- Specific vendors whose role in trial conduct requires their unblinding (e.g. IRT)
- Global Clinical Supply (GCS)
- An independent Data Monitoring Committee (DMC) and the independent statistician & programmer supporting the DMC activities
- Novartis associates who are involved the analysis before final DBL described in Section 4.4

The following measures must be applied by the study site to keep the participant and study site personnel blinded to the identity of the treatment:

- The study drug must be administered by an independent drug administrator or unblinded pharmacist who is not involved in the performance of any of the study assessments.
- Apart from the independent drug administrator or unblinded pharmacist, study site staff should **NOT** handle the Investigational Medicinal Product (IMP) and no information regarding the IMP should be discussed with the site study staff

For the primary analysis at Week 12 (Section 4.4), a limited number of pre-specified members of the program team from Novartis will be unblinded in a phasic manner. After the primary analysis at Week 12 and until study completion, the study will be under the management of a separate blinded team, replacing pre-specified unblinded team members, who will be responsible for study conduct. To maintain the integrity of the study data, the blinded team members will not have access to any of the unblinded data.

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

treatment code has been broken inadvertently or for any non-emergency reason will be discontinued from study treatment. These participants will transition into the follow up period. The investigator must maintain an accurate record of the shipment and dispensing of investigational treatment in a drug accountability log.

Table 6-4 Blinding level

Role	Time or Event					
	Randomization list generated	Study treatment and allergen allocation & dosing	Safety event (single subject unblinded)	Interim analysis: 60 adolescent completers	Primary analysis at Week 12	Analysis at Week 52
Participants	B	B	B	B	B	B
Investigator and site staff	B	B	B	B	B	B
Site staff: Pharmacy staff and IMP administrator	B	UI	B	B	B	B
Global Clinical Supply and Randomization Office	UI	UI	UI	UI	UI	UI
sponsor staff: CRA	B	B	B	B	B	B
Sponsor staff: Pharmacovigilance staff	B	B	UI	B	B	B
Sponsor staff: Bioanalysis [redacted]	B	UI	B	B	B	B
Independent statistician and programmer	B	B	B	B	B	B
Adjudication committee	B	B	B	B	B	B
All other sponsor staff not identified above but defined in the unblinding charter	B	B	B	UI	UI	UI

B Remains blinded

UI Allowed to be unblinded on individual participant level. The results of the DBPCFC at screening will be unblinded to assess eligibility.

6.6 Dose escalation and dose modification

Study drug dose adjustments and/or interruptions are not permitted.

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

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

6.6.1 Dose modifications

Not applicable

6.7 Additional treatment guidance

6.7.1 Treatment compliance

Participants will receive two injections SCq4w at 14 visits during the treatment period. Compliance is assured as long as the participant attends all study visits according to the Schedule of Assessments (Table 8-1). Study drug is administered at the site only at designated study visits. The administration of study drug must be recorded in the source documents and the corresponding eCRF.

6.7.2 Recommended treatment of adverse events

Any treatment deemed necessary by the investigator for the safety of the participant is allowed.

For treatment of severe allergic reactions including anaphylaxis, epinephrine and SABA are typically used.

Treatments of adverse events should align with prohibited medication (Section 6.2.2, Table 6-3) and medications allowed under certain conditions (Section 6.2.1.1, Table 6-2). Medication used to treat adverse events (AEs) must be recorded on the appropriate CRF.

For adverse events associated with the DBPCFC, please consult Section 16.4.

6.7.3 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the participant safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study participant who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a participant, he/she must provide the requested participant identifying information and confirm the necessity to break the treatment code for the participant. The investigator will then receive details of the investigational drug treatment for the specified participant and a fax or email confirming this information. The system will automatically inform Novartis monitor for the site and the study team that the code has been broken.

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

- protocol number
- participant number

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

In case of emergency code breaks, the respective participant is not eligible for joining the extension study anymore.

7 Informed consent procedures

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

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

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

The Investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant or their legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representatives will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.

A copy of the ICF(s) must be provided to the participant or their legally authorized representative.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Per Section 4.6 during a Public Health emergency as declared by Local or Regional authorities (i.e. pandemic, epidemic or natural disaster), that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, the investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference) if allowable by local Health Authorities.

Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g. the presence of an impartial witness, sign/dating separate ICFs by trial participant and person obtaining informed consent, etc.).

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC. Likewise, Novartis will also provide to investigators in separate documents proposed age-appropriate child assent forms.

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

[redacted]

This ICF will contain a separate section that addresses the use of remaining mandatory samples for optional additional research. The Investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for additional research. Participants who decline to participate in this optional additional research will document this.

- Parent/Guardian study consent including the subsections mentioned above.
- Child Assent for ages 6-11 years
- Adolescent Assent for ages 12-17 years
- As applicable, Pregnancy Outcomes Reporting Consent for female participants who took study treatment

[redacted]

If a minor participant reaches the age of legal majority in the course of the study, he/she/they must be re-consented as an adult.

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

[redacted]

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

Participants might be asked to complete an optional questionnaire to provide feedback on their clinical trial experience.

8 Visit schedule and assessments

The Assessment Schedule (Table 8-1) lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the participant's source documentation. The table indicates which data are entered into the eCRF from the source data (X), or remain in the source documents only (S).

Participants should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1) or as close to the designated day/time as possible. The participant should be instructed to contact the investigator if he/she is unable for any reason to attend the visit as planned and the visit should be rescheduled as close as possible to the original date. In case of a rescheduled visit, all upcoming visits need to follow the original schedule. Missed or rescheduled visits should not lead to automatic treatment or study discontinuation.

Participants who discontinue from study or withdraw their consent/oppose the use of their data/biological samples should be scheduled for a final evaluation visit if they agree, as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled and the adverse event and concomitant medications not previously reported must be recorded on the CRF.

All participants who complete the treatment period will be expected to attend all follow-up visits (Visit Week 56 to EOS).

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the investigator as the situation dictates. If allowable by a local Health Authority and depending on operational capabilities, phone calls, virtual contacts (e.g. tele consult) or visits by site staff/ home nursing staff to the participant´s home, can replace on-site study visits, for the duration of the disruption until it is safe for the participant to visit the site again. If the Investigator delegates tasks to any on-site or off-site healthcare professional, the Investigator must ensure the individual(s) is/are qualified and appropriately trained to perform assigned duties. The Investigator must oversee their conduct and remain responsible for the evaluation of the data collected.

Please refer to the assessment schedule (Table 8-1) to understand which assessments have to be carried out in what order. Assessments at the top of the table have to be done before assessments at the bottom of the table. This is especially critical for days on when the DBPCFC is carried out: (e.g.: Cellular biomarker blood draw has to be done before SPT.)

Administration of study drug has to be done **before** the DBPCFC. There must be a minimum of **1 hour between study drug administration and DBPCFC.**

Please make sure the order of assessments is respected consistently.

Table 8-1 Assessment Schedule

Period	**Screening**			**Treatment**															
Visit Name	**SCRN1** [1]	**SCRN 2 Part 1-OFC**	**SCRN 2 Part 2-OFC**	**Day 1 (Randomization)**	**WK 1**	**WK 4**	**WK 8**	**WK12 Part 1-OFC**	**WK12 Part 2-OFC**	**WK16**	**WK20**	**WK24**	**WK28**	**WK32**	**WK36**	**WK40**	**WK44**	**WK48**	**WK52 Part 1-OFC**	**WK52 Part 2-OFC**
Days	**-28 to -1**			**1**	**8**	**29**	**57**	**85**	**87 to 92**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**367 to 372**
Informed consent and assent	X																			
Inclusion / Exclusion criteria	X	X	X	X																
Demography/ Medical history	X																			
Concomitant medications, therapies, procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient reported outcomes (PROs)				X				approx. 10 days before the OFC	approx. 3 days after the OFC										approx. 10 days before the OFC	approx. 3 days after the OFC
Physical Examination	S	S	S	S				S	S										S	S
Body Weight	X							X											X	
Body Height [2]	X			S		S		S							S				S	
Electrocardiogram (ECG)	X							X											X	

Period	**Screening**			**Treatment**															
Visit Name	**SCRN1**[1]	**SCRN 2 Part 1-OFC**	**SCRN 2 Part 2-OFC**	**Day 1 (Randomization)**	**WK 1**	**WK 4**	**WK 8**	**WK12 Part 1-OFC**	**WK12 Part 2-OFC**	**WK16**	**WK20**	**WK24**	**WK28**	**WK32**	**WK36**	**WK40**	**WK44**	**WK48**	**WK52 Part 1-OFC**	**WK52 Part 2-OFC**
Spirometry in co-morbid asthma only	X	X	X					X	X										X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	X			X		X		X							X				X	
Clinical Chemistry	X			X		X		X							X				X	
Coagulation lab	X			X																
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Liver Safety Monitoring	S			S		S		S							S				S	
Renal Safety Monitoring	S			S		S		S							S				S	
Urine pregnancy test		S		S	S	S	S	S		S	S	S	S	S	S	S	S	S	S	
Serum Pregnancy test	X																			
Urinalysis dipstick	S							S							S				S	

Period	**Screening**			**Treatment**																
Visit Name	**SCRN1**[1]	**SCRN 2 Part 1-OFC**	**SCRN 2 Part 2-OFC**	**Day 1 (Randomization)**	**WK 1**	**WK 4**	**WK 8**	**WK12 Part 1-OFC**	**WK12 Part 2-OFC**	**WK16**	**WK20**	**WK24**	**WK28**	**WK32**	**WK36**	**WK40**	**WK44**	**WK48**	**WK52 Part 1-OFC**	**WK52 Part 2-OFC**
Stool Sample (ova & parasitic test) by local lab	S																			
Total IgE and peanut specific IgE (sIgE)	X																			
[redacted]																				
Blood collection for peanut [redacted] specific IgE and IgG4				X				X		X									X	
[redacted]																				
Skin Prick Test[3]	X									X										
[redacted]																				

Period	**Screening**			**Treatment**																
Visit Name	**SCRN1**[1]	**SCRN 2 Part 1-OFC**	**SCRN 2 Part 2-OFC**	**Day 1 (Randomization)**	**WK 1**	**WK 4**	**WK 8**	**WK12 Part 1-OFC**	**WK12 Part 2-OFC**	**WK16**	**WK20**	**WK24**	**WK28**	**WK32**	**WK36**	**WK40**	**WK44**	**WK48**	**WK52 Part 1-OFC**	**WK52 Part 2-OFC**
Contact IRT	S	S	S	S		S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
Study drug administration				X		X	X	X		X	X	X	X	X	X	X	X	X	X	
Study drug Accountability				S		S	S	S		S	S	S	S	S	S	S	S	S	S	
Providing rescue medication, counseling, training & accountability	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
DBPCFC[4]		X	X					X	X										X	X
Trial Feedback Questionnaire																				S
Extension Study participation discussion																		S		
Study disposition			X						X											X

Period	**Follow- up**			
Visit Name	**WK56**	**WK60**	**WK64**	**EOS/PSD**
Days	**393**	**421**	**449**	**477**
Informed consent and assent				
Inclusion / Exclusion criteria				
Demography/ Medical history				

Period	**Follow- up**			
Visit Name	**WK56**	**WK60**	**WK64**	**EOS/PSD**
Days	**393**	**421**	**449**	**477**
Concomitant medications, therapies, procedures	X	X	X	X
Patient reported outcomes (PROs)				
Physical Examination				S
Body Weight				
Body Height [2]				S
Electrocardiogram (ECG)				X
Spirometry in co-morbid asthma only				
Vital Signs	X	X	X	X
Hematology				X
Clinical Chemistry				X
Coagulation lab				
Adverse Events	X	X	X	X
Liver Safety Monitoring				S
Renal Safety Monitoring				S
Urine pregnancy test	S	S	S	S
Serum Pregnancy test				
Urinalysis dipstick				S
Stool Sample (ova & parasitic test) by local lab				S
Total IgE and peanut specific IgE (sIgE)				
[redacted]				
Blood collection for peanut [redacted] specific IgE and IgG4	X	X	X	X
[redacted]				
Skin Prick Test[3]	X			X
[redacted]				

Period	**Follow- up**			
Visit Name	**WK56**	**WK60**	**WK64**	**EOS/PSD**
Days	**393**	**421**	**449**	**477**
[redacted]				
Contact IRT				S
Study drug administration				
Study drug Accountability				
Providing rescue medication, counseling, training & accountability	S	S	S	S
[redacted]				
DBPCFC[4]				
Trial Feedback Questionnaire				
Extension Study participation discussion				
Study disposition				X

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[S] Assessment to be recorded in the source documentation only
[1] Re-screening may be allowed for participants who failed initial screening; only 1 re-screening will be allowed (See Section 8.1)
[2] Body Height needs to be measured for children and adolescents at all visits where clinical chemistry is analyzed. The results need to be captured in source data. Body height only needs to be captured at SCR1 for adults (18 years and older).
[3] Please check the medications prior to skin prick test.
[4] The DBPCFC will be done on two separate days and within a window of one to seven days (See Section 8.3.1)

8.1 Screening

Screening

In order to enroll in the study, participants must meet inclusion and none of the exclusion criteria (Section 5.1 and Section 5.2). Participants will have up to a 4 week screening period to establish study eligibility. During the screening period participants will be required to attend two visits; Screening Visit 1 and Screening Visit 2 (Part 1 and Part 2). Prior to the Screening Visit 2 Part 1 (DBPCFC) screening can be extended one additional week if any information concerning eligibility to proceed to the DBPCFC is outstanding.

Rescreening will be allowed only once for participants who failed initial screening (Screening Visit 1) and still fulfill ALL the study eligibility criteria (Section 5). If a participant rescreens for the study, the participant must sign a new informed consent (and assent if applicable) and will be issued a new participant number. Informed consent (and assent if applicable) for a rescreened participant must be obtained prior to performing any study-related assessments or collecting any data for the Screening visit.

8.1.1 Information to be collected on screening failures

Participants who sign an informed consent form and are subsequently found to be ineligible prior to randomization will be considered as a screen failure. The reason for screen failure should be recorded on the appropriate CRF. The demographic information, informed consent, inclusion/exclusion pages, disposition, total IgE and peanut specific IgE, medical history, DBPCFC and SPT must also be collected for screen failure participants. No further data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a serious adverse event during the screening phase (Section 10.1.3). Adverse events that are not SAEs will be followed by the investigator and collected only in the source data. If the participant fails to be randomized, the IRT must be notified within 2 days of the screen fail that the participant was not randomized. Participants who are randomized and fail to start treatment, e.g. participants randomized in error, will be considered an early terminator. The reason for early termination should be recorded on the appropriate CRF.

8.2 Participant demographics/other baseline characteristics

Participant demographics and baseline characteristics will be collected at Screening (Screening Visit 1), as specified in the assessment schedule (Table 8-1).

Data collected will include age; sex; race; ethnicity; height and weight; relevant medical history, and prior and concomitant medications. A detailed medical history (including family medical history) and current medical conditions present before signing of informed consent will be recorded. Investigators will have the discretion to record abnormal test findings on the CRF capturing medical history whenever in their judgment, the test abnormality occurred prior to the informed consent signature. Participant race and ethnicity are collected and analyzed to identify variations in safety or efficacy due to these factors as well as to assess the diversity of the study population as required by Health Authorities.

8.2.1 Spirometry

For participants with a documented diagnosis of asthma, spirometry testing should be performed at screening (Screening Visit 1) to assess the participant's eligibility for study participation. Per Section 5.2, exclusion criterion 8, participants with uncontrolled asthma defined as FEV1 < 80% of predicted normal value and/or the history of one hospitalization for asthma within 12 months, are excluded.

Furthermore, spirometry is performed prior to the DBPCFCs at Screening Visit 2 - parts 1 and 2, week 12 parts 1 and 2, and at week 52 parts 1 and 2. If the FEV1 % predicted normal value is below 80% (< 80%) before the DBPCFC at any of the beforementioned visits, the DBPCFC should not be performed and rescheduled as appropriate.

For each spirometry measurement, the accurate participant data (e.g., age, gender and height) should be used for the calculation of FEV1 predicted normal value at the site.

The spirometry assessment should be performed in accordance with the standard practice at the site including the quality check. It is recommended to follow the ATS/ERS standard (ATS/ERS Task Force: Standardization of Lung Function Testing, Graham et al 2019) if possible.

8.3 Efficacy

8.3.1 Double Blind Placebo Controlled Food Challenge (DBPCFC)

The DBPCFC is the critical assessment needed to evaluate the primary objective. It is performed at baseline (Screening Visit 2), Week 12 and Week 52. Details of this procedure are outlined in Section 16.4 and preparation of the allergen is outlined in the QGE031G12301 Pharmacy Manual.

Conducting the food challenge requires the physical facility to prepare material as well as an **unblinded** and independent study nurse or staff to execute preparation. The assessment itself is conducted under medical supervision by blinded study personnel. Sites should be equipped with supplies to treat allergic reactions (including severe anaphylaxis) (Section 16.4), as well as access to emergency care units.

To ensure participant safety, on study visits where the DBPCFC is conducted, it is critical to follow the order of assessments as outlined in Table 8-1., i.e. concomitant medication check, physical examination, ECG, vital signs, spirometry (for asthma participants only), urine pregnancy (if applicable), laboratory evaluations and study drug administration (Weeks 12 and 52) must be performed prior to the start of the DBPCFC.

The site should be prepared react to immediate and late hypersensitivity reactions, including anaphylaxis. At the completion of the DBPCFC participants must remain under observation at the site for a minimum of 2 hours after the last OFC dose (or for a positive challenge at least for 1 hour after all allergic symptoms have improved). After the observation period, discharge from the study site is at the discretion of the investigator. Prior to discharge, all participants should be briefed about the signs and symptoms of anaphylaxis and provided with an epinephrine auto-injector.

DBPCFC data will be captured on a designated electronic case report form (eCRF).

If a participant fails to receive study medication for any reason AT the week 12 visit, do not proceed with the DBPCFC. Additionally, if a participant misses more than one dose of study treatment BEFORE week 12, they should not undergo the DBPCFC at the week 12 visit.

8.3.2 Appropriateness of efficacy assessments

The procedures of oral food challenge have been endorsed in principle by the Adverse Reactions to Foods Committee of the American Academy of Allergy and Immunology, and there are well established guidelines such as the PRACTALL protocol (Cox et al (2017), Sampson et al 2012) and the CoFAR definition of dose-limiting symptoms (Table 16-8). The DBPCFC is the state-of-the-art technique to confirm or refute histories of adverse reactions to foods. It is the "gold standard" by which all studies of food allergy should be judged (Bock et al 1988).

Threshold doses can only be determined using DBPCFCs with low doses of the offending food. This approach has been previously used in a clinical study to determine the ability of an anti-IgE monoclonal to shift the dose-response curve of a peanut DBPCFC (Leung et al 2003).

