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Clinical Trial Protocol Title

A three-year, multi-center, double-blind, extension study to evaluate the long-term safety and efficacy of ligelizumab in patients who completed ligelizumab's Phase III studies in food allergy

Clinical Trial Protocol Number: CQGE031G12303B / NCT05678959

Version Number: V02 (Amended Protocol) (Clean)

Compound: QGE031 (ligelizumab)

Brief Title: Long term extension study of ligelizumab in food allergy

Study Phase: III

Sponsor Name: Novartis Pharma AG

Sponsor Address in the EEA: Novartis Pharma AG, Lichtstrasse 35, 4056, Basel Town, Switzerland

Regulatory Agency Identifier Number(s): 2022-502366-25-00 (EU trial number)

Approval Date: 14-Aug-2023 (content final)

Clinical Trial Protocol Template Version 5.0 dated 14-Jan-2022

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Amendment 2 (14-Aug-2023)

Amendment rationale

The protocol is being amended to clarify that the present protocol is dedicated to include only peanut allergic patients from the CQGE031G12301 study. It also clarifies that the duration of the period elapsed since end of treatment in the core study until Day 1 of study CQGE031G12303B will be derived from collected CRF data.

At the time of this amendment, participants have already started transitioning to the extension study in countries with all required approvals in place. These protocol changes are expected to have minimal impact on the study population or results.

Changes to the protocol

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 are non-substantial and do not require IRB/IEC approval prior to implementation.

The changes herein do NOT affect the Informed Consent.

Amendment 1 (25-Jul-2023)

Amendment rationale

The protocol is being amended to emphasize that future protocol amendments will be submitted for approval to update study features, if needed, to account for new study populations from other core studies, for the results of the CQGE031G12301 study once available, and to clarify that there is no placebo arm in the study. Clarification has also been included about the transition of participants from core to extension study in the case of operational delays.

At the time of this amendment, participants have already started transitioning to the extension study in countries with all required approvals in place. These protocol changes are expected to have minimal impact on the study population or results.

Changes to the protocol

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 are non-substantial and do not require IRB/IEC approval prior to implementation.

The changes herein do NOT affect the Informed Consent.

1 Protocol summary

1.1 Summary

Protocol Title:

A three-year, multi-center, double-blind, extension study to evaluate the long-term safety and efficacy of ligelizumab in patients who completed ligelizumab's Phase III studies in food allergy

Brief Title:

Long-term extension study of ligelizumab in food allergy

Purpose

Long-term safety and efficacy

Study Indication /Medical Condition:

Food allergy

Treatment type

Biological (monoclonal antibody)

Study type

Interventional

Objectives and Endpoints:

Table 1-1 Study objectives and endpoints

Objectives	Endpoints
Primary	
To evaluate the long-term safety and tolerability of ligelizumab in participants with food allergy	Overall incidence and exposure-adjusted occurrence rates of treatment-emergent AEs and SAEs
Secondary	
To describe the long-term efficacy of ligelizumab as measured by the tolerance of an allergen food protein during an open-label OFC at scheduled timepoints.	Proportion of participants tolerating a single dose of ≥ 600 mg of peanut protein without dose limiting symptoms during an open label OFC at scheduled timepoints
To assess the safety and tolerability of ligelizumab in all participants who are administered study treatment at home by self-administration or parent/caregiver	Overall incidence and exposure-adjusted occurrence rates of treatment-emergent AEs and SAEs
To assess the long-term impact of ligelizumab on the health related quality of life (HRQoL) of patients with food allergy	Summaries of total scores in the FAQLQ, FAIM and SF-36v2 by age and responder (participants and/or caregiver) at scheduled timepoints

Trial Design:

This is a multi-center, double-blind, 3-year, extension study to evaluate the long-term safety and efficacy of ligelizumab in participants who completed ligelizumab Phase III studies in food allergy. Novartis conducts this study as a basket extension study which enables the participants

from planned multiple Phase III "core" studies to roll over to this extension study (CQGE031G12303B) once the participants have completed a "core" study and agreed to consent to participate in Study CQGE031G12303B.

A subset of participants will also be offered administration of study treatment at home either by the participant him/herself (self-administration) or by parent/caregiver following training at a number of clinic visits.

Brief Summary:

This is an extension study to evaluate the long-term safety and efficacy of ligelizumab in participants who have completed a ligelizumab Phase III study in food allergy. Participants will receive up to 3 years treatment with ligelizumab after which they will enter a follow-up period for 16 weeks. During the study, participants will undergo allergy testing by a Skin Prick Test and Oral Food challenge to test if the treatment is working or not. Accordingly, this study will generate data that should provide guidance relative to the long-term (chronic) use of ligelizumab in food allergic patients in terms of safety, efficacy, pharmaco-dynamics, biomarkers and Quality of Life, and potential discontinuation from treatment.

During the study, treatment will be administered every 4 weeks and while this can take place in the hospital clinic, some participants will be trained to administer study treatment at home by either the participant or parent/caregiver. Participants at home will record administration of the study treatment on a dosing log and return this to the clinic for review.

Table 1-2 Study Treatment and Treatment Form:

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

* Placebo will only be administered alongside the 120mg/1ml dose to protect the dose blinding. There is no placebo arm

Study Duration:

3 years (172 weeks including 16 weeks follow-up)

Treatment Duration:

3 years (Up to 156 weeks)

Visit Frequency:

The visit frequency will be every 4 weeks for those who are administered study treatment in the clinic, and every 12 to 16 weeks for home administration participants, with a phone call every 4 weeks. At week 156, when the study treatment period is complete, all participants will have visits every 4 weeks for follow-up for a period of 16 weeks.

Treatment of interest

Participants will receive ligelizumab treatment allocated in the core study. There is a possibility to discontinue the study treatment in the Maximum Responder (MR) participants who successfully continue "conditional discontinuation of study treatment" (Section 4.1.1). Please refer to the detailed definition of responder status in Table 1-3 (or Table 4-1).

Number of Participants

This study population will consist of participants who have successfully completed ligelizumab Phase III studies in food allergy including (but not limited to) Study CQGE031G12301 (peanut allergy). The expectation is that approximately 550 participants will enroll in this extension study. This extension study will be opened for participants joining from additional QGE031 food allergy trials.

In line with each core study, this extension will involve male and female participants who have successfully completed a core study and are eligible to continue to extension study.

Key Inclusion criteria

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

- Signed informed consent form (ICF) and assent form (where applicable) obtained from the participant/legal representative before study participation. If a minor participant reaches the age of legal majority (as defined by local law), they must be re-consented at the next study visit
- Participants have completed the treatment period in any ligelizumab Phase III studies in food allergy (e.g., Study CQGE031G12301). Please refer to the Section 4.1 for the timing of transition.
- Participants who are willing to adhere to the study visits and procedures, including receiving injections (study treatment) and participating in the OL-OFC (open label oral food challenge)
- Participants who agree to continue avoiding exposure to allergens (per core study) and any other foods they are allergic to throughout this study
- Participants who are able to safely continue into the study as judged by the investigator

Key Exclusion criteria

- Development of a severe or life-threatening episode of an allergic reaction that required intubation and/or ICU admission during the core studies
- Development of a serious adverse event which is suspected to be related to the study treatment judged by the investigator during the core study
- Development of uncontrolled asthma during the core study that could compromise the safety of the participants judged by the investigator
- Development of clinically significant cardiovascular, neurological, and or psychiatric conditions during the core study 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 judged by the investigator

- Participants who failed to comply with the protocol requirements and procedures during the core study, and in the Investigator's opinion they should not participate in this extension study
- Platelets <75,000/ul at EoT of the core study

Treatment Groups:

Ligelizumab 120 mg SC q4w

Ligelizumab 240 mg SC q4w

There is a possibility to discontinue the study treatment in participants who successfully continue "conditional discontinuation of study treatment" (Section 4.1.2).

Data Monitoring/Other Committee:

Yes, Section 10.1.4

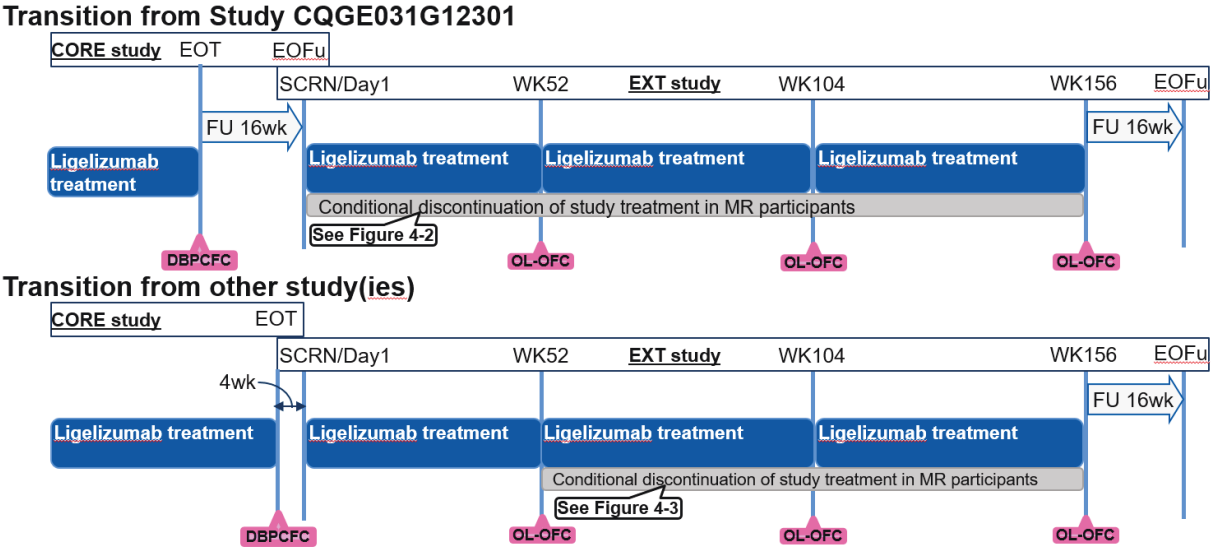
Key words

Food allergy, peanut allergy, oral food challenge, IgE, ligelizumab

1.2 Schema

Participants from Study CQGE031G12301 will enter the extension study after completing the follow-up period of the core study. The participants from other future study(ies) may then enter the extension study immediately after completion of the treatment period of a core study, hence without treatment interruption (Figure 1-1).

Figure 1-1 Study design including transition from the core study



DBPCFC: Double Blind Placebo Controlled OFC, OL-OFC: Open Label Oral Food Challenge, MR: Maximum Responder, EOT: End of Treatment, EOFu: End of Follow-Up.

Transition from Study CQGE031G12301 at the end of the post treatment follow-up period of the core study:

The participants from Study CQGE031G12301 will transition into the extension study after completion of the follow-up period (washout) in the core study. The end of follow-up visit of the core study will become the first visit of this extension study (Screening/Day 1) for these participants. Some of the assessments at EOFu of the core study will form the baseline at Screening/Day 1 in the extension study. The informed consent must be obtained before initiating any study related activities of the extension study at Screening/Day 1.

Transition from other future study(ies) at the end of treatment period of the core study:

The participants from other future study(ies) who complete the study treatment period of the core study and are willing to participate in the extension study will consent to the extension study. The first visit of the extension study (Screening/Day 1) will be scheduled four weeks after the end of the treatment visit of the core study and participants will consent on Screening/Day 1 of the extension study.

Conditional discontinuation of study treatment in the Maximum Responder Participants (See Figure 1-1):

Interruption of treatment until the next OL-OFC to explore the long-term objective of achieving discontinuation of ligelizumab treatment. The detailed process will be described in Section 4.1.2.

Table 1-3 Definition of Maximum Responder based on the DBPCFC/OL-OFC

Responder status	Dose of allergen (food)
Maximum Responder (MR)	Maximum Tolerated Dose (MTD) of CCI . ● Participant WITHOUT Dose Limiting Symptom (DLS) at any dose including the maximum dose, CCI
DBPCFC will be conducted at the end of treatment period of a core study OL-OFC will be conducted during the extension study	

1.3 Schedule of activities (SoA)

The Schedule of Assessments (Table 1-4) lists all of the assessments and when they are performed. All data obtained from these assessments must be supported in the participant's source documentation. The "X" in the table denotes the assessments to be recorded in the clinical database or received electronically from a vendor. The "S" in the table denotes the assessments that are only in the participant's source documentation and do not need to be recorded in the clinical database.

Participants should be seen for all visits/assessments as outlined in the SoA or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. The only remote procedures for this study are the ePRO questionnaires and for a subset of participants the safety phone calls, "at home study drug administration", completion of "Study Drug Dosing Log" and CCI "urine pregnancy test".

Participants who permanently discontinue from study treatment are to complete the end of treatment visit as soon as possible, and attend the follow-up visits as indicated in the SoA. The participants performing conditional discontinuation of study treatment need to visit the clinic for the necessary on site activities such as SPT & OFC, blood collection and safety assessments. Otherwise they will be contacted by the site via phone call every 4 weeks according to the study schedule to monitor safety.

Participants who discontinue from study 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 events and concomitant medications not previously reported must be recorded on the case report form (CRF).

Patient Reported Outcomes (PRO) measure(s) must be completed before any assessments are performed at any given visit.

As per Section 4.5, 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, national and local regulations and depending on operational capabilities, phone calls, virtual contacts (e.g., tele consultation) or visits by site staff/ off-site healthcare professional(s) staff to the participant´s home, can replace certain protocol assessments, for the duration of the disruption until it is safe for the participant to visit the site again. If the Investigator delegates tasks to an 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 1-4 to understand which assessments have to be carried out in what order. This is especially critical for days on when the OFC is carried out: (e.g., Cellular biomarker blood draw has to be done before SPT). Please refer to Table 4-2 for the assessment schedule specific to the participants administering study treatment at home.

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

Please make sure the order of assessments is respected consistently.

Table 1-4 Assessment Schedule

Period	**Extension-Treatment[1]**	**Treatment**																	
Visit Name	**SCRN/Day 1**	**WK 4**	**WK 8**	**WK 12**	**WK 16**	**WK 20**	**WK 24**	**WK 28**	**WK 32**	**WK 36**	**WK 40**	**WK 44**	**WK 48**	**WK 52-OFC**	**WK 56**	**WK 60**	**WK 64**	**WK 68**	**WK 72**	**WK 76**
Weeks	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**68**	**72**	**76**
Days	**1**	**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**	**364**	**392**	**420**	**448**	**476**	**504**	**532**
Informed consent	X																			
Inclusion / Exclusion criteria	X																			
Demography/Medical history	X																			
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications, therapies, procedures		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PRO Completion Reminder													S							
Patient reported outcomes (PROs)	X													approx. 10 days before and 3 days after the OFC						
Physical Examination	S						S							S						S
Electrocardiogram (ECG)	*													X						
Body Weight	X													X						
Body Height	*													S						
Vital Signs	*	X	X	X	X	X	X							X						X
Spirometry in co-morbid asthma only	X													X						
Urine pregnancy test	*	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
Serum Pregnancy test	X[2]																			
Chemistry & Hematology	*						X							X						X
Urinalysis dipstick	*						S							S						
Stool Sample (ova & parasitic test) by local lab	*																			

Period	Extension-Treatment[1]	Treatment																	
Visit Name	SCRN/Day 1	WK 4	WK 8	WK 12	WK 16	WK 20	WK 24	WK 28	WK 32	WK 36	WK 40	WK 44	WK 48	WK 52-OFC	WK 56	WK 60	WK 64	WK 68	WK 72	WK 76
Weeks	1	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	76
Days	1	28	56	84	112	140	168	196	224	252	280	308	336	364	392	420	448	476	504	532
CCI																				
Safety Phone Call[3]		X	X	X	X	X		X	X	X	X	X	X		X	X	X	X	X	
Skin Prick Test[4]	*						X							X						X
Contact IRT (on-site visit)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Treatment Administration[5,6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Treatment Accountability	S	S	S	S	S	S	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
OL-OFC	X[7]						X[8]							X				X[9]		X[8]
Study disposition	X																			

Period	**Treatment**																			
Visit Name	**WK 80**	**WK 84**	**WK 88**	**WK 92**	**WK 96**	**WK 100**	**WK 104-OFC**	**WK 108**	**WK 112**	**WK 116**	**WK 120**	**WK 124**	**WK 128**	**WK 132**	**WK 136**	**WK140**	**WK 144**	**WK 148**	**WK 152**	**WK 156-OFC**
Weeks	**80**	**84**	**88**	**92**	**96**	**100**	**104**	**108**	**112**	**116**	**120**	**124**	**128**	**132**	**136**	**140**	**144**	**148**	**152**	**156**
Days	**560**	**588**	**616**	**644**	**672**	**700**	**728**	**756**	**784**	**812**	**840**	**868**	**896**	**924**	**952**	**980**	**1008**	**1036**	**1064**	**1092**
Informed consent																				
Inclusion / Exclusion criteria																				
Demography/ Medical history																				
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	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
PRO Completion Reminder						S													S	
Patient reported outcomes (PROs)							approx. 10 days before and 3 days after the OFC													approx. 10 days before and 3 days after the OFC
Physical Examination							S						S							S
Electrocardiogram (ECG)							X													X
Body Weight							X													X
Body Height							S													S
Vital Signs							X						X							X
Spirometry in co-morbid asthma only							X													X
Urine pregnancy test	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
Serum Pregnancy test																				
Clinical Chemistry & Hematology							X						X							X
Urinalysis dipstick							S													S
Stool Sample (ova & parasitic test) by local lab																				

Period	Treatment																			
Visit Name	**WK 80**	**WK 84**	**WK 88**	**WK 92**	**WK 96**	**WK 100**	**WK 104-OFC**	**WK 108**	**WK 112**	**WK 116**	**WK 120**	**WK 124**	**WK 128**	**WK 132**	**WK 136**	**WK140**	**WK 144**	**WK 148**	**WK 152**	**WK 156-OFC**
Weeks	**80**	**84**	**88**	**92**	**96**	**100**	**104**	**108**	**112**	**116**	**120**	**124**	**128**	**132**	**136**	**140**	**144**	**148**	**152**	**156**
Days	**560**	**588**	**616**	**644**	**672**	**700**	**728**	**756**	**784**	**812**	**840**	**868**	**896**	**924**	**952**	**980**	**1008**	**1036**	**1064**	**1092**
[redacted]																				
Safety Phone Call[3]	X	X	X	X	X	X		X	X	X	X	X		X	X	X	X	X	X	
Skin Prick Test[4]							X						X							X
Contact IRT (on-site visit)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Treatment Administration[5,6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Treatment Accountability	S	S	S	S	S	S	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
OL-OFC							X				X[9]		X[8]							X
Study disposition																				

Period	**Follow-up**			
Visit Name	**WK 160**	**WK 164**	**WK 168**	**EoS/PSD**
Weeks	**160**	**164**	**168**	**172**
Days	**1120**	**1148**	**1176**	**1204**
Informed consent				
Inclusion / Exclusion criteria				
Demography/ Medical history				
Adverse Events	X	X	X	X
Concomitant medications, therapies, procedures	X	X	X	X
PRO Completion Reminder				
Patient reported outcomes (PROs)				
Physical Examination				S
Electrocardiogram (ECG)				X
Body Weight				
Body Height				
Vital Signs				X
Spirometry in co-morbid asthma only				
Urine pregnancy test				
Serum Pregnancy test				
Clinical Chemistry & Hematology				X
Urinalysis dipstick				S
Stool Sample (ova & parasitic test) by local lab				S
CCI				

Period	**Follow-up**			
Visit Name	**WK 160**	**WK 164**	**WK 168**	**EoS/PSD**
Weeks	**160**	**164**	**168**	**172**
Days	**1120**	**1148**	**1176**	**1204**
CCI				
Safety Phone Call[3]				
Skin Prick Test[4]				X
Contact IRT (on-site visit)				
Study Treatment Administration[5,6]				
Study Treatment Accountability				
Providing rescue medication, counseling, training & accountability	S	S	S	S
OL-OFC				
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] * Assessments collected at last visit of core study
[2] Serum pregnancy test to be done at day 1 visit and thereafter, only in case the Urine pregnancy test is positive, then this assessment must be performed at site.
[3] Only for MR participants when not attending site for SPT, OFC or blood collection
[4] Please check the medications prior to skin prick test.
[5] Depending on the responder status, participants may not receive study treatment at every visit. If participant is a Maximum Responder, they will conditionally discontinue treatment until the next scheduled OFC for Maximum Responders.

