Statistical Analysis Plan (SAP)

EPITOPE – V712-304

Study Title: A DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED PHASE III TRIAL TO ASSESS THE SAFETY AND EFFICACY OF DBV712 IN PEANUT-ALLERGIC YOUNG CHILDREN 1-3 YEARS OF AGE

Study Product: Viaskin® Peanut (DBV712)

Version 4.0, 15 March 2022

DBV APPROVAL SIGNATURES

The main signatories of the document in DBV are the CMO and the Head of Biometrics.

Author:

Name	Signature	Date
PPD		16 March 2022

Reviewers:

Name	Signature	Date
PPD		16 March 2022
PPD		16 March 2022

TABLE OF CONTENTS

[redacted]

LIST OF ABBREVIATIONS

AE / AESI	Adverse Event / Adverse Event of Special Interest
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
(B)DRM	(Blinded) Data Review Meeting
(m)BOCF	(modified) Baseline Observation Carried Forward
CI	Confidence Interval
CRD	Cumulative Reactive Dose
CRF	Case Report Form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
COVID-19	Coronavirus Disease 2019
DBPCFC	Double-Blind Placebo-Controlled Food Challenge
DSMB	Data Safety Monitoring Board
ED	Eliciting Dose
EPIT	EPicutaneous ImmunoTherapy
FAIM	Food Allergy Independent Measure
FAQLQ	Food Allergy Quality of Life Questionnaire
FAS	Full Analysis Set
FC	Food Challenge
GM	Geometric Mean
IgE, IgG4	Immunoglobulin E, immunoglobulin G4 subtype
IMP	Investigational Medicinal Product
IQR	Interquartile Range
IWRS	Interactive Web Response System
LLT	Lowest Level Term
LS Mean	Least-Square Mean
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
Phc	Phone contact

PD	Protocol Deviation
PP	Per Protocol
PT	Preferred Term
Q1, Q3	First, Third Quartile
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SCORAD	Scoring Atopic Dermatitis
SD	Standard Deviation
SE	Standard Error
SOC	System Organ Class
SPT	Skin Prick Test
TEAE	Treatment Emergent Adverse Event
TFL	Tables, Listings and Figures
V	Visit
WHO	World Health Organization

1 INTRODUCTION

This Statistical Analysis Plan (SAP) describes the statistical methods to be used for the reporting and analyses of data collected under the DBV Technologies EPITOPE study (Part B).

This SAP is based upon the following study documents:

- Study protocol, Version 7.0 (15 November 2019)
- eCRF, Version 12.0 (08 February 2021)

2 STUDY OBJECTIVES

The part B objective of this study is to verify the safety and local tolerance of the DBV712 250µg dose and to assess the efficacy and safety of DBV712 to induce desensitization to peanut in peanut-allergic subjects 1 to 3 years of age after a 12-month treatment period by EPicutaneous ImmunoTherapy (EPIT).

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

3.1.1 Study design

- **Design**: Randomized Phase III, Multicenter
- **Centers**: 51 sites in 8 countries
- **Study groups**: The EPITOPE study Part B population will consist of 2 groups:
  - Subjects who received placebo
  - Subjects who received DBV712 250µg
- **Treatment**: DBV712 (Viaskin® Peanut) 250µg patch.
- **Blinding**: Double-blind
- **Data collection**: electronic Case Report Form (eCRF), central laboratory data and subject e-diaries

3.1.2 Study flow chart

Study Assessments	Screening (Max 42d; more if DBPCFC postponed[1])				Treatment Period (12 months)												End of Study	Early Term	Unsch. Visit
Visit tags – PC (Phone Call)	**V1**	**V2**	**V3[2]**	**V4[2]**	**PC1**	**V5**	**PC2**	**V6**	**PC3**	**V7**	**PC4**	**V7bis[3]**	**V8**	**PC5**	**V9**	**V10**	**V11**	**V12**	**ET**	**UV[5]**
Duration in study	**D-42/D-3**			**D1**	**D4**	**D8**	**D22**	**M1**	**M2**	**M3**	**M4.5**	**M3-12**	**M6**	**M7.5**	**M9**	**M12**	**M12**	**M12**		
Time Windows	42d (max) before V4	Any-time up to D-2	Within 1 w of V2 up to D-1		±2 d	±3 d	±2 d	±3 d	±3 d	±7 d	±7 d	±7 d	±7 d	±7 d	±7 d	±7 d	Max V10 + 1 w	V11 + 4 w[4]		
Informed consent	X																			
Check eligibility[6] (inclusion/exclusion criteria)	X			X																
Disease/Medical history[7]	X																			
Parental medical history of atopy	X																			
Demographics	X																			
Physical examination[8]	X	X[10]	X[10]	X		X		X		X		X	X		X	X[10]	X[10]	X	X	X
Vital signs[9]	X	X[10]	X[10]	X		X		X		X		X	X		X	X[10]	X[10]	X	X	X
SCORAD	X									X			X			X				
CCI																				
Laboratory tests[12]	X									X			X			X			X	X
FAQLQ/FAIM/EQ-5D-5L[13]	X															X		X		
Epigenetic analyses	X									X			X			X				

CCI

Study Assessments	Screening (Max 42d; more if DBPCFC postponed[1])				Treatment Period (12 months)													End of Study	Early Term	Unsch. Visit
Visit tags – PC (Phone Call)	V1	V2	V3[2]	V4[2]	PC1	V5	PC2	V6	PC3	V7	PC4	V7bis[3]	V8	PC5	V9	V10	V11	V12	ET	UV[5]
Duration in study	D-42/D-3			D1	D4	D8	D22	M1	M2	M3	M4.5	M3-12	M6	M7.5	M9	M12	M12	M12		
Time Windows	42d (max) before V4	Any-time up to D-2	Within 1 w of V2 up to D-1		±2 d	±3 d	±2 d	±3 d	±3 d	±7 d	±7 d	±7 d	±7 d	±7 d	±7 d	±7 d	Max V10 + 1 w	V11 + 4 w[4]		
BAT[14]	X									X			X			X			X	
DBPCFC[1]		X	X													X	X			
Randomization				X																
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense food sampling kit and instructions				X																
Check for any accidental peanut consumption					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Subject participation card	X																			
Subject diary (dispense/check)				X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Dispense IMP to the subject				X		X		X		X		X	X		X	X				
Apply 1 Viaskin® patch at site				X																
Check the used/unused IMP dispensed to the subject						X		X		X		X	X		X	X	X		X	X

[redacted]

CCI

Study Assessments	Screening (Max 42d; more if DBPCFC postponed[1])				Treatment Period (12 months)												End of Study	Early Term	Unsch. Visit
Visit tags – PC (Phone Call)	V1	V2	V3[2]	V4[2]	PC1	V5	PC2	V6	PC3	V7	PC4	V7bis[3]	V8	PC5	V9	V10	V11	V12	ET	UV[5]
Duration in study	D-42/D-3			D1	D4	D8	D22	M1	M2	M3	M4.5	M3-12	M6	M7.5	M9	M12	M12	M12		
Time Windows	42d (max) before	Any-time up to	Within 1 w of V2 up to														Max V10	V11 +		
[redacted]																				
patch and grading[16]				X		X		X		X		X	X		X	X	X		X	X
Photographs of the back and download the photos taken by subject's parents (if any)				X		X		X		X		X	X		X	X	X		X	X
Dispense epinephrine auto-injector and anaphylaxis emergency action plan (Safety leaflet) / camera or a specific device/hydrocortisone 1%				X																
Review utilization of epinephrine auto-injector and anaphylaxis emergency action plan (when required)						X		X		X		X	X		X	X				
Time under observation before discharge		3 h	3 h	3 h												3 h	3 h			

Abbreviations: BAT = Basophil activation test; D = Day; DBPCFC = Double-blind, placebo-controlled food challenge; d = days; ET = Early termination; FAQLQ/FAIM = Food Allergy Quality of Life Questionnaire/Food Allergy Independent Measure; h = hours; IMP = Investigational medicinal Product; M = Month;

CCI

PC = Phone contact; SCORAD = Scoring atopic dermatitis; SPT = Skin prick test; UV = Unscheduled Visit; V = Visit.

1 If the subject has a concomitant disease which temporarily contra-indicates the performance of the DBPCFC, the test is to be postponed until at least 7 days after recovery

2 Visit 4 may take place on the same day as Visit 3, but this would result in a very long day for the subject (parents/guardians) as all Visit 4 procedures would then have to take place that same day.

3 The Visit 7bis was to be conducted for Part A subjects only in the eventuality of a dose switching for safety reason. After review of the 3-month safety data, both doses of DBV712 were considered as safe, and no dose switching is required. As a consequence, Visit 7bis will not be performed.

4 Visit 12 will take place only for subjects not rolling over into the extension follow-up study

5 Unscheduled Visit could be conducted in case of AEs, need for treatment re-supply, etc. Procedures will be optional and performed as deemed necessary by the investigator.

6 At V1, all selection criteria could be verified except for those that depend on the results of the immunological markers testing (peanut-specific IgE) and on the outcome of the entry/screening DBPCFC.

7 Including history of peanut allergy.

8 Including a complete skin examination, body weight and height.

9 Blood pressure, heart rate and respiratory rate.

10 These examinations are to be done before the DBPCFC. Additionally, they can be repeated during the DBPCFC procedure on both days anytime if judged necessary by the Investigator.

11 Peanut-specific IgE, peanut-specific IgG4, peanut-specific IgE and peanut specific IgG4 to Ara h 1, Ara h 2, Ara h 3, and total IgE will be evaluated at Visits 1, 7, 8, 10. Total IgE will be assessed in Part B subjects only. IgE specific to cow's milk, egg white, house dust mites, and grass pollen will be assessed at Visit 1 and Visit 10 only and in case of an early termination visit.

12 Laboratory tests performed centrally. Hematology: hemoglobin, hematocrit, platelets, red blood cells, white blood cells with differential cell count. Biochemistry: aspartate aminotransferase, alanine aminotransferase, total bilirubin, total protein, blood urea nitrogen, creatinine.

13 For both FAQLQ and FAIM, Parental Form will be used. The translated forms of FAQLQ and FAIM will be completed in countries where they are available in local languages. The EQ-5D-5L questionnaire will be completed by parents/guardians for subjects randomized in part B only.

14 BAT performed centrally in US eligible sites only.

[redacted]

16 16 Check the reaction of the skin on the back of the subject and grade the severity of the local skin reactions. At Visit 4, grading is to be assessed: before patch application, 30 minutes, 1 hour and 2 hours during the patch application and 1h after the patch removal, to document any reaction. Photographs will be taken at each grading time point.

3.1.3 Study duration

The overall maximum study duration in EPITOPE for each subject is approximatively 62 weeks (6-week screening period, 12-month treatment period and 4-week follow-up period).

Due to the Covid-19 pandemic, some sites have been temporarily closed and study visits were postponed. Therefore, the maximum study duration can exceed 62 weeks for the subjects concerned (see Section 5.3.8 for more details).

3.2 Efficacy Endpoints

3.2.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the difference between the percentage of treatment responders at Month 12 in the selected active DBV712 group (250 µg) compared to the placebo group in the overall population. A subject is defined as a treatment responder if:

- The initial Eliciting Dose (ED) was ≤10 mg peanut protein and the ED is ≥300 mg peanut protein at the post-treatment DBPCFC at Month 12 or
- The initial ED was >10 mg peanut protein and the ED is ≥1,000 mg peanut protein at the post-treatment DBPCFC at Month 12.