Although the average amount of peanut consumed in an accidental exposure has not been accurately quantified, it is generally believed to be no more than one or two peanuts, or the equivalent of approximately 160 to 325 mg of peanut protein. Therefore, as proposed in this study, an increase in the threshold of peanut flour required to provoke symptoms should serve as a proxy to estimate the level of protection against unintended ingestion.

8.4 Safety

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

For details on AE collection and reporting, refer to AE section:

- AEs and SAEs, including AEs leading to treatment discontinuation and events of interest such as injection site reactions, anaphylaxis, pre-malignancy/malignancy, cardio-cerebrovascular events
- Physical examination
- Vital signs
- Laboratory evaluations
- Spirometry (for asthma participants only, Section 8.2.1)
- ECG (Electrocardiogram)

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

Table 8-2 Physical Assessments

Assessment	Specification
Physical examination	A complete physical examination will be performed as specified in the Table 8-1, and includes the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate eCRF that captures medical history. Significant findings made after signing the informed consent which meet the definition of an AE must be recorded as an AE.
Vital signs	Vital signs include blood pressure and pulse measurements. After the participant has been sitting for 5 minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured using an automated validated device e.g. OMRON, with an appropriately sized cuff. In case the cuff sizes available are not large enough for the participant's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used. Clinically notable vital signs are defined in Section 16.1.
Height and weight	Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured as specified in the Table 8-1.

8.4.1 Laboratory evaluations

A central laboratory will be used for analysis of all specimens detailed in this section unless noted otherwise. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual. The blood volume collected for pediatric participants aligns with "The Hospital for Sick Children (SickKids) Research Ethics Board Blood Sampling Guidelines" (Howie 2011) and is outlined in detail in the QGE031G12301 Laboratory Manual. If local regulatory requirements stipulate more stringent limits for blood volumes for pediatric participants, the Novartis Clinical Team should be consulted for implementation of prioritization of lab evaluations.

If health authorities require additional testing on biological samples, such tests will be done, wherever possible.

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

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

A serum β-hCG will be collected at screening (Screening Visit 1) for all after menarche and pre-menopausal women who are not surgically sterile.

Table 8-3 Laboratory Evaluations

Test Category	Test Name
Hematology	Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential and platelet count
Coagulation	International Normalized Ratio (INR), Activated partial thromboplastin time (APTT).
Chemistry	Albumin, total bilirubin, direct bilirubin, alkaline phosphatase, AST, ALT, LDH, GGT, chloride, sodium, potassium, magnesium, calcium, phosphate, creatinine, urea/BUN, uric acid, amylase, lipase, and glucose. If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reacting bilirubin should be differentiated.
Urinalysis	A midstream urine sample (approximately 30 mL) will be obtained, in order to avoid contamination with epithelial cells and sediments, and allow proper assessments. Semi-quantitative “dipstick” evaluation for specific gravity, glucose, protein, bilirubin, ketones, leukocyte esterase and blood will be performed at site. When a dipstick evaluation is abnormal, e.g., positive for WBC and/or blood, a urine sample must be sent to the Central Lab for microscopic examination including RBC and WBC. (Details on collection of urine for analysis by central laboratory are provided to investigators in the laboratory manual.)
Parasite screening	Assessment of stool samples for parasitic infections is done by the local laboratory (refer to Assessment of parasitic infections Section 8.4.3)
Pregnancy Test	Serum / Urine pregnancy test (refer to Pregnancy and assessments of fertility Section 8.4. 4)

8.4.2 Electrocardiogram (ECG)

ECGs will be measured at Screening Visit 1 (for eligibility), week 12, week 52 and EOS visits Table 8-1. ECGs must be recorded after 10 minutes rest in the supine position to ensure a stable baseline/according to the ECG investigator manual. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood sampling. The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

Single 12 lead ECGs are collected, and the original trace should be printed on non-heat sensitive paper. Each ECG will be sent electronically for central review directly from the ECG machine. One print-out will be generated and kept at the investigator site as source documentation and will be dated and signed. The subject's number, the date, actual time of the tracing, and Study Code must appear on each page.

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

Clinically significant abnormalities must be recorded on the CRF as either medical history/current medical conditions or adverse events as appropriate.

8.4.3 Pregnancy and assessments of fertility

All pre-menopausal female participants, including adolescent females of 12 to less than 18 years of age, who are not surgically sterile will have pregnancy testing. Post-menopausal status should be recorded in the Medical History CRF.

At Screening Visit 1, all pre-menopausal female participants who are not surgically sterile will have serum β-hCG collected.

At Screening Visit 2 Part 1 and subsequent study visits until Visit EOS, all pre-menopausal female participants who are not surgically sterile will have urine pregnancy testing performed BEFORE administration of the study treatment. A positive urine test needs to be confirmed with a central lab serum test prior to study drug administration. If positive, the participant must be discontinued from study treatment.

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

Assessments of fertility

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

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

In the absence of the above medical documentation, FSH testing is suggested of any female participant regardless of reported reproductive/menopausal status at Screening Visit 1.

8.4.4 Other safety evaluations

Assessment of parasitic infection

Reduction in IgE levels may confer increased susceptibility to parasitic infections. The risk of acquiring or activating infections with helminths during or after treatment with anti-IgE therapy such as ligelizumab is suspected to be low. Data from the Phase II study in the CSU indication (QGE031C2201) in this regard was unremarkable, but limited due to study sample size.

All participants with no symptoms suggestive of parasitic infection will be given a stool sample collection kit at Screening Visit 1 and EOS visit by the site or the site's local laboratory. Participants will take the stool sample kit home and collect a stool samples within seven days of Screening Visit 1 and in the week prior to EOS visit. Participants will return the stool sample to the site or local laboratory as soon as possible after Screening Visit 1 (in order to allow processing within the screening period) and EOS visit.

All participants with symptoms suggestive of parasitic infection at Screening Visit 1 and/ or EOS visit will be given three stool sample collection kits. These participants have to collect stool samples from three different days, ideally on three different days, within seven days of Screening Visit 1 and in the week prior to EOS visit and as soon as possible return the samples.

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

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

Assessment of anaphylactic events

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

Assessment of cardio-cerebrovascular events

An AC will be put in place to review all cases identified through a search algorithm based on the Standardized MedDRA Queries of cardio-cerebrovascular events. The clinical presentation and association of these events with pre-existing risk factors will be part of the assessment. See Section 10.3.2 for details

Assessment of neoplastic events

An AC will be put in place to review all cases identified through a search algorithm based on the Standardized MedDRA Queries of neoplastic events. The clinical presentation and association of these events with pre-existing risk factors will be part of the assessment. See Section 10.3.2 for details.

8.4.5 Appropriateness of safety measurements

In addition to safety assessments that are standard in this population, participants are not eligible to join the study if they have a history of a severe or life-threatening hypersensitivity event needing an ICU admission or intubation within 60 days prior to baseline DBPCFC (Screening Visit 2) or uncontrolled asthma at Screening Visit 1.

Also, study treatment will be discontinued if the participant experiences a life-threatening hypersensitivity event needing an ICU admission or intubation OR a serious hypersensitivity event suspected to be related to study treatment.

8.5 Additional assessments

8.5.1 Clinical Outcome Assessments (COAs)

Patient reported outcomes (PRO)

The impact of ligelizumab on the health-related quality of life (HRQoL) of participants with a food allergy will be assessed by the following measures based on age group and responder type:

- FAQLQ-CF: Food Allergy Quality of Life Questionnaire – Child Form
- FAIM-CF: Food Allergy Independent Measure – Child Form
- FAQLQ-TF: Food Allergy Quality of Life Questionnaire – Teenager Form
- FAIM-TF: Food Allergy Independent Measure – Teenager Form
- FAQLQ-AF: Food Allergy Quality of Life Questionnaire – Adult Form
- FAIM-AF: Food Allergy Independent Measure – Adult Form
- FAQLQ-PF: Food Allergy Quality of Life Questionnaire – Parental Form
- FAQL-PB: Food Allergy Quality of Life - Parental Burden Questionnaire
- SF-36v2 Acute Version – Medical Outcomes Study 36-Item Short Form Version 2 Acute Version (recall period is past week)

Table 8-4 PROs based on participant's age

Age Group/ Respondent Type	**Day 1 Randomization**	**Week 12 10 days Before D1 OFC**	**Week 12 3 days After D2 OFC**	**Week 52 10 days Before D1 OFC**	**Week 52 3 days After D2 OFC**
Children aged 6-7	*Children aged 6-7 will NOT be completing any PRO measures.* *Parents/Caregivers of children aged 6-17 will complete specific PROs designed for Parents/Caregivers.* *Note: Children aged 8-12 will self-complete PROs (next row) and their parents/caregivers will also complete PROs.*				
Children aged 8-12	FAQLQ-CF FAIM-CF	FAQLQ-CF FAIM-CF	FAQLQ-CF FAIM-CF	FAQLQ-CF FAIM-CF	FAQLQ-CF FAIM-CF
Adolescents aged 13-17	FAQLQ-TF FAIM-TF	FAQLQ-TF FAIM-TF	FAQLQ-TF FAIM-TF	FAQLQ-TF FAIM-TF	FAQLQ-TF FAIM-TF
Adults aged 18+	FAQLQ-AF FAIM-AF SF-36v2	FAQLQ-AF FAIM-AF	FAQLQ-AF FAIM-AF SF-36v2	FAQLQ-AF FAIM-AF	FAQLQ-AF FAIM-AF SF-36v2
Parents/Caregivers of Children 6-12	FAQLQ-PF FAQL-PB	FAQLQ-PF	FAQLQ-PF FAQL-PB	FAQLQ-PF	FAQLQ-PF FAQL-PB
Parents/Caregivers of Adolescents13-17	FAQL-PB		FAQL-PB		FAQL-PB

The Food Allergy Quality of Life Questionnaire (FAQLQ) is a self-reported instrument intended to assess the effect of food allergy on the particpant's HRQoL (i.e., domains consist of risk of accidental exposure, emotional impact, allergen avoidance and dietary restrictions). The FAQLQ- Child Form (aged 8-12) (Flokstra-de Blok et al 2009 a), FAQLQ-Teenager Form (aged 13-17) Flokstra-de Blok et al 2008) and FAQLQ-Adult Form (≥18 years of age) (Flokstra-de Blok et al 2009 b), are self-administered, validated, food allergy-specific HRQoL questionnaires. The FAQLQ-parental form (FAQLQ-PF) is completed by parents of children aged 0-12 with food allergy (DunnGalvin et al 2008)

The number of items and domains varies by FAQLQ instrument administered. Each question is scored on a seven-point scale from 1 to 7 (i.e., from 'no' to 'maximal' impairment in HRQoL, respectively). The total score is the arithmetic average of all non-missing items. Domain scores are calculated similarly.

The Food Allergy Independent Measure (FAIM) reflects the participant's perceived food allergy severity and food allergy-related risk. The total score for the FAIM ranges from 1 to 7 (i.e., from 'limited' to 'the greatest' severity perception). If less than 80% of the items are complete, then the total score will not be calculated. Similarly, if less than 80% of the items within a domain are complete, then the domain score will not be calculated. (van der Velde et al 2010)

The Food Allergy Quality of Life-Parental Burden (FAQL-PB) Questionnaire is a self-administered, disease-specific instrument developed to measure the effect of pediatric food allergy on HRQoL among caregivers. The instrument includes 17 items investigating the effect of having a child with food allergy on family/social activities, school, meal preparation, health concerns and emotional issues, using a 7-point Likert scale (Cohen et al 2004).

The SF-36v2® Health Survey is a 36-item instrument for measuring health status and outcomes via participant self-report. It is designed for use in surveys of general and specific populations, health policy evaluations, and clinical practice and research. The SF-6Dv2 (Brazier et al 2020) will be derived from the SF-36v2 (Maruish 2011) for health economic evaluations. The SF-6Dv2 captures the impacts of food allergy on social activities and depression/nervousness.

All questionnaires will be completed in the language most familiar to the respondent. The same parent/caregiver should complete the assessments throughout the study.

The participant should be given sufficient instruction, space, time and privacy to complete the questionnaire during the Randomization visit. The study coordinator should encourage the participants to complete all of the available questionnaires.

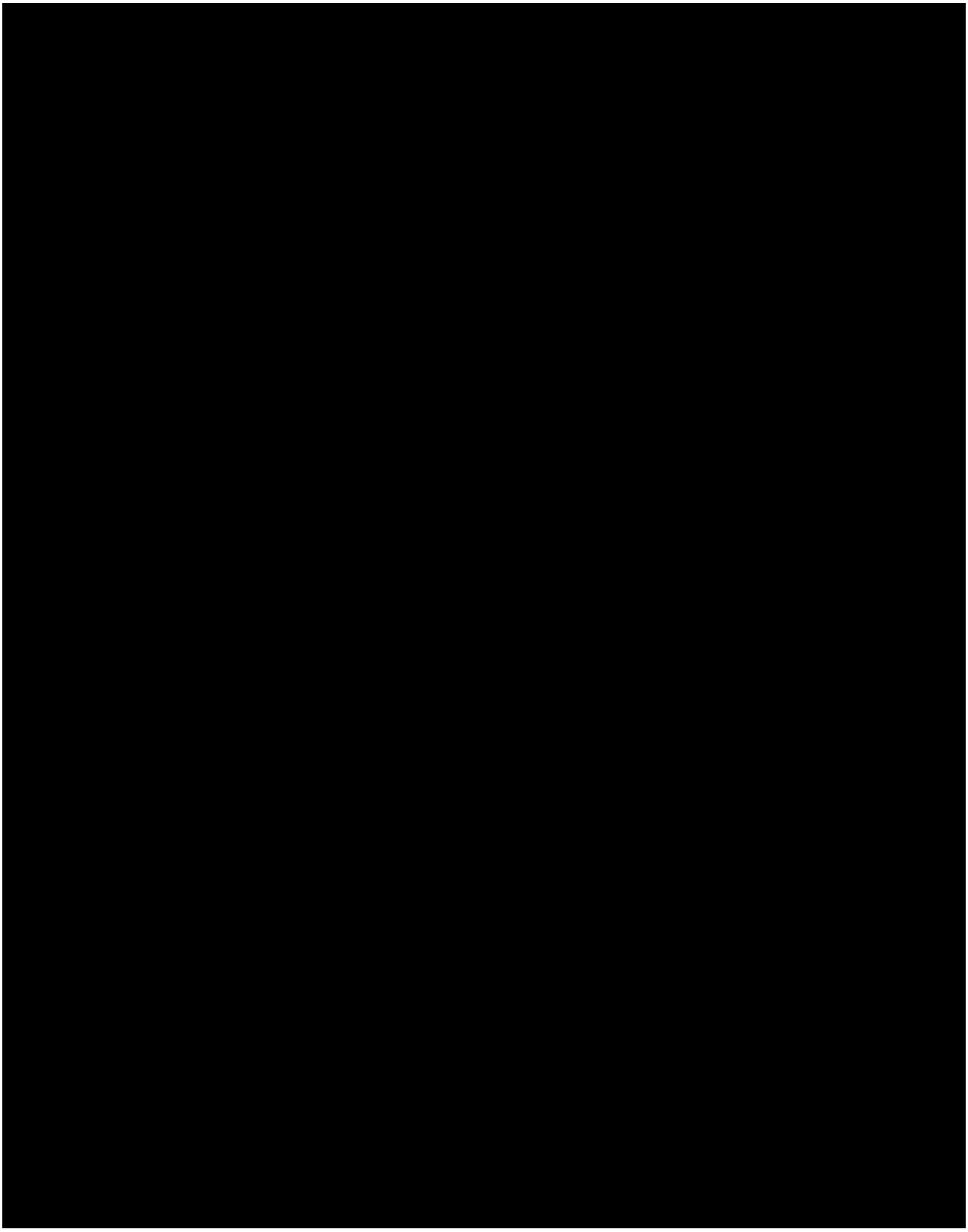
All participants will complete the PRO questions via a handheld electronic device (note: children aged 6-7 will NOT be completing any PRO measures*)*. Participants will take the device home and should complete them 10 days before Day 1 of the OFC and 3 days after Day 2 of the OFC at 12 weeks and at 52 weeks. If participants experience any difficulties with submission after completing the PROs, they should contact the study staff for assistance. Available training materials related to the administrative procedures of the questionnaires will be provided to the sites.

Participant refusal to complete study PROs are not protocol deviations. The participant should be made aware that completed measure(s) are not reviewed by the investigator/ study personnel.

Trial Feedback Questionnaire

This study includes an optional questionnaire for trial participants (18-55 years) to provide feedback on their clinical trial experience. Individual trial participant responses will not be reviewed by investigators. Responses may be used by the sponsor to understand where improvements can be made in the clinical trial process. This questionnaire does not ask

questions about the trial participant's disease, symptoms, treatment effect, or adverse events, and, therefore is not considered as trial data.



8.5.4 Other Assessments

8.5.4.1 Skin prick testing (SPT)

An allergen specific SPT is a commonly used diagnostic tool. In this study a titration SPT using peanut allergen will provide additional information on the impact of IgE suppression on skin mast cells. Milk and/or egg allergens will also be tested based on the participant's medical history.

In performing the test, the skin of the participant's back is the preferred site of testing, alternatively the forearm may be used. For consistency it is important to perform the skin prick test at the same location throughout the study. Skin reactions are to be recorded after 15 minutes of applying allergen to the pricked location. Medications to be washed out prior to the SPT are listed in Table 16-9.

This study specifies the use of BOTH a titration SPT (TSPT) and non-TSPT. All patients will perform a TSPT to peanut. In addition, all patients should perform a non-titration SPT (undiluted) to milk and/or egg according to medical history.

Skin prick testing is scheduled at Screening Visit 1, Week 16, Week 56 and EOS. At Week 16, skin prick testing should be performed before dosing of study treatment.

The size of the wheal and flare (the longest diameter and the midpoint orthogonal diameter) at each site will be recorded in the eCRFs.

The SPT may rarely cause serious allergic reactions, including anaphylaxis, and the site should be prepared to provide immediate treatment should that occur. If the participant experiences a systemic allergic reaction and/or an event which is judged by the investigator as an adverse reaction, it should be reported on the designated CRF.

The SPT procedure is summarized separately in Appendix Section 16.5.