Period	**Follow-up**			
Visit Name	**WK 160**	**WK 164**	**WK 168**	**EoS/PSD**
Weeks	**160**	**164**	**168**	**172**
Days	**1120**	**1148**	**1176**	**1204**

[6] For MR participants defined by previous OFC which have changed responder status (no longer MR), the study treatment should be administered at least 24-hours after OFC.
[7] Only for participants transitioning from Study CQGE031G12301 who were MR at DBPCFC at EoT
[8] Ad hoc OL-OFC visits based on the SPT at Weeks 24, 76, 128 (scheduled time points) or prior to Week 104 and/or 156 (unscheduled time points) to allow the Investigator to check the level of desensitization. Investigator may conduct ad hoc OL-OFC in case of positive (or shift from prior assessment) SPT. The same (SPT followed by OL-OFC) is allowed in case of suspected allergic event during the extended wash out. The results of the ad hoc OL-OFC might lead to the resumption of study treatment (same dose as in the core study or in the previous year) for patients currently undergoing conditional discontinuation.
[9] Ad hoc OL-OFC visit for patients who meet the definition of MR at weeks 52 and 104 and have completed a 16-week wash-out period to determine if the study treatment should be restarted.

2 Introduction

In the last years, food allergy is rising worldwide affecting people of all ages and nations, with an increase in prevalence and costs associated with the disease making it an emerging population health priority (Gupta et al 2013, Gupta et al 2019, Warren et al 2020). Recent data demonstrate that between one-third and one-half of food allergy patients, including adults, are likely to be allergic to more than one food (Gupta et al 2019). Among food types, peanut, milk and egg represent a high prevalence of food allergens and the ingestion of even small quantities of the these allergens may lead to a severe and potentially life-threatening allergic reaction (Savage et al 2003, Fair Health White Paper 2017).

The National Institute of Health (NIH) Food Allergy Expert Panel defines food allergy as a specific IgE-mediated adverse reaction to a given food (Boyce et al 2011). 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).

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, 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).

The diagnosis of food allergy begins with the clinical history of immediate allergic symptom(s) after intake of food allergen(s) together with either a combination of skin prick tests (SPT) and/or specific IgE (sIgE). However the predictive rate of this varies ranging from 50% to 100%. Therefore oral food challenge (OFC) which is the current gold standard is required to confirm the diagnosis of food allergy. Because of the potential of outgrowing a food allergy, re-evaluation of tolerance to the food by OFC might be needed and the interval of OFC is dependent on the food allergen, e.g., every 6 – 12 months in milk and egg and every 2 years in peanut (Muraro et al 2014).

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, 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 Food and Drug Administration (FDA) to mitigate allergic reactions during accidental exposure to peanuts

(Jan-2020) and by European Medicines Agency (EMA) for the treatment of peanut allergy (Dec-2020). However, this treatment is not fundamentally changing the unmet medical need in this space, as it is only targeting one allergen; it is indicated only for a subset of age groups and might not be suitable for all peanut allergic patients.

2.1 Study rationale

This is a multi-center, double-blind, 3-year, extension study with a 16 week follow-up period which is designed to establish ligelizumab's long-term safety, and explore its long-term efficacy, in participants with food allergy who have completed the Phase III studies with ligelizumab in food allergy including (but not limited to) Study CQGE031G12301 (peanut allergy). This protocol is designed as a basket extension study, open to the participants from multiple planned Phase III "core" studies in addition to the Study CQGE031G12301**. Of note, the present protocol is dedicated to include only peanut allergic patients from study CQGE031G12301. Future amendments will be submitted for approval to update study features, if needed, before the extension study CQGE031G12303B is opened to participants from future core studies other than study CQGE031G12301**.

This study will generate data that should provide guidance relative to the long-term (chronic) use of ligelizumab in food allergic patients in terms of safety, efficacy, pharmacodynamics (PD), biomarkers, quality of life (QoL), and potential discontinuation from treatment. Indeed some of the important clinical points that this study will explore focus on:

- Longer-term (>1y) sustainability of ligelizumab efficacy
- CCI [redacted]
- Alignment with international guidelines (Muraro et al 2014) that recommend regular assessment of the underlying phenotype including the option to discontinue treatment (further supported by the analysis of the operating characteristics of several biomarkers that strengthen the decision making)
- A subset of participants will also be offered administration of study treatment at home either by the participant him/herself (self-administration) or by parent/caregiver following appropriate training at three visits in the clinic.

In addition, the 3-year treatment period of this study will also fulfill the Novartis commitment to provide post trial access (PTA) to the participants who have completed ligelizumab Phase III studies in food allergy. In case ligelizumab is not commercially available in some countries at completion of this study, every effort will be made to continue provision of ligelizumab for the participants in those countries that in the opinion of the investigator might still benefit from longer treatment with ligelizumab.

2.2 Background

A recognized medical need in developing novel therapies for food allergy is forthcoming due to rising prevalence of food allergy (including allergy to multiple foods) (Sicherer, Sampson 2018), and the limited therapeutic options leading to potentially lifelong disease burden in many patients. 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 have been developed that recognized the IgE binding site 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, 18 Ed.]). CCI [redacted] 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).

During the treatment 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). Omalizumab is the only humanized anti-IgE antibody currently commercially available. Multiple studies suggest it has efficacy in food allergy in reducing the risk of peanut-induced allergic reactions in a double-blind-placebo-controlled food challenge (Sampson et al 2011, Savage et al 2012, Schneider et al 2013).

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, Renard 2011), reduced IgE and B cell numbers (Ota et al 2009) and reduced cytokine production by T cells (Coyle et al 1996).

Consequently, in the ongoing Study CQGE031G12301 (peanut allergy) and planned other food allergy study(ies), it is hypothesized that the very high level of suppression elicited by ligelizumab will result in a very efficient desensitization against the food allergens hence ensuring protection against food allergic reactions by decreasing the sensitivity to those allergens.

2.3 Benefit/Risk assessment

The risks to participants in this study will be minimized by compliance with all of the eligibility criteria including completion of the core study and by close clinical monitoring including periodic review of data by an independent Data Monitoring Committee (DMC). To further minimize risk the study will be conducted in selected highly specialized centers involved in the phase III studies with ligelizumab in food allergy, who have great experience in the treatment of food allergies and in conducting oral food challenges.

Mechanism of action

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. Multiple studies have supported this therapeutic approach (Leung et al 2003, Savage et al 2012, Schneider et al 2013). CCI [redacted] hence supporting its use in food allergy and anticipating a therapeutic benefit (basophil/ mast cell desensitization).

Available safety data

As of the cut-off date of 22-Jan-2022, approximately 2976 participants have been exposed to ligelizumab across completed, prematurely terminated and ongoing studies, covering the indications of Chronic Spontaneous Urticaria (CSU), asthma, atopic dermatitis, and bullous pemphigoid. The longest exposure to ligelizumab is approximately 17 months. The following doses have been tested in the clinical programs: 12 mg, 24 mg, 36 mg, 72 mg, 120 mg, 180 mg and 240 mg subcutaneous (SC) q2w/q4w, 280 mg SC q2w and 240 mg and 420 mg SC single dose.

In the CSU Phase II program, 291 participants have been exposed to ligelizumab at doses up to 72 mg, 120 mg and 240 mg SC q4w ([Investigator Brochure, 18 Ed.]). In addition, in the most recent CSU Phase III program (Studies CQGE031C2302 and CQGE031C2303), a total of 2150 patients (including 93 adolescent patients) received ligelizumab 72 mg, 120 mg, omalizumab 300 mg and placebo. Overall, no apparent dose-dependent safety signals (except for a trend in injection site reactions, which can be managed in the clinic) 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 SC q2w, 240 mg SC q4w, 180 mg SC q2w, and 120 mg SC q2w treatment arms) and ligelizumab low dose group (12.5% of 40 participants, pooled from ligelizumab 36 mg SC q2w and 12 mg SC 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 SC q4w or 120 mg single dose), omalizumab and placebo. The exceptions were adverse

events (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 (Study CQGE031B2201 in asthma and Study 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 are theoretically applicable to the study treatment. CCI [redacted] In all completed studies to date, four cases have been positively adjudicated as anaphylaxis: three in asthma studies and one in a CSU study. Two out of four cases occurred after restart of ligelizumab. 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.

IgE is an antibody that may have an adaptive role in immunity to parasitosis, particularly helminthic infections. Blocking the interaction of IgE and its receptors with ligelizumab may therefore alter immunologic responsiveness to parasites. For this reason, monitoring for the occurrence of infection and response to therapy is recommended for participants who receive ligelizumab and are at high risk of geohelminth infection. There is insufficient data 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.

In the most recent CSU Phase III program (Studies CQGE031C2302 and CQGE031C2303), a total of 2150 patients (including 93 adolescent patients) received ligelizumab 72 mg, 120 mg, omalizumab 300 mg and placebo. Ligelizumab was well-tolerated, consistent with previous studies.

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

The non-clinical safety evaluation for ligelizumab supports the clinical treatment of children down to the age of 2 years. In a juvenile toxicity study that was conducted in 6-month-old cynomolgus monkeys there was no evidence to suggest that ligelizumab will have a different mode of action or will be cleared differently in pediatric versus adult participants. No new or unexpected safety signals were identified in the Study CQGE031C2201 (CSU dose-ranging) study in adults and in the Study CQGE031C2202 (CSU) in adolescents

Study treatments

Transition from the core study:

There are two groups of core study participants that will be enrolled in the extension study:

- from the Study CQGE031G12301, after completion of post treatment follow-up period of the core study (Figure 1-1)
- from other future study(ies) after completion of the treatment period of a core study (Figure 1-1).

For both groups, participants have to maintain strict avoidance of the inciting food(s) and symptomatic (rescue) treatment of allergic symptoms (e.g., epinephrine, antihistamines, corticosteroids and saline bolus) should be available to reduce the risk to the participants.

As the risk of anaphylaxis related to the reintroduction of treatment after the interruption has not yet been characterized in this population, participants who transition to the extension study at the end of the follow-up period of core Study CQGE031G12301 must remain on-site for observation for a period of 2 hour (h) post-dose for the first three visits after drug administration following the reintroduction of study treatment.

Conditional discontinuation of study treatment in Maximum Responder Participants

This study is exploring long-term treatment strategies based on the efficacy levels (responder status) achieved by the participants at the end of the core study and during the extension study.

For the participants who meet the definition of Maximum Responder (MR, see below), the interruption of the study drug will be commenced, and participants will remain off-treatment unless the sensitivity to the food returns based on the results of the OFC (no longer MR). The rest of the participants continue the study treatment throughout the extension study.

- Definition of Maximum Responder (MR)
  - No dose limiting symptom (DLS) at any dose including the maximum dose of OFC, CCI of peanut protein.

A maximum responder (MR) status might reflect either an optimal effect of the investigational drug and/or a change in the underlying phenotype (loss of disease either following natural history or through potential disease modification by the study treatment). In this case, conditional termination will be carried out to assess whether further treatment is still required, as determined by the following OL-OFC. In case of sustained un-responsiveness, the participants will remain in the study without treatment to keep monitoring his/her condition through selected biomarkers. In case of resurgence of the phenotype, participants will be brought back to the study drug dose that led to MR status

- Conditional discontinuation of study treatment is only for the participants who showed maximum response by DBPCFC (EOT of the core study)/OL-OFC (the extension study). Conditional discontinuation will be allowed only once in any given participant through the entire study. After start of the interruption of study treatment, participants will be allowed to re-start treatment in case of clinical (allergic reactions to food) or other findings (e.g., SPT) suggesting of resurgence of the allergic phenotype. Following these indications, the investigator proposes an optional OL-OFC to more formally re-assess the level of reactivity of the participants and decide on reintroduction of study treatment. As the risk of

anaphylaxis related to the reintroduction of treatment after the washout period has not yet been characterized in this population, participants who will restart study treatment must remain on-site for observation for a period of 2 h post-dose for the first three drug administrations.

Study treatment administration at home:

Ligelizumab will be administered using a single-use, disposable combination product, intended for the subcutaneous (SC) application of a fixed dose of ligelizumab. The combination product consists of a pre-filled syringe (PFS) pre-assembled within a needle safety device (NSD) from the Becton Dickinson UltraSafe Passive™ NSD X100L Plus series (hereinafter called QGE031 PFS in X100L Plus). The design and technical features of the QGE031 PFS in X100L Plus combination product are based on well-established technology and are in line with the current common treatment technology for self-injection drugs. It is permitted for adult participants to do self-administration with QGE031 PFS in X100L Plus while children and adolescent participants must be administered QGE031 PFS in X100L Plus by parent/caregiver. Parent/caregiver can also administer QGE031 PFS in X100L Plus to adult participants, if necessary.

Eligibility criteria

The participants in this basket extension study should have successfully completed a core study. Therefore, the participants who developed any condition meeting discontinuation criteria during a core study, AND/OR participants who developed any clinically significant medical condition listed in the exclusion criteria of a core study judged by the investigator, must not be rolled over into this study.

Oral food challenge (OFC)

In this extension study, open-label OFC will be conducted.

OFC is a standard procedure to diagnose the food allergy. OFC has 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, Kim 2019). To further limit the risks associated with this procedure the following measures have been applied:

- Only highly trained experts representing experienced facilities that are equipped and have the expertise to handle potentially life-threatening hypersensitivity events can participate in this study.
- A Data Monitoring Committee (DMC) will monitor the safety in this study including events incurred during OFC. The DMC will review the data generated externally and independently of Novartis according to the DMC charter. Based on the safety implications of the data, the DMC may recommend modification or termination of the study.

Female participants

Female participants of childbearing potential (defined as all females physiologically capable of becoming pregnant which includes female pediatric participants who are menarchal or who

become menarchal during the study) must be informed that taking the study treatment may involve unknown risks to the fetus, if pregnancy were to occur during the study, they must agree that in order to participate in the study they are required to 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 continue in the study. Female children participants who became older than 12 years during the core studies should be reassessed in regards to contraception requirements established in the respective exclusion criterion.

It is important to be sensitive in introducing this issue, as understanding and comprehension of puberty, sexual activity, pregnancy and contraception is influenced by age, as well as factors such as precocity, socio(educational) economic and familial background. These discussions with the patient and her parents/caregivers are therefore best performed by investigators familiar with the pediatric subject and her family and should be guided by requirements of the local regulatory authorities. These discussions should take into account the socio-economic, cultural factors and religious beliefs of the adolescent participant and her family. The investigator should also discuss the management of the pregnancy test results with the patient and her parents/caregivers. The privacy of the patient should be considered in accordance with the local law and ethics.

COVID-19

With respect to the ongoing COVID-19 pandemic, IgE suppression is not expected to increase the risk of infection. (Teach et al 2015). For participants, vaccination against COVID-19 (inactivated, non-live vaccine) is permitted during the study but not administered within 48 h prior to the study visit (Table 6-5).

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 the treatment for allergic reaction. There is an unmet medical need for therapeutic interventions. As the pathophysiology of IgE mediated food allergy is not affected by the age, IgE suppression is expected to provide a benefit in younger patients as well.

The evaluations specified in this study (including SPT and OL-OFC) are clinically accepted and widely used in clinical research that investigates food allergy in adults, adolescents and children. The experience with the OFC is very much established in children where most publications have developed (Nowak-Wegrzyn et al 2009). Blood volume for laboratory evaluations for children 6-11 years is in line with The Hospital for Sick Children (SickKids) Research Ethics Board Blood Sampling Guidelines (Howie 2011), (Section 8.4.4).

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

3 Objectives, endpoints, and estimands

Table 3-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
● To evaluate the long-term safety and tolerability of ligelizumab in participants with food allergy	● Overall incidence and exposure-adjusted occurrence rates of treatment-emergent AEs and SAEs
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
● To describe the long-term efficacy of ligelizumab as measured by the tolerance of an allergen food protein during an open-label OFC at scheduled timepoints	● Proportion of participants tolerating a single dose of ≥ 600 mg of peanut protein without dose-limiting symptoms during an open label OFC at scheduled timepoints
● To assess the safety and tolerability of ligelizumab in all participants who administered study treatment at home by self-administration or parent/caregiver	● Overall incidence and exposure-adjusted occurrence rates of treatment emergent-AEs and SAEs
● To assess the long-term impact of ligelizumab on the health-related quality of life (HRQoL) of patients with food allergy	● Summaries of total scores in the FAQLQ, FAIM, and SF-36v2 by age and responder (participants and/or parent/caregiver) at scheduled timepoints
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**
CCI	

Objective(s)	Endpoint(s)
CCI	

3.1 Primary estimands

Not Applicable.

3.2 Secondary estimands

Not Applicable.

4 Study design

4.1 Overall design

This is a multi-center, double-blind, 3-year, extension study with a 16 week follow-up period, which is designed to establish ligelizumab's long-term safety and tolerability, and to explore its long-term efficacy in participants with food allergy who have completed Phase III studies with ligelizumab in food allergy. Novartis conducts this study as a basket extension study, which enables the participants from planned multiple Phase III "core" studies to roll over to this extension study once the participants have completed predefined minimal requirements (completion of a treatment or a follow-up period, see Section 4.1.1) of a "core" study and agreed to consent to participate in this study.

