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Clinical Development

CQGE031G12303B / NCT05678959

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

Statistical Analysis Plan (SAP)

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CCI

Table of contents

List of tables

List of figures

List of abbreviations

AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
AUC	Area under Curve
CCI	[redacted]
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
CCV	Cardiovascular and cerebrovascular
CD23	IgE (low affinity) receptor
CI	confidence intervals
CM	Concomitant Medication
Covid-19	Corona Virus Disease 2019
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract research organization
CSR	Clinical study report
CV	Coefficient of variation
DBL	Database Lock
DBPCFC	Double Blind Placebo Controlled Food Challenge
DLS	Dose limiting symptom
EAIR	Exposure adjusted
ECG	Electrocardiogram
eCRF	Electronic case report form
eCRS	Electronic case retrieval strategy
EOS	End of study
FAIM	Food Allergy Independent Measure
FAQLQ	Food Allergy Quality of Life Questionnaire
FAS	Full Analysis Set
FcεRI	IgE (high affinity) receptor
h	Hour
HR	Heart rate
HRQoL	Health-Related Quality of Life
IgE	Immunoglobulin E *(specific and un-specific for the study allergen)*
IgG	Immunoglobulin G
IS	Independent Statistician
L	Liter
CCI	[redacted]
MedDRA	Medical dictionary for regulatory activities
mg	Milligram(s)
mL	Milliliter(s)
mm	Millimeter
mmHg	Blood pressure unit millimeters of mercury
MR	Maximum responder
ms	Millisecond
OFC	Oral Food Challenge
PD	Pharmacodynamic(s)
CCI	[redacted]

PRO	Patient Reported Outcomes
PT	Preferred term
q4W	Every 4 weeks
RR	Responder rate
SAE	Serious Adverse Event
SAF	Safety analysis set
SAP	Statistical analysis plan
SC	Subcutaneous
SCq4W	Subcutaneous injection every 4 weeks
SD	Standard deviation
CCI	[redacted]
SMQ	Standardized MedDRA Query
SOC	System organ class
SPT	Skin Prick Test
TEAE	Treatment-emergent adverse events
TESAE	Treatment-emergent serious adverse events
Total IgE	Drug-bound and free IgE
µL	Microliter

1 Introduction

The purpose of this Statistical Analysis Plan (SAP) is to describe the statistical analyses mentioned in version of the Phase 3 study CQGE031G12303B protocol. This document covers the statistical and analytical plans for the Clinical Study Report (CSR).

After thorough consideration, Novartis decided to terminate the study early. This was a consequence of a broader Novartis company strategic decision and was by no means due to the detection of any potential safety signal. Due to the early termination, the scope of analysis will be limited.