3.2.2 Secondary Efficacy Endpoints

The following secondary efficacy endpoints will be analyzed:

- ED at Month 12 in the selected active DBV712 group (250 µg) versus the placebo group;
- Cumulative Reactive Dose (CRD) at Month 12 in the selected active DBV712 group (250 µg) versus the placebo group;

3.2.3 Other Efficacy Endpoints

- The percentage of subjects reaching a cumulative reactive dose ≥1,444 mg peanut protein at the post treatment DBPCFC at Month 12 in the selected active DBV712 group (250 µg) *versus* the placebo group;
- The percentage of subjects reaching a cumulative reactive dose ≥3,444 mg peanut protein at the post-treatment DBPCFC at Month 12 in the selected active DBV712 group (250 µg) *versus* the placebo group;
- The percentage of subjects unresponsive (those showing no symptoms leading to DBPCFC stop) to the highest dose of peanut protein (2,000 mg of peanut protein) in the selected active DBV712 group (250 µg) *versus* the placebo group.
- The change from baseline in peanut-specific IgE and immunoglobulin G4 subtype (IgG4) at months 3, 6 and 12 in the selected active DBV712 group (250 µg) *versus* the placebo group;
- The change from baseline in peanut SPT average wheal diameters at months 3, 6 and 12 in the selected active DBV712 group (250 µg) *versus* the placebo group,

- Description of the quality of life questionnaires (Food Allergy Quality of Life Questionnaire [FAQLQ]/Food Allergy Independent Measure [FAIM]) and change from baseline in FAQLQ/FAIM scores at Month 12 in the selected active DBV712 group (250 µg) *versus* the placebo group (for those countries where the translated and validated questionnaires are available and used).

3.3 Safety Endpoints

The following IMP safety criteria will be evaluated:

- Treatment emergent adverse events (TEAEs) by System Organ Class (SOC) and Preferred Terms (PTs);
- TEAEs by maximum severity and relatedness to DBV712;
- Incidence, duration and maximum severity of local cutaneous DBV712-induced AEs as assessed by the subject in the diary;
- Incidence and severity of local cutaneous DBV712-induced AEs as assessed by the Investigator;
- Local adverse events of special interest (AESIs) (i.e., reactions at patch sites potentially leading to skin barrier disruption) and systemic AESIs (i.e. anaphylaxis, or systemic hypersensitivity reactions leading to epinephrine intake), whatever the causal relationship to the IMP;
- SAEs by SOC and PTs, and relatedness to DBV712;
- Laboratory data, physical examinations and vital signs;

The following study procedure safety criteria will be evaluated:

- Symptoms elicited during the entry/screening DBPCFC and post-treatment DBPCFC at Month 12 by severity;
- Change in severity of symptoms elicited during the DBPCFC from baseline to Month 12 in the selected active DBV712 group (250 µg) *versus* the placebo group;
- SAEs elicited during the entry/screening DBPCFC and post treatment DBPCFC at Month 12.

3.4 Exploratory Endpoints

The following exploratory criteria will be evaluated:

- The change from baseline in IgE and IgG4 specific to peanut protein components at 3, 6 and 12 months for both DBV712 groups versus the placebo group;
- The change from baseline in total IgE at 3, 6 and 12 months for both DBV712 groups versus the placebo group;
- Enumeration and characterization of reactions triggered by accidental consumption of peanut during the study and analysis of “risk-taking behavior” of parents’ subjects (voluntary peanut consumption) during the study;

[redacted]

- Sensitization status to other allergens (e.g., cow's milk, egg, house dust mites, grass pollen) and their evolution over the study period;
- SCORAD evolution over time;
- [redacted]
- Quality of Life analysis using the EQ-5D-5L;
- Basophil activation test (BAT) analyses (US eligible sites only).

4 ANALYSES SETS

4.1 Enrolled Set (ENRL)

The Enrolled set consists of subjects whose parents/guardians have signed informed consent in the Part B of the study.

4.2 Full Analysis Set (FAS)

The FAS will include all subjects who are randomized in Part B of the study.

All analyses describing the FAS will be performed according to the randomized treatments (i.e treatments allocated by randomization).

4.3 Per-protocol Set (PP)

This PP set will include all subjects from the FAS who do not have major protocol deviations that may affect the primary efficacy endpoints. The deviations to consider are listed more exhaustively in section 5.3.2 and in Appendix 8.1 and will be reviewed during the Blinded Data Review Meeting (BDRM). This population will be analyzed according to study treatment that was actually received by the subjects. In case the wrong IMP is taken, the subject will be analyzed according to the IMP received for the longest period of time.

The PP set will be used to evaluate the robustness of the primary and secondary efficacy analyses.

4.4 Safety Set (SAF)

The Safety population will be comprised of all subjects from the FAS who have received at least 1 dose of IMP in Part B. This population will be used to assess comparative safety information. In case the wrong IMP is dispensed, the subject will be analyzed according to the IMP received for the longest period of time.

Analyses sets summary

The following table lists the analyses performed on each dataset:

	ENRL	FAS	PP	SAF
Screen failures	x			
Subject disposition		X	x	
Demographic variables and Baseline Characteristics		X	(x)	
Medical history				x
Disease history				x
Study duration / Exposure / Compliance				x
Primary efficacy analyses		X	x	
Secondary efficacy analyses		X	x	
Other efficacy analyses		X		
Safety analyses				x
Exploratory analyses		X		
(x) Only if PP Set is more than 10% less than FAS				

5 STATISTICAL METHODOLOGY

5.1 General considerations

The following conventions will be used when presenting summary statistics and analyzing continuous study data:

- Continuous data will be summarized in terms of number of subjects or observations with non-missing data (n), mean, standard deviation (SD), first quartile (Q1), median, third quartile (Q3), minimum (min) and maximum (max), unless otherwise stated.
- For data not normally distributed, a log transformation will be implemented before analysis.
- Compared to the number of decimals recorded for the raw data in the database, the statistics will be reported with the following number of decimals, unless otherwise specified:
  - Minimum and maximum: same number
  - Mean, median, Q1, Q3: one extra decimal
  - Standard deviation: two extra decimals.
- For any parameter at a specific visit or timepoint:
  - Change from Baseline will be calculated as the value of that parameter at that visit minus the Baseline value of that parameter

- Relative change from Baseline will be calculated as the value of that parameter at that visit minus the Baseline value of that parameter divided by the Baseline value of that parameter multiplied by 100.

- For laboratory parameters, values below a detection limit or above a specific value (e.g. <0.35 kU/L or >100 kU/L) will be considered as equal to that limit/value (e.g. =0.35 or 100) in the statistical analyses (except in listing where the reported value will be presented).

  In case of change of detection limit during the course of the study (e.g. from <0.35 kU/L to <0.1 kU/L), all values lower than the highest limit value will be imputed to this threshold (e.g. all values lower than 0.35 kU/L will be considered as equal to 0.35 kU/L). This conservative approach will ensure that changes from Baseline are consistent.

The following conventions will be used when presenting summary statistics for categorical study data:

- Categorical data will be summarized in terms of the number of subjects or observations providing non-missing data at the relevant time point (n), frequency counts and percentages. Any planned collapsing of categories will be detailed in the SAP text and the data displays.
- Percentages will be rounded to one decimal place. Percentages will not be presented for zero counts. Percentages will be calculated using number of subjects in each treatment group as the denominator. If sample sizes are small, the data displays will show the percentages, but any textual report must describe the frequencies.
- Change from Baseline will be summarized using shift tables where appropriate.

The following conventions will be considered regarding p-values:

- P-values greater than or equal to 0.001, in general, will be presented to three decimal places. P-values less than 0.001 will be presented as "<0.001".

Unless otherwise specified, summaries will be presented overall and by treatment group (Placebo / DBV712 250µg).

Titles for tables and listings produced will specify the type of data reported as well as the analysis set concerned (in parentheses).

Listings will generally include variables e.g.: subject identifier, sex and age, treatment group…

Unless otherwise specified, complete dates will be reported in listings using a DDMMMYYYY format (i.e.: 01JAN2015) and time using a 24h clock-time (i.e.: 20:35).

Partial dates will be reported as MMMYYYY or YYYY.

Unless otherwise specified, all report outputs will be produced using SAS® version 9.4 or a later version in a secure and validated environment. Each report output will be provided in a Microsoft Word document (one document per output). All report outputs will be also pooled in one single PDF document with bookmarks and a comprehensive table of contents.

5.2 Statistical and Analytical Strategy

5.2.1 Statistical Testing Strategy

The primary measure of treatment effect will be the difference in response rates at Month 12 between active and placebo treatment groups. The primary analysis will be based on the 2-sided Farrington-Manning 95% confidence interval (CI) for the difference in response rates.

- Definitions -

The Peanut Protein ED is the individual dose of peanut protein administered to subjects during the food challenge procedure, which triggers objective allergic reactions, leading to stopping the challenge. It is capped to 300 mg for the screening food challenge and 2,000 mg for the post-treatment food challenge at 12 months, with the starting dose of 1 mg. The ED is taken from the eCRF.

In the following two cases, the ED at the Month 12 DBPCFC is not documented in the eCRF by the investigator:

- if the Month 12 DBPCFC is stopped without symptoms leading to ending the DBPCFC (stopping rules). This situation is defined as intercurrent events in Table 3.
- if the subject took the 2,000 mg dose without any objective symptom leading to ending the DBPCFC. In this case, the last dose given at Month 12 DBPCFC will be considered for ED value.

Case of Partially ingested dose:

If the last dose given is only partially ingested by the subject prior to the DBPCFC stop, then the ED reported by the investigator is:

- the previous dose given if the quantity of the last dose given actually ingested by the subject is ≤ to the previous dose ingested;
- the last dose given if the quantity of the last dose given actually ingested by the subject is > than the previous dose ingested.

Examples: If the last dose given is 1,000mg but only 200mg is actually ingested, then the recorded ED is 300mg. If the last dose given is 1,000mg and 400mg is actually ingested, then the recorded ED is 1000mg.

The Peanut Protein CRD is defined as the sum of all peanut protein doses taken by the subject during the DBPCFC (including the ED and any partial dose given before the reaction).

The CRD will be calculated as follow:

- If the ED reported by the investigator in the eCRF is missing, then the CRD is missing
- If the ED reported by the investigator in the eCRF is not missing then the CRD is calculated as the sum of all doses given, including also the partial doses; Example: If the set of recorded

doses is {1, 3, 10, 30, 100, 90 (out of 300)}, and recorded ED = 100mg, then CRD = 1 + 3 + 10 + 30 + 100 + 90= 234mg.

Note that ED and CRD will be recorded both for the placebo and the peanut day of the DBPCFC. Only the peanut day of DBPCFC and corresponding ED and CRD will be considered for the analyses.

5.2.2 Multiple Comparisons/Multiplicity

To handle multiple comparisons versus placebo, the overall type-I error will be controlled at a level of 5% (2-sided) by the use of a hierarchical inferential approach. The primary analysis in the FAS must be positive according to the success criterion (pre-specified threshold described in section 5.4.1). The first secondary efficacy analysis (difference in cumulative reactive dose) must meet its success criterion before drawing an inferential conclusion about the next secondary comparison (difference in peanut protein ED).

Table 1 - Pre-defined hierarchical Order for Analysis of Efficacy Endpoints

Order	Efficacy endpoints (at Month 12)	Population	Success criterion
1	Percentages of treatment responders	FAS	95% CI lower bound ≥15%
2	Peanut protein Cumulative Reactive Dose at Month 12	FAS	p ≤0.05
3	Peanut protein Eliciting Dose at Month 12	FAS	p ≤0.05

5.2.3 Stratification

An Interactive Web Response System (IWRS) randomized subjects and assigned the appropriate treatment number or kit number.

In the part B, the randomization scheme was on a 2:1 ratio to DBV712 at the selected dose (250 µg).

Randomization was stratified by center and managed centrally. The randomization scheme ensured that the ratio of active treatments to placebo was maintained.

However, due to the large number of centers, the analyses will not be stratified by center.

5.2.4 Handling of Missing Data

Primary analysis

Analyses of the primary efficacy endpoint will be based on the FAS. Depending on the type of intercurrent events, missing data will be imputed using:

- missing=failure imputation method for intercurrent event 1 (see section 5.4). Those subjects with missing peanut eliciting dose value at Month 12 will be considered as non-responders.
- multiple imputation for subjects with intercurrent events 2 and 5 (see section 5.4), who were unable to perform the DBPCFC (procedure cannot be perform due to Covid-19, child refused to

ingest the formula due to fear, aversion…). For those subjects, the probability distribution that imputes the missing response will rely on placebo subjects with an available response and so the missing data would mimic placebo response. Imputations will be performed using SAS® MI procedure generating 100 sets of imputed data. Seed used for imputation will be specified (details on the implementation of multiple imputations are given in Appendix 8.2)

- modified Baseline Observation Carried Forward (mBOCF) method imputation for subjects with intercurrent event 3 (see section 5.4), who starting the DBPCFC at Month 12 and refusing to ingest the formula left due to fear, aversion, without any of the objective symptoms leading to ending the DBPCFC (stopping rules). This method will rely on mBOCF for ED detailed in next section "Secondary analyses".