Participants will receive ligelizumab treatment allocated in the core study, except for MR participants performing conditional discontinuation of study treatment. CCI

A subset of participants will also be offered administration of study treatment at home either by the participant him/herself (self-administration) or by parent/caregiver following training at three visits at the clinic (Section 4.1.3).

4.1.1 Transition from the core study

Transition from Study CQGE031G12301 at the end of follow-up period:

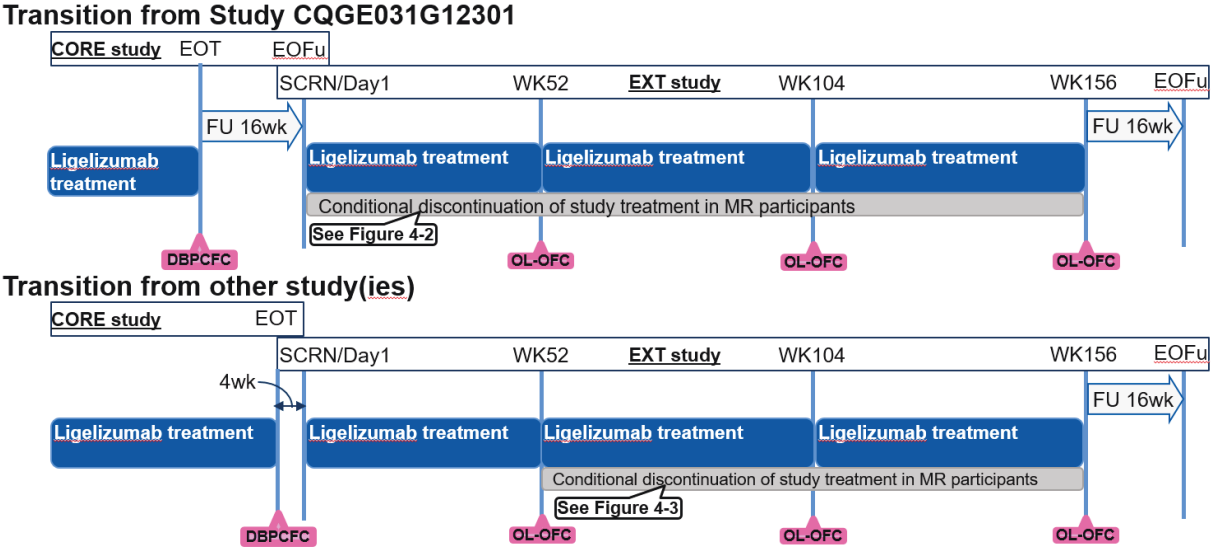
The participants will transition into the extension study after completion of the follow-up period (washout) in the core study (see Figure 4-1). CCI The end of follow-up

visit of the core study will also become the first visit of this extension study (Screening/Day 1). Some of the assessments at EOFu of the core study will form the baseline at Screening/Day 1 of the extension study. The informed consent must be obtained before initiating any study related activities of the extension study at Screening/Day 1.

Transition from other study(ies) at end of treatment period of core study (no post treatment follow-up period):

The participants will transition into the extension study after completion of the study treatment period of the core study. The first visit of the extension study (Screening/Day 1) will be scheduled four weeks after the end of the treatment visit of the core study and participants will consent on Day 1 of the extension study.

Figure 4-1 Study design including transition from the core study



DBPCFC: Double Blind Placebo Controlled OFC, OL-OFC: Open Label Oral Food Challenge, MR: Maximum Responder, EOT: End of Treatment, EOFu: End of Follow-Up.

Should operational reasons prevent timely scheduling of Day 1 during transition from any core study, participants may still be eligible to be included in the extension study based on a case by case assessment as long as all inclusion and exclusion criteria are fulfilled at the time of the assessment.

The duration of period elapsed since the end of treatment in the core study until Day 1 of study CQGE031G12303B will be derived from collected CRF data.

4.1.2 Conditional discontinuation of study treatment in Maximum Responder Participants

In some participants the study treatment might no longer be required because of disease modification by ligelizumab and/or by simply outgrowing the allergy (Savage, Johns 2015). Therefore, conditional discontinuation of study drug is started in all participants whose responder status is MR (maximum responder) as shown in Figure 4-2 (for the participants from

Study CQGE031G12301 who transition at EOFu of the core study and Figure 4-3 for the participants from other study(ies) who transition at End of Treatment (EoT) of the core study).

For the participants who meet the definition of Maximum Responder (MR, see below), the interruption of the study drug will be commenced and participants will continue off-treatment, unless the sensitivity to the food returns based on the OFC (no longer MR).

The detailed process of the treatment for the MR participants is summarized in the Section 4.1.2.1.

This conditional discontinuation of study drug will be controlled by Interactive Response Technology (IRT) which informs the investigator about the treatment/off-treatment in each participant based on the outcome from DBPCFC (at EoT of a core study) / OL-OFC (in the extension study).

Table 4-1 Maximum Responder during the DBPCFC/OL-OFC

Responder status	Dose of allergen (food)
Maximum Responder (MR)	Maximum Tolerated Dose (MTD) of [redacted] ● Participant WITHOUT Dose Limiting Symptom (DLS) at any dose including the maximum dose, [redacted]
DBPCFC will be conducted at the end of treatment period of the core study OL-OFC will be conducted during the extension study	

4.1.2.1 Detailed process for study treatment and conditional discontinuation of study treatment in MR participants

The conditional discontinuation of study treatment can only be performed once. In other words, if following study treatment interruption, the MR responder status is not confirmed at the next OFC, the study treatment should be restarted and continue until the end of treatment (Week 156), (unless participants are permanently discontinued from study treatment earlier see Section 7.1).

The processes of study treatment and conditional discontinuation of study treatment in the first, second and third year of the extension study are summarized below.

The participants who transition from Study CQGE031G12301 (Figure 4-2)

First year

- Participants who meet the definition of MR by DBPCFC at EoT of the core study and transition from the core study at EOFu will perform an OL-OFC at Screening/Day 1:
  - If the participants still meet the definition of MR by OL-OFC on Day 1, the off-treatment period will be continued until Week 52.
  - If the participants are no longer MR by OL-OFC on Day 1, the study treatment will be started (same dose as in the core study) after at least 24 h from completion of the OL-OFC on Day 1. If participants become MR again at a later timepoint, no interruption of treatment is commenced. The study treatment will continue until the EoT of the extension study (Week 156).
- NOTE: The Investigator is able to check the level of desensitization by SPT at Week 24 (scheduled time point) and can decide to conduct ad hoc OL-OFC in case of positive (or

shift from prior assessment) SPT. The same (SPT followed by OL-OFC) is allowed in case of suspected allergic event during the off-treatment period. The results of the ad hoc OL-OFC may lead to the resumption of study treatment (same dose as in the core study) after at least 24 h from completion of the OL-OFC and treatment will continue until the EoT of the extension study (Week 156).

- Participants who did not meet the definition of MR by DBPCFC at EoT of the core study and transition from the core study at EOFu will not perform an OL-OFC at Screening/Day 1. Study treatment will be started (same dose as in the core study) until week 52.

Second year:

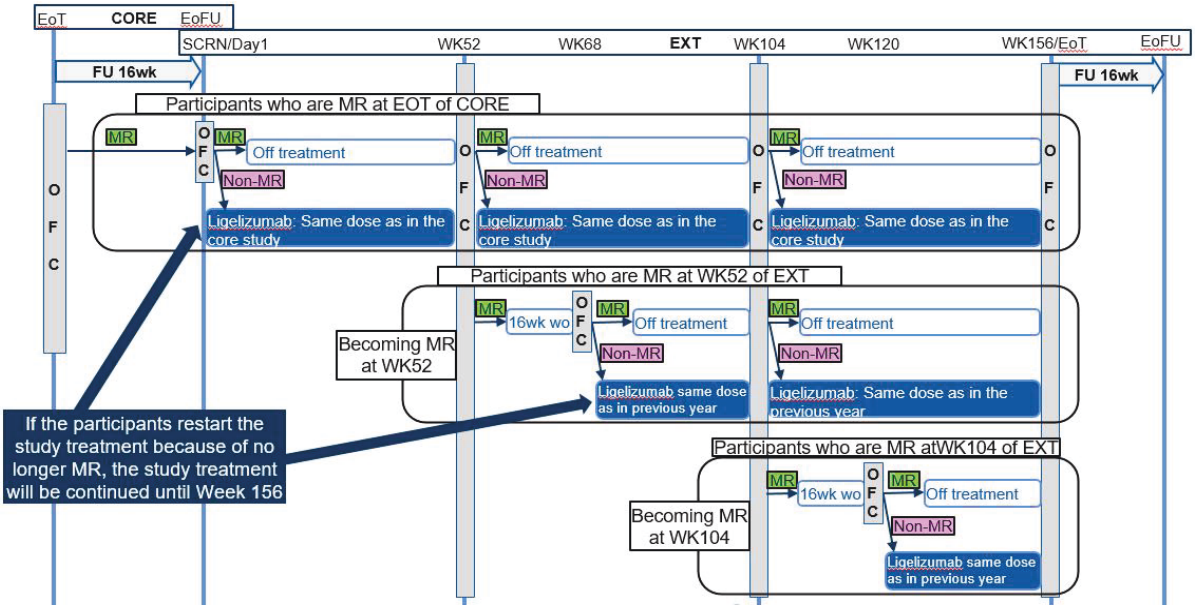
- For participants who have been off-treatment in the first year until Week 52 (i.e., MR participants since Day 1):
  1. If the participants still meet the definition of MR by OL-OFC at Week 52, the off-treatment period will continue up to Week 104 of the extension study.
  2. If the participants are no longer MR by OL-OFC at Week 52, the study treatment will be re-started (same dose as in the core study) after at least 24 h from completion of the OL-OFC. If the participants become MR again at a later timepoint, no interruption of treatment is commenced. The study treatment will continue until the EoT of the extension study (Week 156).
- NOTE: The Investigator is able to check the level of desensitization by SPT at Week 76 (scheduled time point) and can decide to conduct an ad hoc OL-OFC in case of positive (or shift from prior assessment) SPT. The same (SPT followed by OL-OFC) is allowed in case of a suspected allergic event during the off-treatment period. The results of the ad hoc OL-OFC may lead to the resumption of study treatment (at the same dose as in the core study) after at least 24 h from completion of the OL-OFC, and treatment will continue until the EoT of the extension study (Week 156).
- For participants who have received the study treatment in the first year until Week 52 (i.e., participants who did not have OL-OFC at Screening/Day 1):
  1. If the participants meet the definition of MR by OL-OFC at Week 52, the interruption of study treatment (off-treatment) will be initiated.
     - If the participants still meet the definition of MR by OL-OFC after 16 weeks of study treatment interruption (at Week 68), the interruption (off-treatment) period will be extended up to Week 104.
     - If the participants are no longer MR by OL-OFC after 16 weeks of study treatment interruption (at Week 68), the study treatment will be re-started (same dose as in previous year) after at least 24 h from completion of the OL-OFC. If the participants become MR again at a later timepoint, no interruption of treatment is commenced. The study treatment will continue until the EoT of the extension study (Week 156).
- NOTE: The investigator is able to check the level of desensitization by SPT at an unscheduled time point prior to Week 104, and the results of the ad hoc OL-OFC may lead to the resumption of study treatment (same dose as taken previously) after at least 24 h from completion of the OL-OFC and treatment will continue until the EoT of the extension study (Week 156).

- If the participants do not meet the definition of MR by OL-OFC at Week 52, the study treatment will be continued (same dose as in the previous year) until Week 104.

Third year:

- For participants who have been off-treatment in the second year until Week 104:
  1. If the participants meet the definition of MR by OL-OFC at Week 104, the off-treatment period will continue up to Week 156.
  2. If the participants are no longer MR by OL-OFC at Week 104, the study treatment will be re-started (same dose as in previous year) after at least 24 h from completion of the OL-OFC. The study treatment will continue until the EoT of the extension study (Week 156).
- NOTE: The Investigator is able to check the level of desensitization by SPT at Week 128 (scheduled time point) and can decide to conduct an ad hoc OL-OFC in case of positive (or shift from prior assessment) SPT. The same (SPT followed by OL-OFC) is allowed in case of suspected allergic event during the off-treatment period. The results of the ad hoc OL-OFC may lead to the resumption of study treatment (same dose as in core or previous year) after at least 24 h from completion of the OL-OFC, and treatment will continue until the EoT of the extension study (Week 156).
- For participants who have received the study treatment continuously until Week 104:
  - If the participants meet the definition of MR by OL-OFC at Week 104, the off-treatment period will be initiated (unless the participants met MR earlier and already had treatment interruption, in which case treatment continues with the same dose).
    1. If the participants still meet the definition of MR by OL-OFC after 16 weeks of study treatment interruption (at Week 120), the off-treatment period will be extended up to Week 156.
    2. If the participants are no longer MR by OL-OFC after 16 weeks of study treatment interruption (at Week 120), the study treatment will be re-started (same dose as in previous year) after at least 24 h from completion of the OL-OFC. The study treatment will continue until the EoT of the extension study (Week 156).
- NOTE: The investigator is able to check the level of desensitization by SPT at an unscheduled time point prior to Week 104, and the results of the ad hoc OL-OFC may lead to the resumption of study treatment (same dose as previously) after at least 24 h from completion of the OL-OFC, and treatment will continue until the EoT of the extension study (Week 156).
  - If the participants do not meet the definition of MR by OL-OFC at Week 104, the study treatment will be continued (same dose as in previous year) until Week 156.

Figure 4-2 Conditional discontinuation for the MR participants who transition from Study CQGE031G12301



The participants who transition from other study(ies) (Figure 4-3)

First year:

No conditional discontinuation is allowed even if the participants meet the definition of MR by DBPCFC at EoT of the core study. The first visit of the extension study (Screening/Day 1) will be scheduled 4 weeks after EoT of the core study, and the study treatment will be continued (same dose as in the core study) for the first year of extension study.

Second year:

- If the participants meet the definition of MR by OL-OFC at Week 52 of the extension study, the interruption of study treatment (off-treatment) will be initiated:
  1. If the participants still meet the definition of MR by OL-OFC after 16 weeks of study treatment interruption (at Week 68), the interruption (off-treatment period) will be extended up to Week 104.
  2. If the participants are no longer MR by OL-OFC after 16 weeks of interruption (at Week 68), the study treatment will be re-started (same dose as in previous year) after at least 24 h from completion of the OL-OFC. If the participants become MR again at a later timepoint, no interruption is commenced. The study treatment will continue until the EoT of the extension study (Week 156).
- NOTE: The Investigator is able to check the level of desensitization by SPT at an unscheduled time point prior to Week 104 and can decide to conduct ad hoc OL-OFC in case of positive (or shift from prior assessment) SPT. The same (SPT followed by OL-OFC) is allowed in case of suspected allergic event during the off-treatment period. The results of the ad hoc OL-OFC may lead to the resumption of study treatment (same dose as in the core

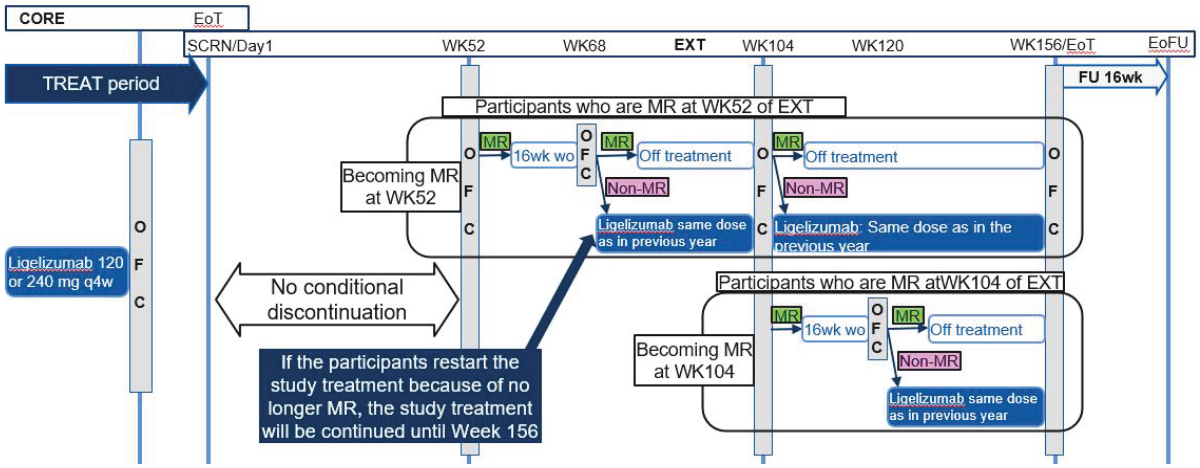
study) after at least 24 h from completion of the OL-OFC, and treatment will continue until the EoT of the extension study (Week 156).

- If the participants do not meet the definition of MR by OL-OFC at Week 52, the study treatment will be continued (same dose as in previous year) until Week 104.

Third year:

- For participants who have been off-treatment in the second year until Week 104
  1. If the participants meet the definition of MR by OL-OFC at Week 104, the off-treatment period will continue up to Week 156.
  2. If the participants are no longer MR by OL-OFC at Week 104, the study treatment will be re-started (same dose as in previous year) after at least 24 h from completion of the OL-OFC. The study treatment will continue until the EoT of the extension study (Week 156).
- NOTE: The Investigator is able to check the level of desensitization by SPT at an unscheduled time point prior to Week 156 and can decide to conduct ad hoc OL-OFC in case of positive (or shift from prior assessment) SPT. The same (SPT followed by OL-OFC) is allowed in case of suspected allergic event during the off-treatment period. The results of the ad hoc OL-OFC may lead to the resumption of study treatment (same dose as in previous year) after at least 24 h from completion of the OL-OFC. The study treatment will continue until the EoT of the extension study (Week 156).
- For participants who have received the study treatment continuously until Week 104
  - If the participants meet the definition of MR by OL-OFC at Week 104, the interruption of study treatment (off-treatment period) will be initiated.
    1. If the participants still meet the definition of MR by OL-OFC after 16 weeks of the study treatment interruption (at Week 120), the interruption (off-treatment period) will be extended up to Week 156.
    2. If the participants are no longer MR by OL-OFC after 16 weeks of interruption (at Week 120), the study treatment will be re-started (same dose as in previous year) after at least 24 h from completion of the OL-OFC. The study treatment will continue until the EoT of the extension study (Week 156).
- NOTE: The Investigator is able to check the level of desensitization by SPT at an unscheduled time point prior to Week 156 and can decide to conduct ad hoc OL-OFC in case of positive (or shift from prior assessment) SPT. The same (SPT followed by OL-OFC) is allowed in case of suspected allergic event during the extended washout. The results of the ad hoc OL-OFC may lead to the resumption of study treatment (same dose as in previous year) after at least 24 h from completion of the OL-OFC. The study treatment will continue until the EoT of the extension study (Week 156).
  - If the participants do not meet the definition of MR by OL-OFC at Week 104, the study treatment will be continued (same dose as in previous year) until Week 156.