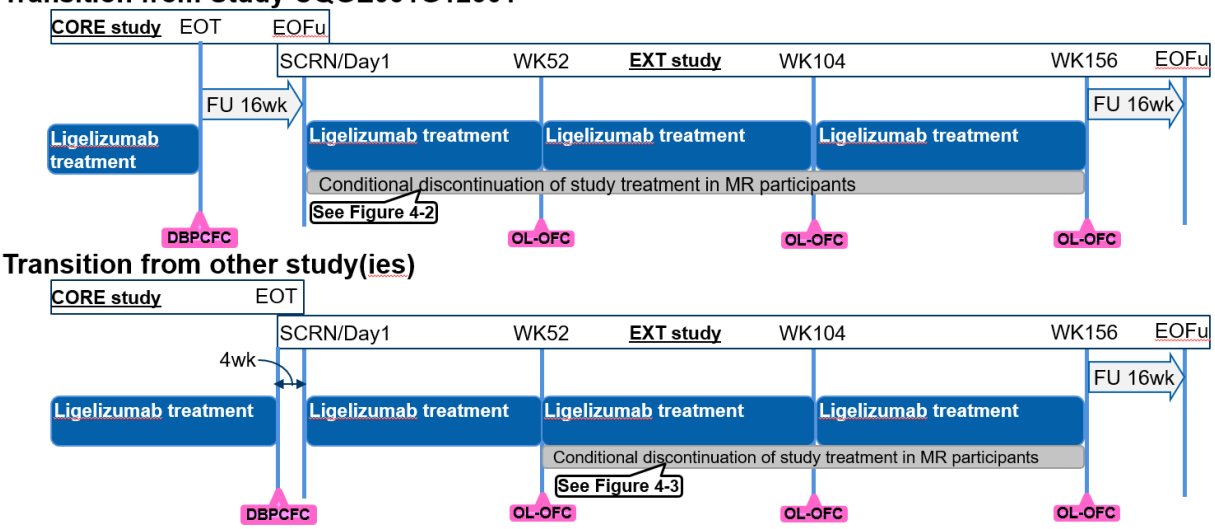
1.1 Study design

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. This is 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. Please refer below to the schematic diagram of the study, including transition from core study (Figure 1-1).

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 the level of desensitization. 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.

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.

The participants from study CQGE031G12301 will transition into the extension study after completion of the follow-up period (washout) in the core study (Refer Figure 4-1 from the protocol). 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.

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 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 (Refer Figure 4-2 from the protocol).

For the participants who meet the definition of Maximum Responder (MR), 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.

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

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.

1.2 Study objectives, endpoints and estimands

Due to the early termination of the study, purely descriptive analyses will be performed for primary, secondary endpoints, and part of exploratory endpoints.

Table 1-1 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)

1.2.1 Primary estimand(s)

Not Applicable.

1.2.2 Secondary estimand(s)

Not Applicable.

2 Statistical methods

2.1 CCI

2.1.1 General definitions

2.1.1.1 CCI

2.1.1.2 CCI

2.1.1.3 CCI

2.1.1.4 CCI

2.1.1.5 CCI

2.1.1.6 CCI

2.2 CCI

CCI

2.2.1 CCI

CCI

2.3 CCI

CCI

2.3.1 CCI

CCI

2.3.2 CCI

CCI

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

Study treatment and compliance will be summarized for SAF-1.

2.4.1 Study treatment / compliance

The duration of exposure in weeks to each treatment group will be summarized using descriptive statistics.

Duration of exposure to study treatment will be calculated as the number of weeks between the first dose date and the last dose date exposed to that treatment over the specified period (Duration of exposure = (date of last known study treatment – date of first known study treatment + 28)/7).

In addition, the number of doses, total cumulative dose and number of missed doses will be summarized using descriptive statistics (see Section 2.1.1).

Listings on dose administration records will be provided.

2.4.2 Prior, concomitant and post therapies

Not required for CSR analysis.

2.5 Analysis supporting primary objective(s)

2.5.1 Primary safety 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 (EAOR) of treatment-emergent adverse events (TEAEs) and serious adverse events (TESAEs), however, due to early termination of the study, EAOR will not be calculated.

TEAEs are defined as events that either:

1) Where an AE either started after the first dose of extension study treatment and within 16 weeks after the last administered study treatment dose 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.

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.

This analysis will be based on SAF-1.

For all adverse events tables the events that the investigator classified as reactions associated to the Oral Food Challenge (OFC)or Skin Prick Test (SPT) will not be included in reporting of treatment-emergent adverse events (TEAEs).

2.5.2 Statistical method of analysis

Summary statistics for primary endpoints overall incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (TESAEs) will be provided as follows:

The number and percentages of participants with at least one event (incidence rates)

The crude incidence rate is defined as the percentage of participants with a specific adverse event divided by the total number of participants in each study group.

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

2.5.2.1 Exposure-Adjusted Incidence rate and 95% confidence interval

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

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

1. Time to the first episode of the i^{th} type event (if the event occurs),
2. Time to the end of observation period, or
3. duration of study treatment plus the 16-week washout period (approximately corresponding to five half-lives) after last treatment dose

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

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

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

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

1. TEAE and TESAE: Primary SOC level, PT level
2. Further safety analyses are defined in safety analyses (Section 2.8)

2.5.2.2 Adverse Events (AEs)

The following treatment-emergent AE summaries will be provided by overall and by treatment group for the Safety Set 1 (SAF-1), presented by dose and cumulative duration of exposure:

- Overview of all TEAEs: Number of participants with at least one (Any AE, Any SAE, Any AE related to study drug, Any AE leading to discontinuation of study treatment, Deaths etc.)
- TEAEs by primary system organ class and preferred term,
- TEAEs by primary Standardized MedDRA Query (SMQ) and preferred term,
- TEAEs by primary system organ class, preferred term and maximum severity,
- TESAEs by primary system organ class and preferred term,
- TEAEs leading to permanent discontinuation of study-drug by primary system organ class and preferred term,
- Treatment Emergent Adverse events of special interest (AESI),
- Study treatment-related adverse events by primary system organ class and preferred term,
- Deaths by primary system organ class and preferred term including listing of deaths,

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.