Sensitivity analyses will be performed on different sets and using other imputation methods for missing data (see section 5.4).

Secondary analyses

Analyses of ED and CRD as continuous endpoints will be based on the FAS using:

- multiple imputation for subjects who were unable to perform the DBPCFC (intercurrent events 2 and 5, see section 5.4). For those subjects, the probability distribution that imputes the missing ED/CRD will rely on placebo subjects with an available response and so the missing data would mimic placebo response. Imputations will be performed using SAS® MI procedure generating 100 sets of imputed data. Seed used for imputation will be specified (details on the implementation of multiple imputations are given in Appendix 8.2)
- mBOCF method to impute missing data at Month 12 for subjects with intercurrent events 1 and 3 (see section 5.4):
  - mBOCF for ED is defined as follow:
    - If the DBPCFC is stopped without symptoms leading to ending the DBPCFC (stopping rules) or if the subject took the 2,000mg dose without any objective symptom leading to ending the DBPCFC, the ED value at Month 12 is considered as the maximum between:
      - the last dose given at Month 12 DBPCFC (if the last dose given at Month 12 DBPCFC is only partially ingested by the subject, then the rules as defined under partially ingested dose in section 5.4.1 will apply) AND
      - the ED value at screening
    - For the subjects who did not undergo the Month 12 DBPCFC, ED value at screening is carried forward at Month 12 using BOCF method.
  - mBOCF for CRD is defined as follows:
    - If the DBPCFC is stopped without symptoms leading to ending the DBPCFC (stopping rules) or if the subject took the 2,000mg dose without any objective symptom leading to ending the DBPCFC, the CRD value at Month 12 is considered as the maximum between:
      - the sum of all doses given at Month 12, including also the partial doses AND

- the CRD value at screening

- For the subjects who did not undergo the Month 12 DBPCFC, CRD at screening is carried forward at Month 12 using BOCF method.

No imputation will be performed for other efficacy, safety and exploratory parameters. In those instances, observed data will be used, excepted for laboratory results reported as below the lower detection limit (or reported above a specific value) which will be imputed as described in Section 5.1 and safety data where partial or missing data will be imputed according to the most conservative approach. (See section 5.5.1.2).

Dates of birth

- If only the day is missing, it will be imputed using the first day of the documented month.
- If the day and the month are missing, it will be imputed using the first of January of the documented year.

For analyses based on the actual age at baseline, the documented age in the IWRS will be used. Imputed date of birth will only be used for analyses based on age during the study, where the calculation using date of birth would be needed (e.g. date of 4th anniversary).

Dates of events

- Imputation rules of Treatment dates are defined in the section 5.2.6.1
- Imputation rules of AEs dates are defined in the section 5.5.1.2
- Imputation rules of Concomitant Medications dates are defined in the section 5.3.7

Dates of findings (Physical exams, ECG, LAB, Vital Signs and Questionnaires)

- If the assessment date (--DTC) is partial
  - If only the day is missing, it will be imputed to the 15th of the month unless month and year are the same as month and year of the visit date then impute visit date
  - If day and month are missing, it will be imputed to the 15th of June unless year is the same as year of the visit date then impute visit date
- If the assessment date (--DTC) is missing, it will be imputed with the visit date.

Diary Data

Two methods will be applied:

- 0-imputation: Patches without assessable duration are imputed as 0 hours.
- No imputation will be performed on time of application/removal unless explicitly described for specific analyses.

5.2.5 Subgroup Efficacy Analysis/es

Analyses of continuous variables will in general include the baseline value as a covariate and treatment group as a factor. The randomization was stratified by center for logistic reasons only. Hence, center will in general not be considered as a factor in the statistical analysis models.

The following subgroups will be defined:

- Screening ED group (ED ≤10 mg, ED >10 mg)
- Age group (1-year, 2-years, 3-years)
- IgE levels at screening
  - <17.5 kU/L, 17.5 to 50 KU/L, 50 to 100 kU/L, >100 kU/L
  - <17.5 kU/L, ≥ 17.5 kU/L
  - <100 kU/L, ≥ 100 kU/L
- Region (Australia, Europe, North America)
- Gender (Male, Female)
- Race (White, Black or African American, Asian, Other [incl. American Indian or Alaska Native, and Native Hawaiian or Other Pacific Islander], not collected)
- Ongoing Medical history of asthma at baseline (Yes / No)
- Ongoing Medical history of allergy other than peanut at baseline (Yes/No) (see section 5.3.4)
- Ongoing Medical history of food allergy other than peanut at baseline (Yes / No) (see section 5.3.4)
- Ongoing Medical history of eczema/atopic dermatitis at baseline (Yes / No) (see section 5.3.4)
- Ongoing Medical history of rhinitis allergic at baseline (Yes / No) (see section 5.3.4)

Subgroup analyses of the primary and secondary efficacy endpoints will be performed as specified in the respective sections below. Analyses with subgroups containing less than 15 subjects should be interpreted with caution.

5.2.6 Key dates, Relative days

5.2.6.1 Key dates

- **The date of first patch application** of each subject will be taken from the first exposure date from eCRF.
  - If only the day is missing, it will be imputed using the day of the latest date between the randomization date and the first dispensation date.
  - If day and month are missing, they will be imputed using the day/month of the latest date between the randomization date and the first dispensation date.
  - If the date is missing, it will be taken from first dispensation date.
- **The date of last patch application** of each subject will be taken from the last exposure date from eCRF.
  - If only the day is missing, it will be imputed to the last day of the month unless month and year are the same as month and year of study end date then impute study end date

- If day and month are missing, they will be imputed to the 31st of December unless year is the same as year of study end date then impute study end date.
- If the date is missing because the subject was lost to follow-up, it will be derived from the study end date.

- **The study end date** will be derived as the study completion date or study discontinuation date from the disposition domain.
  - If the date is missing, it will be derived as the last date available from the visits, the examination, the assessments.

5.2.6.2 Relative days

Relative days will be calculated from the reference date and will be used to classify the assessments.

The reference date also called Day 1, is defined as the first day of study treatment.

The relative days are derived using the formula below:

- (date of assessment) - (reference date) + 1 if the date of assessment is ≥ reference date
- (date of assessment) - (reference date) if the date of assessment is < reference date

Relative days will be missing for the records of subjects not treated.

5.2.6.3 Treatment periods

The following timing variables will be included in analysis datasets for modelling the trial.

Phase (APHASE)	Analysis period	Numeric analysis period (ASPER)	Planned treatment for period (APERIOD)
SCREENING			
TREATMENT	DOUBLE-BLIND TREATMENT	1	TRT01P
FOLLOW-UP			

The treatment period will be defined by a start date (ADSL.TRTSDT) and an end date (ADSL.TRTEDT).

5.2.7 Analysis Windows

For subjects who received at least one patch, all records (including unscheduled, re-tests and early termination visits) are classified in time windows, according to their relative days.

The analysis visit labels (AVISIT) to be used in the analysis datasets and in the TFLs are described below.

Table 2 - Time Window for Efficacy / Safety / Laboratory analyses

Analysis Visit (AVISIT)	Target	Time Window (1)
Baseline	Day1 pre-dose	Not applicable
Day 8	Day 8	±5 d
Month 1	Day 30	±14 d
Month 3	Day 90	±21 d
Month 6	Day 180	±21 d
Month 9	Day 270	±21 d
Month 12 (V10)	Day 365	- 21 d to + 90 d
Month 12 (V11)	Day 372	V10 + 1 to the earliest between V11 and V10 + 2 w
Month 12 (EOS)	Day 400	End of the V11 time window + 1 to V11 + 8 w

(1) In the event that a record does not fall within any predefined analysis timepoint window, AVISIT is populated as "Not Windowed". Assessments not assigned to any visit will be kept in the analysis dataset and in Listings.

For primary and secondary analyses, the DBPCFC entered in the eCRF at Visit 10 or Visit 11 (Month 12) will be taken into account without using the analysis window.

For other efficacy analysis, if an assessment cannot be performed during a planned visit (e.g. SPT postponed due to wash-out period), unscheduled visits occurring within 7 days will be taken into account. Re-tests and other unscheduled visits will not be considered in the analysis (only described in listings). For safety analysis and exposure to treatment, data including re-tests and unscheduled visits will be used in the analysis.

- If more than one assessment is included in a time window the assessment closest to the target day should be used.
- If there are more than one observation with equal distance to the target day the more recent will be used in the analyses.
  - For efficacy related analyses, if multiple measurements for a particular parameter are collected on the same day for the same subject, the more recent of those measurements will be used.
  - For safety related analyses, if multiple measurements are made for a particular laboratory or vital sign parameter on the same day for the same subject, the more recent of those measurements will be used in the analyses.
- If there are visits reported twice in the eCRF, i.e. in an analysis visit and in an unscheduled visit (in case assessment pages are available in one of the visit and not others), all assessments recorded in both visits will be used in the analyses.

The record chosen in a time window is indicated by the analysis flag variable (ANLzzFL).

For summaries and listings of shift from baseline and potentially clinically significant values, all values will be considered in the analyses.

All data collected at unscheduled visits will be listed.

5.2.8 Baseline definition

The baseline assessment will be the latest, non-missing pre-dose assessment available.

All data collected before (<) Day 1 are considered as pre-dose.

At day 1, all following examples are considered as pre-dose:

- if the time is collected and is before (<) treatment start time
- if the time is not collected but the examination/assessment/event is planned before treatment in the protocol (Physical examination, Vital signs, Laboratory tests, Questionnaires planned at day 1 before the first IP, SCORAD, SPT)
- other findings will be considered as post-dose and not included in the baseline calculation.

If a patient is not treated, the baseline value for a parameter is the last non-missing value.

5.2.9 Potential impact of Covid-19 pandemic

Covid-19 pandemic have impacted the timing of the study and efficacy measurements.

Assessments visits were delayed for some subjects enrolled in this study. Therefore, analysis windows were extended as defined in section 5.2.7.

Sensitivity efficacy analyses will be performed to account for the subjects impacted by Covid-19 pandemic in section 5.4.1.

5.3 Subject characteristics

5.3.1 Subject disposition

A clear accounting of the disposition of all subjects who enter the study will be provided, from screening to study completion. Subject disposition will be summarized for all subjects, overall and by treatment group. Percentages will be based on the number of subjects in the Full Analysis Set (FAS). The following descriptions will be performed on all enrolled subjects:

- Number of enrolled subjects, number of screen failures, reasons for non-randomization,
- Analysis sets: number and percentage of subjects in each population used for the analyses. The populations are defined in Section 4.
- Number and percentage of subjects who completed the study treatment, subjects who discontinued the study treatment and reasons why subjects discontinued the study treatment,
- Number and percentages of subjects who discontinued the study treatment:
  - Before Month 12 (exposure < 358 days)

- At Month 12 or after (exposure ≥ 358 days)

- Number and percentages of subjects who performed the Month 12 Food Challenge:
  - As per Month 12 time-window
  - Out of Month 12 time-window (visit delayed due to covid-19 pandemic)
- Number and percentage of subjects randomized by region, country and site,
- An enrolment summary will be presented overall, by region, country and site, showing the number of subjects enrolled, randomized and completing the study, the first date of consent, the last study visit date, the study duration (in days, calculated as the end of study date for randomized subjects – first date of consent for the first screened subject +1).

Study disposition and termination details will be listed for each subject. Listings will also be created to show the study analysis set classifications and randomization assignments.

5.3.2 Protocol Deviations

Protocol Deviations (PD) including violations of inclusion/exclusion criteria will be assessed as "minor" or "major" in cooperation with the Sponsor prior to database lock and unblinding.

Major PDs are defined as those deviations from the protocol likely to have an impact on the perceived efficacy and or safety of the study. Major protocol deviations that may affect the primary analysis will lead to exclusion of the subject from the PP set.

Appendix 8.1 provides preliminary categorization of major protocol deviations and actions to be taken with regards to analysis. Major deviations will be listed separately from minor deviations.

The number and percentage of subjects with major protocol deviations will be summarized by type of deviation, overall and by treatment group for the randomized population. All protocol deviations will also be listed.