[redacted]

8.5.4.3 Additional research using coded data

For participants who consent for additional research, their coded data including biological samples may be used for additional research. The purpose of the additional research would be limited to:

- help better understand how the study treatment works;
- learn more about the disease;
- help develop ways to detect, monitor, and treat related human diseases;
- improve the way clinical studies are conducted

9 Discontinuation and completion

9.1 Discontinuation from study treatment and from study

9.1.1 Discontinuation from study treatment

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

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

Study treatment must be discontinued under the following circumstances:

- Participant/guardian decision
- AEs for which continued exposure to the study drug would be detrimental
- Abnormal renal laboratory results requiring discontinuation (see Section 16.3)
- Abnormal liver laboratory results requiring discontinuation (see Section 16.2)
- Platelets < 75000/µL
- Pregnancy (see Section 5 and Section 8.4.3)
- Participant develops a medical condition that requires use of prohibited treatment as per Section 6.2.2 or if participant exhibits a behavior of non-compliance regarding prohibited medications
- Participant experiences a life-threatening hypersensitivity event due to any reason needing an ICU admission or intubation
- Participant experiences a serious hypersensitivity event suspected to be related to study treatment
- Any other protocol deviation that results in a significant risk to the participant's safety
- Any situation in which study participation might result in a safety risk to the participant
- Following emergency unblinding

If discontinuation of study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the participant's premature discontinuation of study treatment and record this information. The investigator must also contact the IRT to register the participant's discontinuation from study treatment.

Participants who discontinue from study treatment should be encouraged to return for all upcoming visits indicated in the Assessment Schedule (Table 8-1).

If the participant cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the participant, or with a person pre-designated by the participant. This telephone contact should preferably be done according to the study visit schedule and at a minimum information on new/ concomitant treatments and adverse events /serious adverse events should be obtained.

Participants who discontinue study treatment will no longer undergo any DBPCFC that may be planned on the remaining visit(s).

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

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

If discontinuation occurs because treatment code has been broken, please refer to Section 6.7.3.

9.1.2 Discontinuation from study

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

If the participant agrees, a final evaluation at the time of the participant's study discontinuation should be made as detailed in the assessment table (Table 8-1).

9.1.3 Lost to follow-up

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

9.2 Withdrawal of informed consent and exercise of participants' data privacy rights

Withdrawal of consent/opposition to use of data and/ or biological samples occurs in countries where the legal justification to collect and process the data is consent and when a participant:

Explicitly requests to stop use of their data and

- No longer wishes to receive study treatment

and

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

This request should be as per local regulations (e.g. in writing) and recorded in the source documentation.

Withdrawal of consent impacts the ability to further contact the participant, collect follow-up data (e.g. to respond to data queries) and potentially other country-specific restrictions. It is therefore very important to ensure accurate recording of withdrawal vs. discontinuation based on the protocol definitions of these terms.

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the participant's decision to withdraw their consent/exercise data privacy rights and record this information. The Investigator shall clearly document if the participant has withdrawn his/her consent for the use of data in addition to a study discontinuation.

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

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

If the participant agrees, a final evaluation at the time of the participant's withdrawal of consent/ exercise data privacy rights should be made as detailed in the assessment table (refer to

Section 8). Further details on withdrawal of consent or the exercise of participants' data privacy rights are included in the corresponding informed consent form.

9.3 Study completion and post-study treatment

Study completion is defined as when the last participant finishes the End of Study (EOS) visit (Week 68). This includes any repeat assessments associated with this visit with full documentation and follow-up by the Investigator or, in the event of an early study termination decision, the date of that decision.

An Extension Study is planned. Participants who would like to join the Extension study will transition at one of the following timepoints:

1. Approximately the first one third of participants will join the Extension study after completion of the follow-up period at week 68. For those participants, the week 68 Visit is the Study Completion Visit in study QGE031G12301.

2. The remaining participants will join the Extension study after completion of the treatment period at week 52. For those participants, the week 52 Visit is the Study Completion Visit in study QGE031G12301.

Participation in the Extension Study will be optional.

Participants not entering the Extension Study will complete the 16 weeks follow-up period. Their Study Completion Visit is at Week 68.

9.4 Early study termination by the sponsor

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

- Unexpected, significant, or unacceptable safety risk to participants enrolled in the study
- Decision based on recommendations from applicable board(s) or regulatory authorities after review of safety and efficacy data
- Discontinuation of study drug development
- Practical reasons (including slow enrollment)
- Medical reasons

In taking the decision to terminate, Novartis will always consider the participant’s welfare and safety. Should early termination be necessary, participants must be seen as soon as possible and treated as a prematurely withdrawn participant. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant’s interests. The investigator or sponsor, depending on the local regulation, will be responsible for informing IRBs/IECs of the early termination of the trial. For more information on AE and SAE definition and reporting requirements, please see the respective sections.

10 Safety monitoring, reporting and committees

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a clinical investigation participant after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The investigator has the responsibility for managing the safety of individual participant and identifying adverse events.

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

The occurrence of adverse events must be sought by non-directive questioning of the participant at each visit during the study. Additionally, the investigator should proactively query the participants about the occurrence of specific adverse events suggestive of hypersensitivity reactions during and after the DBPCFC, the administration of study drug, and in the event of accidental food ingestion. Adverse events also may be detected when they are volunteered by the participant during or between visits or through physical examination findings, laboratory test findings, or other assessments.

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

1. The severity grade

- mild: usually transient in nature and generally not interfering with normal activities
- moderate: sufficiently discomforting to interfere with normal activities
- severe: prevents normal activities

2. Its relationship to the study treatment. If the event is due to lack of efficacy the assessment of causality will usually be ‘Not suspected.’ The rationale for this guidance is that the symptoms of a lack of efficacy are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy can only be evaluated meaningfully by an analysis of cohorts, not on a single participant;
3. Its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported;
4. Whether it constitutes a SAE (Section 10.1.2 for definition of SAE) and which seriousness criteria have been met;
5. Action taken regarding with study treatment. All adverse events must be treated appropriately. Treatment may include one or more of the following:

- Dose not changed,
- Drug interrupted/permanently discontinued.

- Dose increases or reductions are not permitted.

6. Its outcome: not recovered/ not resolved; recovered/ resolved; recovering/ resolving; recovered/ resolved with sequelae; fatal or unknown

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

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

Adverse event monitoring should be continued until the end of study visit or for at least 30 days or 5 half-lives following the last dose of study treatment, whichever is longer.

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

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

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in participant with the underlying disease. Alert ranges for laboratory and other test abnormalities are included in Section 16.1.

Please refer to Section 16.4 for the assessment, reporting and management of hypersensitivity reactions observed during the DBPCFC and the post-DBPCFC observation period.

10.1.2 Serious adverse events

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

- fatal
- life-threatening

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

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

- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - social reasons and respite care in the absence of any deterioration in the participant's general condition
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above

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

All new malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

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

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred.

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until 30 days after the last study visit (EOS visit week 68) must be reported to Novartis safety immediately, without undue delay, but under no circumstances later than within 24 hours of obtaining knowledge of the events (Note: If more stringent, local regulations regarding reporting timelines prevail, those need to be followed) Any SAEs experienced after the 30 day period should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment, unless otherwise specified in local regulations. Any SAEs reported up to the participant's last visit will be reported in the eCRF. SAEs beyond that date will only be recorded in the Novartis Safety database. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

Information about all SAEs is collected and recorded on the electronic Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode immediately, without undue delay, but under no circumstances later than within 24 hours of the investigator receiving the follow-up information (Note: If more stringent, local regulations regarding reporting timelines prevail, those need to be followed). An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

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

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

Screen Failures: SAEs occurring after the participant has signed the ICF until the time the participant is deemed a Screen Failure must be reported to Novartis.

Randomized or treated participants: SAEs occurring after the participant has signed the ICF until 120 days (5 half-lives of ligelizumab) after the participant has withdrawn consent or discontinued study must be reported to Novartis.

Please refer to Section 16.4 for the assessment, reporting and management of serious hypersensitivity reactions observed during the DBPCFC and the post-DBPCFC observation period.

10.1.4 Pregnancy reporting

Details of all pregnancies in female participants will be collected after the start of study treatment and until 5 half-lives, after last dose of ligelizumab.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

Any post study pregnancy-related SAE considered reasonably related to the study treatment by the Investigator will be reported to Novartis. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Pregnancies

If a female trial participant becomes pregnant, the study treatment should be stopped, which should be documented on the respective CRF. The pregnancy consent form should be presented to the trial participant. The participant must be given adequate time to read, review and sign the

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

Pregnancy should be recorded and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship of the study treatment to any pregnancy outcome. After providing consent, the follow-up should take place during the pregnancy and up to 12 months following the expected delivery date. Any SAE experienced during pregnancy must also be reported.

10.1.5 Reporting of study treatment errors including misuse/abuse

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

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

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

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE. Study treatment errors and uses outside of what is foreseen in the protocol, misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness. For more information on AE and SAE definition and reporting requirements, please see the respective sections.

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

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

The following 2 categories of abnormalities / AEs have to be considered during the course of the study (irrespective of whether classified/reported as AE/SAE):

·Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter

·Liver events, which will require close observation, follow-up monitoring and contributing factors are recorded on the appropriate CRFs

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

Every liver event defined in Table 16-2 should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 16-3 and Table 16-4. Repeat liver chemistry tests (i.e. ALT, AST, TBL, PT/INR, ALP and G-GT) to confirm elevation.

- These liver chemistry repeats will be performed using the central laboratory. If results will not be available from the central laboratory, then the repeats can also be performed at a local laboratory to monitor the safety of the participant. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results recorded on the appropriate CRF.
- If the initial elevation is confirmed, close observation of the participant will be initiated, including consideration of
  - Treatment interruption if deemed appropriate
  - Discontinuation of the investigational drug (refer to Section 9.1.1), if appropriate
  - Hospitalization of the participant if appropriate
  - Causality assessment of the liver event should include:
    - A thorough follow-up of the liver event should include (based on investigator's discretion) serology tests, imaging and pathology assessments, gastroenterologist or hepatologist's consultancy, obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease, imaging such as abdominal ultrasound, CT or MRI scans and obtaining a history of exposure to environmental chemical agents

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

10.2.2 Renal safety monitoring

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

Table 10-1 Base Renal Monitoring

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

- Every renal laboratory trigger or renal event as defined in Table 16-5 should be followed up by the investigator or designated personnel at the trial site as summarized in Table 16-6.

10.3 Committees

10.3.1 Data Monitoring Committee

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

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

10.3.2 Adjudication committee

The role of the Adjudication Committee (AC) is to ensure that all treatment outcomes are judged uniformly, using standard criteria and processes. The AC will be composed of clinical experts to evaluate disease progression and harmonize endpoint assessment criteria using data provided by the sponsor (Section 8.4.4).

All personnel involved in the adjudication process will remain blinded to treatment allocation throughout the trial. Specific details regarding endpoint definitions can be found in the adjudication charter.

11 Data Collection and Database management

11.1 Data collection

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

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

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

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

11.2 Database management and quality control

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

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

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

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

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked **and the treatment codes will be unblinded** and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. eSource DDE or eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of participant records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

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

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria,

documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the participants will be disclosed.

12 Data analysis and statistical methods

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

12.1 Analysis sets

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 to.

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. According to the intent to treat principle, participants will be analyzed according to the treatment they have been assigned to during the randomization procedure. FAS will be used for all efficacy variables, unless otherwise stated.

The Safety Analysis Set (SAF) includes all participants who received at least one dose of study treatment. Participants will be analyzed according to the treatment they received, where treatment received is defined as the randomized/assigned treatment if the participant took at least one dose of that treatment or the first treatment received if the randomized/assigned treatment was never received. The safety set will be used in the analysis of all safety variables.

12.2 Participant demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be summarized descriptively by treatment group for the RAS.

Categorical data will be presented as frequencies and percentages. For continuous data, mean (geometric mean for non-normal variables), standard deviation, median, minimum, and maximum will be presented.

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term, by treatment group.

12.3 Treatments

The Safety analysis set will be used for the analyses below. The duration of exposure (in weeks) to study treatment will be summarized by treatment group. In addition, the number of doses, total cumulative dose, and number of missed doses will be presented. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be summarized according to the Anatomical Therapeutic Chemical (ATC) classification system, and preferred term by treatment group.

12.4 Analysis supporting primary objectives

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

12.4.1 Definition of primary endpoint(s)

Definition of primary estimand is provided in Section 2.1.

12.4.2 Statistical model, hypothesis, and method of analysis

The trial will be considered positive, if at least one of the two ligelizumab doses demonstrate a statistically significant result in comparing the proportion of responders as described below. The two doses will be tested in parallel for 12 weeks treatment on the primary endpoint.

Let p_j denote the responder rate for treatment regimens j, j=0, 1 or 2 where

- 0 corresponds to placebo
- 1 corresponds to ligelizumab 120 mg treated for 12 weeks
- 2 corresponds to ligelizumab 240 mg treated for 12 weeks

Responder rate is defined as the proportion of participants tolerating a single dose of ≥ 600 mg (1044 mg cumulative tolerated dose) of peanut protein without dose-limiting symptoms during the DBPCFC conducted at Week 12. For participants with treatment discontinuation or missing more than 1 doses of study drug prior to Week 12 due to reasons other than operational complications caused by public health emergency, they will be considered non-responders.

The following hypotheses will be tested:

$H_{0\ 120\ RR600}: p_1 / (1- p_1) \leq p_0 / (1- p_0)$ versus $H_{A\ 120\ RR600}: p_1 / (1- p_1) > p_0 / (1- p_0)$

$H_{0\ 240\ RR600}: p_2 / (1- p_2) \leq p_0 / (1- p_0)$, $H_{A\ 240\ RR600}: p_2 / (1- p_2) > p_0 / (1- p_0)$

$H_{0\ 120\ RR600}$: ligelizumab 120mg is not superior to placebo with respect to the responder rate at a level of 600 mg peanut protein (1044 mg cumulative tolerated dose) without dose-limiting symptoms at Week 12

$H_{0\ 240\ RR600}$:ligelizumab 240mg is not superior to placebo with respect to the responder rate at a level of 600 mg peanut protein (cumulative tolerated dose 1044 mg) without dose-limiting symptoms at Week 12

The primary endpoint will be analyzed based on a logistic regression model, including treatment, age subgroup (6 – 11 years, 12 –17 years, 18 - 55 years), region as fixed class effects and log-transformed total IgE at Screening Visit 1 as a covariate. Odds ratio and 95% confidence intervals (CI) will be presented comparing each Ligelizumab dose to Placebo with respect to the proportions of responders.

The detailed testing strategy for primary and key secondary endpoints is provided in Section 12.5.1.

12.4.3 Handling of intercurrent events of primary estimand

The analysis will account for different intercurrent events as explained in the following:

Intercurrent events unrelated to public health emergency (e.g. COVID-19 pandemic)

- Discontinuation of treatment prior to Week 12 : a composite variable strategy will be used to handle these intercurrent events. Participants who discontinue treatment prior to Week 12 due to reasons unrelated to public health emergency will be considered non-responder to reflect potential treatment failure at Week 12 in clinical practice.
- Missing more than one dose of study drug prior to Week 12 : participants who miss more than 1 treatment doses prior to Week 12 due to reasons unrelated to public health emergency will be considered non-responders to reflect potential treatment failure at Week 12 in clinical practice.
- Intake of rescue medication before starting DBPCFC assessment at Week 12 : epinephrine, SABA, anti-histamines and saline bolus are typically used as rescue medication to treat allergic reactions. Considering participants must be in good health and only minimal or no symptomatic medications are allowed before starting the DBPCFC, DBPCFC collected after intake of rescue medication will be used for the primary analysis.

Intercurrent events related to operational complications caused by public health emergency (hypothetical strategy)

- Discontinuation of treatment or missing more than one dose of study drug prior to Week 12 : the interest lies in DBPCFC data at Week 12 that would be observed if the participant had completed 12 week of randomized treatment without the impact of operational complications caused by public health emergency. The responder status at Week 12 will be multiply imputed using the missing at random (MAR) assumption for all treatment arms included in the primary analysis.

The multiple imputation model will be built based on similar participants (i.e. with the same covariates and observed measurement history) in the same treatment arm. More details on the imputation model will be pre-specified in the Statistical Analysis Plan (SAP).

Intercurrent events due to non-operational public health emergency related reasons will be classified as intercurrent events unrelated to public health emergency.

12.4.4 Handling of missing values not related to intercurrent event

Missing DBPCFC data at Week 12 not related to aforementioned intercurrent events are assumed to be unrelated to response or compliance status, hence their missing data will be handled with a missing at random approach and imputed consequently.

The full specification will be provided in the SAP.

12.4.5 Sensitivity analyses

The following sensitivity analysis will be performed for the primary estimand, to assess the robustness of the estimation in the presence of deviations from the assumptions specified in the primary analysis.

A two-dimensional tipping point analysis will be conducted to identify the points at which conclusions from primary analysis will be overturn, in a stepwise manner for both arms independently. After such tipping points are determined, clinical judgment can be applied as to the plausibility of the assumptions underlying these tipping points.

12.4.6 Supplementary analysis

The target population, the primary variable and handling of intercurrent events for the supplementary estimand are the same as for the primary estimand. Differently from the primary estimand, the summary measure for this supplementary estimand is the relative risk that would provide additional insights for clinical interpretation of a treatment effect.

The estimation method is the same as for the primary estimand except that a marginal standardization method will be used to calculate the relative risk of being a responder and its 95% confidence interval. This method uses the same fitted logistic model as for the primary estimand, but involves averaging predictions for each treatment group.

12.4.7 Supportive analyses

As supportive analyses to the primary analyses, subgroups for primary efficacy endpoint will be analyzed but not be limited to the following:

- By age group (6 – 11 years, 12 – 17 years, 18-55 years)
- By total IgE at Screening Visit 1 (<350 IU/ mL; ≥350 IU/ mL)
- By age group and total IgE at Screening Visit 1
- By allergy status (mono- vs poly-sensitized participants)
  Mono-sensitized participants are only sensitized to peanut protein. Poly-sensitized participants are sensitized to peanut protein and at least one of the other proteins in the panel. Poly-sensitization is defined as sIgE ≥0.35 kUA/L for a food allergen in the panel other than peanut.

The subgroup analyses for primary endpoint will be conducted using the same model as for the main analysis but with additional model terms for the subgroup (if not already included in the model), and subgroup-by-treatment interaction terms.

12.5 Analysis supporting secondary objectives

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

Key secondary endpoints

Definitions of secondary estimands for key secondary objectives are provided in Section 2.2.