Figure 4-3 Conditional discontinuation for the MR participants who transition from other studies



4.1.3 Administration of study treatment at home

This study will also assess the safety of ligelizumab administered in the home setting by either the adult participant (self-administration) or parent/caregiver (in case of adolescent and children) during the extension study.

There are several potential benefits associated with home administration of medication (including self-administration) (Richardson et al 2014):

- it reduces the burden and cost on patients, caregivers, healthcare professionals and the overall health care systems
- it improves patients' knowledge about the disease and medication, and increases sense of responsibility and independence of managing their condition
- the sense of ownership may decrease the chance of medication errors
- a better compliance leading to improved effectiveness of disease management

Participants or parents/caregivers are asked if they are interested in administration in the home setting. Participants or parents/caregivers will undergo required training at three clinic visits under supervision of the site personnel. After undergoing 3 consecutive training visits at the site, participants will then be provided with medication kits to permit their first administration at home. The administration of study treatment at home may take any of the following forms (see Section 6.2.3):

- adult participant: appropriately trained and aware of the responsibility relating to the injection procedure of the study treatment;
- adult participant's parent/caregiver: in case an adult participant is not able to perform the procedure, an adult participant's parent/caregiver appropriately trained by the site can take responsibility for the injection procedure of the study treatment to the adult participant;
- adolescent (12 - 17 years)/child (6 - 11 years) participant: adult parent/caregiver appropriately trained by site, takes complete responsibility for the injection procedure of the study treatment to the adolescent/child participant.

The importance of study treatment administration at home in this Phase III extension study in addition to the benefits detailed above, will:

- allow evaluation of the safety of administration at home of ligelizumab in the treatment for food allergy over a long period of time
- reduce the burden required for participants to make on-site visits, with all the associated benefits described above.

Administration at home will be commenced in the first year of the study in the non MR participants who transition at the end of follow-up period of the core study as well as non MR participants who transition at the end of treatment period of other studies. For those participants, who started the home-administration in year 1 and continue the treatment in years 2 and 3, they will be able to continue the administration at home for the remainder of the study.

It will be possible to start the administration at home also in the second/third year for participants no longer MR at the end of first/second year or in participants who express the interest in administration at home after the first/second year of treatment.

The detailed process of administration at home is written in Section 6.2.3.

Rationale for starting points of administration at home

To allow sufficient training to participant or parent/caregiver on the use of pre-filled syringe (PFS), training will commence at Week 16 and thereafter take place at Weeks 20 and 24. The first self-administration outside the clinic could start at Week 28 of the extension treatment period. However, if the investigator feels it is in the best interest of the participant, they can defer the training until a suitable timepoint, in agreement with the site staff and participant. In addition, before start of training, the clinical data of the participants who will be administered at home should be frozen in the electronic data capture (EDC) system (confirmed by Novartis Data Management) so that the blinded data of the core study can be protected despite potential un-blinding occurring during the administration at home without "unblinded" administrator.

For participants starting the administration at home after the first/second year the training visits will be:

- **after first year:** training at weeks 56, 60 and 64 with the first administration at home on week 68
- **after second year:** training at weeks 108, 112 and 116 with the first administration at home on week 120

Table 4-2 Home Administration Assessment Schedule

Period	**Screening-Treatment**	**Treatment**																	
Visit Name	**SCRN/Day 1**	**WK 4**	**WK 8**	**WK 12**	**WK 16**	**WK 20**	**WK 24**	**WK 28**	**WK 32**	**WK 36**	**WK 40**	**WK 44**	**WK 48**	**WK 52-OFC**	**WK 56**	**WK 60**	**WK 64**	**WK 68**	**WK 72**	**WK 76**
Week	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**68**	**72**	**76**
Days	**1**	**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**	**364**	**392**	**420**	**448**	**476**	**504**	**532**
Informed consent	X																			
Inclusion / Exclusion criteria	X																			
Demography/ Medical history	X																			
Adverse Events	*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications, therapies, procedures		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 / 3 days after OFC						
Physical Examination	S						S							S						S
ECG	*													X						
Body Weight	X													X						
Body Height	*													S						
Vital Signs	*	X	X	X	X	X	X							X						X
Spirometry in co-morbid asthma only	X													X						
Urine pregnancy test[2]	*	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S

Period	**Screening-Treatment**	**Treatment**																	
Visit Name	**SCRN/Day 1**	**WK 4**	**WK 8**	**WK 12**	**WK 16**	**WK 20**	**WK 24**	**WK 28**	**WK 32**	**WK 36**	**WK 40**	**WK 44**	**WK 48**	**WK 52-OFC**	**WK 56**	**WK 60**	**WK 64**	**WK 68**	**WK 72**	**WK 76**
Week	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**68**	**72**	**76**
Days	**1**	**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**	**364**	**392**	**420**	**448**	**476**	**504**	**532**
Serum Pregnancy test	X[3]																			
Chemistry & Hematology	*						X							X						X
Urinalysis dipstick	*						S							S						
Stool Sample (ova & parasitic test) by local lab	*																			
CCI																				
Skin Prick Test[4]	*						X							X						X
Contact IRT							X			X				X			X			X
Home Administration Training					X	X	X								X[5]	X[5]	X[5]			

Period	**Screening-Treatment**	**Treatment**																	
Visit Name	**SCRN/Day 1**	**WK 4**	**WK 8**	**WK 12**	**WK 16**	**WK 20**	**WK 24**	**WK 28**	**WK 32**	**WK 36**	**WK 40**	**WK 44**	**WK 48**	**WK 52-OFC**	**WK 56**	**WK 60**	**WK 64**	**WK 68**	**WK 72**	**WK 76**
Week	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**68**	**72**	**76**
Days	**1**	**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**	**364**	**392**	**420**	**448**	**476**	**504**	**532**
Study Drug Administration (on-site)	X	X	X	X	X	X	X			X				X[6]			X			X
Dispense Home Administration Dosing Log							S													
Study Drug Administration (at home)								X	X		X	X	X		X	X		X	X	
Safety Phone Call (at home)								X	X		X	X	X		X	X		X	X	
Study Drug Accountability	S	S	S	S	S	S	S			S				S			S			S
Review Home Administration Dosing Log										X				X			X			X
Providing rescue medication, counseling, training & accountability	S	S	S	S	S	S	S			S				S			S			S
OL-OFC	X[7]													X						
CCI																				
Study disposition	X																			

Period		**Treatment Period**																		
Visit Name	**WK 80**	**WK 84**	**WK 88**	**WK 92**	**WK 96**	**WK 100**	**WK 104-OFC**	**WK 108**	**WK 112**	**WK 116**	**WK 120**	**WK 124**	**WK 128**	**WK 132**	**WK 136**	**WK140**	**WK 144**	**WK 148**	**WK 152**	**WK 156-OFC**
Weeks	**80**	**84**	**88**	**92**	**96**	**100**	**104**	**108**	**112**	**116**	**120**	**124**	**128**	**132**	**136**	**140**	**144**	**148**	**152**	**156**
Days	**560**	**588**	**616**	**644**	**672**	**700**	**728**	**756**	**784**	**812**	**840**	**868**	**896**	**924**	**952**	**980**	**1008**	**1036**	**1064**	**1092**
Informed consent																				
Inclusion / Exclusion criteria																				
Demography/ Medical history																				
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	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)							approx. 10 days before and 3 days after the OFC													approx. 10 days before and 3 days after the OFC
Physical Examination							S						S							S
Electrocardiogram (ECG)							X													X
Body Weight							X													X
Body Height							S													S
Vital Signs							X						X							X

Period		**Treatment Period**																		
Visit Name	**WK 80**	**WK 84**	**WK 88**	**WK 92**	**WK 96**	**WK 100**	**WK 104-OFC**	**WK 108**	**WK 112**	**WK 116**	**WK 120**	**WK 124**	**WK 128**	**WK 132**	**WK 136**	**WK140**	**WK 144**	**WK 148**	**WK 152**	**WK 156-OFC**
Weeks	**80**	**84**	**88**	**92**	**96**	**100**	**104**	**108**	**112**	**116**	**120**	**124**	**128**	**132**	**136**	**140**	**144**	**148**	**152**	**156**
Days	**560**	**588**	**616**	**644**	**672**	**700**	**728**	**756**	**784**	**812**	**840**	**868**	**896**	**924**	**952**	**980**	**1008**	**1036**	**1064**	**1092**
Spirometry in co-morbid asthma only							X													X
Urine pregnancy test[2]	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
Serum Pregnancy test																				
Clinical Chemistry & Hematology							X						X							X
Urinalysis dipstick							S													S
Stool Sample (ova & parasitic test) by local lab																				

CCI

Period		**Treatment Period**																		
Visit Name	**WK 80**	**WK 84**	**WK 88**	**WK 92**	**WK 96**	**WK 100**	**WK 104-OFC**	**WK 108**	**WK 112**	**WK 116**	**WK 120**	**WK 124**	**WK 128**	**WK 132**	**WK 136**	**WK140**	**WK 144**	**WK 148**	**WK 152**	**WK 156-OFC**
Weeks	**80**	**84**	**88**	**92**	**96**	**100**	**104**	**108**	**112**	**116**	**120**	**124**	**128**	**132**	**136**	**140**	**144**	**148**	**152**	**156**
Days	**560**	**588**	**616**	**644**	**672**	**700**	**728**	**756**	**784**	**812**	**840**	**868**	**896**	**924**	**952**	**980**	**1008**	**1036**	**1064**	**1092**
CCI																				
Skin Prick Test[4]							X						X							X
Contact IRT			X				X			X			X			X				X
Home Administration Training								X[5]	X[5]	X[5]										
Study Treatment Administration (on-site)			X				X[6]			X			X			X				X[6]
Dispense Home Administration Dosing Log																				
Study Treatment Administration (at home)	X	X		X	X	X		X	X		X	X		X	X		X	X	X	
Safety Phone Call (at home)	X	X		X	X	X		X	X		X	X		X	X		X	X	X	
Study Treatment Accountability			S				S			S			S			S				S
Review Home Administration Dosing Log			X				X			X			X			X				X
Providing rescue medication, counseling, training & accountability			S				S			S			S			S				S

Period		Treatment Period																		
Visit Name	**WK 80**	**WK 84**	**WK 88**	**WK 92**	**WK 96**	**WK 100**	**WK 104-OFC**	**WK 108**	**WK 112**	**WK 116**	**WK 120**	**WK 124**	**WK 128**	**WK 132**	**WK 136**	**WK140**	**WK 144**	**WK 148**	**WK 152**	**WK 156-OFC**
Weeks	**80**	**84**	**88**	**92**	**96**	**100**	**104**	**108**	**112**	**116**	**120**	**124**	**128**	**132**	**136**	**140**	**144**	**148**	**152**	**156**
Days	**560**	**588**	**616**	**644**	**672**	**700**	**728**	**756**	**784**	**812**	**840**	**868**	**896**	**924**	**952**	**980**	**1008**	**1036**	**1064**	**1092**
OL-OFC							X													X
CCI																				
Study disposition																				

Period	Follow-up			
Visit Name	**WK 160**	**WK 164**	**WK 168**	**EOS/PSD**
Weeks	**160**	**164**	**168**	**172**
Days	**1120**	**1148**	**1176**	**1204**
Informed consent				
Inclusion / Exclusion criteria				
Demography/ Medical history				
Adverse Events	X	X	X	X
Concomitant medications, therapies, procedures	X	X	X	X
Patient reported outcomes (PROs)				
Physical Examination				S
Electrocardiogram (ECG)				X
Body Weight				
Body Height				
Vital Signs				X
Spirometry in co-morbid asthma only				
Urine pregnancy test[2]				

Period	**Follow-up**			
Visit Name	**WK 160**	**WK 164**	**WK 168**	**EOS/PSD**
Weeks	**160**	**164**	**168**	**172**
Days	**1120**	**1148**	**1176**	**1204**
Serum Pregnancy test				
Clinical Chemistry & Hematology				X
Urinalysis dipstick				S
Stool Sample (ova & parasitic test) by local lab				S
CCI				
Skin Prick Test[4]				X
Contact IRT				
Home Administration Training				
Study Treatment Administration (on-site)				
Dispense Home Administration Dosing Log				
Study Treatment Administration (at home)				
Safety Phone Call (at home)	X		X	

Period	**Follow-up**			
Visit Name	**WK 160**	**WK 164**	**WK 168**	**EOS/PSD**
Weeks	**160**	**164**	**168**	**172**
Days	**1120**	**1148**	**1176**	**1204**
Study Treatment Accountability				
Review Home Administration Dosing Log				
Providing rescue medication, counseling, training & accountability	S	S	S	S
OL-OFC				
CCI				
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] * Assessments collected at last visit of Core Study.

[2] Urine pregnancy tests will be provided to all self-administration patients who are women of child-bearing age, for home use. In the event that the home test is positive, the patient must call site and arrange for an immediate visit to perform a serum pregnancy test.

[3] Serum pregnancy test to be done at day 1 visit and thereafter, only in case the Urine pregnancy test is positive, then this assessment must be performed at site.

[4] Please check the medications prior to skin prick test.

[5] This training only applies to patients who started treatment after the first/second year of treatment.

[6] Study drug must be administered on site at least one hour before OFC.

[7] Only for participants transitioning from CORE Study QGE031G12301 who were MR at DBPCFC at EoT.

4.2 Scientific rationale for study design

The current standard of care for the patients with food allergy is strict avoidance of the inciting food(s) and symptomatic treatment of allergic symptoms (e.g., epinephrine and antihistamines). Anti-IgE medication is not currently indicated for the prevention of allergic events in patients with food allergy and there is limited knowledge and experience in the clinical research setting.

Ligelizumab is an investigational treatment aimed at the protection of patients against allergic reactions due to an accidental exposure to the allergen(s). Therefore it is important to understand the long-term safety and efficacy of ligelizumab in food allergy.

Table 4-3 Rationale for study design

Study Design Aspect	Rationale
Overall	This Phase III extension study of ligelizumab is designed to build on ongoing study data by further evaluating long-term (3 years) safety and efficacy in the participants who have completed the treatment period of the ligelizumab food allergy Phase III studies.
Randomization	No randomization for the study treatment will occur. The participants in this extension study will receive the same dose as in the core studies.
Blinding	The purpose of double-blind design in this extension study is to protect the blinding of data in the core studies. The participants from the core studies will not be unblinded in order to enter this extension study.
Population	The participants who have completed the treatment period of the core studies are considered suitable to continue the study treatment in this extension study from an ethical and safety perspective.
Duration of study periods	Long-term safety data of ligelizumab is critical in food allergy patients and to assess the sustainability of the effect of the clinical response. As described in the earlier section, the exploration of efficacy in ligelizumab based on the “response driven approach” is planned in this study (e.g., conditional discontinuation of study treatment in the maximum responder participants). The long-term safety and efficacy data of ligelizumab could support the practicing physician's treatment plan for the management of food allergy patients with ligelizumab. In addition, the extended duration of treatment in this study will support Novartis' commitment to Post Trial Access (PTA) for participants completing Phase III studies.
Administration at home	There are several potential benefits associated with home self-administration of medication (Richardson et al 2014): In this study protocol, the term "administration at home" refers to the process by which the study treatment is administered to the participants in the home setting outside of the clinic. Self-administration is allowed only for adult participants. If adult participants do not want to self-administer, the parent/caregiver of adult participants can administer the study treatment to the adult participants. In the participants aged 6 to 17 years, self-administration is NOT allowed, and trained parent/caregiver will administer study treatment to the participants aged 6 to 17 years. The data collected will be used to evaluate the safety of ligelizumab in the participants who express interest in the administration of the study treatment at home and fulfill the suitability requirements.

4.2.1 Participant input into design

There was engagement with a Food Allergy Advocacy group composed of parents and parents/caregivers.

They provided some feedback on study design. They welcomed the opportunity for the administration of the study treatment at home. In addition they welcomed frequent contact at home by their study doctor or study site personnel during administration at home in case they had questions or anything to report. Participants and parents/caregivers also expressed interest in having a dosing log to record their medication.

4.3 Justification for dose

The same ligelizumab doses and regimen used in the core studies will be evaluated in this extension study. CCI [redacted]

4.3.1 Rationale for choice of background therapy

Strict avoidance of the inciting food(s) and symptomatic treatment of allergic symptoms with epinephrine, anti-histamines and corticosteroids represent the current standard of care. No other anti-IgE medication is currently indicated for the prevention of allergic events in food allergy patients. In addition, oral immunotherapy is currently only approved for peanut, in a limited age group and in few geographies.

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

Not applicable.

4.5 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. At the investigator's direction based on benefit-risk considerations of the participant's clinical condition, qualifying participants may be offered the option to have certain clinical trial procedures according to SoA performed at a remote location such as the patient's home, in the event that the patient cannot attend site during a public health emergency. 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.

4.6 Purpose and timing of interim analyses/design adaptations

One or more interim analyses may be conducted to support decision-making in relation to the current clinical study, the future of the sponsor's clinical development plan, or the long-term safety and efficacy of ligelizumab. Additional details will be provided in the Statistical Analysis Plan (SAP).

4.7 End of study definition

The end of the study is defined as the date of the last visit (end of follow-up period) of the last participant according to the Section 1.3 Schedule of Activities globally.

Study completion in each participant is defined as when the participant finishes their last study visit (end of follow-up period) and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator.

5 Study population

This study population will consist of participants who have successfully completed ligelizumab Phase III studies in food allergy including (but not limited to) Study CQGE031G12301 (peanut allergy). Considering the estimated drop out rate of the core study (15%) and a limited alternative standard of care in the patients with food allergy, the expectation is that approximately 550 participants will enroll in this extension study. This extension study will be opened for participants joining from additional ligelizumab food allergy studies.

In line with each core study this extension study will involve male and female participants who have successfully completed a core study and are eligible to continue to the extension study.

5.1 Inclusion criteria

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

1. Signed informed consent form (ICF) and assent form (where applicable) obtained from the participant/legal representative before study participation. If a minor participant reaches the age of legal majority (as defined by local law), they must be re-consented at the next study visit.
2. Participants have completed the treatment period in any ligelizumab's Phase III studies in food allergy (e.g., CQGE031G12301). Please refer to the Section 4.1 for the timing of transition.
3. Participants who are willing to adhere to the study visits and procedures, including receiving injections (study treatment) and participating in the OL-OFC.
4. Participants who are willing to continue avoiding exposure to allergens (per core study) and any other foods they are allergic to throughout this study.
5. Participants who are able to safely continue into the study as judged by the investigator

5.2 Exclusion criteria

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

1. Development of a severe or life-threatening episode of an allergic reaction that requires intubation and/or Intensive Care Unit (ICU) admission during a core study.
2. Development of a serious adverse event which is suspected to be related to the study treatment judged by the investigator during a core study.
3. Development of uncontrolled asthma during a core study that could compromise the safety of the participants as judged by the investigator.