Separate summaries will be provided for study treatment-related adverse events, death, serious adverse events, and other significant adverse events leading to discontinuation.

2.5.2.3 Adverse events of special interest / grouping of AEs

AEs of special interest (AESI) are defined in the latest version of the compound electronic Case Retrieval Strategy (eCRS). The classification reflects the safety topics of interest identified in the current version of the QGE031 Development Safety Profiling Plan and may be updated based on review of accumulating data. The number and percentage of participants with treatment emergent AEs of special interest will be summarized by risk category, PT and treatment. The search criteria in the latest eCRS corresponding the MedDRA version at the database lock will be used and reported in the CSR:

- Hypersensitivity reactions (including anaphylaxis)
- Cardiovascular and Cerebrovascular (CCV) events

- Neoplastic conditions
- Injection site reactions
- Serum Sickness
- Eosinophilic Conditions / Churg-Strauss Syndrome
- Parasitic (Helminthic) infections
- Thrombocytopenia

Adjudicated AEs

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

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

2.5.3 Handling of intercurrent events

Not Applicable.

2.5.4 Handling of missing values not related to intercurrent event

Missing data will not be replaced.

2.5.5 Sensitivity analyses

Not Applicable.

2.6 Analysis supporting secondary objectives

2.6.1 Secondary endpoint(s)

Secondary objective [1] is 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.

To satisfy the above secondary objectives the following endpoint will be taken into consideration:

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. This analysis will be based on FAS.

Secondary objective [2] is to assess the safety and tolerability of ligelizumab in all participants who administered study treatment at home by self-administration or parent/caregiver.

To satisfy the above secondary objectives the following endpoint will be taken into consideration:

Overall incidence rates of treatment emergent-AEs and SAEs will be analysis based on SAF-1.

Secondary objective [3] is to assess the long-term impact of ligelizumab on the health-related quality of life (HRQoL) of patients with food allergy.

To satisfy the above secondary objectives the following endpoint will be taken into consideration:

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

This analysis will be based on FAS and latest available value at each visit will be used for summary.

Note: SF-36v2 completed by adults only.

For all efficacy endpoints, if missing Week 52-OFC assessments, Week 156-OFC assessments performed within 380 days (inclusive) after first extension dose date will be considered as Week 52-OFC assessments.

2.6.2 Statistical method of analysis

The analysis of 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 will be summarized with number and percentage of responders at Week 52, Week 104 and Week 156 by treatment group and overall.

To evaluate for all participants who administered study treatment at home by self-administration or parent/caregiver under the second secondary endpoints analysis for overall incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (TESAEs) will be summarized as per Section 2.5.2.

Summaries for change from baseline in FAQLQ, SF-36v2 and FAIM domain and total scores will also be provided by age group and responder (participants and/or parent/caregiver) at scheduled timepoints (Refer Section 2.12).

2.6.3 Handling of intercurrent events

Not Applicable.

2.6.4 Handling of missing values not related to intercurrent event

Missing data will not be imputed.

2.6.5 Sensitivity analyses

Not Applicable.

2.7 Exploratory analyses

CCI [redacted].

2.8 Safety analyses

All safety endpoints i.e. AEs, laboratory data and vital signs will be conducted on SAF-1, only wherever required summary and listings will be provided on SAF-2. All listings and tables will be presented by treatment group.

2.8.1 Requirements of ClinicalTrials.gov and EudraCT

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on treatment emergent AEs: non-serious AEs with an incidence greater than 3%, and deaths and serious AEs (SAEs) including the events suspected to be related to study treatment, will be provided by SOC and PT on the Safety Set. The cut-off of 3% can be re-evaluated based on number of patients.

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

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

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

2.8.2 Deaths

The number of deaths resulting from TEAEs will be summarized by SOC and PT. All the deaths in the clinical database including those occurring during screening will be listed.