The key secondary efficacy endpoints are:

- Responder status defined as tolerating a single dose of ≥ 1000 mg (2044 mg cumulative tolerated dose) peanut protein without dose-limiting symptoms at Week 12. The proportion of responders will be analyzed using the logistic regression model in a similar fashion as the primary estimand. Intercurrent events and missing data will be handled following the same principle as for the primary estimand.
- Responder status defined as tolerating a single dose of 3000 mg (5044 mg cumulative tolerated dose) peanut protein without dose-limiting symptoms at Week 12. The proportion of responders will be analyzed using the logistic regression model in a similar fashion as the primary estimand. Intercurrent events and missing data will be handled following the same principle as for the primary estimand.
- Maximum severity of symptoms occurring at any challenge dose of peanut protein up to and including 1000 mg during the DBPCFC conducted at Week 12. Symptom severity will be categorized as 4 levels: None, Mild, Moderate, Severe. The odds of developing less severe level of symptoms will be analyzed with a proportional odds model, including treatment, age group (6 – 11years, 12 – 17 years, 18 - 55 years), region as fixed class effects and log-transformed total IgE at Screening Visit 1 as a covariate. Missing data at Week 12 corresponding to the intercurrent events of category 1 as described in Section 2.2.3 will be multiply imputed in line with the treatment policy strategy. For participants in the active treatment arms, missing data will be imputed based on placebo data. For participants in the placebo arm, missing data will be imputed based on the observed placebo arm data under a missing at random (MAR) assumption (treatment policy strategy). Other intercurrent events and missing data will be handled with a similar hypothetical strategy as for the primary estimand.
- Responder status defined as participants tolerating a single dose of ≥ 1000 mg (2044 mg cumulative tolerated dose) peanut protein without dose-limiting symptoms at Week 12 (8 weeks of placebo + 4 weeks of ligelizumab treatment vs. 12 weeks of placebo). The proportion of responders will be analyzed using the logistic regression model in a similar fashion as the primary estimand. Intercurrent events will be handled with a hypothetical strategy as described in Section 2.2.4 and missing data will be imputed under a MAR assumption. The familywise type I error rate will be controlled at the one-sided 0.025 level across the primary and key secondary null hypotheses in a closed testing procedure (Bretz et al 2009).

Key secondary null hypotheses:

$H_{0\,120\,RR1000}$: ligelizumab 120 mg is not superior to placebo with respect to the responder rate at a level of 1000 mg peanut protein (cumulative tolerated dose 2044 mg) at Week 12

$H_{0\,240\,RR1000}$: ligelizumab 240 mg is not superior to placebo with respect to the responder rate at a level of 1000 mg peanut protein (cumulative tolerated dose 2044 mg) at Week 12

$H_{0\,120\,RR3000}$: ligelizumab 120 mg is not superior to placebo with respect to the responder rate at a level of 3000 mg peanut protein (cumulative tolerated dose 5044 mg) at Week 12

$H_{0\,240\,RR3000}$: ligelizumab 240 mg is not superior to placebo with respect to the responder rate at a level of 3000 mg peanut protein (cumulative tolerated dose 5044 mg) at Week 12

$H_{0\ 120\ severity}$: ligelizumab 120 mg is not superior to placebo with respect to the odds of developing less severe level of symptoms evaluated by maximum severity of symptoms at any challenge dose of peanut protein up to and including 1000 mg during the DBPCFC conducted at Week 12

$H_{0\ 240\ severity}$: ligelizumab 240 mg is not superior to placebo with respect to the odds of developing less severe level of symptoms evaluated by maximum severity of symptoms at any challenge dose of peanut protein up to and including 1000 mg during the DBPCFC conducted at Week 12

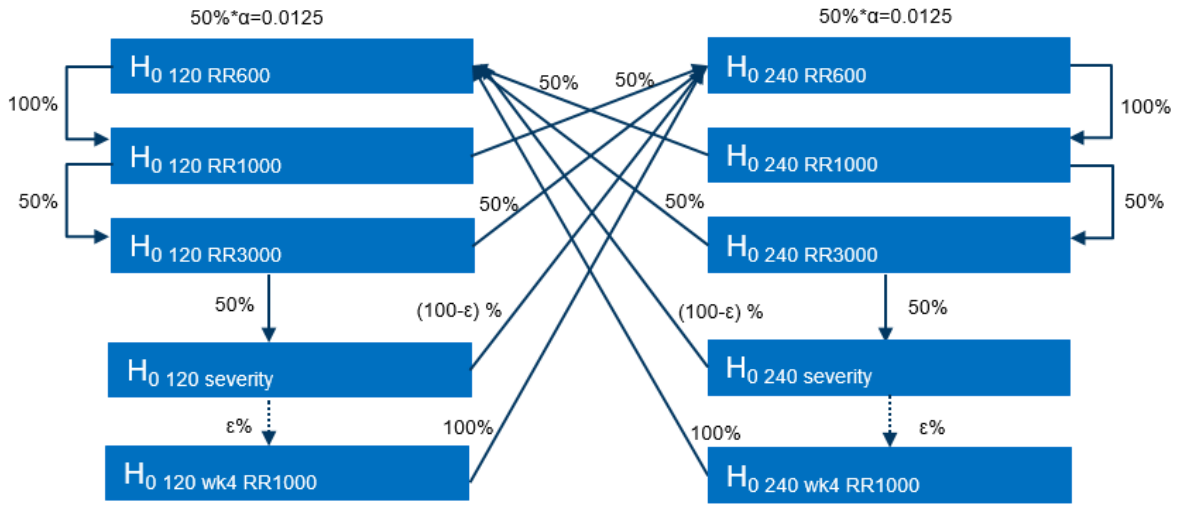
The following secondary hypotheses will be used to evaluate onset of action of ligelizumab (8 weeks of placebo + 4 weeks of ligelizumab treatment):

$H_{0\ 120\ wk4\ RR1000}$: ligelizumab 120 mg (8 weeks of placebo + 4 weeks of ligelizumab treatment) is not superior to placebo with respect to the responder rate at a level of 1000 mg peanut protein (cumulative 2044 mg) at Week 12

$H_{0\ 240\ wk4\ RR1000}$: ligelizumab 240 mg (8 weeks of placebo + 4 weeks of ligelizumab treatment) is not superior to placebo with respect to the responder rate at a level of 1000 mg peanut protein (cumulative 2044 mg) at Week 12

The graphical approach of Bretz et al 2009 for sequentially rejecting testing procedures is used to illustrate the testing strategy in Figure 12-1.

Figure 12-1 Testing strategy



- The hypotheses will be tested in two branches constituting ligelizumab 120 mg versus placebo (left branch) and ligelizumab 240 mg versus placebo (right branch). Initially, the full alpha level of 0.025 (one-sided) is equally split across the primary hypotheses for the two branches.
- Once this first primary null hypothesis $H_{0\ 120\ RR600}$ or $H_{0\ 240\ RR600}$ for a dose has been rejected at the initial alpha level of 0.0125 (one-sided), the alpha will be fully distributed to $H_{0\ 120\ RR1000}$ or $H_{0\ 240\ RR1000}$ for the same dose.

- If $H_{0\ 120\ RR1000}$ or $H_{0\ 240\ RR1000}$ is rejected for a dose, then 50% of its local significance level is reassigned to the primary null hypothesis for the other dose, and 50% of its local significance level is reassigned to $H_{0\ 120\ RR3000}$ or $H_{0\ 240\ RR3000}$ for the same dose.
- If $H_{0\ 120\ RR3000}$ or $H_{0\ 240\ RR3000}$ is rejected for a dose, 50% of its local significance level is reassigned to the primary null hypothesis for the other dose, and 50% of its local significance level is reassigned to $H_{0\ 120\ severity}$ or $H_{0\ 240\ severity}$ for the same dose.
- If $H_{0\ 120\ severity}$ or $H_{0\ 240\ severity}$ is rejected for a dose, (100-ε)% of its local significance level is reassigned to the primary null hypothesis for the other dose. ε is set to a very small number in practice, e.g., 10^{-10}. The dotted dashed edges with a weight of ε indicate the local significance level will only be reassigned to $H_{0\ 120\ wk4\ RR1000}$ or $H_{0\ 240\ wk4\ RR1000}$, once both $H_{0\ 120\ severity}$ and $H_{0\ 240\ severity}$ are rejected.
- If $H_{0\ 120\ wk4\ RR1000}$ or $H_{0\ 240\ wk4\ RR1000}$ is rejected for a dose, 100% of its local significance level is reassigned to the primary null hypothesis for the other dose.

Other secondary endpoints

Other secondary endpoints which are not part of testing strategy include:

- Proportion of participants tolerating a single dose of ≥ 1000 mg (2044 mg cumulative tolerated dose) of peanut protein without dose-limiting symptoms during DBPCFC conducted at Week 52 : number and percentage of responders will be summarized by treatment group. In addition, the responder rate at Week 52 will be compared to the responder rate at Week 12 in ligelizumab 120 mg arm and 240 mg arm with a non-inferiority test, respectively. The choice of non-inferiority margin and detailed analysis will be pre-specified in SAP.
- Change in maximum tolerated dose (MTD) of peanut protein without dose-limiting symptoms during the DBPCFC at Week 52 compared to Week 12 : MTD (log-transformed scale) at Week 52 along with changes from baseline and changes from Week 12 will be summarized descriptively.
- Change from baseline in peanut-specific IgE and IgG4 at Week 12, Week 16 and Week 52: Summary statistics, including geometric means and geometric standard deviations, will be presented for peanut-specific IgE and IgG4 along with changes from baseline by time point and treatment group. Change from baseline in log-transformed levels of peanut specific-IgE and peanut specific-IgG4 at Week 12 and Week 16 will be analyzed using an ANCOVA model with terms for treatment group, age group, region, log-transformed total IgE at Screening Visit 1 and log-transformed baseline peanut specific-IgE or peanut specific-IgG4.
- Change from baseline (screening) in mean wheal diameters by SPT at Week 16, Week 56 and Week 68: Summary statistics for the SPT mean wheal diameter and changes from baseline will be presented at each visit by treatment group. Change from baseline in SPT mean wheal diameter at Week 16 will be analyzed using an ANCOVA model with terms for treatment group, age group, region, log-transformed total IgE at Screening Visit 1, and baseline SPT mean wheal diameter.
- Change from baseline in total and domain scores in the FAQLQ at various timepoints by age and responder (subject or caregiver): The scores along with change from baseline will be summarized descriptively at Day 1, before and after the DBPCFC at Week 12 and

Week 52 by treatment arm. Comparative statistical analyses will be performed to evaluate differences between treatment groups.

- Change from baseline in total and domain scores in the FAIM at various timepoints by age and responder (subject or caregiver): similar analysis will be performed as for FAQLQ.
- Change from baseline in total and domain scores in the SF-36v2 at various timepoints: The scores along with change from baseline will be summarized descriptively at Day 1, before and after the DBPCFC at Week 12 and Week 52 by treatment.

Further details of analysis for other secondary endpoints will be provided in the SAP.

12.5.2 Safety endpoints

All safety endpoints (i.e. AEs, laboratory data, vital signs, and ECG) will be summarized by treatment for all participants on the safety set. In addition, subgroup analysis by age (6-11 years, 12-17 years, 18-55 years) will be evaluated for all the safety endpoints listed in this section.

Adverse events

Treatment emergent adverse events are defined as events started after the first dose of study treatment or events present prior to the first dose of study treatment but increased in severity based on preferred term. All events that the investigator classifies as reactions associated to the DBPCFC or SPT will not be included in reporting of treatment-emergent AEs. The number (and percentage) of participants with treatment emergent adverse events will be summarized in the following ways:

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

Separate summaries will be provided for study treatment related adverse events, death, serious adverse events, other significant adverse events leading to discontinuation. If a participant reported more than one AE with the same preferred term, the AE with the greatest severity will be presented. If a participant reported more than one AE within the same primary system organ class, the participant will be counted only once with the greatest severity at the system organ class level, where applicable.

All AEs with onset in the follow-up period will also be considered as treatment emergent. Data from the placebo arm after switching to ligelizumab will be summarized separately. The number and percentage of participants with treatment emergent adverse events of special interest will be summarized by risk category, preferred term and treatment.

In addition, summaries will be provided by subgroups of age and allergy status (mono-sensitized and poly-sensitized).

Vital signs

Summary statistics will be provided by vital sign, treatment group and visit/time as appropriate. Change from baseline will only be summarized for participants with both baseline and post-baseline values. Participants 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 and children aged 6-11 years:

- See Section 16.1 for upper and lower limits for vital signs.

12-lead ECG

Summary statistics will be provided by treatment and visit/time.

Clinical laboratory evaluations

Summary statistics will be provided by treatment and visit/time.

[redacted]

[redacted]

12.7 Interim analyses

As previously noted in Section 4.4, there will be three analyses before the final database lock, in addition to the DMC analyses.

Interim Analysis:

At the start or the study, recruitment will be restricted to 12-55 year old participants. When approximately 60 adolescent participants (defined as 12-17 years of age) have completed all week 12 assessments, an interim analysis on [redacted], safety [redacted] data ([redacted]) will be performed. The intent of this analysis is to confirm the dosing strategy for the youngest age cohort. Once confirmed, recruitment will open to participants aged 6-11 years. Dosing would be either only 120 mg or 120 mg and 240 mg for this age cohort.

Primary Analysis at Week 12:

The Primary Analysis will be performed once all participants have reached Week 12 in the study and completed its assessments or prematurely withdrawn from the study prior to Week 12. Formal testing of primary and key secondary endpoints will be performed according to testing strategy specified in Figure 12-1 with full alpha. Since the primary and key secondary objectives will be performed only for the Primary Analysis, adjustment to the overall type I error rate is not required. In addition, a Dose-Exposure-Response model to describe the responder rate and the factors impacting the response will be developed. This model will be used to select the dose for registration in the participants 6 years and older, and select the dose for pediatric trial in younger population.

Analysis at Week 52:

The study will subsequently continue as planned in a blinded manner for the full 52 weeks treatment period and 16 weeks follow up. A final analysis will be performed after all participants have completed Week 52 or prematurely withdrawn from the study prior to Week 52.

DMC analyses

The DMC will assess, at defined intervals, the progress of a clinical trial, safety data, and critical efficacy variables and recommend to the sponsor whether to continue, modify, or terminate a trial, as defined in the DMC charter. Analysis of selected efficacy variables will be provided only for the purpose of helping for safety evaluation. Such assessments do not inflate the type I error for the primary efficacy hypothesis testing and thus no adjustment for multiplicity is required.

12.8 Sample size calculation

A total sample size of approximately 486 randomized participants is targeted to achieve sufficient power for the primary and key secondary endpoints and provide adequate precision in estimating AE rates in this study.

Participants will receive one of three treatments (ligelizumab 240mg SCq4w, ligelizumab 120mg SCq4w, or placebo SCq4w) and will be randomized into five treatment arms with a ratio 2:2:2:2:1. At the start of the study, recruitment is restricted to 12-55 years old participants and children 6-11 years will be recruited upon confirmation of the dosing strategy (120 mg and 240 mg, or 120 mg only).

[redacted]

12.8.1 Primary endpoint(s)

The primary objective is to demonstrate that ligelizumab doses are superior to placebo in responder rate at a level of 600 mg peanut protein (1044 mg cumulative tolerated dose) after 12 weeks of treatment.

The responder rate at 600 mg dose of peanut protein in placebo and ligelizumab groups have been assumed approximately 20% and at least 80%, respectively for participants with evaluable DBPCFC at Week 12. These assumptions are considered highly clinically relevant based on the PALISADE trial conducted in similar populations (Vickery et al 2018). In the PALISADE trial , the responder rate at 600 mg single challenge dose of peanut protein in placebo and AR101 were 4.3% (95% CI: 1.9% , 9.7%) and 84.5% (95% CI: 79.9, 88.1), respectively. Approximately 15% of participants were assumed to discontinue treatment before week 12 and will be

considered non-responders in power calculations. Therefore, the responder rate at 600 mg single dose of peanut protein in placebo and ligelizumab were assumed 17% and 68%, respectively for randomized participants. For the purpose of evaluating the power for the primary trial objectives, it was assumed that none of the secondary null hypotheses would be rejected and the full alpha level of 0.025 (one-sided) would be equally split across the primary hypotheses for each dose (i.e., 0.0125 one-sided for each testing). Under the outlined assumptions, a two group Fisher's exact test with a 0.0125 one-sided significance level will have above 99% power to detect the difference of responder rate between each ligelizumab group and placebo, when the sample size is 108 participants on each ligelizumab dose and 54 participants on placebo. In case the dosing will only be limited to 120 mg for children, the anticipated sample size also provides greater than 99% power to detect the difference of responder rate between each ligelizumab group and placebo at a 0.0125 one-sided significance level. These power calculations are an approximation of the power achieved with the logistic regression approach. The table below shows the sensitivity of the power to deviations from the assumptions.

Table 12-1 Sensitivity of the power for each dose for the primary variable

RR in each QGE031 group with evaluable DBPCFC at Week 12	RR in placebo group with evaluable DBPCFC at Week 12	Dropout rate	RR in each QGE031 group	RR in placebo group	Sample size in each QGE031 group	Sample size in placebo	Power
80%	20%	15%	68%	17%	108	54	>99.9%
80%	20%	15%	68%	17%	144	54	>99.9%
80%	20%	15%	68%	17%	72	36	>99.9%
70%	20%	15%	59.5%	17%	108	54	99.8%
70%	20%	15%	59.5%	17%	144	54	>99.9%
70%	20%	15%	59.5%	17%	72	36	98.6%

RR = responder rate. Approximately 15% of participants were assumed to discontinue treatment before week 12 and be considered as non-responders in power calculations.
Power results were calculated with East 6 version 6.4.

The consistency trend of treatment effect on primary endpoint will be evaluated in age subgroups. Participants will be stratified based on region, total IgE at screening and by age at screening (6-11 years, 12-17 years, and 18-55 years) in randomization. Approximately one third of randomized participants are expected in each age subgroup. This yields approximately 36 participants in each ligelizumab group per age subgroup and 18 participants in placebo group per age subgroup in the base case scenario. In case the dosing will only be limited to 120 mg for children, approximately 72 children will be allocated to each of the two ligelizumab 120 mg arms. The number of participants per age subgroup may be varied in actual recruitment. To ensure a high probability (90%) of observing the point estimates of odds ratio for the treatment effect greater than 1 in all age subgroups, the sample size for the smallest age subgroup should be at least 9.4% of the number of participants included for primary analysis based on an approach to partition sample size in a multiregional trial (Kawai et al 2008). In practice, the estimation of responder rate based on this limited sample size may be easily affected by a few

extreme random observations. Therefore, it is suggested to enlarge the sample size for the smallest age subgroup whenever feasible. Additional consideration from safety aspects for number of participants in age subgroups are provided in Section 12.8.2.1.

12.8.2 Secondary endpoint(s)

If statistical significance is achieved in the primary test, the tests for the key secondary variables included in the testing strategy will be performed. The local significance level for each key secondary null hypothesis will be determined based on the closed testing procedure shown in Figure 12-1.