4. Development of clinically significant cardiovascular, neurological, and/or psychiatric conditions during a core study 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 as judged by the investigator.
5. Development of malignancy of any organ system during a core study (except for basal cell carcinoma; actinic keratoses; Bowen disease (carcinoma in situ) that has been treated, with no evidence of recurrence in the past 12 weeks and carcinoma in situ of the cervix or non-invasive malignant colon polyps that have been removed).
6. Development of clinically significant abnormality in laboratory testing, ECG, and/or vital signs during a core study 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 as judged by the investigator.
7. Use of prohibited medications (Table 6-5) or medication that is not allowed under certain conditions (Table 6-4).
8. Participants who discontinued from a core study, irrespective of the reason.
9. Participants who failed to comply with the protocol requirements and procedures during a core study, and in the Investigator's opinion should not participate in this extension study.
10. Platelets <75,000/uL at EoT of core study.
11. Pregnant or nursing (lactating) females.
12. Sexually active children below the age of 12 years.
13. Female participants, incl. adolescent females of 12 to less than 18 years of age at the entry of the extension study, of childbearing 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 (appr. 4 months, e.g., 5 half-lives, after the last dose of ligelizumab). Basic (acceptable and 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 Medicinal Product (IMP). In the 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 deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the ICF/assent.

5.3 Screen failures

A screen failure occurs when a participant who consents to participate in the clinical study is subsequently found to be ineligible and therefore will not receive the study treatment. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

5.3.1 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. The participant number will be different to the core study participant number. The Participant No. consists of the Site Number (Site No.) (as assigned by Novartis to the investigative site) with a sequential participant number suffixed to it, so that each participant's participation is numbered uniquely across the entire database. Upon signing the informed consent form, the participant is assigned to the next sequential Participant No. available. In order to link between the core study and the extension study, the participants No. of the core study will be recorded in the respective CRF in the extension study.

6 Study treatment(s) and concomitant therapy

6.1 Study treatment(s)

During the extension study, participants will be receiving the same dose of ligelizumab as assigned at randomization in the core studies. There is a possibility to discontinue the study treatment in the MR participants who successfully continue "conditional discontinuation of study treatment" (Section 4.1.2).

Study treatment includes investigational drug ligelizumab (120 mg/ml) and placebo, all participants will receive 2 injections, so participants on 120mg/ml will also receive a matching placebo injection to protect the study blinding. Study treatment must be administered by an independent drug administrator or unblinded pharmacist at the study site who is not involved in any of the study assessments. The procedure for the administration at home is summarized in the Section 6.2.3.1. The administration will be performed by the participant and/or parent/caregiver in the case of a child/adolescent at home.

Novartis will supply ligelizumab (QGE031) 120 mg per 1 mL as prefilled syringe (PFS) pre-assembled within a needle safety device (NSD) from the Becton Dickinson UltraSafe Passive™ NSD X100L Plus series and placebo.

Table 6-1 Investigational and control drug

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

* Placebo will only be administered alongside the 120mg/1ml dose to protect the dose blinding. There is no placebo arm

6.1.1 Bio-batch retention samples

Not applicable.

6.1.2 Additional study treatments

No other treatment beyond investigational drug and control drug are included in this trial.

6.1.3 Treatment arms/group

Participants will be assigned to one of the following two treatment arms depending on responder status in the previous study/ies) as per Section 4.1.1 and Section 4.1.2.

Each participant (except the MR participants undergoing conditional discontinuation) will receive two (2) SC injections every four weeks starting at Day 1.

1. ligelizumab 240 mg arm: 2 injections of 1.0 mL ligelizumab
2. ligelizumab 120 mg arm: 1 injection of 1.0 mL ligelizumab and 1 injection of 1.0 mL placebo

The assignment to receive 120 mg or 240 mg ligelizumab will be determined by treatment received during the previous study(ies). All participants (except the MR participants undergoing conditional discontinuation (Section 4.1.2)) will receive study drug (ligelizumab). There is no placebo arm.

Of note, based on CQGE031G12301 core study results, Novartis will assess the need to switch participants in CQGE031G12303B to a different dose than the one they were receiving in CQGE031G12301.

6.1.4 Treatment duration

The planned duration of treatment is up to 156 weeks (three years). There is a possibility of a shorter treatment period than three years in the MR participants who successfully continue "conditional discontinuation of study treatment" (Section 4.1.2).

6.1.5 Medical devices

Not applicable.

6.2 Preparation, handling, storage, and accountability

Each study site will be supplied with study treatment in packaging as described under Table 6-1 Investigational and control drugs section.

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

An independent unblinded administrator will identify the study treatment kits to dispense to the participant by contacting the Interactive Response Technology (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.

The guidelines for the storage, preparation and administration of study treatment are described in the pharmacy manual (provided separately).

As per Section 4.5, 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, delivery of IMP directly to a participant's home may be permitted for the participants or parents/caregivers who have completed the training of injection (if allowed by local or regional health authorities and ethics committees, as appropriate) or in the event the Investigator has decided that an on-site visit by the participant is no longer appropriate or possible. The dispatch of IMP from the site to the participant's home remains under the accountability of the Investigator. Each shipment/provisioning will be for either 12 or 16 weeks as per IRT supply. In this case, regular phone calls or virtual contacts (every 4 weeks or more frequently if needed) will occur between the site and the participant for instructional purposes, safety monitoring, investigation of any adverse events, ensuring participant continues to benefit from treatment, and discussion of the participant's health status until the participant can resume visits at the study site.

6.2.1 Handling of study treatment

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

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

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

The Investigator or designated site staff (blinded or unblinded, as applicable) 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 field monitors during site or remote monitoring visits, and at the completion of the trial. The Investigator must provide accountability also 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. If study treatment is administered at home, participants will be asked to return all unused study treatment and packaging at the end of the study, and as appropriate during the course of the study or at the time of discontinuation of study treatment.

6.2.2 Handling of other 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:

- Short-acting Beta-agonist (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.

6.2.3 Instruction for prescribing and taking study treatment

The independent study treatment 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 un-blind the participant or any of the study site personnel.

The subcutaneous 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. 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 who join the study after the follow-up period of the core study will remain on site for observation for a period of **2 h post-dose** for the first three drug administration visits, this equates to week 0, 4 and 8. Thereafter a 30 minute wait will suffice. Participants who join the extension study from continuous treatment will only require a 30 minute wait at the site. The 2-hour observation period for the first three drug administrations must be observed in all instances where study treatment is reintroduced after a washout/interruption period (e.g., restart of the

study treatment after the conditional discontinuation of study treatment because of no longer MR).

At Week 52, 104, and 156 there must be **a minimum of 1 hour between administration of study treatment and performing the OFC** (Section 8.3.1). Study treatment must be given **before the OFC**.

In case the study treatment should be started based on the responder driven approach (Previous MR is no longer MR after off-treatment, Section 4.1.2), the time interval between OFC and restart of study treatment must be a minimum of 24 h.

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 managed by the IRT.

All study treatment dosages prescribed and dispensed to the participant and all dosing errors or missed administrations during the study must be recorded on the appropriate electronic case report form (eCRF).

All kits of study treatment assigned by the IRT will be recorded in the IRT system. The investigator must promote compliance by instructing the participant to take the study treatment exactly as prescribed and by stating that compliance is necessary for the participant's safety and validity of the study. The participant must also be instructed to contact the investigator if he/she is unable, for any reason, to take the study treatment as prescribed.

6.2.3.1 Administration at home by participant or parent/caregiver

The study treatment should only be administered via PFS by adults. In other words, if the participant is below 18 years (< 18), the administration should be done by his/her parent/caregiver. Even an adult participant who is willing to be part of the administration at home **BUT** not comfortable with self administration, in this instance the parent/caregiver can be an administrator.

The participant will be given the option to start administration at home once their training is completed. The participants doing conditional discontinuation of study treatment won't be offered the opportunity of drug administration at home.

Before initiation of training visit, participants who are willing to take part in administration at home should be evaluated according to the below criteria. If the criteria are satisfied, then the Instruction For Use (IFU) Guide will be provided to the participants or caregiver who will then undergo training in administration of the study treatment.

The clinical eligibility criteria for administration at home of ligelizumab are below:

- participant/caregiver should be capable and willing to self-administer ligelizumab.
- participant/caregiver should know how to recognize symptoms/signs of severe hypersensitivity reactions

For the first and second use of PFS, the injection will take place as a site staff assisted injection i.e., with the help of the site staff performing the injection steps. At the third use of PFS, the self-injection will take place under supervision however without the help of the site staff, i.e., the site staff only observes and does not help in performing the injection steps. The training of each injection, be it assisted or under supervision, will be provided individually by the site staff to the participant/caregiver.

Participants who administered ligelizumab at home in the first year of the extension study and continue into the second/third year of the study, will continue the home-administration. However, those participants who are unable to adhere to administration at home in the first year of study can then revert to clinic visits, they will subsequently be supported by the clinic to do home administration and training during the second/third year.

First dose of PFS: Assisted administration of study treatment

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

Second dose of PFS: Assisted supervision of study treatment

- Study staff should ask the participant whether they wish to be retrained prior to injection. If needed, site staff will retrain the participant.
- Participant will perform the injection into the appropriate injection site of the body with the site staff **actively assisting** him/her during the injection. If the site staff observes that the participant is performing an action that may jeopardize the participant's safety, site staff will intervene to prevent any potential harm and guide/correct the participant.

Third dose of PFS: Supervised administration of study treatment

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

Thereafter, outside of clinic administrations should be done at pre-defined time points as per assessment schedule (Table 1-4). **If self-administration is performed by a parent/caregiver, the parent/caregiver will then be trained as outlined above.**

All participants self-administering study treatment at home should remain under observation by a family member or colleague, for symptoms and signals of hypersensitivity in a quiet environment for 30 minutes after each administration.

Participants carrying out administration outside the clinic setting will:

- have in-clinic safety and efficacy assessments done at least at Weeks 24, 52, 76, 104, 128 and 156 intervals
- on site visits will take place every 12-16 weeks, to collect study treatment (2 or 3 kits), review dosing log and safety check
- At the site visits, participant or parent/caregiver will be offered the opportunity to perform a self administration under the supervision of the study staff and to be retrained on the injection technique upon request or if whenever required.
- be assessed remotely (i.e., outside of clinic) by safety phone call from the site every 4 weeks either on the day of study treatment administration or 1 to 3 days after, unless there is an in-clinic visit scheduled (at Weeks 24, 52, 76, 104, 128 and 156 as per protocol).

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

At any time during the study, should a participant or parent/caregiver or investigator decide not to continue with administration of study treatment at home, the participant must contact the site, or the site staff must contact the participant, to arrange for all subsequent visits and treatments to be administered at the site.

6.3 Measures to minimize bias: randomization and blinding

6.3.1 Treatment assignment, randomization

No randomization will be performed in this study. Clinical trial treatment randomization codes are generated in the core studies and the same will be used in the extension study. The assignment of treatment will depend on the previous study treatment assignment during the core study, as well as a response driven approach.

At screening, all eligible participants will be allocated via Interactive Response Technology (IRT) to the treatment dose that the participant was assigned to in the core study, except in some scenarios described in Section 4.1.2. The Investigator or his/her delegate will contact the IRT after confirming that the participant fulfills all the inclusion/exclusion criteria. The IRT will assign the participant to a treatment and will specify a unique medication number for the package of investigational treatment to be dispensed to the participant. All kits of study treatment assigned by the IRT will be recorded in the IRT system.

MR participants will continue off-treatment or re-start study treatment (if no longer MR) during the study as part of "conditional discontinuation" which will be controlled by IRT.

6.3.2 Treatment blinding

The purpose of the double-blind design in this extension study is to protect the blinding of data in the core studies.

Participants, investigator, study staff and the Novartis Clinical Trial Team will remain blinded to the identity of the treatment assignment from the time of enrollment 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) if required, and the independent statistician & programmer supporting the DMC activities.
- Novartis associates who are involved the analysis before final Database lock (DBL) described in Section 4.6

The following measures must be applied by the study site to keep the data integrity of the core studies in terms of the identity of the treatment:

- As per Section 6.1, two completely identical syringes will be supplied for the ligelizumab 120 mg (120mg and placebo) or 240 mg (120 mg x 2).
- The study treatment 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 blinded site staff
- An independent administrator or unblinded pharmacist will not be involved for the participants who are part of study treatment administration at home. Although the appearance of syringes (ligelizumab 120 mg, placebo) is the same, there is a potential risk to be unblinded by the speculation of participant or parent/caregiver. Therefore before start of training for the study treatment administration at home, the clinical data of the participants who will be administered at home should be frozen in the EDC system (confirmed by Novartis Data Management).

For any interim analysis before final database lock (Section 9.8) a limited number of pre-specified members of the program team from Novartis will be unblinded in a phasic manner. 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.

Un-blinding 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

of the study. The investigator must maintain an accurate record of the shipment and dispensing of investigational treatment in a drug accountability log.

Table 6-2 Blinding level

	Time or Event			
Role	**Treatment assignment list generated**	**Treatment allocation & dosing**	**Safety event (single participant unblinded)**	**Interim analysis**
Participants	B	B	B	B
Investigator and site staff	B	B	B	B
Site staff: Pharmacy staff and IMP administrator	B	UI	B	B
Global Clinical Supply and Randomization Office	UI	UI	UI	UI
sponsor staff: CRA	B	B	B	B
Sponsor staff: Pharmacovigilance staff	B	B	UI	B
Sponsor staff: Bioanalysis CCI	B	UI	B	B
DMC independent statistician and programmer	B	UI	UI	UI
Data monitoring committee	B	UI	UI	UI
Adjudication committee	B	B	B	B
All other sponsor staff not identified above but defined in the charter	B	B	B	UI

B Remains blinded UI Allowed to be unblinded on individual participant level *DMC will review unblinded data.

6.3.3 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, discontinuation from study treatment and knowledge of the possible treatment assignments are sufficient to treat a study participant who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. 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 the Novartis monitor for the site and the study team that the code has been broken.

It is the Investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT/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 his/her backup in cases of emergency, or when he/she is unavailable, to ensure that un-blinding can be performed at any time.

6.4 Study treatment compliance

Participants will receive two injections SC q4w during the treatment period. Compliance is assured as long as the participant attends all study visits according to the Schedule of Assessments (Table 1-4). For participants receiving study treatment at the site, compliance is assured, as study treatment must be administered by study personnel (independent study treatment administrator or unblinded pharmacist) via SC injection.

For administration at home by participant or parent/caregiver: The Investigator must promote compliance by instructing the participant to take the study treatment exactly as prescribed and by stating that compliance is necessary for the participant's safety and the validity of the study. The participant must also be instructed to contact the Investigator if he/she is unable for any reason to take the study treatment as prescribed. In addition compliance will be measured by a dosing log for those undergoing administration at home. The administration of study treatment must be recorded in the dosing log and compliance should be monitored by the Investigator and/or study personnel. All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

6.4.1 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 short-acting beta2-agonist (SABA) are typically used.

Treatments of adverse events should align with medications allowed under certain conditions (Section 6.8.1.1) and prohibited medication (Table 6-5) where possible. Medication used to treat AEs must be recorded on the appropriate CRF.

For adverse events associated with the OFC, please see the Appendix 7 (Section 10.7).

6.5 Dose modification

6.5.1 Definitions of dose limiting toxicities (DLTs)

Not applicable.

6.5.2 Dose modifications

Study treatment dose adjustments are not permitted.

Any interruption of study treatment administration should be discussed with Novartis or delegate regarding the participant's eligibility to continue study treatment except for the cases based on the response driven approach (Section 4.1.2).

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

6.5.3 Follow-up for toxicities

6.5.3.1 Follow-up on potential drug-induced liver injury (DILI) cases

Participants with transaminase increase combined with total bilirubin increase may be indicative of potentially severe DILI and should be considered as clinically important events and assessed appropriately to establish the diagnosis. The required clinical information, as detailed below, should be sought to obtain the medical diagnosis of the most likely cause of the observed laboratory abnormalities.

The threshold for potential DILI may depend on the participant's baseline AST/ALT and total bilirubin value; participants meeting any of the following criteria will require further follow-up as outlined below:

- For participants with normal ALT and AST and total bilirubin value at baseline: AST or ALT > 3.0 x ULN combined with total bilirubin > 2.0 x ULN
- For participants with elevated AST or ALT or total bilirubin value at baseline: [AST or ALT > 2 x baseline] OR [AST or ALT >300 U/L], whichever occurs first combined with [total bilirubin > 2 x baseline AND > 2.0 x ULN]

As DILI is essentially a diagnosis of exclusion, other causes of abnormal liver tests should be considered and their role clarified before DILI is assumed to be the cause of liver injury.

A detailed history, including relevant information such as review of ethanol consumption, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.

Laboratory tests should include ALT, AST, total bilirubin, direct and indirect bilirubin, GGT, prothrombin time (PT)/INR, alkaline phosphatase, albumin, and creatine kinase. If available, testing of Glutamate Dehydrogenase (GLDH) is additionally recommended.

Perform relevant examinations (Ultrasound or MRI, Endoscopic retrograde cholangiopancreatography (ERCP)) as appropriate to rule-out an extrahepatic cause of cholestasis. Cholestasis (is defined as an ALP elevation > 2.0 x ULN with R value < 2 in participants without bone metastasis, or elevation of the liver-specific ALP isoenzyme in participants with bone metastasis).

Note: The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic ($R \leq 2$), hepatocellular ($R \geq 5$), or mixed ($R > 2$ and < 5) liver injury. For children, there are caveats to calculating the R-ratio as normal levels of ALP are higher than in adults with standard ranges varying by developmental age. In clinical situations where it is suspected that ALP elevations are from an extrahepatic source, the GGT can be used if available. GGT may be less specific than ALP as a marker of cholestatic injury, since GGT can also be elevated by enzyme induction or by ethanol consumption. It is more sensitive than ALP for detecting bile duct injury.

Table 6-3 provides guidance on specific clinical and diagnostic assessments which can be performed to rule-out possible alternative causes of observed Liver function test (LFT) abnormalities.