The COVID-19 pandemic requires specific attention on the Protocol Deviations that may impact the conduct of the study and the follow-up of the subjects. The number and percentage of subjects that experienced at least one Covid-19 deviation will be described together with the major protocol deviation table. Also, Protocol Deviations that are specifically related to COVID-19 will also be described in a separate table and identified in the listing of deviations.

5.3.3 Demographic variables and Baseline Characteristics

5.3.3.1 Demographics

Descriptive statistics will be produced for demographic baseline characteristics by treatment group and overall. Demographics data include:

- Age (years), continuous, recalculated based on date of birth and informed consent, populated by IWRS system
- Age in category (1-year, 2-years,3-years)
- Gender (Male, Female, Undifferentiated, Unknown)

- Race as collected in the eCRF:
  - American Indian or Alaska Native
  - Asian,
  - Black or African American,
  - Native Hawaiian or Other Pacific Islander,
  - White,
  - Other,
  - Not collected ("Not applicable", "Not reported" or missing)
- Race using the following mapping: White (e-CRF value = "White"), Black or African American (e-CRF value = "Black or African American"), Asian (e-CRF value =" Asian"), Other (e-CRF value = "Native Hawaiian or Other Pacific Islander", "American Indian or Alaska Native" or "Other"), Not collected ("Not applicable", "Not reported" or missing)

Summaries will be provided for the FAS. Replicating this table for various analysis sets is not useful, however, if the PP Set is more than 10% less than FAS, a new table with PP Set will be presented.

The demographics data will be provided in data listing.

5.3.3.2 Baseline Characteristics

Descriptive statistics will be produced for baseline characteristics by treatment group and overall. Baseline characteristics data include:

- Height (cm), Weight (kg)
- Peanut-specific IgE (kU/L)
- Peanut-specific IgG4 (mg/L)
- Skin Prick Test (SPT): Mean and longest wheal diameter for undiluted peanut extract (mm)
- ED in continuous
- ED in categories:
  - 1, 3, 10, 30, 100, 300 mg;
  - < 10mg, ≥ 10mg
- CRD in continuous

Summaries will be provided for the FAS. The full baseline characteristics data will be presented in a listing.

5.3.4 Medical history

Medical history covers the collections of information on past or current conditions (with the exclusion of peanut allergy). In addition to the coding performed, the following medical history classes are defined:

- Any allergy other than peanut
  - PT terms which contains "ALLERG" (excluding LLT "Peanut allergy") and PT terms which contains "HYPERSENSITIVITY" (excluding LLT "Peanut allergy")
- Any food allergy other than peanut:

- PT "Food allergy" (excluding LLT "peanut allergy")
  - + PT "Milk allergy"
  - + PT "Allergy to fermented products".

- Other atopic conditions:
  - Asthma
    - SMQ Asthma/bronchospasm MedDRA Version 20.1 from narrow terms: List of PT terms: Asthma, asthma exercise induced, asthma late onset, asthmatic crisis, bronchospasm, bronchial hyperreactivity, infantile asthma, status asthmaticus, wheezing
  - Eczema/Atopic Dermatitis
    - List of PT terms: Dermatitis atopic, Dermatitis allergic, Eczema, Application site eczema.
  - Allergic Rhinitis
    - List of PT terms: Rhinitis allergic, Seasonal allergy, Rhinitis perennial, Conjunctivitis allergic

The exhaustiveness of the lists specified above will be reviewed during the data review meeting and may be extended with further terms prior to database lock as applicable.

The medical history of specific interest description will also be presented for:

- medical history ongoing at Baseline
- medical history not ongoing at Baseline

Medical history will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) and will be reported by SOC and PT. The table will be sorted by descending frequency of SOC, and, within each SOC, by descending frequency of PT in all subjects. The number and percentage of subjects with at least one medical history term will also be provided.

Medical history will be summarized overall and by treatment group for the Safety set. Medical history data will be also provided in listings.

5.3.5 Parental atopic medical history

Parental (father and/or mother) atopic history is recorded on the Parental Atopic History eCRF page and will be summarized as the number and percentage of subjects with father / mother having any of the following conditions:

- asthma,
- seasonal allergies,
- perennial allergies,
- food allergies,
- eczema/atopic dermatitis,

- other allergic diseases.

The number and percentages of subjects with at least one parental atopic medical history will also be provided.

Parental atopic medical history will be summarized overall and by treatment group for the Safety set. Parental atopic medical history data will be also provided in listings.

In case a subject's parent is not the biological parent, no parental medical history is collected about this parent.

5.3.6 Disease history

Disease history covers the collection of information about the peanut allergy of the subject and will be reported using the following characteristics:

- Age at peanut allergy diagnosis (in months, calculated as 12 * (Date of diagnosis – Date of birth) / 365.25),
- Time since peanut allergy diagnosis (in months, calculated as 12 * (Date of Informed consent - Date of diagnosis) / 365.25),
- Category of the physician who made the diagnosis,
- Main reason having led to the diagnosis (reaction after ingestion, parental/sibling history of atopy, other risk factors)
- Diagnosis criteria (Allergic reaction(s) following peanut consumption, Positive SPT to peanut, Positive titer of peanut-sIgE, Positive Double-Blind Placebo-Controlled FC to peanut, Positive Single-Blind Placebo-Controlled FC to peanut, Positive Open FC to peanut)
- Most recent results of peanut allergy diagnostic tests performed,
- Description of allergic reactions:
  - Number of allergic reactions after ingestion of peanut,
  - Number of allergic reactions after ingestion of peanut in the previous 12 months,
  - Time since last reaction after ingestion of peanut (in months, calculated as 12 * (Date of Informed consent - Date of last reaction) / 365.25). When the date of last reaction is partial (only year available or year and month), the latest possible date will be assumed (e.g. 31st of December or last day of the month).
  - Allergic reaction after ingestion of peanut after the age of 2 years old.

When the date of diagnosis is partial (only year available or year and month), the latest date between the date of birth and the earliest possible date of diagnosis (e.g. first of January or first day of the month) will be considered.

Disease history will be summarized by treatment group and overall for the Safety set. Disease history data will be also provided in data listings.

5.3.7 Prior and concomitant medications

All medications taken before the study entry, at study entry and during the study will be recorded and coded using the World Health Organization (WHO) Drug Dictionary (Sept. 2017).

Medications will be classified either as "Prior only" (P), "Both Prior and Concomitant" (PC) or "Concomitant only" (C).

This classification will be made by comparing the medication start and stop dates with the date of first/last application of study medication.

Medications starting after the completion/withdrawal date will be listed but will not be classified or summarized.

"Prior only" (P) medications will be:

- Medications that were taken within 6 months prior to the first dose of study medication and that stopped before the first dose of study medication,
- Medications with partial start/stop date where there is clear evidence to suggest that the medication stopped prior to the first dose of study medication.

"Both prior and concomitant" (PC) medications will be:

- Medications starting before the first dose of study medication and stops on or after the first dose of study medication,
- Medications with partial start/stop date where there is clear evidence to suggest that the medication started prior to the first dose of study medication (no evidence for the stop date).

"Concomitant only" (C) medications will be:

- Medications with a start date on or after the first dose of study medication,
- Medications with partial start/stop date where there is clear evidence to suggest that the medication started after the first dose of study medication,
- Medications with partial or complete stop date where there is clear evidence to suggest that the medication stopped after the first dose of study medication (no evidence for the start date),
- All other medications with partial start/stop date where there is no clear evidence to suggest that the medication started or stopped before or after the first dose of study medication.

In addition to the WHO Drug coding performed, the following medication classes are defined:

- Epinephrine,
  - They will be identified on PT that contains "EPINEPHRINE" and ATC level 1 = "CARDIOVASCULAR SYSTEM".
- Systemic or inhaled corticosteroids,
  - They will be identified as:
    - Any medication ATC codes starting with "H02"

- Any medication ATC code starting with “A07EA”, “C05”, “R01AD” and (ROUTE in “ORAL” “PO” “RECTAL” “RESPIRATORY (INHALATION)” “INTRAVENOUS”)

- Topical corticosteroids,
  - They will be identified as:
    - Any medication ATC code starting with “D07”
    - Any medication ATC code starting with “A07EA”, “C05”, “R01AD” and ROUTE = Topical.

For prior and/or concomitant medications, number and percent of subjects overall and per ATC class (level 3) and preferred drug name will be calculated. The following summaries will be presented overall and by treatment group for the Safety set:

- Prior medications (other than the ones taken during the food challenge at Baseline), prior only medications (P) will be taken into account;
- Concomitant medications (other than the ones taken for the food challenge at Month 12 and the ones taken for voluntary or accidental consumption of peanut), both prior and concomitant (PC) and concomitant (C) medications will be taken into account;
- Medications taken for food challenges, by time point;
- Concomitant medications taken due to accidental/voluntary consumption of peanut.

Number of antihistamine and number of epinephrine administrations during food challenges will also be tabulated separately (for the Peanut and Placebo days of DBPCFC separately), overall and by treatment group for the Safety set.

Non-drug therapies and surgical procedures are collected and will be coded using the version 20.1 of the MedDRA Dictionary. They will be also presented by SOC and preferred term overall and by treatment group for the Safety set.

All prior and concomitant medications, non-drug therapies and surgical procedures will be listed for the Safety set. The listing will be provided with a flag to indicate the prior and concomitant medications.

5.3.8 Study duration, treatment exposure and compliance

The overall study duration for each subject will be approximately 62 weeks (6-week screening period, 52-week treatment period and 4-week follow-up period).

Study duration (days) will be calculated as:

- End of study date - Date of informed consent +1.

Due to the Covid-19 pandemic, some visits were postponed, and study duration can exceed 62 weeks (6-week screening period, 12-month treatment period and 4-week follow-up period) for the concerned subjects. Study duration will be summarized for the Safety set overall and by treatment group. The number (%) of subjects with a study duration exceeding 62 weeks will also be tabulated.

Treatment exposure will be based on:

- The exposure duration (in days, regardless of treatment interruption), calculated over the whole study period as:
  - Date of last patch application – Date of first patch application) +1,
- The total dose of peanut protein (in mg) received via the patch during the study, calculated over the whole study period as:
  - Exposure duration (in days) * Actual treatment dosage

Exposure duration and total peanut protein dose will be summarized for the Safety set overall and by treatment group (except total peanut protein dose that will only be described for the active arm).

Number and percentage of subjects per category of exposure duration (in days) will be presented using the following categories:

- 0 to 6 months (Day 1 to Day 180),
- 6 to 12 months (Day 181 to Day 365),
- 12 to 18 months (Day 366 to Day 545),
- > 18 months (> Day 546)

The compliance (%) determined over the whole study period as:

$$100 \text{ x } \left(\frac{Number\ of\ patches\ dispensed - Number\ of\ patches\ returned}{Exposure\ duration\ in\ days}\right)$$

Global compliance will be summarized for the Safety set overall and by treatment group.

Treatment compliance will be summarized using frequency tables (<80%, 80% to 100%, >100) and by means of descriptive statistics (n, mean, SD, median, Q1, minimum, Q3, and maximum) with compliance > 100% set to 100%.

If a subject did not bring back unused patches, the amount of patches that have been applied cannot be accurately assessed. During the Data Review Meeting, before database lock, each subject having unreturned kit will be evaluated and a decision will be taken whether the subject compliance should be considered as missing.

The study medication must be applied on the skin for 24 hours every day (±4 hours), except during the initiation of treatment, where the duration of application of the study medication will be progressively increased as follows:

- During the first week (from Day 1 through Day 7), the patches will be applied for 2 hours (± 30 minutes) every day;
- During the second week (from Day 8 through Day 14), the patches will be applied for 4 hours (± 30 minutes) every day;
- During the third week (from Day 15 through Day 21), the patches will be applied for 8 hours (± 1 hour) every day;
- During the fourth week (from Day 21 through Day 28), the patches will be applied for 12 hours (± 2 hours) every day;

- From the fifth week onwards (Day 29), the patches will be applied for the entire 24 hours (± 4 hours) every day.

The time to first 24 hours (±4 hours) patch application will be summarized by means of descriptive statistics (n, mean, SD, median, Q1, minimum, Q3, and maximum) and described using a Kaplan Meier curve.

The daily application duration (in hours) will be summarized descriptively using the subject e-diary data for the following periods:

- Overall,
- D1 to D7,
- D8 to D14,
- D15 to D21,
- D22 to D28,
- D29 to D90,
- D91 to D185,
- D186 to D275,
- D276 to D365,
- > D365,
- D29 to D365,
- > D29

If more than one patch is applied the same day, the daily duration considered is the cumulative application duration of these patches (if the end date/time of first patch is not documented, the application date/time of the next patch will be used for imputation).