Assuming a treatment discontinuation rate of 15% before week 12 and responder rates in each treatment group as shown in the table below, the local power (unconditional) of each hypothesis was estimated using 10,000 simulations with package gMCP in R 3.6.1. [redacted]

Table 12-2 Power of each dose for the analyses of primary and key secondary variables in the base case scenario

Variable	Assumptions of treatment effect				Local power (unconditional)	
		QGE031 240 mg	QGE031 120 mg	Pbo	QGE031 240 mg	QGE031 120 mg
RR of tolerating 600 mg peanut protein	RR* (RR in rand)	80% (68%)	80% (68%)	20% (17%)	>99.9%	>99.9%
RR of tolerating 1000 mg peanut protein	RR* (RR in rand)	70% (59.5%)	70% (59.5%)	20% (17%)	>99.9%	>99.9%
RR of tolerating 3000 mg peanut protein	RR* (RR in rand)	60% (51%)	60% (51%)	15% (12.75%)	>99.9%	>99.9%
Maximum severity of symptoms at	% None	38%	38%	2%	>99.9%	>99.9%
	% Mild	32%	32%	28%		
	% Moderate	25%	25%	59%		

any challenge dose up to and including 1000 mg#	% Severe	5%	5%	11%		
RR of tolerating 1000 mg peanut protein with 4 weeks of ligelizumab treatment	RR^	50%	45%	20%	98.3%	93.0%

RR=responder rate; Pbo=placebo; The proposed number of participants for comparisons between ligelizumab and placebo are 108 in each ligelizumab arm and 54 in placebo arm.

*RR is based on the anticipated proportion of responders in participants with evaluable DBPCFC at Week 12. Approximately 15% of participants are assumed to discontinue treatment before week 12 and considered non-responders for randomized population in power calculation (RR in rand).#For maximum severity of symptoms, the assumed proportion of participants in each category is based on randomized population.
Power calculations were performed in R 3.6.1 with package gMCP.
^RR is based on the anticipated proportion of responders in participants with evaluable DBPCFC at Week 12. Same treatment effect is expected for randomized population in power calculation, assuming participants had taken study treatment at Week 8 and conducted DBPCFC at Week 12.

[redacted]

[redacted]

12.8.2.1 Precision for adverse events

All participants will have the opportunity of receiving treatment for ligelizumab 120 mg or 240 mg in the 52 weeks of treatment period with a ratio of 50%: 50% (n=243 for each group). For each ligelizumab dose group, approximately one third of randomized participants are in each age subgroup (6-11 years, 12-17 years and 18-55 years). This yields approximately 81 participants per age group exposed with each ligelizumab dose for at least 9 months in the base case scenario. [redacted] The table below shows the sensitivity of the precision level (95% CI) based on the assumptions of different incidence rates and number of participants per age group.

Table 12-4 Precision levels (95% CI) for sensitivity of safety incidence rate per age group

Event rate (proportion of participants with an event)	Number of participants	95% CI
0%	81	(0, 4.5%)
1%	81	(0, 6.3%)
2%	81	(0.2%, 7.9%)
0%	162	(0, 2.3%)
1%	162	(0.1%, 4%)
2%	162	(0.4%, 5.5%)

Meanwhile, all the participants (486 participants) randomized in the study would be exposed with ligelizumab treatment for at least 9 months. For any adverse event with 1% incidence rate, the exact 95% Clopper-Pearson CI for the proportion of participants would be (0.3%, 2.3%).

Table 12-4 shows the sensitivity of the precision (95% CI) based on the assumptions of different incidence rates and total number of participants.

Table 12-5 Precision levels (95% CI) for sensitivity of safety incidence rate for overall population

Event rate (proportion of participants with an event)	Number of participants	95% CI
0%	486	(0, 0.8%)
1%	486	(0.3%, 2.3%)
2%	486	(1%, 3.7%)

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

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

13.2 Responsibilities of the investigator and IRB/IEC

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

13.3 Publication of study protocol and results

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

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

13.4 Quality Control and Quality Assurance

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

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

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

13.5 Participant Engagement

Participant engagement initiatives are included in this study and will be provided, for distribution to study participants. If compliance is impacted by cultural norms or local laws and regulations, sites may discuss modifications to these requirements with Novartis.

- Thank You letter
- Plain language trial summary - after CSR publication
- Trial Feedback Questionnaires (TFQ)

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of participants should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

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

14.1 Protocol amendments

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

Only amendments that are required for participant safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any participant included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

15 References

References are available upon request

Ankerst J, Nopp A, Johansson SG, et al (2010) Xolair is effective in allergics with a low serum IgE level. International Archives of Allergy and Immunology;152:71-4.

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

Baniyash M, Kehry M, Eshhar Z (1988) Anti-IgE monoclonal antibodies directed at the Fc epsilon receptor binding site. Molecular Immunology; 25:705-11.

Bock SA, Sampson HA, Atkins FM, et al (1988) Double-blind, placebo-controlled food challenge (DBPCFC) as an office procedure: A manual. J. Allergy Clinical Immunology; 82:986-97.

Boyce JA, Assa'ad A, Burks AW, et al (2010) Guidelines for the Diagnosis and Management of Food Allergy in the United States: Summary of the NIAID-Sponsored Expert Panel Report. J. Allergy Clinical Immunology; 126:1105-18.

Brazier JE, Mulhern BJ, Bjorner JB, et al (2020) Developing a New Version of the SF-6D Health State Classification System From the SF-36v2: SF-6Dv2. Medical Care; 58:557-65.

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

Byrne AM, Malka-Rais J, Burks AW, et al (2010) How do we know when peanut and tree nut allergy have resolved, and how do we keep it resolved? Clin Exp Allergy; 40(9):1303-11

Casale TB, Haselkorn T, Ciaccio CE, et al (2019) Harmonization of Terminology for Tolerated and Reactive Dose in Food Allergy Immunotherapy. J Allergy Clinical Immunology Practice; 7:389-92.

Chinthrajah RS, Jones SM, Kim EH, et al (2022) Updating the CoFAR Grading Scale for Systemic Allergic Reactions in Food Allergy. J Allergy Clin Immunology; S0091-6749(22)00007-0.

Cohen BL, Noone S, Muñoz-Furlong A, et al (2004) Development of a questionnaire to measure quality of life in families with a child with food allergy. J. Allergy Clinical Immunology; 114:1159-63.

Cox L, Platts-Mills TA, Finegold I, et al (2007) American Academy of Allergy, Asthma & Immunology/American College of Allergy, Asthma and Immunology Joint Task Force Report on omalizumab-associated anaphylaxis. J. Allergy Clinical Immunology; 120:1373-7.

Cox LS, Sanchez-Borges M, Lockey RF (2017) World Allergy Organization Systemic Allergic Reaction Grading System: Is a Modification Needed? J Allergy Clinical Immunology Practice; 5:58-62.e5.

Coyle AJ, Wagner K, Bertrand C, et al (1996) Central role of immunoglobulin (Ig) E in the induction of lung eosinophil infiltration and T helper 2 cell cytokine production: inhibition by a non-anaphylactogenic anti-IgE antibody. J. Exp. Medicine; 183:1303-10.

DunnGalvin A, de BlokFlokstra BM, Burks AW, et al (2008) Food allergy QoL questionnaire for children aged 0-12 years: content, construct, and cross-cultural validity. Clinical Exp. Allergy; 38:977-86.

Feng C, Kim JH (2019) Beyond Avoidance: the Psychosocial Impact of Food Allergies. Clinical Reviews in Allergy & Immunology; 57:74-82.

Fleming S, Thompson M, Stevens R, et al (2011) Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. Lancet; 377: 1011-8.

Flokstra-de Blok BM, DunnGalvin A, Vlieg-Boerstra BJ, et al (2008) Development and validation of the self-administered Food Allergy Quality of Life Questionnaire for adolescents. J. Allergy Clinical Immunology; 122:139-44, 144.e1-2.

Flokstra-de Blok BM, DunnGalvin A, Vlieg-Boerstra BJ, et al (2009) a Development and validation of a self-administered Food Allergy Quality of Life Questionnaire for children. Clinical. Exp. Allergy; 39:(1)127-37.

Flokstra-de Blok BM, van der Meulen GN, DunnGalvin A, et al (2009) b Development and validation of the Food Allergy Quality of Life Questionnaire - Adult Form. Allergy; 64(8): 1209-17.

Flokstra-de Blok BM, van der Velde JL, Vlieg-Boerstra BJ, et al (2010) Development, validity and reliability of the food allergy independent measure (FAIM). Allergy 65(5): 630-5.

Flynn JT, Kaelber DC, Baker-Smith CM, et al (2017) Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents. Pediatrics; 140(3):e20171904.

GINA (2020) Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention.

Gasser P, Tarchevskaya SS, Guntern P, et al (2020) The mechanistic and functional profile of the therapeutic anti-IgE antibody ligelizumab differs from omalizumab. Nat Commun 11(1): 165.

Gauvreau GM, Arm JP, Boulet LP, et al (2016) Efficacy and safety of multiple doses of QGE031 (ligelizumab) versus omalizumab and placebo in inhibiting allergen-induced early asthmatic responses. J. Allergy Clinical Immunology; 138(4):1051-1059

Graham BL, Steenbruggen I, Miller MR, et al (2019) Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. Am J Respir Crit Care Medicine. 200(8):e70-e88

Gupta R, Holdford D, Bilaver L, et al (2013) The economic impact of childhood food allergy in the United States. JAMA Pediatr 167(11):1026-31

Gupta RS, Springston EE, Warrier MR, et al (2011) The prevalence, severity, and distribution of childhood food allergy in the United States. Pediatrics 128(1):e9-17

Gupta RS, Warren CM, Smith BM, et al (2019) Prevalence and Severity of Food Allergies Among US Adults. JAMA Netw Open 2(1):e185630

Howie SR (2011) Blood sample volumes in child health research: review of safe limits. Bull World Health Organ 89(1):46-53

ICH-E2D guideline (2003) ICH E2D Post-approval safety data management (Available from: https database.ich.org/sites/default/files/E2D_Guideline.pdf (Accessed 22042022).

Jones SM, Burks AW (2017) Food Allergy. N. Engl. J. Med. 377(12):1168-1176

Kawai N, Chuang-Stein C, Komiyama O & Li Y(2008) An Approach to Rationalize Partitioning Sample Size into Individual Regions in a Multiregional Trial. Drug Information Journal 42;(2) 139–47.

Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group (2013) KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease Kidney Int Suppl, 3 (2013) p. pp. 1-150.

Kjellman NM, Johansson SG, Roth A (1976) Serum IgE levels in healthy children quantified by a sandwich technique (PRIST). Clinical Allergy; 1976 (1):51-9.

Leung DY, Sampson HA, Yunginger JW, et al (2003) Effect of anti-IgE therapy in patients with peanut allergy. N. Engl. J. Medicine; 348(11):986-93

Lowe PJ, Renard D (2011) Omalizumab decreases IgE production in patients with allergic (IgE-mediated) asthma; PKPD analysis of a biomarker, total IgE. Br J Clin Pharmacology; 72(2):306-20

Lowe PJ, Tannenbaum S, Gautier A, et al (2009) Relationship between omalizumab pharmacokinetics, IgE pharmacodynamics and symptoms in patients with severe persistent allergic (IgE-mediated) asthma. Br J Clin Pharmacol; 68(1):61-76.

MacGlashan D, McKenzie-White J, Chichester K, et al (1998) In vitro regulation of FcepsilonRIalpha expression on human basophils by IgE antibody. Blood; 91(5):1633-43.

MacGlashan DW (1993) Releasability of human basophils: cellular sensitivity and maximal histamine release are independent variables. J. Allergy Clin. Immunol.; 91(2):605-15

MacGlashan DW, Bochner BS, Adelman DC, et al (1997) Down-regulation of Fc(epsilon)RI expression on human basophils during in vivo treatment of atopic patients with anti-IgE antibody. J. Immunol.; 158(3):1438-45.

Maruish, M. E. (Ed.). (2011) User's manual for the SF-36v2 Health Survey (3rd ed.). Lincoln, RI: QualityMetric Incorporated.

Maurer M, Giménez-Arnau AM, Sussman G, et al (2019) Ligelizumab for Chronic Spontaneous Urticaria. N. Engl. J. Medicine; 381(14):1321-1332

Muraro A, Werfel T, Hoffmann-Sommergruber K, et al (2014) EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. Allergy; 69(8):1008-25

National Kidney Foundation (2002) K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis. ;39 (2 Suppl 1):S1.

Niggemann B, Beyer K (2007) Diagnosis of food allergy in children: toward a standardization of food challenge. J. Pediatr. Gastroenterol. Nutr.; 45(4):399-404.

Nowak-Wegrzyn A, Assa'ad Amal H, Bahna SL. et al (2009): Work Group report: oral food challenge testing, J Allergy Clin Immunol. Jun; 123(6 Suppl) 365S-83S

Ota T, Aoki-Ota M, Duong BH, et al (2009) Suppression of IgE B cells and IgE binding to Fc(epsilon)RI by gene therapy with single-chain anti-IgE. J Immunol; 182(12):8110-7

Peavy RD, Metcalfe DD (2008) Understanding the mechanisms of anaphylaxis. Curr Opin Allergy Clin Immunol; 8(4):310-5

Sampson HA, Gerth van Wijk R, Bindslev-Jensen C, et al (2012) Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology-European Academy of Allergy and Clinical Immunology PRACTALL consensus report. J. Allergy Clin. Immunol; 130(6):1260-74

Sampson HA, Leung DY, Burks AW, et al (2011) A phase II, randomized, double-blind, parallel-group, placebo-controlled oral food challenge trial of Xolair (omalizumab) in peanut allergy. J. Allergy Clin. Immunol; 127(5):1309

Sampson HA, Muñoz-Furlong A, Campbell RL, et al (2006) Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J. Allergy Clin. Immunol.; 117(2):391-7

Savage JH, Courneya JP, Sterba PM, et al (2012) Kinetics of mast cell, basophil, and oral food challenge responses in omalizumab-treated adults with peanut allergy. J. Allergy Clin. Immunol. 130(5):1123-1129

Schneider LC, Rachid R, LeBovidge J, et al (2013) A pilot study of omalizumab to facilitate rapid oral desensitization in high-risk peanut-allergic patients. J. Allergy Clin. Immunol; 132(6):1368-74

Schwartz GJ, Muñoz A, Schneider MF, et al (2009) New equations to estimate GFR in children with CKD. J. Am. Soc. Nephrol.; 20(3):629-37

Sicherer SH, Sampson HA (2018) Food allergy: A review and update on epidemiology, pathogenesis, diagnosis, prevention, and management. J. Allergy Clin. Immunol.; 141(1):41-58

Taylor SL, Hefle SL, Bindslev-Jensen C, et al (2004) A consensus protocol for the determination of the threshold doses for allergenic foods: how much is too much? Clin. Exp. Allergy; 34(5):689-95

Teach SJ, Gill MA, Togias A, et al (2015) Preseasonal treatment with either omalizumab or an inhaled corticosteroid boost to prevent fall asthma exacerbations. J. Allergy Clinical Immunology; 136(6):1476-1485

Vadas P, Gold M, Perelman B, et al (2008) Platelet-activating factor, PAF acetylhydrolase, and severe anaphylaxis. N. Engl. J. Med.; 358(1):28-35

Vander Leek TK, Liu AH, Stefanski K, et al (2000) The natural history of peanut allergy in young children and its association with serum peanut-specific IgE. J. Pediatr.; 137(6):749-55

Vickery BP, Vereda A, et al (2018) AR101 Oral Immunotherapy for Peanut Allergy. N. Engl. J. Med.; 379(21):1991-2001

Warren CM, Jiang J, Gupta RS (2020) Epidemiology and Burden of Food Allergy. Curr Allergy Asthma Rep; 20(2):6

Wood RA (2003) The natural history of food allergy. Pediatrics; 111(6 Pt 3):1631-7

Xepapadaki P, Kostoudi S, Tzeli K, et al (2019) A pilot study to investigate the influence of upper respiratory infections on IgE reactivity to food allergens. Pediatr Allergy Immunol; 30(1):127-130

16 Appendices

16.1 Appendix 1: Clinically notable laboratory values and vital signs

Laboratory assessments

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

Refer to Section 16.3 for clinically notable laboratory values for nephrotoxicity

The following other specific criteria have been identified for this study:

- Platelets < 75 000/µL
- Any participant who has platelets < 75 000/µL after being randomized should discontinue study treatment.

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

Vital signs

Notable values for vital signs for adults are:

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

For children (6-11years) and adolescents, the notable values are described in Table 16-1:

Table 16-1 Notable values for Heart Rate (HR) and Blood Pressure in children and adolescents

	HR (bpm)			
Age range	Low		High	
6-8 years	<74		>111	
8-12 years	<67		>103	
12-15 years	<62		>96	
≥ 15 years	<58		>92	
Age (years)	Blood pressure (mmHg)			
	Boys		Girls	
6	105	66	105	67
7	106	68	106	68
8	107	69	107	69
9	107	70	108	71
10	108	72	109	72
11	110	74	111	74
12	113	75	114	75
13	120	80	120	80
Heart Rate (HR) Adapted from Fleming et al 2011; Blood Pressure (BP) adapted from Flynn et al 2017				

ECG

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

For children, a QTc ≤450 ms is recommended as the upper limit of normal for children up to 12 years of age. In children older than 12 years, the same thresholds apply as for adults i.e. QTc <450 ms in males and QTc <460 ms in females (Novartis ECG and QTc Clinical Development Safety Guideline, 2017)

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

Table 16-2 Liver event and Laboratory trigger definitions

	Definition/ threshold
Liver laboratory triggers If ALT, AST and total bilirubin normal at baseline:	· ALT or AST > 5 × ULN · ALP > 2 × ULN (in the absence of known bone pathology) · Total bilirubin > 3 × ULN (in the absence of known Gilbert syndrome) · ALT or AST > 3 × ULN and INR > 1.5 · Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and Total bilirubin > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) · Any clinical event of jaundice (or equivalent term) · ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia · Any adverse event potentially indicative of a liver toxicity*
If ALT or AST abnormal at baseline:	· ALT or AST > 2x baseline or > 300 U/L (whichever occurs first)
*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; non-infectious hepatitis; benign, malignant and unspecified liver neoplasms ULN: upper limit of normal	

Table 16-3 Follow up requirements for liver laboratory triggers

	ALT	**TBL**	**Liver Symptoms**	**Action**
ALT increase without bilirubin increase:				
	If normal at baseline: ALT > 3 x ULN **If elevated at baseline:** ALT > 2 x baseline or > 300 U/L (whichever occurs first)	Normal For participants with Gilbert's syndrome: No change in baseline TBL	None	• **No change to study treatment** • Measure ALT, AST, ALP, GGT, TBIL, INR, albumin, CK, and GLDH in 48-72 hours. • Follow-up for symptoms.
	If normal at baseline: ALT > 5 x ULN for more than two weeks **If elevated at baseline:** ALT > 3 x baseline or > 300 U/L (whichever occurs	Normal For participants with Gilbert's syndrome: No change in baseline TBL	None	• **Interrupt study drug** • Measure ALT, AST, ALP, GGT, TBIL, INR, albumin, CK, and GLDH in 48-72 hours.