Table 6-3 Guidance to rule-out possible alternative causes of LFT abnormalities

Disease	Assessment
Hepatitis A, B, C, E	● IgM anti-HAV; HBsAg, IgM & IgG anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
CMV, HSV, EBV infection	● IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	● Antinuclear Antibodies (ANA) & Anti-Smooth Muscle Antibody (ASMA) titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	● Ethanol history, GGT, MCV, CD-transferrin
Nonalcoholic steatohepatitis	● Ultrasound or MRI
Hypoxic/ischemic hepatopathy	● Medical history: acute or chronic congestive heart failure, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.
Biliary tract disease	● Ultrasound or MRI, ERCP as appropriate.
Wilson disease (if <40 yrs old)	● Caeruloplasmin
Hemochromatosis	● Ferritin, transferrin
Alpha-1-antitrypsin deficiency	● Alpha-1-antitrypsin

Other causes should also be considered based upon participants' medical history (hyperthyroidism / thyrotoxic hepatitis – T3, T4, TSH; cardiovascular disease / ischemic hepatitis – ECG, prior hypotensive episodes; Type 1 diabetes mellitus / glycogenic hepatitis).

Following appropriate causality assessments, as outlined above, the causality of the treatment is estimated as "probable" (i.e.,>50% likely), if it appears greater than all other possible causes of liver injury combined. The term "treatment-induced" indicates probably caused by the treatment, not by something else, and only such a case can be considered a DILI case and should be reported as an SAE.

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified, should be considered as "medically significant" and thus, meet the definition of SAE and should be reported as a SAE using the term "potential treatment-induced liver injury." All events should be followed up with the outcome clearly documented.

6.5.4 Retreatment criteria

Restart of study treatment is only possible for the participants undergoing conditional discontinuation of study treatment, but becoming sensitive to the food allergen, as defined by the OFC (no longer MR) after being off-treatment.

6.6 Continued access to study treatment after the end of the study

6.6.1 Post trial access

This is an extension study to the core studies of ligelizumab Food Allergy Program which will provide access to ligelizumab to those participants who decide to join the study until it is commercially available or accessible in the participating countries (up to 3 years in some regions). The 3-year treatment period of this study will also fulfill the Novartis commitment to provide post trial access (PTA) to the participants who have completed ligelizumab Phase III studies in food allergy. For the participants who complete this extension study prior to the ligelizumab becoming available in the country of the participant and is, in the opinion of the

investigator still deriving clinical benefit from ligelizumab, every effort will be made to continue provision of ligelizumab.

6.7 Treatment of overdose

In the event of an overdose for participants administering study treatment at home, e.g., when more than 2 doses were given to the participant, the participant or parent/caregiver should:

- Contact the study site staff immediately.
- Site should then contact the medical monitor
- Advise the participant or parent/caregiver to report any untoward events to the study site staff and continue to closely monitor the participant
- Evaluate the participant to determine, in consultation with the medical monitor, whether study treatment should be interrupted
- Document the quantity of the excess dose as well as the duration of the overdose.

6.7.1 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.

6.8 Concomitant and other therapy

6.8.1 Concomitant therapy

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

Each concomitant drug must be individually assessed against all exclusion criteria and against the medication allowed under certain conditions (listed in Table 6-4) and prohibited medication listed in Table 6-5. If in doubt, the Investigator should contact the Novartis medical monitor before starting Screening/Day 1 visit or allowing a new medication to be started. If the participant is already enrolled, contact Novartis to determine if the participant should continue participating 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.

6.8.1.1 Permitted concomitant therapy requiring caution and/or action

The following medications below are allowed under certain conditions:

Table 6-4 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 in the maintenance phase for the treatment of allergies (except food allergies)	SC (subcutaneous) immunotherapy: time window of 1 week between OFC or study treatment administration and immunotherapy shot. SLIT (sublingual immunotherapy): Hold SLIT dose on the day of OFC
Inactivated, non-live vaccines (including Covid19 vaccine)	Not administered within 48 hours prior to a study visit
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 OFC
Short Acting Beta Agonist (SABA)	Not used within 6h of all spirometry assessments for asthma participants and within 6h prior to start of OFC
Short-term burst of systemic corticosteroids for the treatment of acute signs and symptoms	Not administered within 5 half-lives prior to SPT and OFC.
Oral H2 receptor antagonists (e.g., cimetidine, ranitidine, famotidine, nizatidine)	Not administered within 24 hours prior to SPT and OFC
Corticosteroids nasal spray	In recommended doses and dosage regimens
Anti-Histamine nasal spray	

6.8.2 Prohibited medication

Use of the treatments displayed below is not allowed after the start of the study treatment.

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/Day 1 to the end of the study, investigational treatment and OL-OFC must be discontinued.

Table 6-5 Prohibited medication

Medication	Prohibition period	Action taken
Any monoclonal antibody treatment (including any Fab fragments); e.g., omalizumab (Xolair®), dupilumab (Dupixent®), benralizumab (Fasenra™), mepolizumab (Nucala®), reslizumab (Cinqair®)	Any time	Discontinue investigational treatment
Immunotherapy for the treatment of food allergies	Any time	Discontinue investigational treatment
Other systemic immunosuppressive medications including but not limited to methotrexate, cyclosporine A, cyclophosphamide, tacrolimus and mycophenolate mofetil, Janus Kinase inhibitors	Any time	Discontinue investigational treatment

Medication	Prohibition period	Action taken
Chronic use of systemic corticosteroids	Any time (See Table 6-4 above for short-term burst)	Discontinue investigational treatment
Beta blockers	Any time	Discontinue investigational treatment
ACE inhibitors	Any time	Discontinue investigational treatment
Tricyclic antidepressants	Any time	Discontinue investigational treatment
Other investigational drugs	Any time	Discontinue investigational treatment
Live attenuated vaccines	Any time	Discontinue investigational treatment

6.8.3 Rescue medicine

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.

Rescue medication can either be provided directly at the study center or prescribed to the participant.

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 the 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.

These two rescue medications are to be provided to the participant locally at the transition to this extension study (or continuously carrying the rescue med from the core study). Participants should be instructed to bring them to each visit.

Epinephrine:

In alignment with treatment guidelines for food allergy, all study participants will be provided with rescue medication epinephrine (e.g., EpiPen® 150 µg, 300 µg, 500 µg, Jext® 150 µg or 300 µg) to be used to treat any allergic reactions and potential anaphylactic events that occur throughout the study as needed. This qualifies as authorized auxiliary medicinal product (AxMP) under the European Clinical Trial Regulation 536/2014. If the participant is treated with epinepherine (e.g., EpiPen®, Jext®) outside of a study visit, the participant or parent/caregiver should contact the study site staff immediately.

SABA (salbutamol/albuterol):

Participants with a documented diagnosis of asthma will additionally be provided with SABA rescue medication. This qualifies as authorized auxiliary medicinal product (AxMP) under the European Clinical Trial Regulation 536/2014. As listed in Table 6-4, the participant should not use SABA rescue medication within 6 hours of a spirometry assessment and/or OFC.

7 Discontinuation of study treatment and participant discontinuation/withdrawal

7.1 Discontinuation of study treatment

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

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

Discontinuation from study treatment is required under the following circumstances:

- Participant/guardian decision
- Pregnancy
- AEs for which continued exposure to the study drug would be detrimental
- Abnormal liver and/or renal laboratory results requiring discontinuation
- Platelets <75000 /uL
- 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
- Use of prohibited treatment as per recommendations in the prohibited treatment section
- Any situation in which continued study participation might result in a safety risk to the participant
- Following emergency unblinding

If discontinuation from study treatment occurs, the Investigator should make a reasonable effort to understand the primary reason for the participant’s discontinuation from study treatment and record this information.

Participants who discontinue from study treatment agree to return for the end of treatment and follow-up visits indicated in Section 1.3 Schedule of Activities.

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. Participants who discontinue study treatment will no longer undergo any OFC that may be planned on the remaining visit(s). After discontinuation from study treatment, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

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

The Investigator must also contact the IRT to register the participant’s discontinuation from study treatment.

7.2 Participant discontinuation from the 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 Section 1.3 Schedule of Activities.

7.3 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 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 Section 1.3 Schedule of Activities.

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

7.4 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits or fail to respond to any site attempts to contact them without stating an intention to discontinue from

study treatment or discontinue from study or withdraw consent (or exercise other participants' data privacy rights), 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.

7.5 Early study termination by the Sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination (but not limited to):

- Unexpected, significant, or unacceptable safety risk to participants enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data
- Discontinuation of study treatment development

In taking the decision to terminate, Novartis will always consider participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible and treated as a participant who discontinued from study treatment. The Investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant's interests. The Investigator or Novartis depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

8 Study Assessments and Procedures

- Study procedures and their timing are summarized in Section 1.3 Schedule of Activities. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with Novartis upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in Section 1.3 Schedule of Activities, is essential and required for study conduct.
- Safety/laboratory/analyte results that could un-blind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Screening

In this extension study, Screening and Day 1 with the first administration of study treatment will occur on the same day, except the MR participants who transition at the end of the follow-up period of the core study, when the first administration of study treatment will be given on a different day (Section 4.1.2).

Each participant must have completed the treatment period in the Phase III studies with ligelizumab in food allergy including (but not limited to) Study CQGE031G12301 (peanut allergy).

Participants who are from Study CQGE031G12301 will transition into the extension study after completion of the follow-up period (washout) of the core study. The end of follow-up visit of the core study will also become the first visit of this extension study (Screening/Day 1). The informed consent must be obtained before initiating any study related activities in the extension study at Screening/Day 1 (Figure 4-1).

Participants from other study(ies) who complete the study treatment period of a core study and are willing to participate in the extension study will consent to the extension study. Four weeks after the end of the final treatment visit of a core study, the first visit of this extension study will be scheduled (Screening/Day 1) (Figure 4-1).

Participants who sign an informed consent form (and assent form if applicable) for this extension study and are subsequently found to be ineligible prior to the first dose of study treatment administration (Day 1) will be considered as a screen failure. The reason for screen failure should be recorded on the appropriate CRF.

8.2 Participant demographics/other baseline characteristics

Participant demographics and baseline characteristics will be collected at Screening, as specified in Section 1.3 Schedule of Activities.

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 entering the extension study will be recorded, including any ongoing adverse events from the core study. Clinically relevant abnormal test findings should also be captured in medical history once it 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.

8.3 Efficacy assessments

8.3.1 Oral Food Challenge (OFC)

In this extension study, the open-label OFC will be conducted to evaluate the level of desensitization to the food(s) every year as well as for MR to extend the off-treatment (washout) period. Details of this procedure are outlined in the Appendix 7 (Section 10.7) and preparation of the allergen is outlined in the Pharmacy Manual.

Although OL-OFC will be conducted in this study, it is recommended that same site personnel (unblinded and independent) as in the core study continues the preparation of the challenge material. However it is not necessary to keep blinding because the participants will receive allergen food protein (and not placebo).

Conducting the food challenge requires the physical facility to store and prepare material, as well as the assessment itself conducted under medical supervision. Sites should be equipped with supplies to treat allergic reactions (including severe anaphylaxis) (Section 10.7), as well as access to emergency care units.

To ensure participant safety, on study visits where the OFC is conducted, it is critical to follow the order of assessments as outlined in Table 1-4. i.e., concomitant medication check, physical examination, ECG, vital signs, spirometry (for asthma participants only), urine pregnancy (if applicable), laboratory evaluations, skin prick test (SPT) and study treatment administration must be performed prior to the start of the OFC. CCI [redacted]

The site should be prepared to react to immediate and late hypersensitivity reactions, including anaphylaxis. At the completion of the OFC 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 in possession of an epinephrine auto-injector consistent with local guideline.

OFC data will be captured on a designated page of the electronic case report form (eCRF).

8.3.1.1 Spirometry before OFC

For participants with a documented diagnosis of asthma, spirometry is performed prior to the OFC and if the Forced Expiratory Volume during the 1st second (FEV1) % predicted normal value is below 80% (< 80%), the OFC 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 American Thoracic Society / European Respiratory Society (ATS/ERS) standard (ATS/ERS Task Force: Standardization of Lung Function Testing, Graham et al 2019) if possible.

8.3.2 Skin Prick Test (SPT)

An allergen specific SPT is a commonly used diagnostic tool (Heinzerling et al 2013). 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.

SPT is scheduled every 6 months during the extension study Table 1-4. At the visit where dosing of study treatment, SPT and OFC are scheduled, SPT should be performed before dosing of study treatment followed by OFC.

The SPT procedure is summarized separately in Appendix 8 (Section 10.8).

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.

8.3.3 Appropriateness of efficacy assessments

OFC

The Oral Food Challenge (OFC) represents the gold standard for diagnosing food allergies. It is also the most objective method to clinically estimate threshold doses for allergenic foods in highly sensitive individuals. In this study, the OFC is based upon several available guidelines, PRACTALL (Cox, Nowak-Wegrzyn 2018) and the CoFAR Grading Definition of Dose-Limiting Symptoms. The test itself corresponds most closely to the natural ingestion of food.

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

SPT assessment

Skin prick Test is used in clinical practice as a diagnostic modality to detect the presence of sIgE antibodies to the food source. The size of the SPT wheal correlates with an increased likelihood of clinical food allergy. However, a positive result alone indicates sensitization and does not equate to food allergy (Foong et al 2021)

8.4 Safety assessments

Safety assessments are specified below with Table 1-4 Assessment Schedule detailing when each assessment is to be performed.

For details on AE collection and reporting, refer to Section 8.6:

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 (asthma patients only) refer to Section 8.3.1.1

Electrocardiogram (ECG)

As per Section 4.5, during a public health emergency as declared by local or regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, regular phone or virtual calls can occur (every 4 weeks or more frequently if needed) for safety monitoring and discussion of the participant´s health status until it is safe for the participant to visit the site again.

8.4.1 Physical examinations

A complete physical examination will be performed as specified in the schedule of activities table (Table 1-4) and will include 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.

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

Information on 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 CRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event.

8.4.2 Vital signs

Vital signs include blood pressure and pulse measurements will be measured as specified in the schedule of assessments Table 1-4. After the participant has been sitting for five minutes, with the back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured three times using an automated validated device, e.g., OMRON, with an appropriately sized cuff. The repeat sitting measurements will be made at 1 - 2 minute intervals and the mean of the three measurements will be used. In case the cuff sizes available are not large enough for the participant's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.

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

Clinically notable vital signs are defined in Appendix 3 (Section 10.3.1).

8.4.3 Electrocardiograms

ECGs will be measured once a year as specified in the schedule of assessments in Table 1-4.

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 participant's number, the date, actual time of the tracing, and Study Code must appear on each page.

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.

Additional, unscheduled, safety ECGs may be repeated at the discretion of the investigator at any time during the study as clinically indicated. For any ECGs with participant safety concerns, 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.

8.4.4 Clinical safety laboratory tests

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 QGE031G12303B 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.

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

Clinically notable laboratory findings are defined in Appendix 3 (Section 10.3.1). 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 capturing medical history/current medical conditions/AEs.

A serum β-hCG will be collected at Screening/Visit 1 as specified in the schedule of assessments in Table 1-4 for all after menarche and pre-menopausal women who are not surgically sterile.

As per Section 4.5, 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, if participants cannot visit the site for protocol-specified safety lab assessments, an alternative lab (local) collection site may be used.

Table 8-1 Laboratory evaluations

Test category	Test name
Hematology	Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential and platelet count
Chemistry	Albumin, Alkaline phosphatase (ALP), ALT, Amylase, AST, Calcium, Chloride, Creatinine, Direct Bilirubin, Gamma-glutamyl-transferase (GGT), Glucose, Lactate dehydrogenase (LDH), Lipase, Magnesium, Phosphate, Potassium, Sodium, Total Bilirubin (If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reacting bilirubin should be differentiated), Urea/BUN, Uric Acid
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 8.4.6.1.

Test category	Test name
Pregnancy Test and Assessments of Fertility	Serum / Urine pregnancy test (refer to Pregnancy and assessments of fertility Section 8.4.5). Confirmatory serum pregnancy required in case of positive urine pregnancy test

8.4.5 Pregnancy testing

All pre-menopausal female participants, including female pediatric participants who are menarchal or who become menarchal during the study, who are not surgically sterile will have pregnancy testing. Post-menopausal status should be recorded in the Medical History CRF.

Continuing from the core studies and up to the EOS, all pre-menopausal female participants who are not surgically sterile will have urine pregnancy testing performed BEFORE administration of the study treatment. Females participating in the home administration will receive urine pregnancy kits to test prior to study treatment injection.

A positive urine test requires the participant to contact the site staff and they will then need to confirm the result with a central lab serum test, prior to further study treatment administration, in the interim, they should withhold study medication. If positive after serum test, 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, Follicle Stimulating Hormone (FSH) testing is required of any female participant regardless of reported reproductive/menopausal status at screening.

As per Section 4.5, 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, if participants cannot visit the site to have serum pregnancy tests, urine pregnancy test kits may be used. Relevant participants can perform the urine pregnancy test at home and report the result to the site. It is important that participants are instructed to perform the urine pregnancy test first and only if the test result is negative proceed with the administration of the study treatment. A communication process should be established with the participant so that the site is informed and can verify the pregnancy test results, following any local country procedures.

8.4.6 Other safety evaluations

8.4.6.1 Assessment of parasitic infection

Reduction in IgE levels may confer increased susceptibility to parasitic infections. The risk of acquiring or activating infections with helminthes during or after treatment with anti-IgE therapy such as ligelizumab is suspected to be low.

Stool sampling for the assessment of parasitic infection is scheduled:

- Beginning of the study:
  - No stool sample for the extension study is required (results from the Core study(ies) will be used)
- End of the study:
  - All participants: Single stool sample is required and sample kit will be given at the visit before the end of study visit
- Participants who report diarrhoea, or any other symptoms suggestive of parasitic infection at any time during the study will be given three stool sample collection kits. These participants have to collect stool samples ideally on three different days, and then to return the samples to the clinic or local lab as soon as possible after collection. For home administration participants, they need to arrange to collect kits and return them to the clinic as agreed with the clinic staff.

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 as well as eCRF as an AE. Stool samples negative for pathogenic organisms must be recorded in the source data.

Subjects who develop stools positive for pathogenic helminthic infections during the study should have their infection treated according to current local practice and can continue the study as per schedule.

8.4.6.2 Independent data review by adjudication committee

An adjudication committee (AC) will be put in place to determine whether cases of hypersensitivity identified through a search algorithm based on the Standardized Medical Dictionary for Regulatory Activities (MedDRA) Queries may represent cases of:

- anaphylactic events
- cardio-cerebrovascular events
- neoplastic events

The clinical presentation and association of these events with pre-existing risk factors will be part of the assessment.

Further details regarding the AC will be documented in an AC charter.

8.4.7 Appropriateness of safety measurements

The safety assessments of this extension study are in line with that of each core study and are standard in this population, in addition they are based on the available ligelizumab safety data. Participants have completed a core study before entering to this extension study, therefore it is important to monitor the participants' safety continuously in the same manner.