2.8.3 Laboratory data

For selected parameters (Hematology & Clinical Chemistry) Shift tables using the low/normal/high (low and high) classification will be used to compare baseline to the worst post-baseline value. For the shift tables, the normal laboratory ranges will be used to evaluate whether the worst post-baseline value was normal, low, or high relative to whether or not the baseline value was normal, low or high. These summaries will be presented by laboratory parameter and visit.

Additionally, all-laboratory data will be listed.

2.8.4 Other safety data

2.8.4.1 Vital signs

Summary of abnormal vital signs will be provided for SAF-1 based on following criteria.

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

For adults:

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 2-1:

Table 2-1 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

2.9 CCI [redacted]

CCI [redacted].

2.10 CCI [redacted]

CCI [redacted]

2.11 Patient-reported outcomes

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 (completed by children aged 8-12)
- FAIM-CF: Food Allergy Independent Measure – Child Form (completed by children aged 8-12)
- FAQLQ-TF: Food Allergy Quality of Life Questionnaire – Teenager Form (completed by adolescents aged 13-17)
- FAIM-TF: Food Allergy Independent Measure – Teenager Form (completed by adolescents aged 13-17)
- FAQLQ-AF: Food Allergy Quality of Life Questionnaire – Adult Form (completed by adults aged 18-55)

- FAIM-AF: Food Allergy Independent Measure – Adult Form (completed by adults aged 18-55)
- FAQLQ-PF: Food Allergy Quality of Life Questionnaire – Parental Form (completed by same parent/caregiver of children aged 0-12)
- FAQL-PB: Food Allergy Quality of Life – Parental Burden Questionnaire (completed by same parent/caregiver of children aged 0-17)

Table 2-2 PROs based on participant's age

Age Group/ Respondent Type	Questionnaire	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 12	FAQLQ-CF	x	x	x	x	x	x	x
	FAIM-CF	x	x	x	x	x	x	x
Teenagers aged 13-17	FAQLQ-TF	x	x	x	x	x	x	x
	FAIM-TF	x	x	x	x	x	x	x
Adults aged 18+	FAQLQ-AF	x	x	x	x	x	x	x
	FAIM-AF SF-36v2	x	x	x	x	x	x	x
Parents/ Caregivers of Children aged 13-17	FAQLQ-PF	x	x	x	x	x	x	x
	FAQL-PB	x	x	x	x	x	x	x
Parents/ Caregivers of Children aged 12	FAQL-PB	x		x		x		x

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 (pre) the OFC and 3 days after (post) the OFC at Week 52, 104 and 156. For analysis, will consider latest non-missing measurements. If the 'post-' measurement is missing, then the non-missing 'pre-' measurement will be used. 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.

Scoring of PRO Instruments

The number of items and domains varies by FAQLQ instrument administered. Each question is scored on a 7-point scale (0-6 coded as 1-7 in analysis, with a higher level indicating greater impairment in HRQoL). The total score is the arithmetic average of all completed items. Domain scores are calculated similarly for each form as following:

FAQLQ-CF: Emotional impact (EI) (item no. 19-24), Allergen avoidance (AA) (item no. 4, 6-10, 15), Risk of accidental exposure (RAE) (item no. 11, 13, 14, 16, 17), Dietary restriction (DR) (item no. 1-3, 5, 12, 18)

FAQLQ-TF: Emotional impact (EI) (item no. 5, 12, 19-23), Allergen avoidance and dietary restrictions (AADR) (item no. 1-4, 6-10, 16), Risk of accidental exposure (RAE) (item no. 11, 13-15, 17, 18)

FAQLQ-AF: Emotional impact (EI) (item no. 5, 24-29), Allergen avoidance and dietary restrictions (AADR) (item no. 1-4, 6, 8-12, 20), Risk of Accidental Exposure (RAE) (item no. 7, 13-18, 21), Food allergy related health (FAH) (item no. 19, 22, 23)

FAQLQ-PF: Emotional impact (EI) (item no. 2, 6, 7, 9-11, 23-28, 30), Food anxiety (FA) (item no. 1, 4, 5, 16, 17, 20, 21, 29), Social and dietary limitations (SDL) (item no. 3, 8, 12-15, 18, 19, 22).