	ALT	TBL	Liver Symptoms	Action
	first) for more than two weeks			• Follow-up for symptoms. • Initiate close monitoring and workup for competing etiologies. • Study drug can be restarted only if another etiology is identified and liver enzymes return to baseline.
	If normal at baseline: ALT > 8 x ULN	Normal	None	
ALT increase with bilirubin increase:				
	If normal at baseline: ALT > 3 x ULN	TBL > 2 x ULN (or INR > 1.5) For participants with Gilbert's syndrome: Doubling of direct bilirubin	None	
	If elevated at baseline: ALT > 2 x baseline or > 300 U/L (whichever occurs first)			
	If normal at baseline: ALT > 3 x ULN	Normal or elevated	Severe fatigue, nausea, vomiting, right upper quadrant pain	
	If elevated at baseline: ALT > 2 x baseline or > 300 U/L (whichever occurs first)			

Table 16-4 Follow up requirements for liver laboratory triggers

Criteria	***Actions required***	***Follow-up monitoring***
Total Bilirubin (isolated)		
>1.5 – 3.0 ULN	• *Maintain treatment* • *Repeat LFTs within 48-72 hours*	*Monitor LFTs weekly until resolution[c] to ≤ Grade 1 or to baseline*
> 3 - 10 × ULN (in the absence of known Gilbert syndrome)	• *Interrupt treatment* • *Repeat LFT within 48-72 hours* • *Hospitalize if clinically appropriate* • *Establish causality* • *Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF*	*Monitor LFTs weekly until resolutionc to ≤ Grade 1 or to baseline (ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT)* *Test for hemolysis (e.g. reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)*
> 10 x ULN	• *Discontinue the study treatment immediately* • *Hospitalize the participant* • *Establish causality* • *Record the AE and contributing factors(e.g. conmeds, med hx, lab)in the appropriate CRF*	*ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT until resolutionc (frequency at investigator discretion)*

Criteria	***Actions required***	***Follow-up monitoring***
*Any AE potentially indicative of a liver toxicity**	• *Consider study treatment interruption or discontinuation* • *Hospitalization if clinically appropriate* • *Establish causality* • *Record the AE and contributing factors(e.g., conmeds, med hx, lab)in the appropriate CRF*	*Investigator discretion*
[c]Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death. **These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage – related conditions; non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms.*		

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

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

Table 16-5 Specific renal alert criteria and actions

Renal Event	Actions
Confirmed serum creatinine increase 25% – 49%	• Consider causes and possible interventions • Follow up within 2-5 days
Serum creatinine increase ≥ 50% [+] OR if <18 years old, eGFR ≤ 35mL/min/1.73 m2	• Consider causes and possible interventions • Repeat assessment within 24-48h if possible • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected • Consider participant hospitalization and specialized treatment
New onset dipstick proteinuria ≥ 3+ OR Protein-creatinine ratio (PCR) ≥ 1g/g Cr (or mg/mmol equivalent as converted by the measuring laboratory)	• Consider causes and possible interventions • Assess serum albumin & serum protein • Repeat assessment to confirm • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected
New onset hematuria ≥ 3+ on urine dipstick	Assess & document • Repeat assessment to confirm • Distinguish hemoglobinuria from hematuria • Urine sediment microscopy • Assess sCr • Exclude infection, trauma, bleeding from the distal urinary tract/bladder, menstruation • Consider bleeding disorder
[+] Corresponds to KDIGO criteria for Acute Kidney Injury (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work 2013) Whenever a renal event is identified, a detailed participant history and examination are indicated to identify and potentially eliminate risk factors that may have initiated or contributed to the event: · Blood pressure assessment (after 5-minute rest, with an appropriate cuff size) · Signs and symptoms like fever, headache, shortness of breath, back or abdominal pain, dysuria or hematuria, dependent or periorbital edema · Changes in blood pressure, body weight, fluid intake, voiding pattern, or urine output · Concomitant events or procedures such as trauma, surgical procedures, cardiac or hepatic failure, contrast media or other known nephrotoxin administration, or other diseases or causes, e.g., dehydration due to delirium, tumor lysis	

Table 16-6 Renal event follow-up

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

FOLLOW-UP OF RENAL EVENTS
level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months
Analysis of urine markers in samples collected over the course of the DIN event

16.4 Double-blind Placebo Controlled Food Challenge

16.4.1 Background

The DBPCFC, also referred to as the oral food challenge (OFC), represents the gold standard to diagnose food allergy. It is also the most objective method to clinically estimate threshold doses for allergenic foods in highly sensitive individuals (Taylor et al 2004). In this study the OFC is based upon several available guidelines, PRACTALL (Sampson et al 2012) and the CoFAR Grading Definition of Dose-Limiting Symptoms. The double-blind aspect of the OFC markedly reduces any potential bias of participant and/or supervising health care professionals that could interfere with its appropriate interpretation. The test itself corresponds most closely to the natural ingestion of food.

In general, the OFC is to be strictly performed under medical supervision to document the dose of allergen that provokes a reaction and, if needed, to administer symptomatic treatment which could potentially require the management of anaphylaxis. Participants must be in good health before proceeding with the food challenge and should be advised to avoid physical exercise at least one hour prior to the start of the procedure. A light breakfast is optional on the day of the OFC, in line with local practice. Additionally, participants should be on minimal or no symptomatic medication before starting the OFC (Table 6-2 and Table 6-3). Due to the inherent risk of a severe reaction, participants who have experienced a severe or life-threatening hypersensitivity event needing an ICU admission or intubation within 60 days prior to baseline DBPCFC (at Screening 2 visit) are excluded from study participation.

Intravenous access may be set up before the DBPCFC at the investigator's discretion (e.g., participant at high risk of reaction or severe reaction based upon prior history and medical history).

At the start of the OFC a small dose of peanut allergen is administered. This dose is intentionally lower than any dose expected to induce a reaction (Niggemann and Beyer 2007). While monitoring the participant for any allergic symptoms, the allergen dose is gradually increased until a cumulative dose at least equivalent to the portion of allergen as defined in the objectives (Section 2) is ingested (refer to the QGE031G12301 Pharmacy Manual).

16.4.2 DBPCFC dosing schedule

This study includes three DBPCFCs: the first at Screening Visit 2, the second at 12 weeks, and the third at 52 weeks (end of treatment).

Each DBPCFC consists of two parts, active allergen (peanut) challenge and placebo challenge. Each challenge is to be performed on a separate day (Part 1 and Part 2). The active allergen challenge is either given on the first day or the second day. To ensure and preserve the double-blind nature of the challenge, independent (unblinded) study site staff need to prepare the material for each challenge prior to administration. Study staff/investigator administering the challenge and participants undergoing the challenge remain blinded to the identity of the

challenge on the two test days (i.e. if peanut allergen or placebo is tested on the first or the second day). The time interval between each challenge part **is** approximately **one to seven days**; there must be a minimum of one full day between Part 1 and Part 2 and maximum of 7 days. **There must be at least 24 hours between the completion of the OFC Part 2 and the first administration of study treatment at the Randomization visit.**

At Part 1 (the first challenge day) of week 12 and week 52 visits, study treatment must be administered at least 1 hour before the DBPCFC.

16.4.2.1 Allergen dose escalation

At each DBPCFC, participants will be exposed to increasing amounts of allergen, either peanut protein or corresponding placebo in a randomized fashion, with each dose administration separated by at least 15 minutes (Table 16-7).

At screening the dry weight amounts of 1 mg, 3 mg, 10 mg, 30 mg and 100 mg of peanut protein and corresponding placebo will be tested.

At 12 weeks and at 52 weeks, the dry weight amounts of 1mg, 3 mg, 10 mg, 30 mg, 100 mg, 300 mg, 600 mg, 1000 mg and 3000 mg of peanut protein and corresponding placebo will be tested.

16.4.2.2 Maximum dose

Within the OFC, incremental allergen (or placebo) dose increases continue until the highest dose for the challenge has been reached (100 mg at screening and 3000 mg at 12 weeks and 52 weeks), or until the participant displays (a) dose-limiting symptom(s) (Section 16.4.5).

Three hundred (300) mg peanut protein is estimated to correspond to the amount of allergen generally associated with accidental exposure, while 3000 mg corresponds to the highest peanut protein dose used within this protocol.

The DBPCFC allergen doses are indicated by dry weight (mg) in Table 16-7. The allergen granules are to be reconstituted for administration and given to the participant in portions measured by volume (mL). Refer to the Pharmacy Manual.

16.4.2.3 DBPCFC allergen dose administration instruction

Table 16-7 Dry Weight Dosing Table

Dose No.	Peanut Protein/Placebo (mg)	Cumulative Dose (mg)
1	1	1
2	3	4
3	10	14
4	30	44
5	100	144
6	300	444
7	600	1044
8	1000	2044
9	3000	5044

After each administered dose of reconstituted allergen (or placebo) participants are to be monitored for any reaction. In the presence of an allergic reaction, and at the investigator's discretion, the interval between escalating doses can be increased or the challenge can be stopped. (Section 16.4.5).

The minimum observation time between doses is 15 minutes, the maximum observation time is 30 minutes. If needed, an additional 30 minutes of observation is permitted for further evaluation of symptoms. If continuation of the OFC is still in question after 1 hour of observation, the challenge should be considered positive and should be stopped.

During and up to at least one hour after the completion of the DBPCFC, vital signs should be monitored approximately every 15 minutes and documented in source.

In the event of an allergen dosing error, the site should contact Novartis.

16.4.3 DBPCFC material

Novartis will supply the Oral Food Allergen Peanut Flour Chocolate Meal Base and its placebo globally in an **open-label** fashion.

- high dose: 20%w/w Peanut Flour Chocolate Flavour Challenge Meal Base (20%w/w Peanut Choc)
- low dose: 0.67%w/w Peanut Flour Chocolate Flavour Challenge Meal Base (0.67%w/w Peanut Choc)
- Placebo: 0%w/w Peanut Flour Chocolate Flavour Challenge Meal Base (0%w/w Peanut Choc)

Pharmaceutical Dosage Form: Granules for oral suspension

Route of Administration: Oral

The food challenge material and preparation instructions are described in detail in the QGE031G12301 Pharmacy Manual provided separately.

As previously noted, there should be an independent (unblinded) nurse, or other appropriately trained study site staff to prepare (i.e. NOT TO ADMINISTER) the unblinded material for the DBPCFC after obtaining the randomly assigned test sequence through the IRT system (Section 16.4.2)

16.4.4 Preparing for the food challenge

Prior to DBPCFC material preparation, independent **unblinded** study site personnel need to access the IRT system to obtain the allergen kit number to be used (corresponding to peanut allergen or placebo).

IMPORTANT NOTE: After **completion** of the 2nd day of the DBPCFC at Screening Visit 2 **ONLY**, the BLINDED site staff will access the IRT system to unblind the test and evaluate eligibility for randomization.

This unblinding step is only applicable for the first DBPCFC at Screening and does NOT apply to the DBPCFC at weeks 12 and 52.

16.4.5 Evaluation parameters of the DBPCFC

Objective symptoms exhibited by participants should be evaluated through physical examination. Complaints arising from the participant without observable changes will be classified as subjective.

The DBPCFC will be considered **positive** with the occurrence of any dose-limiting symptom(s). Dose-limiting symptoms indicate a true allergic reaction occurring during administration of a single dose that should preclude the administration of any further doses in the view of the investigator. Investigators should refer to Table 16-8 (CoFAR grading scale) for definition of dose-limiting symptoms. Symptoms can be mild, moderate or severe. Mild symptoms are not usually considered dose-limiting, although a combination of mild symptoms during a single dose might lead to the cessation of the OFC at the discretion of the investigator. All moderate and severe symptoms as defined in Table 16-8 are considered dose-limiting.

Symptoms that require administration of any rescue medication (e.g. SABA, epinephrine or other) are considered dose-limiting symptoms. In this case, the challenge has to be stopped and the challenge is considered positive.

All findings that the investigator classifies as reactions to the DBPCFC should be recorded in source documentation and on a designated eCRF. These events should not be reported on the Adverse Event eCRF unless they constitute an SAE according to the investigator's judgement.

The details and start time of any treatment and/or medication provided to treat DBPCFC-related allergic reactions should be recorded on the respective eCRF. The DBPCFC will be considered **negative** if a participant does not exhibit (a) dose-limiting symptom(s) (= positive challenge) at the end of the challenge.

Table 16-8 Definition of Dose-Limiting Symptoms (per the CoFAR* grading scale, Chinthrajah et al 2022)

MILD (not typically dose limiting)	MODERATE (dose limiting)	SEVERE (dose limiting)
• Skin – limited (few) or localized hives, swelling (e.g., mild lip edema), skin flushing (e.g., few areas of faint erythema) or mild pruritus (e.g., occasional scratching) • Respiratory – rhinorrhea (e.g., occasional sniffling or sneezing), nasal congestion, occasional cough, throat discomfort • GI – mild abdominal discomfort (including mild nausea with or without decreased activity), isolated emesis thought to be secondary to gag	• Skin – systemic hives (e.g., numerous or widespread hives), swelling (e.g., significant lip or face edema), pruritus causing protracted scratching, more than a few areas of erythema or pronounced erythema • Respiratory – throat tightness without hoarseness, persistent cough, wheezing without dyspnea • GI – persistent moderate abdominal pain/cramping/nausea with decreased activity, vomiting	• Skin – severe generalized urticaria/angioedema/erythema • Respiratory – laryngeal edema, throat tightness with hoarseness, wheezing with dyspnea, stridor • GI – severe abdominal pain/cramping/repetitive vomiting • • Neurological – change in mental status • • Circulatory – clinically significant hypotension

16.4.6 DBPCFC completion

At the completion of the DBPCFC (post-administration of the last dose of allergen), participants must remain under observation at the study site for a minimum of 2 hours to confirm a negative challenge. In the event of a positive challenge participants must remain under observation at the study site for a minimum of 1 hour after allergic symptoms have improved to a level compatible with safe discharge. Observation beyond this timepoint remains at the Investigator's discretion and could potentially include hospital overnight observation.

Treatment of positive reactions

Epinephrine, SABA, anti-histamines and saline bolus are typically used to treat allergic reactions. Treatment in line with local clinic provisions/ guidelines is at the investigator's discretion. All treatment must be documented in the corresponding eCRF.

Discharge procedures

Upon discharge from the study site post-DBPCFC participants should be provided with a 24-hour emergency telephone contact. Furthermore, participants should be advised to avoid physical exercise within 2 hours after having received the last dose of the DBPCFC.

Delayed or late-onset reactions to the DBPCFC are defined as reactions occurring after the participant was discharged from the clinic. Since a delayed reaction to the DBPCFC cannot be predicted prior to discharge, all participants should be briefed about the signs and symptoms of anaphylaxis and provided with rescue medication (epinephrine auto-injector and short acting beta-agonists [asthma participants only]). Participants should also receive specific information on how to recognize a late reaction and on how and when to use rescue medication. Delayed or late- onset reactions will not be considered dose-limiting and will be captured on a designated CRF.

Post-discharge, participants who need to use epinephrine due to a suspected reaction should immediately go to the closest emergency room for additional assessment and contact the investigative site.

Adverse event reporting

If the participant experiences an allergic reaction associated with the DBPCFC (immediate, delayed or late-onset) that meets the criteria for a serious adverse event in the investigator's judgment, it should be captured on the designated CFR and reported as described in Section 10.1.3 SAE Reporting.

The administration of study medication will precede the DBPCFC at weeks 12 and 52. Investigators should apply their medical judgement when assessing if reactions occurring during the DBPCFC or during the post-DBPCFC observation period are symptoms caused by the food challenge or whether they are adverse events suspected to be related to the study treatment. Both adverse events suspected to be related to study treatment and allergic reactions due to the DBPCFC should be captured on the designated CRFs, and if serious, be reported as described in Section 10.1.3 SAE Reporting. For such SAEs, a causality assessment to either

study treatment or DBPCFC must be provided and documented together with its medical rationale.

16.5 Guidance for skin prick test

16.5.1 Background of Skin Prick Test

This study includes a Skin Prick Test (SPT) targeting peanut allergen as well as milk and/or egg allergens (if indicated by medical history). SPTs are performed at Screening Visit 1, Week 16 (before study drug dosing), Week 56 and End of Study. The Screening Visit 1 SPT will confirm the eligibility of all participants to peanut allergen and to assess the level of sensitivity to milk and/or egg if medical history indicates that the participant is allergic to milk and/or egg. A positive SPT for peanut allergen is defined as an average diameter of the longest diameter and mid-point orthogonal diameter ≥ 4 mm wheal compared to negative control.

This study specifies the use of BOTH a titration SPT (TSPT) and non-TSPT. All participants will receive the TSPT to peanut. In addition, all participants should receive the non-titration SPT (undiluted) to milk and/or egg based on medical history.

The TSPT will be conducted to the peanut allergen only; undiluted extract, five 10-fold dilutions (1:10, 1:100, 1:1’000, 1:10’000, and 1:100’000).

In addition to peanut, milk stock and egg stock will be tested (if indicated).

Positive and negative control should be tested together.

16.5.2 Material

Preparation for the reagent of titration SPT.

- ~ 5ml Vials (can be purchased from any supplier)
- Diluent (saline) (also purchased from any supplier)
- Pipette with disposable pipette tip or syringe (able to measure 0.1 to 0.9 ml)
- Add 0.9 mL of diluent to each of 5 vials (~ 5 mL in size). Label them from 1:10, 1:100, 1:1’000, 1:10’000, 1:100’000; and include the name of the allergen, the lot number, and the date on which the dilutions were made.
- Take 0.1 mL of the undiluted peanut stock and add to vial 1:10. Mix well.
- Take 0.1 mL from the 1:10 vial and add to vial 1:100. Mix well.
- Take 0.1 mL from the 1:100 vial and add to vial 1:1’000. Mix well.
- Take 0.1 mL from the 1:1,000 vial and add to vial 1:10’000. Mix well.
- Take 0.1 mL from the 1:10,000 vial and add to vial 1:100’000. Mix well.

Only a very small volume of allergen is needed per test – one “drop”. The prepared dilutions should not be used for more than one week after reconstitution.

The non-TSPT will be conducted using the stock (undiluted) of milk and egg if medical history indicates allergy to these foods at Screening 1,

Positive and negative control always need to be tested together.