Also, study treatment will be discontinued if the participant experiences a life-threatening hypersensitivity event needing an Intensive Care Unit (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 – Adolescent Form

FAIM-TF: Food Allergy Independent Measure – Adolescent 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 8-2 PROs based on participant's age

Age Group/ Respondent Type	Day 1 Screening	Week 52 10 days Before OFC	Week 52 3 days After OFC	Week 104 10 days Before OFC	Week 104 3 days After OFC	Week 156 10 days Before OFC	Week 156 3 days After 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	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	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	FAQLQ-AF FAIM-AF	FAQLQ-AF FAIM-AF SF-36v2

Age Group/ Respondent Type	Day 1 Screening	Week 52 10 days Before OFC	Week 52 3 days After OFC	Week 104 10 days Before OFC	Week 104 3 days After OFC	Week 156 10 days Before OFC	Week 156 3 days After OFC
Parents/Caregivers of Children 6-12	FAQLQ-PF FAQL-PB	FAQLQ-PF	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		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 participant'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 2009a), 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 2009b), 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 Screening 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 the OFC and 3 days after the OFC at Week 52, 104 and 156. 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 is not a protocol deviation. The participant should be made aware that completed measures are not reviewed by the investigator/study personnel.

8.6 Adverse events (AEs), serious adverse events (SAEs), and other safety reporting

The definitions of adverse events (AEs) and serious adverse events (SAEs) can be found in Section 8.6.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 8.6.3.

8.6.1 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 OFC, 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 under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 8.6.2):

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 or progression of underlying illness (i.e., progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single participant
3. Its duration (start and end dates or ongoing) and the outcome must be reported
4. Whether it constitutes a SAE (see Section 8.6.2 for definition of SAE) and which seriousness criteria have been met
5. Action taken 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
6. Its outcome

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 for at least 30 days or 5 half-lives following the last dose of study treatment.

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be not recovered/not resolved (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 participants

with the underlying disease. Alert ranges for laboratory and other test abnormalities are included in Section 10.3.1.

Please refer to Section 10.7 for the assessment, reporting and management of hypersensitivity reactions observed during the OFC and the post-OFC observation period.

8.6.2 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, fetal death or a congenital abnormality or 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.

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

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

8.6.3 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 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). 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 last study 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). An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a 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 study 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 European Union (EU) Clinical Trial Regulation 536/2014 or as per national regulatory requirements in participating countries.

8.6.4 Pregnancy

Details of all pregnancies in female participants will be collected after the start of study treatment and until 5 half-lives after the 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 as described in Section 8.6.3. 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, and the pregnancy consent form should be presented to the trial participant. The participant must be given adequate time to read, review and sign the pregnancy consent form. This consent form is necessary to allow the Investigator to collect and report information regarding the pregnancy. To ensure participant safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

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

After consent is provided, the pregnancy reporting will occur up to one year after the estimated date of delivery.

8.6.5 Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs

Not applicable.

8.6.6 Adverse events of special interest

The following safety topics of interest are described in the Investigators Brochure edition 18 “Section 7: Summary of the data and guidance for the investigator”: Injection site reactions, Hypersensitivity reactions (including anaphylaxis), CCI Thrombocytopenia, Parasitic (Helminthic) infection, and Reduction in vaccine efficacy.

8.6.7 Medical device deficiencies

Not applicable.

8.7 CCI

CCI

8.8 CCI

8.8.1 CCI

8.8.2 CCI

8.9 CCI

8.9.1 CCI

CCI

8.9.2 CCI

8.10 Health economics OR Medical resource utilization and health economics

Not applicable.

9 Statistical considerations

CCI

9.1 CCI

9.2 Statistical analyses

9.2.1 CCI

9.2.2 CCI

9.2.3 CCI

9.3 Primary endpoint(s)/estimand(s) analysis

9.3.1 Definition of primary endpoint(s)

The primary objective of the study is to assess the long-term safety and tolerability of ligelizumab in participants with food allergy for an additional three year period after a core study.

Primary endpoints are overall incidence and exposure-adjusted occurrence rates of treatment-emergent adverse events (TEAEs) and serious adverse events (TESAEs).

TEAEs are defined as events that either: 1) started after the first dose of study treatment and within 16 weeks after the last study treatment; or 2) began prior to the first dose of study treatment but increased in severity (based on preferred term) within 16 weeks after the last study treatment.

For all safety analyses, the safety sets defined in Section 9.1 will be used. All participants enrolled into the extension study, regardless of which preceding studies they came from, will be included in the safety analysis. All listings and tables will be presented by treatment dose. All data will be included in the analysis, regardless of rescue medication use.

9.3.2 Statistical model, hypothesis, and method of analysis

There is no pre-specified hypothesis for the primary endpoints, and no inferential analysis will be done for the primary endpoints.

Summary statistics will be provided.

Summaries will include: 1) the number and percentages of participants with at least one event (incidence rates); and 2) exposure-adjusted occurrence rates (the number of events per participant year of exposure). The following treatment-emergent AE summaries will be provided for the Safety Set 1 (SAF-1), presented by dose and cumulative duration of exposure:

- Overall, by primary system organ class and preferred term,
- Overall, by primary Standardized MedDRA Query (SMQ) and preferred term,
- Overall, by primary system organ class, preferred term and maximum severity,
- Suspected drug-related AEs by primary system organ class and preferred term,
- SAEs by primary system organ class and preferred term,
- AEs leading to permanent discontinuation of study-drug by primary system organ class and preferred term,
- Adverse events of special interest (AESI).

Other tables will be generated to summarize safety data for participants in SAF-1 who restarted study treatment after a protocol mandated interruption period (> 16weeks). Details will be provided in the SAP.

Summaries will be performed as well for non-TEAEs for participants who did not receive any study treatment doses during the extension study (SAF-2).

Separate summaries will be provided for study treatment-related adverse events, death, serious adverse events, and 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.

Other safety analyses (laboratory data, vital signs, ECG) are described in Section 9.4.2.

9.3.3 Handling of intercurrent events of primary estimand (if applicable)

Not Applicable

9.3.4 Handling of missing values

Missing data will not be replaced.

9.3.5 Multiplicity adjustment (if applicable)

Not Applicable

9.3.6 Sensitivity analyses

Not Applicable

9.3.7 Supplementary analysis

Supplementary analyses will be described in the SAP

9.4 Secondary endpoint(s)/estimand(s) analysis

No multiplicity adjustment will be carried out for secondary analyses described below.

9.4.1 Efficacy and/or pharmacodynamic endpoint(s)

In order to describe the long-term efficacy of ligelizumab, as measured by the tolerance of an allergen food protein, summaries will be provided for the proportion of participants tolerating a single dose of ≥ 600 mg of peanut protein without dose-limiting symptoms during an open-label OFC at scheduled timepoints. Additional analysis methods may be specified in the SAP.

9.4.2 Safety endpoints

Safety analyses will be conducted on SAF-1 and may be conducted on other safety analysis sets as well. All listings and tables will be presented by treatment group.

Adverse events

Analysis of adverse events has been described in Section 9.3: Analysis of the Primary Endpoint.

Vital signs

Change from baseline in vital sign measurements for each post-baseline visit will be analyzed using summary statistics, for each vital sign and treatment group.

Change from baseline will only be summarized for subjects with both baseline and post-baseline values. Missing values will not be imputed. Subjects with notable vital signs, as defined in Section 10.3, will be listed.

12-lead ECG

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

Clinical laboratory evaluations

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

9.4.3 Patient reported outcomes

As described in Section 8.5.1, the impact of ligelizumab on the HRQoL of participants with a food allergy will be assessed by several measures based on age group and responder type.

Summaries of domain and total scores in the FAQLQ, FAIM and SF-36v2 will be reported by age and responder (participants and/or caregiver) at scheduled timepoints.

Further details will be provided in the SAP.

9.5 Exploratory endpoint(s)/estimand(s) analysis

CCI

9.5.1 CCI

CCI

9.5.2 CCI

CCI

9.5.3 CCI

CCI

9.5.4 DNA

CCI

9.6 (Other) Safety analyses

Refer to the SAP for details

9.7 Other analyses

Not applicable.

9.8 Interim analysis

One or more interim analyses may be conducted to support decision-making in relation to the current clinical study, the future of the sponsor's clinical development plan, or the long-term safety and efficacy of ligelizumab. Additional details will be provided in the SAP.

9.9 Sample size determination

9.9.1 Primary endpoint(s)

The expectation is that approximately 550 participants from the Study CQGE01G12301 and other QGE031 Phase III studies will enroll in this extension study, after accounting for an estimated drop-out rate of 15% during the core phase of the studies.

No hypothesis testing is planned in the extension study.

9.9.2 Secondary Endpoints

All participants will have the opportunity to receive ligelizumab during the study. This sample size is sufficient to yield adequate precision in estimating AE rates in this study. For example, if one percent of 200 participants has an AE, the exact 95% Clopper-Pearson confidence interval for the proportion of participants would be 0.12% to 3.6%. The table below gives the 95% confidence intervals for varying sample sizes and incidence rates, assuming approximately 200 or 300 subjects are in each treatment dose group.

Table 9-1 Precision Levels (95%) for sensitivity of safety incidence rate

Number of Participants	Event Rate (%)	95% Confidence Interval
200	1	(0.12%, 3.6%)
	2	(0.55%, 5%)
	3	(1.10%, 6.4%)
300	1	(0.21%, 2.9%)
	2	(0.74%, 4.3%)
	3	(1.40%, 5.6%)
550	1	(0.35%, 2.2%)
	2	(1.00%, 3.6%)
	3	(1.70%, 4.8%)

Confidence intervals generated using the exact Clopper-Pearson method.

10 Supporting documentation and operational considerations

10.1 Appendix 1: Regulatory, ethical, and study oversight considerations

10.1.1 Regulatory and ethical considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
- Applicable ICH Good Clinical Practice (GCP) guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an Institutional Review Board/Independent Ethics Committee (IRB/IEC) by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments/modifications to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The Investigator will be responsible for the following:

Signing 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

Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC

Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures

Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

Inform Novartis immediately if an inspection of the clinical site is requested by a regulatory authority

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 Clinical Trial Regulation 536/2014, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

10.1.2 Informed consent process

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 (defined as parent/caregiver) 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.

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 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.

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

The 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.

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

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

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

The following informed consents are included in this study:

- Main study consent, which also includes:
  - A subsection that requires a separate signature for the 'Optional Consent for Additional Research' to allow future research on data/samples collected during this study
- Parent/Guardian study consent
- Child Assent for ages 6-11 years
- Adolescent Assent for ages 12-17 years
- As applicable, Pregnancy Outcomes Reporting Consent for female participants

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.

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

As per Section 4.5, during a public health emergency as declared by local or regional authorities i.e., pandemic, epidemic or natural disaster, that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, Investigator may conduct the informed consent discussion remotely (e.g., telephone, videoconference) if allowable by a local health authority.

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

10.1.3 Data protection

Participants will be assigned a unique identifier by Novartis. Any participant records or datasets that are transferred to Novartis will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by Novartis in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Novartis, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Novartis has appropriate processes and policies in place to handle personal data breaches according to applicable privacy laws.

10.1.4 Committees structure

10.1.4.1 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 monitor the safety in this study including events incurred during OFC at defined intervals the progress of a clinical trial and recommend to Novartis whether to continue, modify, or terminate a trial.

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 Novartis and the DMC.

10.1.4.2 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 Novartis.

There are three ACs in this study: anaphylactic events, cardio-cerebrovascular events and 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 above three events. The clinical presentation and association of these events with pre-existing risk factors will be part of the assessment.

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.

10.1.5 Data quality assurance

Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan, contracts.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of Novartis. No records may be transferred to another location or party without written notification to Novartis.

10.1.5.1 Data collection

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

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

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

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

10.1.5.2 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.

10.1.6 Source documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The Investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. The Investigator must also keep the original

informed consent form signed by the participant (a signed copy is given to the participant). Definition of what constitutes source data and its origin can be found in, e.g., source data acknowledgment and/or monitoring guidelines.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF. Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis / delegated CRO /CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

10.1.7 Publication policy

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in CTIS public website. 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, CTIS public website 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.

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

Summary results of primary and secondary endpoints will be disclosed based upon the global Last Participant Last Visit (LPLV) date, since multinational studies are locked and reported based upon the global LPLV.

10.1.8 Protocol adherence and protocol amendments

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.

10.1.8.1 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.

10.2 Appendix 2: Abbreviations and definitions

10.2.1 List of abbreviations

AC	Adjudication Committee
ACE	Angiotensin-converting-enzyme
CCI	[redacted]
AE	Adverse Event
AESI	Adverse Events of Special Interest
AF	Adult form
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANA	Antinuclear Antibodies
ASMA	Anti-smooth muscle antibody
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
ATS/ERS	American Thoracic Society / European Respiratory Society
AUC	Area under the Curve
AxMP	Auxiliary Medicinal Product
CCI	[redacted]
bpm	Beats per minute
BUN	Blood Urea Nitrogen
CD23	IgE (low affinity) receptor
CF	Child form
CIOMS	Council for International Organizations of Medical Sciences
CK	Creatine Kinase
cm	centimetre
CMO&PS	Chief Medical Office and Patient Safety

CMV	Cytomegalovirus
COA	Clinical Outcome Assessment
CoFAR	Consortium of Food Allergy Research
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus pandemic 2019
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSR	Clinical study report
CSU	Chronic Spontaneous Urticaria
CV	coefficient of variation
DBL	Database lock
DBPCFC	Double Blind Placebo Controlled Food Challenge
DILI	Drug-Induced Liver Injury
DIN	Drug Inducted Nephrotoxicity
DLS	Dose Limiting Symptoms
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
EAACI	European Academy of Allergy and Clinical Immunology
EBV	Epstein-Barr virus
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EEA	European Economic Area
EMA	European Medicines Agency
EOFu	End of Follow-up
EoT	End of Treatment
ERCP	Endoscopic Retrograde Cholangiopancreatography
eSource	Electronic Source
EU	European Union
FAIM	Food Allergy Independent Measure
FAQL	Food allergy quality of life
FAQLQ	Food Allergy Quality of Life Questionnaire
FAS	Full Analysis Set
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
GGT	Gamma-glutamyl transferase
GLDH	Glutamate Dehydrogenase
h	Hour
HBsAg	Hepatitis B virus surface antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HEV	High endothelial venules
HRQoL	Health-Related Quality of Life

HSV	Herpes simplex virus
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
IFU	Instructions for Use
IgE	Immunoglobulin E
IMP	Investigational Medicinal Product
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine device
IUS	Intrauterine system
L	Litre
LDH	lactate dehydrogenase
LFT	Liver function test
LLOQ	lower limit of quantification
LPLV	Last patient last visit
mAb	Monoclonal Antibody
CCI	[redacted]
MCV	Mean corpuscular volume
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
mm	millimeter
mmHg	millimeters of mercury, blood pressure measurement
MR	Maximum Responder
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NIH	National Institute of Health
No.	Number
NSD	Needle safety device
OFC	Oral Food Challenge
OHP	Off-site Healthcare Professional
OIT	Oral Immunotherapy
OL-OFC	Open label oral food challenge
PB	Parental burden
PCM	Peanut Challenge Meal
PD	Pharmacodynamic(s)
PF	Parental form
PFS	Pre-filled syringe
CCI	[redacted]
PRACTALL	Practical Allergy
PRO	Patient Reported Outcomes

PSD	Premature Subject Discontinuation
PT	prothrombin time
PTA	Post trial access
q2w	every two weeks
QoL	Quality of Life
QTcF	QT interval corrected by Fridericia's formula
RBC	Red Blood Cells
RNA	Ribonucleic acid
SABA	short-acting ß-agonist
SAE	Serious Adverse Event
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SC	subcutaneous
CCI	[redacted]
SCRN	Screening
SD	standard deviation
SF-36v2	Acute Version – Medical Outcomes Study 36-Item Short Form Version 2 Acute Version (recall period is past week)
CCI	[redacted]
CCI	[redacted]
SLIT	Sublingual immunotherapy
SMQ	Standardized MedDRA Query
SoA	Schedule of Activities
SPT	Skin Prick Test
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBL	Total Bilirubin
TEAEs	Treatment Emergent Adverse events
TESAEs	Treatment Emergent Serious Adverse Events
TF	Adolescent form
TSH	Thyroid stimulating hormone
TSPT	Titration skin prick test
ULN	upper limit of normal
ULQ	Upper limit of quantification
WBC	White blood cells
WHO	World Health Organization
WK	Week
β-hCG	Beta-Human Chorionic Gonadotropin
µL	microlitre

10.2.2 Definitions

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
Auxiliary medicinal product	As per EU CTR Auxiliary Medicinal Product is: Medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product (e.g., rescue medication, challenge agents, background treatment or medicinal products used to assess end-points in the clinical

	trial). Concomitant therapy is not considered as AMP.
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
CE marking	A marking by which a manufacturer indicates that a device is in conformity with the applicable requirements set out in European Union legislation providing for its affixing. CE marking of medical devices is required prior to lawfully placing them on the European Union market.
Clinical Outcome Assessment (COA)	A measure that describes or reflects how a participant feels, functions, or survives
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 intervention (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
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g., q28 days)
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 intervention 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.
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained. The action of enrolling one or more participants
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 Novartis 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.
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.

Investigational drug/ treatment	The drug whose properties are being tested in the study
Investigational Medical Device	Medical Device being assessed for safety or performance in a clinical investigation. This includes devices already on the market and being evaluated for new intended uses, new populations, new materials, or design changes
Medication number	A unique identifier on the label of medication kits
Mis-randomized participants	Mis-randomized participants are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study or the participant allocated to an invalid stratification factor
Off-site	Describes trial activities that are performed at remote location by an off-site healthcare professional, such as procedures performed at the participant's home.
Off-site healthcare Professional (OHP)	A qualified healthcare professional, who performs certain protocol procedures for the participant in an off-site location such as a participant's home.
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e., concomitant or rescue therapy)
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" terminology is used in the protocol whereas term "Subject" is used in data collection
Participant number	A unique number assigned to each participant upon signing the informed consent. 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 participant about the status of a participant's health condition without amendment or interpretation of the participant'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
Remote	Describes any trial activities performed at a location that is not the investigative site.
Rescreening	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
Run-in Failure	A participant who is screened but not randomized/treated after the run-in period (where run-in period requires adjustment to participant's intervention or other treatment)
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

Stage in cancer	The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant
Study device	Study device is a medical device (marketed or investigational) that is used in a circumstance that makes it part of the investigation.
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
Tele-visit	Procedures or communications conducted using technology such as telephone or video-conference, whereby the participant is not at the investigative site where the Investigator will conduct the trial.
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Treatment of interest	The treatment of interest and, as appropriate, the alternative treatment to which comparison will be made. These might be individual interventions, combinations of interventions administered concurrently, e.g., as add-on to standard of care, or might consist of an overall regimen involving a complex sequence of interventions. This is the treatment of interest used in describing the related clinical question of interest, which might or might not be the same as the study treatment.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of consent	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.