The percentage of days with no patch application, per subject e-diary reported data, will also be tabulated, overall and for each of the above periods.

A patch will be considered as "applied" if the date and time of application is documented in the e-diary.

The start date/time and/or end date/time of patch application used to calculate the duration of patch application are extracted from the e-diary.

If the duration calculation leads to an aberrant value (ie. a negative value or a value > 50h), then the duration will be considered as missing.

Average duration of application will be calculated:

- On patches with available duration only
- On all patches using 0-imputation (section 5.2.4) when duration is not available (e.g. missing date or time of removal)

All data including documentation of treatment interruptions will be listed.

5.4 Efficacy Analyses

Intercurrent events defined for efficacy are summarized in the following table.

Table 3 - Intercurrent Event Types

Label	Intercurrent Event Type	Comment (for main estimand)
Intercurrent event 1 (Early treatment Discontinuation before 12 Months*)	Treatment exposure < M12 and missing peanut DBPCFC	Subjects will be included in the FAS. Subjects will be considered as a non-responder.
Intercurrent event 2 (subject/caregiver refusing the Month 12 peanut DBPCFC)	Treatment exposure ≥ M12, subject had not started the peanut DBPCFC and refusing to ingest the peanut formula	Subjects will be included in the FAS. An imputation will be used for missing data.
Intercurrent event 3 (peanut DBPCFC initiated but not finished)	Child starting the DBPCFC and stopped without symptoms leading to ending the peanut DBPCFC (stopping rules) (e.g. refusing to ingest the peanut formula left due to fear, aversion)	Subjects will be included in the FAS. An imputation will be used for missing data.
Intercurrent event 4 (peanut DBPCFC completed at Month 12* falls outside the recommended time-window)	Delayed peanut DBPCFC completed at Month 12 (e.g. due to temporarily closed centers or postponed visits (COVID-19))	Subjects will be included in the FAS. Actual values will be used regardless of whether an intercurrent event has occurred.
Intercurrent event 5 (discontinuation at or after Month 12 * with Month 12 peanut DBPCFC missing)	Treatment exposure ≥ M12 but missing peanut DBPCFC (e.g. due to temporarily closed centers or postponed visits (COVID-19))	Subjects will be included in the FAS. An imputation will be used for missing data.

*Month 12 time windows are comprised between 358 – 407 days (section 5.2.7).

5.4.1 Primary Efficacy Analysis/es

The primary efficacy analysis is based on an endpoint that is derived from the Eliciting dose (ED). Rules of derivation is defined in section 5.2.

The primary efficacy endpoint in this study is the difference between the percentage of treatment responders in the selected active DBV712 group (250 µg) compared to the placebo group after 12 months of treatment. A subject is defined as a treatment responder:

- If the screening ED was ≤10 mg peanut protein and the ED is ≥ 300 mg peanut protein at the post-treatment DBPCFC at Month 12,

  OR

- If the screening ED was >10 mg peanut protein and the ED is ≥ 1,000 mg peanut protein at the post-treatment DBPCFC at Month 12.

The primary endpoint and corresponding estimand is detailed in the below table.

Table 4 - Primary endpoint and Estimand with Rationale for Strategies to Address Intercurrent Events

Estimand description	Treatment efficacy will be evaluated using the difference between the percentage of treatment responders in the selected active DBV712 (250 µg) group compared to the placebo group after 12 months of treatment in the target population. A combination of strategies will be used to treat separately the different intercurrent events.
Target Population	Pediatric subjects aged 1 to 3 years, with diagnosed peanut allergy or high suspicion of peanut allergy, enrolled and randomized following confirmation of all eligibility criteria
Analysis Set	Full Analysis Set
Variable/Endpoint	A subject is defined as a treatment responder: • If the screening ED was ≤10 mg peanut protein and the ED is ≥ 300 mg peanut protein at the post-treatment DBPCFC at Month 12, OR • If the screening ED was >10 mg peanut protein and the ED is ≥ 1,000 mg peanut protein at the post-treatment DBPCFC at Month 12.
Treatment Condition(s)	DBV712 250 µg group or placebo (Reference: Placebo).
Population-Level Summary	Difference in treatment responder rates between DBV712 250µg and placebo.
Intercurrent Event Strategy	
Intercurrent event 1	Composite strategy (subjects considered as non-responders)
Intercurrent event 2	Composite strategy (subjects will mimic placebo response)
Intercurrent event 3	Composite strategy (mBOCF)
Intercurrent event 4	Treatment policy
Intercurrent event 5	Composite strategy (subjects will mimic placebo response)
Rationale for Strategy(s)	Composite strategy is used for intercurrent events 1, 2, 3 and 5 as follows: - Early treatment discontinuations before 12 Months (Intercurrent event 1) are considered as non-responders

	- Subject/caregiver refusing the Month 12 peanut DBPCFC (Treatment exposure ≥ M12, subject had not started the peanut DBPCFC and refusing to ingest the peanut formula – Intercurrent event 2) will be imputed using multiple imputation to mimic placebo response - Discontinuations at or after Month 12 with Month 12 peanut DBPCFC missing (Intercurrent event 5) will be imputed using multiple imputation to mimic placebo response - Peanut DBPCFC initiated but not finished (Intercurrent event 3) will be imputed using mBOCF. Treatment policy strategy is used for intercurrent event 4: - If the Peanut DBPCFC completed at Month 12 falls outside the recommended time-window, subject ED at Month 12 is used as collected.
Imputation/Data	According to the type of intercurrent event, missing value will be imputed based on data in placebo group or on mBOCF.
Analysis Model/Method	<u>Main analysis</u> The primary analysis will be assessed using a 2-sided Farrington-Manning 95% confidence interval (CI) for the difference in response rates. The success criterion will be met if 95% CI lower bound ≥15%. The 2-sided Wilson 95% CIs of individual response rates will be presented. Intercurrent events handling and multiple imputation inference: Step 1: Missing treatment response from intercurrent events 3 will be imputed based on mBOCF method (see section 5.2.4). Step 2: Missing treatment response from intercurrent events 2 and 5 will be imputed using SAS® procedure MI. A response will be imputed based on placebo group subject's responses performing the following steps: I. Subjects with missing treatment response (intercurrent events 2 and 5) and subjects in the placebo arm that started the Month 12 DBPCFC (intercurrent event 3, imputed in step 1) or completed the Month 12 DBPCFC will be selected. II. PROC MI will be used to impute missing values using a monotone logistic statement with baseline ED subgroup (ED ≤10 mg, ED >10 mg) as covariate.

```
PROC MI DATA=<dataset_name> NIMPUTE=100 OUT=MI_out
SEED=223218 ;
CLASS resp ED  subgroup;
MONOTONE LOGISTIC (resp= ED_subgroup /DETAILS) ;
VAR ED_subgroup resp;
RUN;
```

This will generate 100 datasets containing imputed values for those missing (intercurrent events 2 and 5) in the original dataset.

Step 3:

Data for subjects in the active arm with non-missing treatment response and subjects with missing treatment response (intercurrent event 1) will be replicated 100 times.

Missing treatment response from intercurrent event 1 will be imputed as failure (missing=failure imputation method).

Step 4:

Data from step 2 and data from step 3 will be combined. This will generate 100 complete analyses datasets without missing values.

The 2-sided Farrington-Manning 95% confidence interval (CI) for the difference in response rates and the 2-sided Wilson 95% CIs of individual response rates will be performed separately for each of the 100 complete analysis data sets. The results will be combined into one multiple imputation inference (estimated treatment effect/individual response rates and associated confidence intervals) using SAS® procedure MIANALYZE.

All methods described above will be performed using SAS® procedures and detailed in Appendix 8.2.

Sensitivity and other analyses on primary endpoint:

Various sensitivity and other analyses on the primary endpoint will be performed to assess the robustness of the primary analysis results with respect to selected analysis set, missing data handling strategies and adjustment for stratification variables. Results from the sensitivity analyses will be compared with the primary analysis results, but without the need to fulfil a formal success criterion. Variations between the primary analysis results and the sensitivity analysis results are expected and will be subject to discussion within the clinical study report (CSR). The following sensitivity and other analysis analyses will be performed:

- The primary efficacy analysis will be repeated on the FAS using missing=failure imputation method for intercurrent events 1, 2 and 5.
- The primary efficacy analysis will be repeated on the FAS using multiple imputation method for intercurrent events 1, 2 and 5. Specifically, the probability distribution that imputes the missing response will rely on placebo subjects with an available response and so the missing data would mimic placebo response.
- The primary efficacy analysis will be repeated on the FAS: for all missing data using multiple imputation method (intercurrent events 2

	and 5), the probability distribution that imputes the missing response for DBV712 250µg subjects will rely on DBV712 250µg subjects with an available response, and the probability distribution that imputes the missing response for placebo subjects will rely on placebo subjects with an available response. • The primary efficacy analysis will be repeated on the FAS, excluding subjects with intercurrent event 1,2 or 5. • The primary efficacy analysis will be repeated on the FAS, excluding patients whose DBPCFC falls outside the Month 12 time-window (intercurrent event 4). • The primary efficacy analysis will be repeated on the PP set. Additionally, the results from primary analysis and associated sensitive analyses will be presented in a forest plot, giving a visual suggestion of the amount of analyses heterogeneity. As for the primary analysis, with the expected sample size of more than 300 subjects, there are no concerns regarding the validity of proposed analysis approaches, therefore no systematic check of assumptions will be performed. Subgroup analyses To further support the primary analysis, the number and percentage of subjects responding to treatment as determined by the results from the DBPCFC at Month 12, differences in response rates and corresponding 2-sided 95% CI will be computed within defined subgroups of the study population. The analyses will be based on the FAS set using the same imputation method as for the primary efficacy analysis within the subgroups defined in section 5.2.5. Results from the subgroup analyses (estimated difference in response rates and 95% CIs) will also be presented in a forest plot. [redacted]

5.4.2 Secondary Efficacy Analysis/es

In this section the statistical analyses for the defined secondary efficacy endpoints will be described. For all endpoints, descriptive statistics and inferential analyses will be performed. To control the family-wise error rate at a level of 5%, a hierarchical testing procedure will be applied testing the secondary endpoints (after confirmatory significance of the primary analysis). Details on the hierarchical testing procedure and consequent interpretation of the analysis results are given in section 5.2.2.

5.4.2.1 Eliciting dose of peanut protein

The secondary efficacy endpoint evaluating eliciting dose and corresponding estimand is detailed in the below table.