If more than one item in any domain is missing, a domain score should not be calculated for that case. A total score can still be calculated if 20% or fewer of the items are missing.

The FAIM reflects the participant's perceived food allergy severity and food allergy-related risk (van der Velde, Flokstra-de Blok et al. 2010). Each question is scored on a 7-point scale (0-6 coded as 1-7 in analysis, with a greater score indicating a higher level of perceived risk or chance of adverse events occurring). The total score is the arithmetic average of all completed items. If less than 80% of the items within the score are complete, it will not be calculated. Questions 4 and 5 (effectively managing a reaction, receiving sufficient help from others) must be reverse coded.

A threshold of 0.45 points has been suggested and used as a minimal important difference (MID) to interpret clinical relevance (Dunn Galvin, Cullinane et al. 2010). For FAQLQ and FAIM forms, the 0.45 threshold will be used to interpret the clinical relevance of group-level differences and changes, in addition to within-patient changes.

The FAQL-PB is a self-administered, disease-specific instrument developed to measure the effect of pediatric food allergy on HRQoL for caregivers (Cohen, Noone et al. 2004). The instrument includes 17 items (assessing social, dietary and emotional impacts) on the impact of having a child with food allergy on the parents themselves using a 7-point Likert scale ranging from 0 (not limited/troubled) to 6 (extremely limited/troubled). The total score is the arithmetic average of all completed items.

The SF-36v2® Health Survey is a 36-item instrument that measures generic health-related quality of life. It is designed for use in surveys of general and specific populations, health policy evaluations and clinical practice and research. Two forms of this instrument are available and this study will use the one-week recall (acute) form. The SF-36v2 contains 8 scales and 2 component summary indices evaluating physical, social and emotional functioning in addition to general health perceptions and mental health. Responses to items allow for direct calculation of scale scores, while the physical component summary (PCS) and mental component summary (MCS) scores are computed from weighted scale scores. The SF-36v2 scale and composite scores can be converted to a T-score metric, allowing for norm-based scores derived from responses to a 2009 survey conducted by QualityMetric.[4] For all scales and summary measures, higher scores indicate better health outcomes.

The SF-6Dv2 may be derived from the SF-36v2 for health economic evaluations (Brazier, Mulhern et al. 2020). The SF-6Dv2 captures the impact of diseases and conditions on social activities and depression/nervousness. The SF-6Dv2 questionnaire uses a standardized health state descriptive system consisting of 6 dimensions, including social limitations, which was deemed essential to cover in food allergy. All dimensions are expressed over 5 levels, except for pain, which uses 6 levels, allowing for the description of 18,750 different health states. Health states are described using a combination of 6 digits each expressing the level for a dimension. For example, state "111111" indicates perfect health and state "555655" indicates the worst possible health status. The resulting SF-6Dv2 index, scored from 0.0 (worst health

state) to 1.0 (best health state), can be used in the assessment of the quality adjusted life years (QALYs) and the cost-effectiveness of various health care interventions.

2.12 CCI

CCI

2.13 Other Exploratory analyses

Not applicable.

2.14 Interim analysis

Not applicable.

3 Sample size calculation

The expectation is that approximately 200 participants from the study CQGE01G12301 will enroll in this extension study.

4 Change to protocol specified analyses

CCI

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

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

5.1.2 AE date imputation

Rules for imputing the AE end date:

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

Rules for imputing the AE start date:

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

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

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

Impute AE start date:

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

- If the AE month is missing, then the imputed AE start date is set to the AE reference start date + 1 day.
- If the AE month is less than the treatment start month, then the imputed AE start date is set to the mid-month point (15MONYYYY).
- Otherwise, if the AE month is equal to the treatment start date month or greater than the treatment start date month, then the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).

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

5.2 AEs coding/grading

The MedDRA version which will be available at the time of database lock, will be used for the coding purpose of the adverse events.

5.3 Laboratory parameters derivations

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

Refer to Section 10.6 of the protocol 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 being randomized should discontinue study treatment.For all other laboratory assessments, the Central Laboratory will flag laboratory values falling outside of the normal ranges on the Central Laboratory Report (which the investigator should review and sign-off) and the investigator will report any values considered clinically significant in the CRF.

6 Reference

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