10.3 Appendix 3: Clinical laboratory tests

10.3.1 Clinically notable laboratory values and vital signs

Laboratory assessments

Refer to Section 10.5 for clinically notable laboratory values for liver safety monitoring.

Refer to Section 10.6 for clinically notable laboratory values for renal safety monitoring

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

- Platelets < 75 000/µL
- Any participant who has platelets < 75 000/µL after first study drug administration 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 (6-11 years) and adolescents, the notable values are described in Table 10-1:

Table 10-1 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	
	Blood pressure (mmHg)			
Age (years)	**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)

10.4 Appendix 4: Participant Engagement

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

- Thank You letter
- Plain language trial summary - after CSR publication

10.5 Appendix 5: Liver safety monitoring

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

Please refer to Table 10-2 in Appendix 5 for complete definitions of liver laboratory triggers.

Once a participant is exposed to study treatment, every liver event defined in Table 10-3 should be followed up by the Investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 10-4. 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 the Discontinuation of study treatment section), if appropriate
- Hospitalization of the participant if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include
    - These investigations can include based on Investigator's discretion: serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease

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

10.5.1 Liver event and laboratory trigger definitions & follow-up requirements

Table 10-2 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*

	Definition/ threshold
If ALT or AST abnormal at baseline:	● ALT or AST > 3x baseline or > 300 U/L (whichever occurs first)

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; non-infectious hepatitis; benign, malignant and unspecified liver neoplasms ULN: upper limit of normal

Table 10-3 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 AND > 5 x ULN for more than two weeks	Normal For participants with Gilbert's syndrome: No change in baseline TBL	None	● **Interrupt 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 > 8 x ULN	Normal	None	● Initiate close monitoring and workup for competing etiologies.
ALT increase with bilirubin increase:			● Study treatment can be restarted only if another etiology is identified and liver enzymes return to baseline.
If normal at baseline: ALT > 3 x ULN **If elevated at baseline:** ALT > 2 x baseline or > 300 U/L (whichever occurs first)	TBL > 2 x ULN (or INR > 1.5) For participants with Gilbert's syndrome: Doubling of direct bilirubin	None	
If normal at baseline: ALT > 3 x ULN **If elevated at baseline:** ALT > 2 x baseline or > 300 U/L (whichever occurs first)	Normal or elevated	Severe fatigue, nausea, vomiting, right upper quadrant pain	

Table 10-4 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

Criteria	Actions required	Follow-up monitoring
> 3 - 10 × ULN (in the absence of known Gilbert syndrome)	● Interrupt treatment ● Repeat LFT within 48-72 hours ● Hospitalize if clinically appropriate ● Establish causality ● Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	Monitor LFTs weekly until resolution to ≤ Grade 1 or to baseline (ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 10 x ULN	● Discontinue the study treatment immediately ● Hospitalize the participant ● Establish causality ● Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT until resolution (frequency at Investigator discretion)
Any AE potentially indicative of a liver toxicity*	● Consider study treatment interruption or discontinuation ● Hospitalization if clinically appropriate ● Establish causality ● Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	Investigator discretion

[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 an elevated level after a maximum of 6 months, (6) 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.

10.6 Appendix 6: Renal safety monitoring

The following base monitoring for renal laboratory values, as per the Novartis Drug-Induced Nephrotoxicity Guidelines (Nov 2017; Table 10-5 below) of abnormal renal laboratory values will be carried out as part of the assessment schedule (Table 1-4) during the course of the study.

Table 10-5 Base Renal Monitoring

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

Every renal laboratory trigger or renal event as defined in Table 10-6 should be followed up by the investigator or designated personnel at the trial site as summarized in Table 10-7.

10.6.1 Specific Renal Alert Criteria and Actions and Event Follow-up

Table 10-6 Specific renal alert criteria and actions

Renal Event	Actions
Confirmed serum creatinine increase 25% – 49%	• Consider causes and possible interventions • Follow-up within 2-5 days
Serum creatinine increase ≥ 50% [+] OR if <18 years old, eGFR ≤ 35mL/min/1.73 m2	• Consider causes and possible interventions • Repeat assessment within 24-48h if possible • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected • Consider 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 10-7 Renal event follow-up

FOLLOW-UP OF RENAL EVENTS
Assess+, document and record in CRF • Urine dipstick and sediment microscopy evidence of DIN: crystals, red blood cells (dysmorphic/glomerular vs. non-dysmorphic/non-glomerular), white blood cells, tubular epithelial cells • Blood pressure and body weight • Serum creatinine, BUN, electrolytes (sodium, potassium, phosphate, calcium), bicarbonate and uric acid • Urine output
Review and record possible contributing factors to the renal event (co-medications, other co-morbid conditions) and additional diagnostic procedures (MRI etc) in the CRF
Monitor 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 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

10.7 Appendix 7: Oral Food Challenge

10.7.1 Background

The Oral Food Challenge (OFC) represents the gold standard for diagnosing food allergies. 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 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 6-4 and Table 6-5).

Intravenous access may be set up before the OFC 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 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 3) is ingested (refer to the QGE031G12303B Pharmacy Manual)

10.7.2 Dosing Schedule

This study includes OFC as per the Assessment Schedule (Table 1-4). Each OFC consists of an active allergen peanut challenge meal.

Study treatment must be administered at least 1 hour before the OFC. If study treatment is started based on the responder-driven approach (Previous MR is no longer MR after being off-treatment (Section 4.1.2) the time interval between the OFC and restart of study treatment must be a minimum of 24 h.

10.7.2.1 Maximum dose

Within the OFC, incremental allergen dose increases continue until the highest dose for the challenge has been reached or until the participant displays (a) dose-limiting symptom(s) (Section 10.7.5).

For the OFC, three hundred (300) mg of food protein is estimated to correspond to the amount of allergen generally associated with accidental exposure, while CCI corresponds to the highest food protein dose used within this protocol.

The OFC allergen doses are indicated by dry weight (mg) in Table 10-8. The allergen granules are to be reconstituted for administration and given to the participant in portions measured by

volume (mL) starting from the lowest dose. Refer to the Pharmacy Manual for complete preparation and administration instruction.

10.7.2.2 OFC allergen dose administration instruction

Table 10-8 Allergen Dosing Table (active ingredient dry weight)

Allergen dose No.	Food allergen protein (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	CCI	CCI

After each administered dose of reconstituted allergen, 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 10.7.5)

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 the 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 OFC, 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.

10.7.3 Peanut OFC material

Novartis will supply the Oral Food Allergen Peanut Flour Chocolate Meal Base 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)

Pharmaceutical Dosage Form: Granules for oral suspension

Route of Administration: Oral

The Peanut Challenge Meal (PCM001) will be used for the open-label OFC. This Auxiliary Medicinal Product (AxMP) is currently not approved for marketing in any country worldwide. It is important to conduct OFC by using standardized material in this study, however, there is currently no authorized AxMP available appropriate for this trial, therefore PCM001 will be used.

The food challenge material and preparation instructions are described in detail in the QGE031G12301B Pharmacy Manual provided separately.

10.7.4 Preparing for the food challenge

Prior to OFC material preparation, study site personnel need to access the IRT system to obtain the allergen kit number to be used.

10.7.5 Evaluation parameters of the OFC

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 OFC will be considered **positive** with the occurrence of any dose-limiting symptom(s). Dose-limiting symptoms indicate a true allergic reaction occurring during the administration of a single dose that should preclude the administration of any further doses. Investigators should refer to Table 10-9 (CoFAR grading scale) for the 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 10-9 are considered dose-limiting.

Symptoms requiring administration of any rescue medication (e.g., SABA, epinephrine or other) are considered dose-limiting. 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 OFC 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 OFC-related allergic reactions should be recorded on the respective eCRF. The OFC will be considered **negative** if a participant does not exhibit (a) dose-limiting symptom(s) (= positive challenge) at the end of the challenge.

Table 10-9 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	● 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	● 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

without decreased activity), isolated emesis thought to be secondary to gag	• GI – persistent moderate abdominal pain/cramping/nausea with decreased activity, vomiting

10.7.6 OFC completion

At the completion of the OFC (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-OFC participants should be provided with a 24-hour emergency telephone contact. Furthermore, participants should be advised to avoid physical exercise within 2 hours after receiving the last dose of the OFC.

Delayed or late-onset reactions to the OFC are defined as reactions occurring after the participant was discharged from the clinic. Since a delayed reaction to the OFC 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 OFC (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 CRF and reported as described in Section 8.6.3 SAE Reporting.

The administration of study medication will precede the OFC. Investigators should apply their medical judgement when assessing if reactions occurring during the OFC or during the post-OFC 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 OFC should be captured on the designated CRFs, and if serious, be reported as described in Section 8.6.3 SAE Reporting. For such SAEs,

a causality assessment to either study treatment or OFC must be provided and documented together with its medical rationale.

10.8 Appendix 8: Guidance for Skin Prick Test

10.8.1 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). These diagnostic agents to test for allergic diseases (ATC code: V04CL) qualify as auxiliary medicinal products (AxMP) under the European Clinical Trial Regulation 536/2014. The products used in European Economic Area (EEA) countries are authorized at least in one EEA member state. SPT assessments are performed before study drug dosing as per the Assessment Schedule Table 1-4.

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; 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 has to be tested (if indicated by medical history).

Positive and negative controls should be tested together.

10.8.2 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 peanut and milk and/or egg (if indicated in the medical history).

Positive and negative control always need to be tested together.

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 stock (-undiluted), peanut (1:10), peanut (1:100), peanut (1:1'000), peanut (1:10'000), peanut (1:100'000), milk (undiluted), and egg (undiluted).

10.8.3 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.
- Test time: Skin reactions should be recorded after 15 minutes of dropping the allergen to the pricked location.
- Positive/negative control: The SPT must be repeated if the results for the positive control (≥ 3 mm average wheal diameter) and/or negative control (0 mm wheal diameter) were not obtained.
- Medications to be washed out prior to the SPT are listed in Table 10-10.

Table 10-10 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

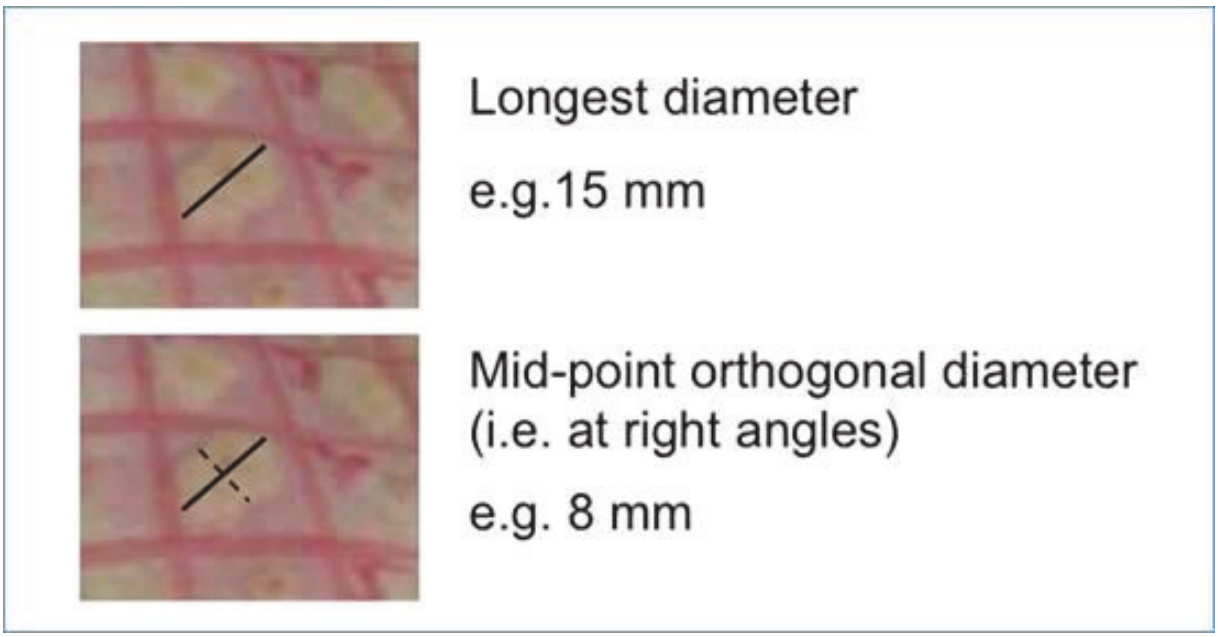
10.8.3.1 Performing the Skin Prick Test

Clean the area of the skin with 70% alcohol and allow it 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 the 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 different 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).

Figure 10-1 Measurement of skin reaction



10.8.4 Completion of the Skin Prick Test

After measurement of skin reaction and recording them in the source document, clean the skin with alcohol to remove the ink from the 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 8.6.3.

10.9 Appendix 9: PRO Measures

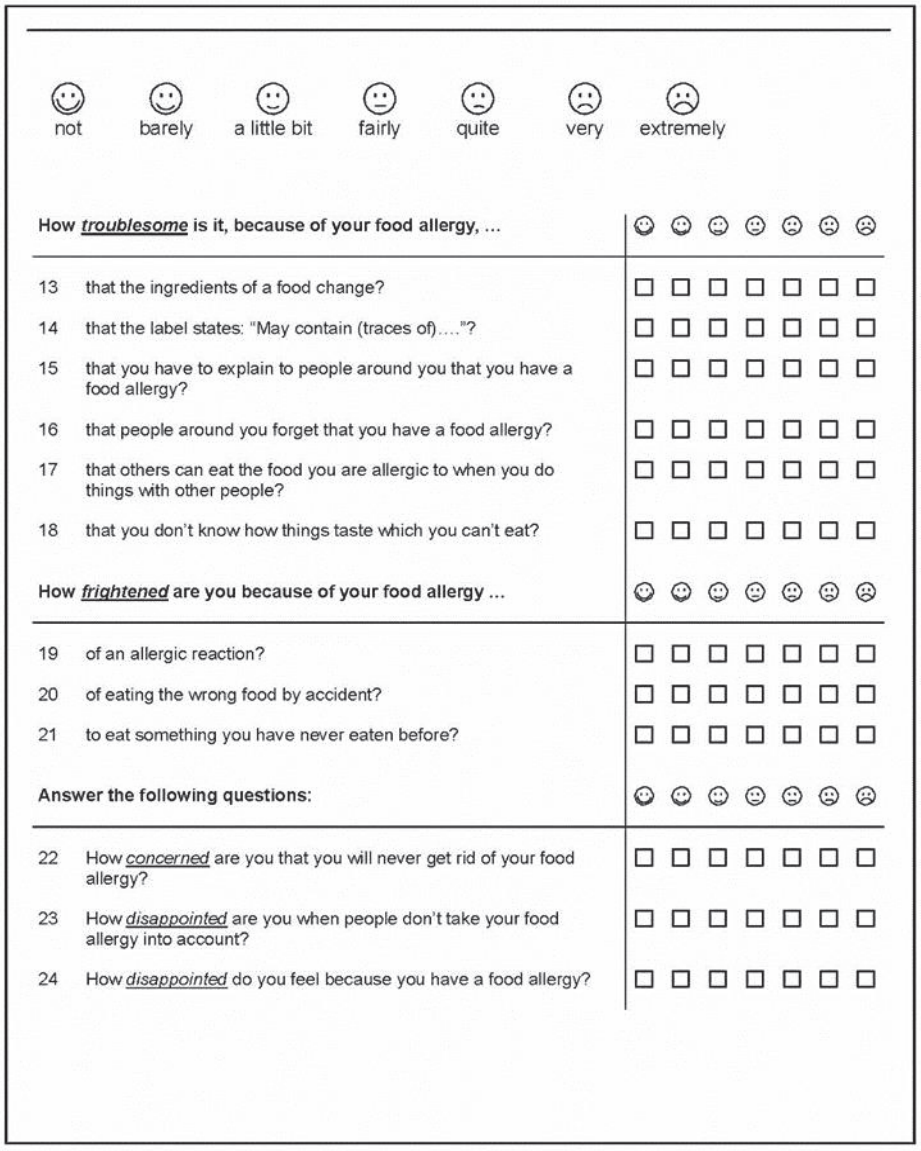
10.9.1 FAQLQ-CF: Food Allergy Quality of Life Questionnaire Child Form

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?	☐



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?	☐	☐	☐	☐	☐	☐	☐

10.9.2 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?**	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?**
☐ almost none	☐ so little I don't actually notice it
☐ very few	☐ very little
☐ a few	☐ little
☐ some	☐ moderately

10.9.3 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	☐	☐	☐	☐	☐	☐	☐

10.9.4 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

10.9.5 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?	☐	☐	☐	☐	☐	☐	☐

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?	☐	☐	☐	☐	☐	☐	☐

10.9.6 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	1	2	3	4	5	6
never (0% chance)	very small chance	small chance	fair chance	great chance	very great chance	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

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

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

10.9.8 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	☐	☐	☐	☐	☐	☐	☐

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?	☐	☐	☐	☐	☐	☐	☐

10.9.9 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	
	SF-36v2® Health Survey © 1992, 2000, 2010, 2012 Medical Outcomes Trust and QualityMetric Incorporated. All rights reserved. SF-36® is a registered trademark of Medical Outcomes Trust. (SF-36v2® Health Survey Acute, United States (English))						

10.9.10 Home Administration Study Drug Diary (example)

CQGE031G12303B – Home Administration Study Drug Diary

	Questions/answers	Triggers
Q1	If you /participant are a female who can get pregnant, please perform a pregnancy test prior to injecting the study treatment. If the result is positive DO NOT inject the study treatment and inform the site personnel.	Only show to female participants
Instruction screen	**Study treatment pre-filled syringe injections** Reminder: The dose includes 2 injections. At each site visit, please return unused/used kit packaging.	
Q2	Has the study drug been injected? Yes / No	If Yes, go to Q3. If No, skip Q3, go to Q4 and end of the diary.
Q3	How many injections did you have? 1 / 2	If 1, go to Q5, Q6, Q7, and Q9. If 2, skip Q4 and go to Q5, Q6, Q7, Q8, and Q9.
Q4	You had 0 or 1 injection, select the reason: Participant decision Parent/Caregiver decision Adverse Event Technical Problems Pregnancy	
Q5	Please enter the date of injection(s): *Date picker*	
Q6	Please enter the time of injections: *Time picker* (Hour: minutes)	
Q7	Select the site of the 1st injection. Left Thigh Right Thigh Left Abdomen Right Abdomen Left Upper Arm Right Upper Arm	
Q8	Select the site of the 2nd injection. Left Thigh Right Thigh Left Abdomen Right Abdomen Left Upper Arm Right Upper Arm	
Q9	Who performed the injections? Myself Parent/Caregiver Study site personnel	

10.9.11 CCI [redacted]

10.9.11.1 CCI [redacted]

10.9.11.2CCI

11 References

References are available upon request

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