Table 5 - Secondary efficacy endpoint evaluating eliciting dose of peanut protein and Estimand with Rationale for Strategies to Address Intercurrent Events

Estimand description	The secondary efficacy endpoint will evaluate eliciting dose of peanut protein in overall and by treatment group. A combination of strategies will be used to treat separately the different intercurrent events.
Target Population	Pediatric subjects aged 1 to 3 years, with diagnosed peanut allergy or high suspicion of peanut allergy, enrolled and randomized following confirmation of all eligibility criteria
Analysis Set	Full Analysis Set
Variable/Endpoint	Peanut protein ED dose at Baseline and at Month 12
Treatment Condition(s)	DBV712 250 µg group or placebo (Reference: Placebo).
Population-Level Summary	The following variables will be tabulated by treatment group using descriptive statistics: • Peanut protein ED dose at Baseline and at Month 12 (Geometric mean and associated Confidence Interval (CI) will also be provided), • Change in Peanut protein ED dose at Month 12 since Baseline (Geometric ratio will also be provided), • Status of Peanut protein ED dose at Month 12 (Decrease / Stable / Increase).
Intercurrent Event Strategy	
Intercurrent event 1	Composite strategy (mBOCF)
Intercurrent event 2	Composite strategy (subjects will mimic placebo response)
Intercurrent event 3	Composite strategy (mBOCF)
Intercurrent event 4	Treatment policy
Intercurrent event 5	Composite strategy (subjects will mimic placebo response)
Rationale for Strategy(s)	Composite strategy is used for intercurrent events 1, 2, 3 and 5 as follows: - For Early treatment discontinuations before 12 Months (Intercurrent event 1), Peanut DBPCFC will be imputed using mBOCF (subject is a non-responder)

	- Subject/caregiver refusing the Month 12 peanut DBPCFC (Treatment exposure ≥ M12, subject had not started the peanut DBPCFC and refusing to ingest the peanut formula – Intercurrent event 2) will be imputed using multiple imputation to mimic placebo response - Discontinuations at or after Month 12 with Month 12 DBPCFC missing (Intercurrent event 5) will be imputed using multiple imputation to mimic placebo response - Peanut DBPCFC initiated but not finished (Intercurrent event 3) will be imputed using mBOCF. Treatment policy strategy is used for intercurrent event 4: If the Peanut DBPCFC completed at Month 12 falls outside the recommended time-window subject ED at Month 12 is used as collected.
Imputation/Data	According to the type of intercurrent event, missing value will be imputed based on data in placebo group or on mBOCF. For descriptive statistics, missing value will be imputed based on mBOCF.
Analysis Model/Method	<u>Main analysis</u> ED is known as violating the normality assumption, thus log10-transformation of the data will be used for the analyses. The ED in each treatment group at Month 12 will be compared using an analysis of covariance (ANCOVA) model. The ANCOVA model will include the treatment group, adjusted for the Baseline ED value. The ANCOVA will be performed through a mixed procedure. A sample of the SAS® code to be used can be found in Appendix 8.2. The following statistics will be presented: • The back transformed Least square means: the Geometric Least Square Means by treatment group • The back transformed difference between the LS Means and the associated confidence interval: the geometric LS Means ratio • The p-value from the hypothesis test of no difference between the treatment groups based on type III sum of squares. Intercurrent events handling and multiple imputation inference: Step 1: Same as for primary efficacy analysis (imputation for intercurrent event 3 using mBOCF method).

	Step 2: Same as for primary efficacy analysis (imputation for intercurrent events 2 and 5). "MONOTONE REG" option will be used instead of a "MONOTONE LOGISTIC" in the SAS® procedure MI. Step 3: Same as for primary efficacy analysis (imputation for intercurrent event 1 using mBOCF method). Step 4: Same as for primary efficacy analysis. ANCOVA analysis will be performed separately for each of the 100 complete analysis data sets. All methods described above will be performed using SAS® procedures and detailed in Appendix 8.2. Sensitivity analysis on ED The main analysis will be repeated on the FAS using mBOCF imputation method for intercurrent events 2 and 5. Other analysis on ED The main analysis will be performed on PP set. [redacted]

5.4.2.2 Cumulative Reactive Dose of peanut protein

The secondary efficacy endpoint evaluating cumulative reactive dose of peanut protein and corresponding estimand is detailed in the below table.

Table 6 - Secondary efficacy endpoint evaluating cumulative reactive dose of peanut protein and Estimand with Rationale for Strategies to Address Intercurrent Events

Estimand description	The secondary efficacy endpoint will evaluate cumulative reactive dose of peanut protein in overall and by treatment group. A combination of strategies will be used to treat separately the different intercurrent events.
Target Population	Pediatric subjects aged 1 to 3 years, with diagnosed peanut allergy or high suspicion of peanut allergy, enrolled and randomized following confirmation of all eligibility criteria
Analysis Set	Full Analysis Set
Variable/Endpoint	Peanut protein cumulative reactive dose (CRD) at Baseline and at Month 12

Treatment Condition(s)	DBV712 250 µg group or placebo (Reference: Placebo).
Population-Level Summary	The following variables will be tabulated overall and by treatment group using descriptive statistics: • Peanut protein CRD at Baseline and at Month 12 (Geometric mean and associated Confidence Interval (CI) will also be provided) • Change in Peanut protein CRD at Month 12 since Baseline (Geometric Ratio will be also provided)
Intercurrent Event Strategy	
Intercurrent event 1	Composite strategy (mBOCF)
Intercurrent event 2	Composite strategy (subjects will mimic placebo response)
Intercurrent event 3	Composite strategy (mBOCF)
Intercurrent event 4	Treatment policy
Intercurrent event 5	Composite strategy (subjects will mimic placebo response)
Rationale for Strategy(s)	Composite strategy is used for intercurrent events 1, 2, 3 and 5 as follows: - For Early treatment discontinuations before 12 Months (Intercurrent event 1) Peanut DBPCFC will be imputed using mBOCF (subject is a non-responder) - Subject/caregiver refusing the Month 12 peanut DBPCFC (Treatment exposure ≥ M12, subject had not started the peanut DBPCFC and refusing to ingest the peanut formula – Intercurrent event 2) will be imputed using multiple imputation to mimic placebo response - Discontinuations at or after Month 12 with Month 12 DBPCFC missing (Intercurrent event 5) will be imputed using multiple imputation to mimic placebo response - Peanut DBPCFC initiated but not finished (Intercurrent event 3) will be imputed using mBOCF. Treatment policy strategy is used for intercurrent event 4: If the Peanut DBPCFC completed at Month 12 falls outside the recommended time-window, subject ED at Month 12 is used as collected.

Imputation/Data	According to the type of intercurrent event, missing value will be imputed based on data in placebo group or on mBOCF. For descriptive statistics, missing value will be imputed based on mBOCF.
Analysis Model/Method	Main analysis The peanut protein CRD in each treatment group at Month 12 will be compared using the same strategy as described in Section 5.4.2.1. Sensitivity analysis on CRD The main analysis will be repeated on the FAS using mBOCF imputation method for intercurrent events 2 and 5. Other analysis on CRD The main analysis will be performed on PP set.

5.4.3 Other Efficacy Analysis/es

In this section the statistical analyses for the defined other efficacy endpoints will be described. For all endpoints, descriptive statistics and inferential analyses will be performed. All statistical measures (p-values and CIs) will only be of descriptive nature with no aim to draw confirmatory conclusions. If not stated otherwise, all analyses will be performed on the FAS.

No imputation for missing data is used for Other Efficacy variables, i.e. only observed data are presented, except for laboratory results reported as below the lower detection limit (or reported above a specific value) which will be imputed as described in section 5.1.

5.4.3.1 Treatment response based on Responder definitions

Based on the ED from the DBPCFC at Month 12 visit, using imputation method rules used for primary analysis (depending on intercurrent event type), the following will be defined:

- Subjects defined as treatment responders:
  - If the screening ED was ≤10 mg peanut protein and the ED is ≥ 1,000 mg peanut protein at the post-treatment DBPCFC at Month 12
    OR
  - If the screening ED was >10 mg peanut protein and the ED is ≥ 2,000 mg peanut protein at the post-treatment DBPCFC at Month 12
- Subjects defined as treatment responders:
  - If the ED is ≥ 1,000 mg peanut protein at the post-treatment DBPCFC at Month 12, regardless the screening ED

Based on the CRD from the DBPCFC at Month 12 visit, using imputation method rules used for primary analysis (depending on intercurrent event type), the following will be defined:

- The percentage of subjects reaching a CRD ≥ 1,444 mg peanut protein at Month 12 post-treatment DBPCFC
- The percentage of subjects reaching a CRD ≥ 3,444 mg peanut protein at Month 12 post-treatment DBPCFC
- The percentage of subjects who passed the Month 12 post-treatment DBPCFC (no stopping criteria leading to stopping the DBPCFC at 2,000 mg)

The number and percentage of subjects will be presented by treatment group.

The analysis will be performed on the FAS and PP set. Data from these endpoints will be included in a listing.

5.4.3.2 Peanut-specific IgE and IgG4 over time

Descriptive summaries of peanut-specific IgE and IgG4 over time will include actual values, absolute and relative changes from Baseline at Month 3, Month 6 and Month 12 for the overall FAS. Geometric Mean (GM) and associated Confidence Interval (CI) will also be provided.

Actual values Median (±IQR), GM and associated CI over time in IgE and IgG4 will be presented graphically, by treatment group, for the overall FAS.

Both parameters are known as violating the normality assumption, thus log-transformation of the data will be used.

Repeated-measures ANCOVA models (using a Compound Symmetry covariance matrix structure) will be built to compare the geometric mean absolute values in peanut-specific IgE and IgG4 using all time points evaluated up to Month 12 in the active group versus the placebo group on the FAS using observed data. Treatment group, treatment-by-time point interaction and Baseline value will be included in the model.

The SAS® code used is listed in Appendix 8.2.

Statistics reported will include: Geometric LS means and standard error at each time point (Baseline, Month 3, 6 and 12), together with the geometric LS means ratio (DBV712 250µg/Placebo), the associated 95% confidence interval and the corresponding p-values at each time point. P-value for treatment effect all time points taken together will also be provided.

5.4.3.3 Ratio between peanut-specific IgG4 and peanut-specific IgE

The log transformation of the ratio between peanut-specific IgG4 and peanut-specific IgE, calculated as:

$$\text{Ratio} = log\left(\frac{Peanut\ specific\ IgG4(mg/L)\times 1000}{Peanut\ specific\ IgE\ (kU/L)\times 2.4}\right)$$

will be tabulated for the FAS at each time point:

- by treatment group and overall;
- for treatment responders vs. non responders (primary endpoint), by treatment group and overall.

5.4.3.4 Skin prick test (SPT) mean wheal diameters

Descriptive analysis of SPT mean wheal diameter over time including actual values and absolute change from Baseline at Month 3, Month 6 and Month 12 will be provided for the overall FAS.

The mean wheal diameter at Month 12 in each treatment group will be compared using an analysis of covariance (ANCOVA) model on the FAS on observed data. The model will include the treatment group, adjusted for the Baseline value as covariates.

All analyses will be performed on the FAS using observed data, with no imputation of missing data. Data will also be listed.

5.4.3.5 Food Allergy Quality of Life Questionnaires Parent Form (FAQLQ-PF)

The FAQLQs are disease-specific health-related quality of life questionnaires for subjects with food allergy. They are considered reliable and valid instruments to measure the impact of food allergy on health-related quality of life.

At screening and at Month 12, the subjects' parents/guardians will complete the FAQLQ-PF questionnaires (in countries where the translated and validated questionnaires are available and used).

Starting from protocol v6.0, a new version of the FAQLQ-PF questionnaire will be used for subjects randomized in Part B, at screening and at Month 12. The template of the questionnaire is provided in Appendix 6 of the protocol.

FAQLQ-PF will be analyzed according to the 3 following domains:

- EI: Emotional impact (Q no: 2, 6-7, 9-11),
- FA: Food-related anxiety (Q no: 1, 4-5),
- SDL: Social and dietary limitations (Q no: 3, 8, 12-14).

Age at Visit 1 will be used to define which questions will be applicable during the study for each subject. Questions not needed will be not used for analysis.

The following instructions from the reference website (www.faqlq.com) will be used for the derivations of (sub-) scales:

1) Each question of the FAQLQ-PF is answered on a 7-point scale (0 to 6) and will be recoded 1 to 7

2) All sub-scores are calculated by dividing the sum of scores by the number of completed questions

3) FAQLQ-PF Total Score = (EI Subscale Score + FA Subscale Score + SDL Subscale Score) / 3

4) If > 20% of items in any (sub-) scale are missing then the respective (sub-) scale is set to missing

5) Total score is calculated only if the 3 sub-scores are completed

The FAQLQ Parent Form (FAQLQ-PF) total score and the Emotional impact domain score at baseline (V1) and Month 12 and the change from baseline at Month 12 will be summarized descriptively by treatment group as continuous data. This analysis will be repeated in the subgroup of responders vs non-responders as per Primary endpoint definition.

Absolute change in FAQLQ-PF total score and each domain scores will be analyzed using ANCOVA models with treatment group as fixed effects and respective baseline value as a covariate. From the statistical model, LS Means, corresponding 2-sided 95% CI, and the LS Mean difference (DBV712 250µg – Placebo) and corresponding 2-sided 95% CI, effect size and p-value from the 2-sided test of no difference between treatment groups will be presented.

All analyses will be performed on the FAS using observed data, with no imputation of missing data. Data will also be listed.

5.4.3.6 Food Allergy Independent Measure Parent Form (FAIM-PF)

The FAIM-PF questionnaires capture the subjects' expectation of something happening because of her/his food allergy. It corresponds to the Section E of the FAQLQ-PF questionnaire.