16.5.3 Starting the Skin Prick Test

- Location of SPT: The skin of the participant's back is the preferred site of testing, alternatively the forearm may be used. For consistency purposes it is important for individual participants to perform the SPT at the same site during the study.

EXAMPLE:

TSPT: if the participant had a positive medical history of milk and egg in addition to peanut, total 10 pricks are needed; positive control, negative control, peanut (extract), peanut (1:10), peanut (1:100), peanut (1:1'000), peanut (1:10'000), peanut (1:100'000), milk, and egg

- Test time: Skin reactions should be recorded after 15 minutes of dropping allergen to the pricked location.
- Positive/negative control: The SPT should be repeated if the valid positive (≥ 3 mm wheal) and negative (no response) control results were not obtained.
- Prohibited/washout medications prior to SPT

Table 16-9 Medications to be washed out prior to SPT

Medication	Prohibited period
Short acting and long acting anti histamines (e.g., chlorpheniramine, prometazine, diphenhydramine, loratadine, cetirizine)	≥5 half-lives
Antihistamine nose spray	12 hours
Oral H2-receptor antagonist (e.g., cimetidine, ranitidine, famotidine, roxatidine, lafutidine)	24 hours
Systemic corticosteroids (including short-term burst of OCS)	≥5 half-lives

16.5.3.1 Performing the Skin Prick Test

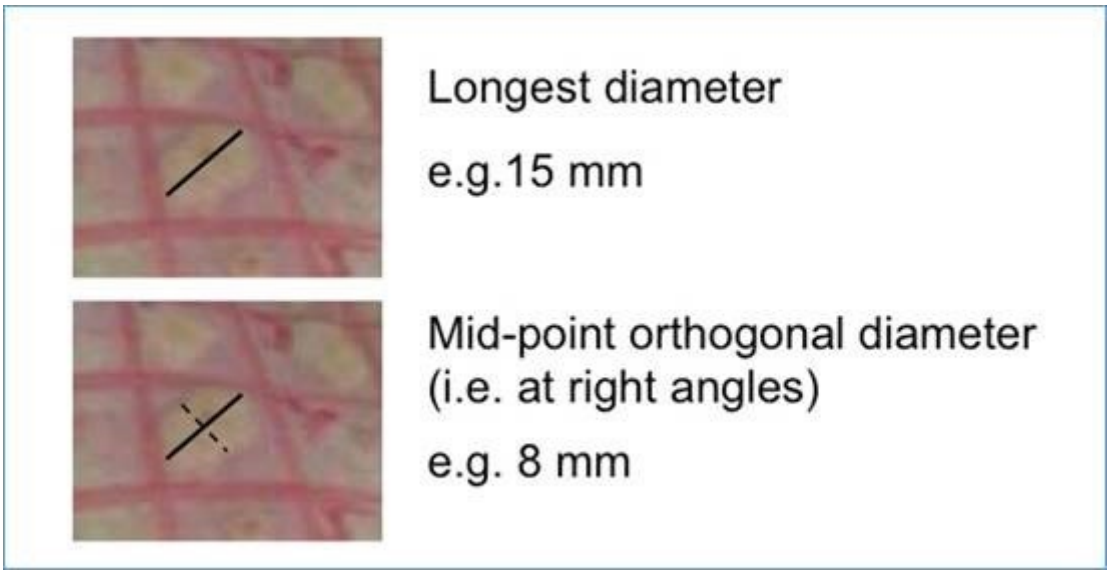
Clean the area of skin with 70% alcohol and allow to dry

1. Use a pen (which can be washed off with an alcohol wipe) to mark the skin with the sites where SPT will be performed. Put a mark beside the area where a particular solution will be placed; or draw boxes on the skin
   - Label allergen: peanut stock, milk stock (if positive Medical History), egg stock (if positive Medical History), and diluted peanut stock for TSPT (from 1:10 to 100'000)
   - Label histamine (positive control) and diluent-saline (negative control)
2. Place one drop of test solution at the appropriate labelled site as above and "prick" the skin with an appropriate SPT device: 1) Start from saline, positive control, then allergen (for TSPT, from the lowest concentration), 2) Use difference lancet for other allergen
3. Start a time (record it)
4. After pricking the skin, immediately blot the skin with tissue paper to absorb excess liquid; avoid letting the liquid run from one site to another
5. After 15 minutes measure the size of the wheal at each site: 1) Start with the site you first pricked and then work your way in the same order in which the pricks were applied. The time taken to do this will be approximately the time it took to apply the solutions and prick

them, 2) Measure and record the longest diameter at each site (record in eCRF), 3) Measure and record the midpoint orthogonal diameter (record in eCRF).

For the eligibility check, the average of longest wheal diameter and the corresponding midpoint orthogonal diameter will be used, e.g. 11.5 mm = (15+8)/2

Figure 16-1 Measurement of skin reaction



16.5.4 Completion of the Skin Prick Test

After measurement of skin reaction and recorded them in the source document, clean the skin with alcohol to remove the ink from marker pen on the skin.

Rarely, SPT can cause a generalized allergic reaction (e.g., hives itchy, runny nose, asthma) or even anaphylaxis. Therefore, at the completion of SPT, the participants should remain under observation at the site as per the investigator's discretion.

Adverse event reporting

If the participant experiences a systemic allergic reaction suspected to be triggered by the SPT, the event should be captured in the designated CRF. Adverse events meeting the criteria for a SAE should be reported as described in Section 10.1.3 SAE Reporting.

16.6 PRO Measures

16.6.1 FAQLQ-CF: Food Allergy Quality of Life Questionnaire Child Form

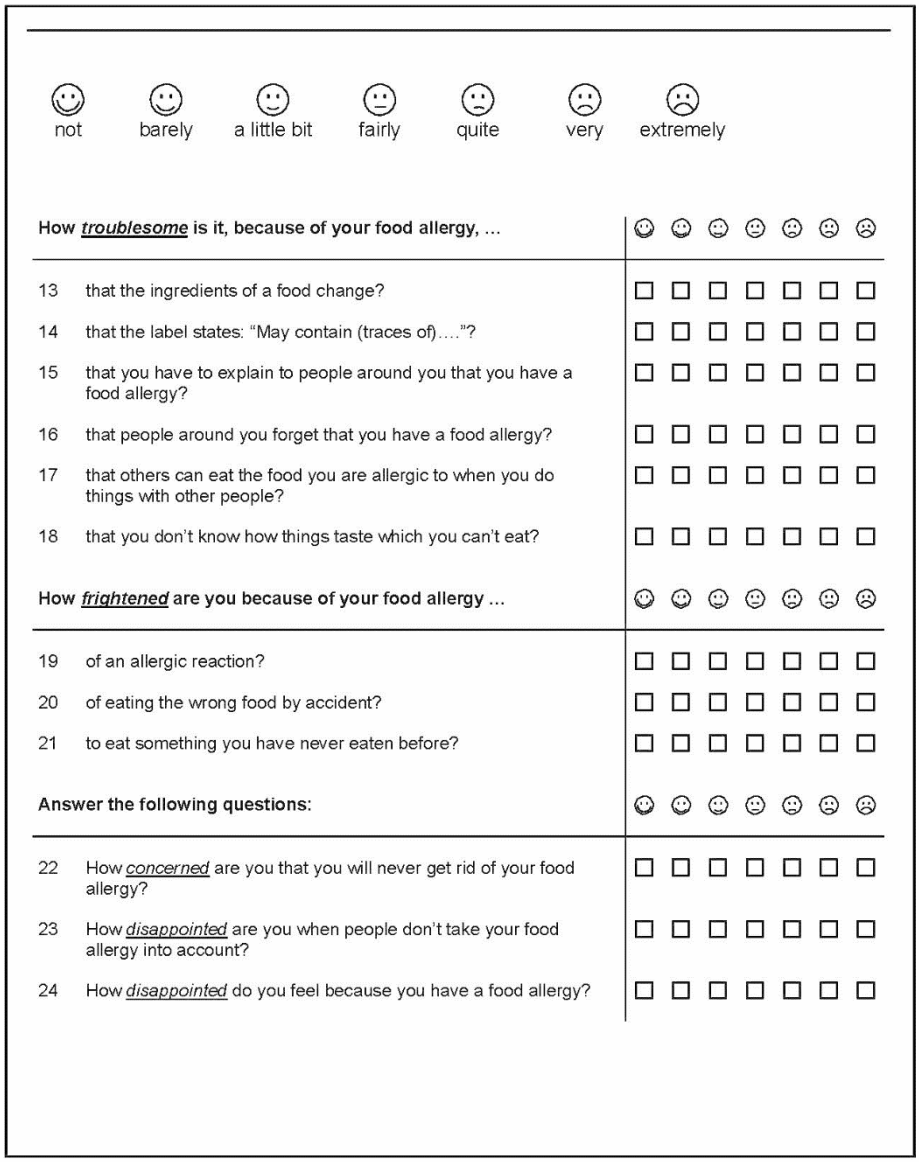
Food Allergy Quality of Life Questionnaire – Child Form (8-12 years)

The questions are about the influence of your food allergy on your quality of life. It is important that you fill in the answers yourself. You may ask your parents for help, but they are not allowed to tell you which answer to give. Answer every question by putting an 'x' in the proper box. You may choose from the following answers.

not barely a little bit fairly quite very extremely

	How *troublesome* do you find it, because of your food allergy, that you …	
1	must always watch what you eat?	☐ ☐ ☐ ☐ ☐ ☐ ☐
2	can eat fewer things?	☐ ☐ ☐ ☐ ☐ ☐ ☐
3	are limited in buying things you like?	☐ ☐ ☐ ☐ ☐ ☐ ☐
4	have to read labels?	☐ ☐ ☐ ☐ ☐ ☐ ☐
5	have to refuse food when you do things with others?	☐ ☐ ☐ ☐ ☐ ☐ ☐
6	can less easily stay for a meal with someone?	☐ ☐ ☐ ☐ ☐ ☐ ☐
7	can taste or try fewer things when eating out?	☐ ☐ ☐ ☐ ☐ ☐ ☐
8	have to tell beforehand about what you are not allowed to eat when eating out?	☐ ☐ ☐ ☐ ☐ ☐ ☐
9	have to check yourself whether you can eat something when eating out?	☐ ☐ ☐ ☐ ☐ ☐ ☐
10	hesitate eating certain foods when you don't know if it is safe?	☐ ☐ ☐ ☐ ☐ ☐ ☐
11	must watch out when touching certain foods?	☐ ☐ ☐ ☐ ☐ ☐ ☐
12	don't get anything when someone is giving treats at school?	☐ ☐ ☐ ☐ ☐ ☐ ☐

XXXXXXXX FAQLQ-CF-English/US 1 of 2 Source, NV V1, 18Jan20201



not barely a little bit fairly quite very extremely

	How ***troublesome*** **is it, because of your food allergy, ...**	
13	that the ingredients of a food change?	☐ ☐ ☐ ☐ ☐ ☐ ☐
14	that the label states: "May contain (traces of)...."?	☐ ☐ ☐ ☐ ☐ ☐ ☐
15	that you have to explain to people around you that you have a food allergy?	☐ ☐ ☐ ☐ ☐ ☐ ☐
16	that people around you forget that you have a food allergy?	☐ ☐ ☐ ☐ ☐ ☐ ☐
17	that others can eat the food you are allergic to when you do things with other people?	☐ ☐ ☐ ☐ ☐ ☐ ☐
18	that you don't know how things taste which you can't eat?	☐ ☐ ☐ ☐ ☐ ☐ ☐
	How *frightened* are you because of your food allergy ...	
19	of an allergic reaction?	☐ ☐ ☐ ☐ ☐ ☐ ☐
20	of eating the wrong food by accident?	☐ ☐ ☐ ☐ ☐ ☐ ☐
21	to eat something you have never eaten before?	☐ ☐ ☐ ☐ ☐ ☐ ☐
	Answer the following questions:	
22	How *concerned* are you that you will never get rid of your food allergy?	☐ ☐ ☐ ☐ ☐ ☐ ☐
23	How *disappointed* are you when people don't take your food allergy into account?	☐ ☐ ☐ ☐ ☐ ☐ ☐
24	How *disappointed* do you feel because you have a food allergy?	☐ ☐ ☐ ☐ ☐ ☐ ☐

16.6.2 FAIM-CF: Food Allergy Independent Measure Child Form

Food Allergy Independent Measure – Child Form (8-12 years)

The following four questions are about the chance that you think you have of something happening to you because of your food allergy. Choose one of the answers. This is followed by two more questions about your food allergy. Answer every question by putting an 'x' in the box next to the proper answer.

0 never (0% chance)	1 very small chance	2 small chance	3 fair chance	4 big chance	5 very big chance	6 always (100% chance)

How big do you think the chance is that you …	0	1	2	3	4	5	6
1. will accidentally eat something to which you are allergic?	☐	☐	☐	☐	☐	☐	☐
2. will have a severe reaction if you accidentally eat something to which you are allergic?	☐	☐	☐	☐	☐	☐	☐
3. will die if you accidentally eat something to which you are allergic?	☐	☐	☐	☐	☐	☐	☐
4. can **not** do the right things for your allergic reaction should you accidentally eat something to which you are allergic?	☐	☐	☐	☐	☐	☐	☐

5. How many foods are you unable to eat because of your food allergy?

- ☐ almost none
- ☐ very few
- ☐ a few
- ☐ some
- ☐ many
- ☐ very many
- ☐ almost all

6. Everyone does things with other people, such as;
- playing with friends,
- going to a birthday party,
- visiting,
- staying over with someone for a meal or eating out.

How much does your food allergy affect things you do with others?

- ☐ so little I don't actually notice it
- ☐ very little
- ☐ little
- ☐ moderately
- ☐ a good deal
- ☐ a great deal
- ☐ a very great deal

16.6.3 FAQLQ-TF: Food Allergy Quality of Life Questionnaire Teenager Form

Food Allergy Quality of Life Questionnaire – Teenager Form (13-17 years)

The following questions concern the influence your food allergy has on your quality of life. Answer every question by marking the appropriate box with an 'x'. You may choose from one of the following answers.

0	1	2	3	4	5	6
not	barely	slightly	moderately	quite	very	extremely

	How *troublesome* do you find it, because of your food allergy, that you …	**0**	**1**	**2**	**3**	**4**	**5**	**6**
1	must always be alert as to what you are eating?	☐	☐	☐	☐	☐	☐	☐
2	are able to eat fewer products?	☐	☐	☐	☐	☐	☐	☐
3	are limited as to the products you can buy?	☐	☐	☐	☐	☐	☐	☐
4	must read labels?	☐	☐	☐	☐	☐	☐	☐
5	have the feeling that you have less control of what you eat when eating out?	☐	☐	☐	☐	☐	☐	☐
6	are less able to spontaneously accept an invitation to stay for a meal?	☐	☐	☐	☐	☐	☐	☐
7	are less able to taste or try various products when eating out?	☐	☐	☐	☐	☐	☐	☐
8	must check yourself whether you can eat something when eating out?	☐	☐	☐	☐	☐	☐	☐
9	hesitate eating a product when you have doubts about it?	☐	☐	☐	☐	☐	☐	☐
10	must refuse treats at school or work?	☐	☐	☐	☐	☐	☐	☐
11	must be careful about touching certain foods?	☐	☐	☐	☐	☐	☐	☐
12	must carry an epinephrine auto injector (e.g. EpiPen, Twinject, Anapen…)? (If you don't have an epinephrine auto injector mark an 'x' here ☐)	☐	☐	☐	☐	☐	☐	☐

0	1	2	3	4	5	6
not	barely	slightly	moderately	quite	very	extremely

How ***troublesome*** is it, because of your food allergy, ...		0	1	2	3	4	5	6
13	that the ingredient s of a product change?	☐	☐	☐	☐	☐	☐	☐
14	that the label states: "May contain traces of…."?	☐	☐	☐	☐	☐	☐	☐
15	that the labeling of the bulk packaging (for example box or bag) is different than the individual packages?	☐	☐	☐	☐	☐	☐	☐
16	that you have to explain to people around you that you have a food allergy?	☐	☐	☐	☐	☐	☐	☐
17	that during social activities others can eat the food to which you are allergic?	☐	☐	☐	☐	☐	☐	☐
18	that during social activities your food allergy is not taken into account enough?	☐	☐	☐	☐	☐	☐	☐

How ***frightened*** are you because of your food allergy ...		0	1	2	3	4	5	6
19	of an allergic reaction?	☐	☐	☐	☐	☐	☐	☐
20	of accidentally eating something wrong?	☐	☐	☐	☐	☐	☐	☐
21	to eat something you have never eaten before?	☐	☐	☐	☐	☐	☐	☐

Answer the following questions:		0	1	2	3	4	5	6
22	How *discouraged* do you feel during an allergic reaction?	☐	☐	☐	☐	☐	☐	☐
23	How *disappointed* are you when people do not take your food allergy into account?	☐	☐	☐	☐	☐	☐	☐

16.6.4 FAIM-TF: Food Allergy Independent Measure Teenager Form

Food Allergy Independent Measure – Teenager Form (13-17 years)

The following four questions are about the chance that you think you have of something happening to you because of your food allergy. Choose one of the answers provided. This is followed by two more questions about your food allergy. Answer every question by putting an 'x' in the box next to the appropriate answer.

0 never (0% chance)	1 very small chance	2 small chance	3 fair chance	4 great chance	5 very great chance	6 always (100% chance)

How great do you think the chance is that you ...	0	1	2	3	4	5	6
1. will accidentally eat something to which you are allergic?	☐	☐	☐	☐	☐	☐	☐
2. will have a severe reaction if you accidentally eat something to which you are allergic?	☐	☐	☐	☐	☐	☐	☐
3. will die if you accidentally eat something to which you are allergic?	☐	☐	☐	☐	☐	☐	☐
4. can **not** effectively deal with an allergic reaction should you accidentally eat something to which you are allergic?	☐	☐	☐	☐	☐	☐	☐

5. How many products must you avoid because of your food allergy?	6. How great is the impact of your food allergy on your social life?
☐ almost none	☐ negligibly small
☐ very few	☐ very small
☐ a few	☐ small
☐ some	☐ moderate
☐ many	☐ great
☐ very many	☐ very great
☐ almost all	☐ extremely great

16.6.5 FAQLQ-AF: Food Allergy Quality of Life Questionnaire Adult Form

Food Allergy Quality of Life Questionnaire – Adult Form (18 years and older)

Instructions

The following questions concern the influence your food allergy has on your quality of life. Answer every question by marking the appropriate box with an 'x'. You may choose from one of the following answers.