Each question of the FAIM-PF is answered on a 7-point scale (0 to 6) and will be recoded 1 to 7. Total FAIM-PF scores will be calculated by dividing the sum of completed items by the number of completed items. Total FAIM-PF scores range from 1 "low perceived disease severity" to 7 "high perceived disease severity". Calculation of total FAIM-PF scores will be done only when 80% or more of the items are completed.

Some specific items mentioned below must be reverse coded.

There are 2 sections in the questionnaire with the same question, one from the perspective of the parents (What chance do you think your child has of.....?) the other reflecting the thoughts of the child (What chance does your child think he/she has of.....?). Both mean scores of the parent's form ("Parent's thoughts" and "Child's thoughts") are calculated as the mean of the single items, only if none of the items is missing. In both scores question 4 will be reverse scored.

The total FAIM-PF-scores will be summarized overall and for each type of questionnaire, in total and by randomized treatment group (Placebo/DBV712 250µg) at baseline (V1) and Month 12, and the change from baseline at Month 12.

Absolute change in FAIM-PF total score and for each type of questionnaire will be analyzed using ANCOVA models with treatment group as fixed effects and respective baseline value as a covariate. From the statistical model, LS Means, corresponding 2-sided 95% CI, and the LS Mean difference (DBV712 250µg – Placebo) and corresponding 2-sided 95% CI, effect size and p-value from the 2-sided test of no difference between treatment groups will be presented.

All analyses will be performed on the FAS using observed data, with no imputation of missing data. Data will also be listed.

5.5 Study Drug Safety Evaluation

Safety analysis will be performed using the Safety Set (SAF). All outputs will be summarized by actual treatment received and presented by treatment group and overall. Unless otherwise specified, missing data will not be replaced/imputed.

5.5.1 Adverse Events

5.5.1.1 Definitions

Treatment-emergent AEs will be defined as any AEs, regardless of relationship to IMP reported during or after the initial application, i.e. AEs where start date/time is on or after date/time of the first study treatment.

- When an AE's start date is equal to the date of first study treatment and the start time of AE is missing, AE will be defined as treatment emergent.
- Where dates are missing or partially missing, adverse events will be assumed to be treatment-emergent, unless there is a clear evidence (through comparison of partial dates) to suggest that the adverse event started prior to the first study treatment. More specifically, See Section 5.5.1.2.

AEs occurring after the end of the study will be recorded only if the investigator considers that there is a causal relationship with the IMP and as such, will be considered also as TEAEs.

Pre-treatment emergent AE will be defined as an AE that begins before the first administration of IMP.

IMP-induced Local TEAEs are defined as TEAEs considered as related to IMP with a High-Level Term equal to "Application and instillation site reactions" and will be flagged in the analysis datasets.

Following medication use will be defined:

- **Epinephrine use** will be identified by a combination of standard medication name that contains "EPINEPHRINE" and ATC level 1 = "CARDIOVASCULAR SYSTEM".
- **Systemic or inhaled corticosteroid use** will be identified by:
  - ATC code starting with "H02"
  - ATC code starting with "R03AK" (Adrenergics in combination with corticosteroids or other drugs, excl. anticholinergics) and "R03BA" (Glucocorticoids)
- **Topical corticosteroid use** will be identified by ATC code starting with "D07" (Corticosteroids, Dermatological preparations)

Treatment emergent adverse events of special interest (AESI), are defined as:

Local AESI:

Local AESIs will be identified by one of the following conditions:

- Any adverse events with a preferred term (PT) corresponding to this prespecified list of PT according to the MedDRA version 20.1:
  - Application site abscess
  - Application site burn
  - Application site cyst
  - Application site discharge

- Application site extravasation
- Application site fissure
- Application site haemorrhage
- Application site injury
- Application site laceration
- Application site necrosis
- Application site scab
- Application site scar
- Application site ulcer
- Application site vesicles
- Application site wound

- Any adverse events with verbatim which contains "GRADE 4 or "GRADE IV" for HLT = "Application and instillation site reactions".

Systemic AESIs:

Systemic AESI is defined as any acute systemic immediate allergic reactions (rapid onset) after exposure to a known or suspected allergen regardless of the causal relationship to the IMP, and occurring outside the DBPCFCs. This includes:

1. Anaphylactic reaction

2. Any systemic hypersensitivity reaction leading to epinephrine intake

Systemic AESIs will be identified by the investigator in the eCRF using the tick box "AESI".

In case of serious events and to avoid duplicated information, SAE form is completed instead of AESI form. Serious systemic AESIs will be identified as any SAE with a preferred term (PT) corresponding to:

- "Anaphylactic reaction"
- "Anaphylactic shock"
- ("Hypersensitivity" or "Food allergy") AND AE leading to an epinephrine intake (Epinephrine use will be retrieved using Standard medication name containing "EPINEPHRINE" and ATC level 1 = "CARDIOVASCULAR SYSTEM")

5.5.1.2 Handling of Missing or Incomplete Data

Partial AE end date will be derived before partial/missing AE start date.

AE end date

- If AE end date is missing or AE is ongoing, the AE end date will not be imputed.
- If AE end date is partial:
  - If AE end day is missing, it will be imputed to the earliest date (last day of the month/Month AE end/Year AE end, death date)
  - If AE end day and month are missing, they will be imputed to the earliest date (31DEC/Year AE end, death date)

AE start date

- If AE start date is missing, the AE start date will not be imputed.
  - If derived AE end date is missing, the AE will be considered as TEAE
  - If derived AE end date is before (<) the Treatment start date, the AE will be considered as pre-TEAE
  - If derived AE end date is on or after (≥) the Treatment start date, the AE will be considered as TEAE
- If AE start date is partial:
  - If derived AE end date is missing:
    - If AE start day is missing it will be imputed to "01" unless month and year are the same as month and year of the TRT start date then impute TRT start date
    - If AE start day/month are missing they will be imputed to "01JAN" unless year is the same as year of the TRT start date then impute TRT start date
  - If derived AE end date is before (<) the Treatment start date:
    - Missing day will be imputed to 01 and Missing month will be imputed to "JAN"
  - If derived AE end date is on or after (≥) the Treatment start date:
    - If AE start day is missing it will be imputed to "01" unless month and year are the same as month and year of the TRT start date then impute TRT start date
    - If AE start day/month are missing they will be imputed to "01JAN" unless year is the same as year of the TRT start date then impute TRT start date

Severity

TEAEs with missing severity will be considered as "severe";

Causality

TEAEs with missing relationship to the IMP will be considered as "drug-related".

TEAEs reported as related, probably related, or possibly related to the IMP will be considered as related to IMP.

5.5.1.3 Analyses

AEs related to accidental peanut consumption will be excluded from analyses (unless otherwise specified) and presented separately (section 5.7.1).

SAEs elicited during DBPCFC will be excluded from any analyses, unless otherwise specified. Nevertheless, these SAEs will be presented in the listings when applicable (section 5.6). Symptoms related to DBPCFC are reported in tables separately from other AEs.

For each summary presented by SOC and PT:

- the SOC "General disorders and administration site conditions" will be tabulated globally as well as split in 2 subsections:
  - General disorders (High Level Term not equal to "Application and instillation site reactions"),
  - Administration site conditions (High Level Term equal to "Application and instillation site reactions").
- Lowest Level Term (LLT) will be tabulated for the PT "Anaphylactic reaction" to help distinguish reactions due to other allergens.

An overall overview table of TEAEs (to be distinguished from symptoms/reactions elicited during the DBPCFCs) will be provided showing the number of subjects, the percentage of subjects and the number of events for the following categories of TEAEs:

- Any TEAEs,
- Any serious TEAEs,
- Any TEAEs considered related to IMP:
  - Any TEAEs reported as related,
  - Any TEAEs reported as probably related,
  - Any TEAEs reported as possibly related,
- Any TEAEs considered unrelated to IMP:
  - Any TEAEs reported as unlikely related,
  - Any TEAEs reported as unrelated,
- Any Serious TEAEs considered related to IMP,
- Any TEAEs leading to permanent study treatment discontinuation,
- Any TEAEs leading to temporary study treatment discontinuation,
- Any TEAEs leading to death,
- Any mild TEAEs,

- Any moderate TEAEs,
- Any severe TEAEs,
- Any severe TEAEs considered related to IMP (reported as related, probably or possibly related),
- Any IMP-induced Local TEAEs,
- Any severe IMP-induced Local TEAEs,
- Any treatment-emergent local AESI,
- Any treatment-emergent systemic AESI:
  - Reported as Anaphylactic reaction
  - Reported as Systemic hypersensitivity reaction leading to epinephrine intake
- Any treatment-emergent systemic AESI considered related to IMP (reported as related, probably or possibly related):
  - Reported as Anaphylactic reaction
  - Reported as Systemic hypersensitivity reaction leading to epinephrine intake
- Any TEAEs leading to an epinephrine intake
  - Considered related to IMP
  - Considered unrelated to IMP,
- Any TEAEs leading to systemic or inhaled corticosteroid use,
- Any TEAEs leading to topical corticosteroid use

Overall overview of TEAEs will be repeated:

- for the subgroups listed in section 5.2.5,
- including APC,
- for subperiod of treatment post 4 years old (from the date turning 4 years old to end of treatment).

The number and percentage of subjects who experienced at least one event and the number of events will further be summarized by SOC and PT for the following types of events:

- any TEAEs,
- any serious TEAEs,
- any potentially drug-related TEAEs,
- any serious potentially drug-related TEAEs,
- any TEAEs leading to permanent study treatment discontinuation,
- any TEAEs leading to temporary study treatment discontinuation,
- any TEAEs leading to death,
- any TEAEs leading to epinephrine intake,

- any TEAEs leading to systemic or inhaled corticosteroid use,
- any TEAEs leading to topical corticosteroids use
- any TEAEs occurring after 407 days (V10 (365 + 7 days) + V11 (7 days) + V12 (4 weeks)).

Additional tables will be created to display the most frequent TEAEs (by preferred term), occurring in at least 5% of the subjects in any of the treatment groups.

For TEAEs and TEAEs considered related to IMP, additional tables will be provided showing number of subjects and percentage of subjects:

- By maximum severity (severe, moderate and mild): Subjects will be counted once per SOC and once per PT at the worst severity. If the severity is missing, the worst severity will be assumed.
- By maximum duration: For these tables TEAEs will be presented by SOC, PT within each SOC and maximum duration within each PT (using the classes for duration in days: (1 to 7 Days, 8 to 15 Days, 16 to 30 Days, 31 to 60 Days, 61 to 90 Days, More than 90 Days). For AEs ongoing at the end of the study, duration will be imputed based on the date of subject end of study. For AEs not ongoing but with missing end date, duration will be imputed based on date of last study treatment.

Additionally, for TEAEs and TEAEs considered related to IMP, tables showing number of subjects, percentage of subjects and number of events by severity will be provided. Subjects will be counted once per SOC, per PT and per severity. For these specific tables, if the severity is missing, no hypothesis will be assumed to replace the missing severity.

Adverse event summaries will be ordered in terms of decreasing frequency for SOC, and PT within SOC, in the active treatment group, and then similarly by decreasing frequency in the placebo group, and then alphabetically for SOC, and PT within SOC.

A by-subject listing of all adverse events will be provided. This listing will be presented by treatment group and will include: treatment group, subject identifier, age, sex, adverse event (SOC, PT, and verbatim term), date/time of onset (and corresponding study day), date/time of resolution (and corresponding study day), duration, severity, treatment required, relationship to IMP, relationship to an accidental peanut consumption, relationship to DBPCFC, and AESI flag, and action taken with the IMP, outcome, and whether the event is classified as serious or not with the corresponding criteria.

Pre-treatment emergent adverse events will be listed separately the same way as the treatment emergent adverse events.

TEAE leading to an epinephrine intake will also be listed.

Finally, SAEs will also be listed the same way with an additional flag for treatment emergent SAEs.

5.5.2 Deaths

A detailed table will be created showing the number of subjects who experienced one SAE leading to Death, the corresponding percentage of subjects and the number of events grouped by SOC and PT.

All deaths will be listed in a summary table.

5.5.3 Local Skin Tolerance

Subject assessment

The severity of local skin reactions will be assessed on a daily basis by the parents/guardians in diaries during the whole treatment duration for Part B subjects. The following data from the subject's diaries will be summarized for itching, redness, swelling and any local reaction (itching, redness or swelling) by treatment group on the SAF:

- Number and percentage of subjects by maximum severity of skin reactions reported during the assessment period (all subjects / subjects with at least one reaction (grade ≥ 1).
- Number and proportion of days with a reaction reported (grade ≥ 1) during the assessment period.
- Number and proportion of days with a reaction reported Grade 0 / Grade 1 / Grade 2 / Grade 3 during the assessment period.