0	1	2	3	4	5	6
Not	barely	slightly	moderately	quite	very	extremely

	How *troublesome* do you find it, because of your food allergy, that you …	0	1	2	3	4	5	6
1	must always be alert as to what you are eating?	☐	☐	☐	☐	☐	☐	☐
2	are able to eat fewer products?	☐	☐	☐	☐	☐	☐	☐
3	are limited as to the products you can buy?	☐	☐	☐	☐	☐	☐	☐
4	must read labels?	☐	☐	☐	☐	☐	☐	☐
5	have the feeling that you have less control of what you eat when eating out?	☐	☐	☐	☐	☐	☐	☐
6	must refuse many things during social activities?	☐	☐	☐	☐	☐	☐	☐
7	sometimes frustrate people when they are making an effort to accommodate your food allergy?	☐	☐	☐	☐	☐	☐	☐
8	are less able to spontaneously accept an invitation to stay for a meal?	☐	☐	☐	☐	☐	☐	☐
9	are less able to taste or try various products when eating out?	☐	☐	☐	☐	☐	☐	☐
10	can eat out less?	☐	☐	☐	☐	☐	☐	☐
11	must personally check whether you can eat something when eating out?	☐	☐	☐	☐	☐	☐	☐
12	hesitate eating a product when you have doubts about it?	☐	☐	☐	☐	☐	☐	☐

0 Not	**1** barely	**2** slightly	**3** moderately	**4** quite	**5** very	**6** extremely

	How *troublesome* is it, because of your food allergy, ...	**0**	**1**	**2**	**3**	**4**	**5**	**6**
13	that the ingredients of a product change?	☐	☐	☐	☐	☐	☐	☐
14	that labels are incomplete?	☐	☐	☐	☐	☐	☐	☐
15	that the lettering on labels is too small?	☐	☐	☐	☐	☐	☐	☐
16	that the label states: "May contain (traces of)…."?	☐	☐	☐	☐	☐	☐	☐
17	that ingredients are different in other countries (for example during vacation)?	☐	☐	☐	☐	☐	☐	☐
18	that people underestimate your problems caused by food allergy?	☐	☐	☐	☐	☐	☐	☐
19	that it is unclear to which foods you are allergic?	☐	☐	☐	☐	☐	☐	☐
20	that you must explain to those around you that you have a food allergy?	☐	☐	☐	☐	☐	☐	☐
21	for your host or hostess should you have an allergic reaction?	☐	☐	☐	☐	☐	☐	☐

	How *worried* are you because of your food allergy ...	**0**	**1**	**2**	**3**	**4**	**5**	**6**
22	about your health?	☐	☐	☐	☐	☐	☐	☐
23	that the allergic reactions to foods will become increasingly severe?	☐	☐	☐	☐	☐	☐	☐

	How *frightened* are you because of your food allergy ...	**0**	**1**	**2**	**3**	**4**	**5**	**6**
24	of an allergic reaction?	☐	☐	☐	☐	☐	☐	☐
25	of accidentally eating the wrong food?	☐	☐	☐	☐	☐	☐	☐
26	of an allergic reaction when eating out despite the fact that your dietary restrictions have been discussed beforehand?	☐	☐	☐	☐	☐	☐	☐

0 Not	**1** barely	**2** slightly	**3** moderately	**4** quite	**5** very	**6** extremely

Answer the following questions:		**0**	**1**	**2**	**3**	**4**	**5**	**6**
27	To what degree do you *feel you are being a nuisance* because you have a food allergy when eating out?	☐	☐	☐	☐	☐	☐	☐
28	How *discouraged* do you feel during an allergic reaction?	☐	☐	☐	☐	☐	☐	☐
29	How *apprehensive* are you about eating something you have never eaten before?	☐	☐	☐	☐	☐	☐	☐

16.6.6 FAIM-AF: Food Allergy Independent Measure Adult Form

Food Allergy Independent Measure – Adult Form (18 years and older)

The following four questions are about the chance that you think you have of something happening to you because of your food allergy. Choose one of the answers provided. This is followed by two more questions about your food allergy. Answer every question by putting an 'x' in the box next to the appropriate answer.

0 never (0% chance)	1 very small chance	2 small chance	3 fair chance	4 great chance	5 very great chance	6 certain (100% chance)

How great do you think the chance is that you ...	0	1	2	3	4	5	6
1. will accidentally eat something to which you are allergic?	☐	☐	☐	☐	☐	☐	☐
2. will have a severe reaction if you accidentally eat something to which you are allergic?	☐	☐	☐	☐	☐	☐	☐
3. will die if you accidentally eat something to which you are allergic?	☐	☐	☐	☐	☐	☐	☐
4. can **not** effectively deal with an allergic reaction should you accidentally eat something to which you are allergic?	☐	☐	☐	☐	☐	☐	☐

5. How many products must you avoid because of your food allergy?	6. How great is the impact of your food allergy on your social life?
☐ almost none	☐ negligibly small
☐ very few	☐ very small
☐ a few	☐ small
☐ some	☐ moderate
☐ many	☐ great
☐ very many	☐ very great
☐ almost all	☐ extremely great

16.6.7 FAQLQ-PF: Food Allergy Quality of Life Questionnaire Parental Form

Food Allergy Quality of Life Questionnaire – Parent Form (FAQLQ-PF)
Children aged 0-12 years

Instructions to Parents

- The following are scenarios that parents have told us affect children's quality of life because of food allergy.
- Please indicate how much of an impact each scenario has on **your child's quality of life** by placing a tick or an x in one of the boxes numbered 0-6.

All information given is completely confidential.
This questionnaire will only be identified by a code number.

Response Options

0 = not at all
1= a little bit
2 = slightly
3 = moderately
4 = quite a bit
5 = very much
6 = extremely

There are 4 sections to this questionnaire: A, B, C, and D.

- If your child is aged 0 to 3 years, please answer Section A ONLY.
- If your child is aged 4 to 6 years, please answer Section A + Section B.
- If your child is aged 7 years and over, please answer Section A + Section B + Section C.

Section D: For ALL age groups.

SECTION A: For all age groups

Because of food allergy, my child feels……	**0**	**1**	**2**	**3**	**4**	**5**	**6**
1 Worried about food in general	☐	☐	☐	☐	☐	☐	☐
2 Different from other children	☐	☐	☐	☐	☐	☐	☐
3 Frustrated by dietary restrictions	☐	☐	☐	☐	☐	☐	☐
4 Reluctant to try unfamiliar foods	☐	☐	☐	☐	☐	☐	☐
5 Concerned that he/she will have a reaction to food	☐	☐	☐	☐	☐	☐	☐

Because of food allergy, my child……	**0**	**1**	**2**	**3**	**4**	**5**	**6**
6 Experiences physical distress	☐	☐	☐	☐	☐	☐	☐
7 Experiences emotional distress	☐	☐	☐	☐	☐	☐	☐
8 Has a lack of variety in his/her diet	☐	☐	☐	☐	☐	☐	☐

Because of food allergy, my child has been affected by……..	**0**	**1**	**2**	**3**	**4**	**5**	**6**
9 Receiving more attention than other children of his/her age	☐	☐	☐	☐	☐	☐	☐
10 Having to grow up more quickly than other children of his/her age	☐	☐	☐	☐	☐	☐	☐
11 His/her environment being more restricted than other children of his/her age	☐	☐	☐	☐	☐	☐	☐

Because of food allergy, my child's social environment is restricted because of limitations on……..	**0**	**1**	**2**	**3**	**4**	**5**	**6**
12 Restaurants we can safely go to as a family	☐	☐	☐	☐	☐	☐	☐
13 Holiday destinations we can safely go to as a family	☐	☐	☐	☐	☐	☐	☐

Because of food allergy, my child's ability to take part has been limited……..	**0**	**1**	**2**	**3**	**4**	**5**	**6**
14 In social activities in other people's houses (*sleepovers, parties, playtime*)	☐	☐	☐	☐	☐	☐	☐
15 In preschool/school events involving food (*class parties/treats/lunchtime*)	☐	☐	☐	☐	☐	☐	☐

SECTION B: For children aged 4 to 12 years.

Because of food allergy, my child feels……	**0**	**1**	**2**	**3**	**4**	**5**	**6**
16 Worried when going to unfamiliar places	☐	☐	☐	☐	☐	☐	☐
17 Concerned that he/she must always be cautious about food	☐	☐	☐	☐	☐	☐	☐
18 'Left out' in activities involving food	☐	☐	☐	☐	☐	☐	☐
19 That family social outings have been restricted by the need to plan ahead.	☐	☐	☐	☐	☐	☐	☐
20 Concerned about accidentally eating an ingredient to which he/she is allergic	☐	☐	☐	☐	☐	☐	☐
21 Worried when eating with unfamiliar adults/children	☐	☐	☐	☐	☐	☐	☐
22 Frustrated by social restrictions	☐	☐	☐	☐	☐	☐	☐

Because of food allergy, my child……	**0**	**1**	**2**	**3**	**4**	**5**	**6**
23 Is more apprehensive in general than other children of his/her age	☐	☐	☐	☐	☐	☐	☐
24 Is more cautious in general than other children of his/her age	☐	☐	☐	☐	☐	☐	☐
25 Cannot be as confident as other children of his/her age in social situations	☐	☐	☐	☐	☐	☐	☐
26 Wishes his/her food allergy would go away	☐	☐	☐	☐	☐	☐	☐

SECTION C: For children aged 7 to 12 years

Because of food allergy, my child feels……	**0**	**1**	**2**	**3**	**4**	**5**	**6**
27 Worried about his/her future (opportunities, relationships)	☐	☐	☐	☐	☐	☐	☐
28 Many people do not understand the serious nature of food allergy	☐	☐	☐	☐	☐	☐	☐
29 Concerned by poor labelling on food products	☐	☐	☐	☐	☐	☐	☐
30 Food allergy limits his/her life in general	☐	☐	☐	☐	☐	☐	☐

SECTION D: For all age groups

Food Allergy Independent Measure (FAIM) for children

Items are answered on a 0-6 or 1-7 point response scale as preferred, with a greater score indicating a higher level of perceived risk. Question 4 must be reverse scored before a Total score is calculated.

	How great do you think is the chance that your child	**0**	**1**	**2**	**3**	**4**	**5**	**6**
1	will accidentally eat something to which he/she is allergic?							
2	will have a severe reaction if he/she accidentally eat something to which he/she is allergic?							
3	Will die if he/she eats something to which he/she is allergic?							
4	will effectively manage a reaction or will receive sufficient help from others if a reaction occurs?							

5. How many foods must your child avoid because of food allergy?	6. How much has your child's food allergy limited the type of activities your child can take part in?
☐ almost none	☐ so little he/she doesn't actually notice it
☐ very few	☐ very little
☐ a few	☐ little
☐ some	☐ moderately
☐ many	☐ a good deal
☐ very many	☐ a great deal
☐ almost all	☐ a very great deal

16.6.8 FAQL-PB: Food Allergy Quality of Life - Parental Burden Questionnaire

Food Allergy Quality of Life – Parental Burden Questionnaire (FAQL-PB)

0	1	2	3	4	5	6
not limited	hardly limited at all	somewhat limited	moderately limited	quite a bit limited	very limited	extremely limited

		0	1	2	3	4	5	6
1)	If you and your family were planning a holiday/vacation, how much would your choice of vacation be limited by your child's food allergy?	☐	☐	☐	☐	☐	☐	☐
2)	If you and your family were planning to go to a restaurant, how much would your choice of a restaurant be limited by your child's food allergy?	☐	☐	☐	☐	☐	☐	☐
3)	If you and your family were planning to participate in social activities with others involving food (e.g., parties, holiday, etc) how limited would your ability to participate in social activities that involve food be because of your child's food allergy?	☐	☐	☐	☐	☐	☐	☐

0 not troubled	**1** hardly troubled at all	**2** somewhat troubled	**3** moderately troubled	**4** quite a bit troubled	**5** very troubled	**6** extremely troubled

		0	1	2	3	4	5	6
4)	In the past week, how troubled have you been by your need to spend extra time preparing meals (i.e. label reading, extra time shopping, preparing meals, etc.) due to your child's food allergy?	☐	☐	☐	☐	☐	☐	☐
5)	In the past week, how troubled have you been about your need to take special precautions before going out of the home with your child because of their food allergy?	☐	☐	☐	☐	☐	☐	☐
6)	In the past week, how troubled have you been by anxiety relating to your child's food allergy?	☐	☐	☐	☐	☐	☐	☐
7)	In the past week, how troubled have you been that your child may not overcome their food allergy?	☐	☐	☐	☐	☐	☐	☐
8)	In the past week, how troubled have you been by the possibility of, or actually leaving your child in the care of others because of their food allergy?	☐	☐	☐	☐	☐	☐	☐
9)	In the past week, how troubled have you been by frustration over other's lack of appreciation for the seriousness of food allergy?	☐	☐	☐	☐	☐	☐	☐
10)	In the past week, how troubled have you been by sadness regarding the burden your child carries because of their food allergy?	☐	☐	☐	☐	☐	☐	☐
11)	In the past week, how troubled have you been about your child's attending school, camp, daycare or other group activity with children because of their food allergy?	☐	☐	☐	☐	☐	☐	☐
12)	In the past week, how troubled have you been by your concerns for your child's health because of their food allergy?	☐	☐	☐	☐	☐	☐	☐
13)	In the past week, how troubled with the worry that you will not be able to help your child if they have an allergic reaction to food?	☐	☐	☐	☐	☐	☐	☐

0 not troubled	**1** hardly troubled at all	**2** somewhat troubled	**3** moderately troubled	**4** quite a bit troubled	**5** very troubled	**6** extremely troubled

		0	1	2	3	4	5	6
14)	In the past week, how troubled have you been with the worry that your child will not have a normal upbringing because of their food allergy?	☐	☐	☐	☐	☐	☐	☐
15)	In the past week, how troubled have you been about concerns for your child's nutrition because of their food allergy?	☐	☐	☐	☐	☐	☐	☐
16)	In the past week, how troubled have you been with issues concerning your child being near others while eating because of their food allergy?	☐	☐	☐	☐	☐	☐	☐
17)	In the past week, how troubled have you been with being frightened by the thought that your child will have a food allergic reaction?	☐	☐	☐	☐	☐	☐	☐

16.6.9 SF-36v2 Acute Version Short Form 36-Health Survey Questionnaire v2

SF-36v2® Health Survey Single-Item Acute Recall for Handheld Device

Item Name	Question Text	Answer Text 1	Answer Text 2	Answer Text 3	Answer Text 4	Answer Text 5	Answer Text 6
	Your Health and Well-Being						
	This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Thank you for completing this survey! For each of the following questions, please select the one response that best describes your answer.						
SF36v2_GH1	In general, would you say your health is:	Excellent	Very good	Good	Fair	Poor	
SF36v2_HT	Compared to one week ago, how would you rate your health in general now?	Much better now than one week ago	Somewhat better now than one week ago	About the same as one week ago	Somewhat worse now than one week ago	Much worse now than one week ago	
	The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?						
SF36v2_PF01	Does your health now limit you in vigorous activities, such as running, lifting heavy objects, participating in strenuous sports? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all			
SF36v2_PF02	Does your health now limit you in moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all			
SF36v2_PF03	Does your health now limit you in lifting or carrying groceries? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all			
SF36v2_PF04	Does your health now limit you in climbing several flights of stairs? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all			
SF36v2_PF05	Does your health now limit you in climbing one flight of stairs? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all			
SF36v2_PF06	Does your health now limit you in bending, kneeling, or stooping? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all			
SF36v2_PF07	Does your health now limit you in walking more than a mile? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all			
SF36v2_PF08	Does your health now limit you in walking several hundred yards? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all			
SF36v2_PF09	Does your health now limit you in walking one hundred yards? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all			
SF36v2_PF10	Does your health now limit you in bathing or dressing yourself? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all			
	During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?						

Item Name	Question Text	Answer Text 1	Answer Text 2	Answer Text 3	Answer Text 4	Answer Text 5	Answer Text 6
SF36v2_RP1	During the past week, how much of the time have you cut down on the amount of time you spent on work or other activities as a result of your physical health?	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
SF36v2_RP2	During the past week, how much of the time have you accomplished less than you would like as a result of your physical health?	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
SF36v2_RP3	During the past week, how much of the time were you limited in the kind of work or other activities as a result of your physical health?	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
SF36v2_RP4	During the past week, how much of the time have you had difficulty performing the work or other activities as a result of your physical health (for example, it took extra effort)?	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
	During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?						
SF36v2_RE1	During the past week, how much of the time have you cut down on the amount of time you spent on work or other activities as a result of any emotional problems (such as feeling depressed or anxious)?	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
SF36v2_RE2	During the past week, how much of the time have you accomplished less than you would like as a result of any emotional problems (such as feeling depressed or anxious)?	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
SF36v2_RE3	During the past week, how much of the time have you done work or other activities less carefully than usual as a result of any emotional problems (such as feeling depressed or anxious)?	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
SF36v2_SF1	During the past week, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?	Not at all	Slightly	Moderately	Quite a bit	Extremely	
SF36v2_BP1	How much bodily pain have you had during the past week?	None	Very mild	Mild	Moderate	Severe	Very severe
SF36v2_BP2	During the past week, how much did pain interfere with your normal work (including both work outside the home and housework)?	Not at all	A little bit	Moderately	Quite a bit	Extremely	
	These questions are about how you feel and how things have been with you during the past week. For each question, please give the one answer that comes closest to the way you have been feeling.						

Item Name	Question Text	Answer Text 1	Answer Text 2	Answer Text 3	Answer Text 4	Answer Text 5	Answer Text 6
SF36v2_VT1	How much of the time during the past week did you feel full of life?	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
SF36v2_MH1	How much of the time during the past week have you been very nervous?	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
SF36v2_MH2	How much of the time during the past week have you felt so down in the dumps that nothing could cheer you up?	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
SF36v2_MH3	How much of the time during the past week have you felt calm and peaceful?	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
SF36v2_VT2	How much of the time during the past week did you have a lot of energy?	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
SF36v2_MH4	How much of the time during the past week have you felt downhearted and depressed?	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
SF36v2_VT3	How much of the time during the past week did you feel worn out?	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
SF36v2_MH5	How much of the time during the past week have you been happy?	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
SF36v2_VT4	How much of the time during the past week did you feel tired?	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
SF36v2_SF2	During the past week, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
	How TRUE or FALSE is each of the following statements for you?						
SF36v2_GH2	I seem to get sick a little easier than other people.	Definitely true	Mostly true	Don't know	Mostly false	Definitely false	
SF36v2_GH3	I am as healthy as anybody I know.	Definitely true	Mostly true	Don't know	Mostly false	Definitely false	
SF36v2_GH4	I expect my health to get worse.	Definitely true	Mostly true	Don't know	Mostly false	Definitely false	
SF36v2_GH5	My health is excellent.	Definitely true	Mostly true	Don't know	Mostly false	Definitely false	
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