The proportion of days with a reaction reported will be calculated as:

$$\left(\frac{\text{Number of days with a reaction reported}}{\text{Number of days with a patch applied}}\right)$$

The number of days with a reaction reported and number of days with patches applied will be calculated based on application dates.

The above defined proportions will be calculated overall (Day 1 to Day 180 or Day 365) and for the following periods of time:

- Month 1 (Day 1 to Day 30),
- Month 2 (Day 31 to Day 60),
- Month 3 (Day 61 to Day 90),
- Month 4 (Day 91 to Day 120),
- Month 5 (Day 121 to Day 150),
- Month 6 (Day 151 to Day 180),
- Month 7 (Day 181 to Day 210),
- Month 8 (Day 211 to Day 240),
- Month 9 (Day 241 to Day 270),
- Month 10 (Day 271 to Day 300),
- Month 11 (Day 301 to Day 330),
- Month 12 (Day 331 to Day 365)
- Above Month 12 (> Day 365)

All data will be presented in a listing for SAF.

Investigator assessment

Examination of the skin at the site of patch application will be performed by the investigator at several visits:

- at Visit 4 the assessment will specifically be performed before patch application, at 30 minutes, 1 hour and 2 hours during patch application and 1 hour after patch removal.
- At each time point, the skin reaction will be graded by the Investigators on a scale of Grade 0 (negative) to Grade 4 (erythema, vesicles) and localization of the skin reaction (under the patch (A)/beyond the patch,(B)), see details in Table 7.

Table 7 - Patch Application Site Skin Reaction Grading (Investigator)

Skin Reaction	Grade if localized under the patch	Grade if extending beyond the patch	Grade regardless of localization
Negative	Grade 0	Grade 0	Grade 0
Only erythema, or erythema and infiltration	Grade 1A	Grade 1B	Grade 1
Erythema and few papules	Grade 2A	Grade 2B	Grade 2
Erythema and many or spreading papules	Grade 3A	Grade 3B	Grade 3
Erythema and vesicles	Grade 4A	Grade 4B	Grade 4

Grade 4B is considered as the most severe leading to 4B > 4A > 3B > 3A > 2B > 2A > 1B > 1A >0.

The number and percentage of subjects with each grade will be presented by visit (and timepoint within visit for visit 4), both overall and by location of site reaction (under the patch / beyond the patch) by treatment group on the FAS.

Additionally, the worst grading overall (during the course of the trial) will be summarized as the number and percentage of subjects in each category on the Safety Set.

Patch site skin reaction data will also be listed on the Safety Set.

5.5.4 Clinical Laboratory Evaluation

Laboratory tests will be performed by a central laboratory. All laboratory data units will be converted to SI units if necessary.

The following laboratory parameters will be assessed at the analysis windows Baseline, Month 3, Month 6 and Month 12:

- Hematology:
  - hemoglobin,
  - hematocrit,
  - platelets,
  - red blood cells,
  - white blood cells (with differential cell count (in %))
- Biochemistry:
  - alanine aminotransferase (ALT),
  - aspartate aminotransferase (AST),
  - total bilirubin,
  - total protein,
  - blood urea nitrogen,
  - creatinine

Clinically significant changes (abnormalities) in laboratory parameters, in the judgment of the Investigator, will be recorded as AEs and appropriate countermeasures taken.

In the event of unexplained abnormal laboratory test values of clinical significance, the tests should be repeated at a reasonable time point and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found.

Those repeated assessments performed outside scheduled visits are taken into account for the analysis and should follow the rules described in section 5.2.7.

The following results will be tabulated for hematology and biochemistry tests on the safety set (in SI units):

- Descriptive statistics for each test result at each timepoint.
- Descriptive statistics for absolute changes from Baseline for each test result at time point.
- Common Toxicity Criteria for Adverse Events (CTCAE version 4.03) grade at each time point and shift from Baseline for each test result at each time point. CTCAE grades for hematology and biochemistry measures will be derived according to Appendix 8.3.
- Shift of test abnormalities (Low, Within normal range, High) between Baseline ant each timepoint

All laboratory data will be listed. Values that are out of normal range will be flagged in the data listings.

Flags used are:

- Low (below normal ranges), based on the following original flags from the laboratory reports:
  - PL, L2 ("Panic Low")

- TL, L1 ("Telephone Low")
- L ("Low")

- High (above normal ranges), based on the following original flags from the laboratory reports:
  - H ("High")
  - TH, H1 ("Telephone High")
  - PH, H2 ("Panic High")

When summarized in tables, all “High” flags will be merged together (“Panic High”, “Telephone High”,” High”); the same for the low flags as well.

In listings, “High” and “Low” flags will be reported.

Listings of all laboratory data will be provided by treatment group, and will include subject identifier, age, sex, weight and visit for the Safety set. Laboratory reference ranges will also be listed for the Safety set.

5.5.5 Vital Signs

The following vital signs will be recorded, before each DBPCFC and at any scheduled and unscheduled visits:

- Systolic blood pressure (in mmHg),
- Diastolic blood pressure (in mmHg),
- Heart rate (beats/minute),
- Respiratory rate (breaths per minute).

The following results will be tabulated for all vital signs:

- Summary statistics of values by visit and changes from Baseline
- Changes from Baseline by visit
- Number and percentage of subjects with vital signs abnormalities by post-baseline visit for heart rate, systolic blood pressure and diastolic blood pressure classified using the criteria defined in Table 8.

Table 8 - Criteria to Determine Clinically Relevant Abnormalities in Vital Signs

Vital Sign Criteria for Abnormalities	Criteria for Abnormalities (any of the following situation)
Heart rate	• value <60 beats/min, • value >130 beats/min, • an increase from pre-dosing of >20 beats/min, or • a decrease from pre-dosing of >20 beats/min
Systolic blood pressure	• value <70 mmHg • value >130 mmHg, • an increase from pre-dosing of > 40 mmHg, or • a decrease from pre-dosing of >30 mmHg
Diastolic blood pressure	• value <45 mmHg • value >85 mmHg, • an increase from pre-dosing of >30 mmHg, or • a decrease from pre-dosing of >20 mmHg

Vital signs data and clinically relevant abnormalities in vital signs will also be listed.

5.5.6 Physical Examination

A Physical examination will be performed, in accordance with the Schedule of Procedures and includes the following parameters and at any unscheduled visit at the discretion of the investigator.

Physical examination will include the measure of the weight (kg) and height (cm) and the examination of the following:

- General appearance,
- Head and Neck,
- Ears, nose and throat,
- Eyes,
- Complete skin examination,
- Cardiovascular system,
- Respiratory system,
- Abdominal system,
- Nervous system,
- Other system(s).

The following results will be tabulated:

- Summary statistic for weight and height by visit and change from Baseline,
- Number and percentage of subjects with abnormal (vs. normal / not done) physical examination by visit for each of the system examined.

Physical examination data will also be listed for the Safety set.

5.6 Study Procedure Safety Evaluation

The symptoms elicited during the DBPCFC (as they are expressly provoked) are differentiated from TEAEs and Treatment Emergent SAEs.

5.6.1 Serious Adverse Events Elicited during DBPCFC

All SAEs elicited during the entry/screening DBPCFC and Month 12 DBPCFC will be tabulated by SOC / PT and by timepoint. It will be discriminated between Peanut- and Placebo-Formula.

SAE elicited during any DBPCFC during the study will also be listed on the Enrolled Set.

5.6.2 Symptomatic Reactions during DBPCFC

The objective symptoms collected during the DBPCFC are the following:

- Skin:
  - Erythematous rash (and % of rash area concerned)
  - Pruritus
  - Urticaria/ angioedema
  - Rash
- Upper respiratory:
  - Sneezing/ itching
  - Nasal congestion
  - Rhinorrhea
  - Laryngeal
- Lower respiratory:
  - Wheezing
- Gastrointestinal:
  - Diarrhea
  - Vomiting
  - Cardiovascular
- Eyes:

- Conjunctivitis
- Any other objective symptoms (not reported, mild, moderate, severe)

The subjective symptoms collected are:

- Itchy mouth
- Itchy throat
- Nausea
- Abdominal pain
- Any other subjective symptoms (not reported, mild, moderate, severe).

With the exception of erythematous rash (recorded as Yes/No), each symptom is graded as: 0=" absent", 1=" mild", 2=" moderate" or 3=" severe". For erythematous rash, the % area involved is collected. The grading corresponding to the area involved is captured in the grading of the "Rash" symptom. No further step is required.

A total symptom score for each subject will be calculated as the sum of all severity score for all objective symptoms (for the Peanut formula only, excluding erythematous rash) and abdominal pain subjective symptom (only when grade is 2 or 3). This will be based on the sum of each of the following symptom being graded for severity as 0, 1, 2 or 3 (respectively absent, mild, moderate and severe):

Pruritus, Urticaria/ angioedema, Rash, Sneezing/ itching, Nasal congestion, Rhinorrhea, Laryngeal, Wheezing, Diarrhea, Vomiting, Cardiovascular, Conjunctivitis, Abdominal pain, Any other objective symptoms (one score for each of the other objective symptoms, 0 if no other objective symptom is recorded or if the answer to the question "Did the subject experienced any objective symptoms" is "No").

The reactions appearing during a DBPCFC will be summarized by group and by formula (peanut, placebo) for the enrolled set, showing:

- The number and percentage of subjects with objective symptoms (by severity) at Baseline and at Month 12 (actual value) (overall and by type of symptom)
- The number and percentage of subjects with subjective symptoms (by severity) at Baseline and at Month 12 (overall and by type of symptom)
- Summary statistics on the Total symptom score at Baseline, at Month 12 (actual value) and the change from Baseline to Month 12 (using observed values).
- Symptoms used to calculate the Total symptom score will also be described using the number and percentage of subjects with symptoms by maximum severity at Baseline and at Month 12 overall and at each dose of DBPCFC. The Month 12 maximum symptom severity in the selected active DBV712 group (250 µg) compared to the placebo group will be analyzed on the FAS set excluding subjects with intercurrent events 1, 2 or 5 using a Cochran-Armitage Trend Test.

5.7 Exploratory Analyses

5.7.1 Accidental Peanut Consumption

In case of possible APC, a dedicated form is to be completed in the eCRF. Associated symptoms are collected in the same CRF page, and the final diagnosis (e.g. Anaphylactic reaction) is recorded in the Adverse Events CRF page. Both forms will be described separately.

The following summaries will be provided:

- Number and percentage of subjects with any peanut consumption overall and by number of consumptions (1, 2, 3, >3),
- Number and percentage of subjects with any peanut consumption confirmed as accidental, overall and by number of consumptions,
- Number and percentage of subjects with any peanut consumption confirmed as non-accidental, overall and by number of consumptions.

All summaries will be created by treatment group and overall for the Safety set.

An overview table of AEs induced by APC will be provided showing the number and percentage of subjects overall and for each treatment group, for the following categories:

- Any AEs induced by APC,
- Any Serious AEs induced by APC,
- Any Anaphylactic reaction induced by APC (Anaphylactic reactions will be retrieved using MedDRA Preferred Term “Anaphylactic reaction” or “Anaphylactic shock”). The LLT level will also be tabulated,
- Any AEs induced by APC leading to Epinephrine intake (Epinephrine use will be retrieved using Standard medication name containing “EPINEPHRINE” and ATC level 1 = “CARDIOVASCULAR SYSTEM”).

All AEs induced by APC will be tabulated by treatment group and overall on the Safety set.

5.7.2 IgE and IgG4 specific to peanut protein components

IgE and IgG4 specific to peanut specific components will include Ara h 1, Ara h 2, and Ara h 3. IgE and IgG4 specific to peanut specific components will be summarized descriptively as continuous data at Visit 1 (baseline), Month 3, Month 6 and Month 12. Absolute and relative change from baseline at each post-baseline visit will also be presented.

Absolute change from baseline in IgE and IgG4 peanut specific components at Month 3, Month 6 and Month 12 will be analyzed using the same approach as described for IgE and IgG4 in section 5.4.3.2.

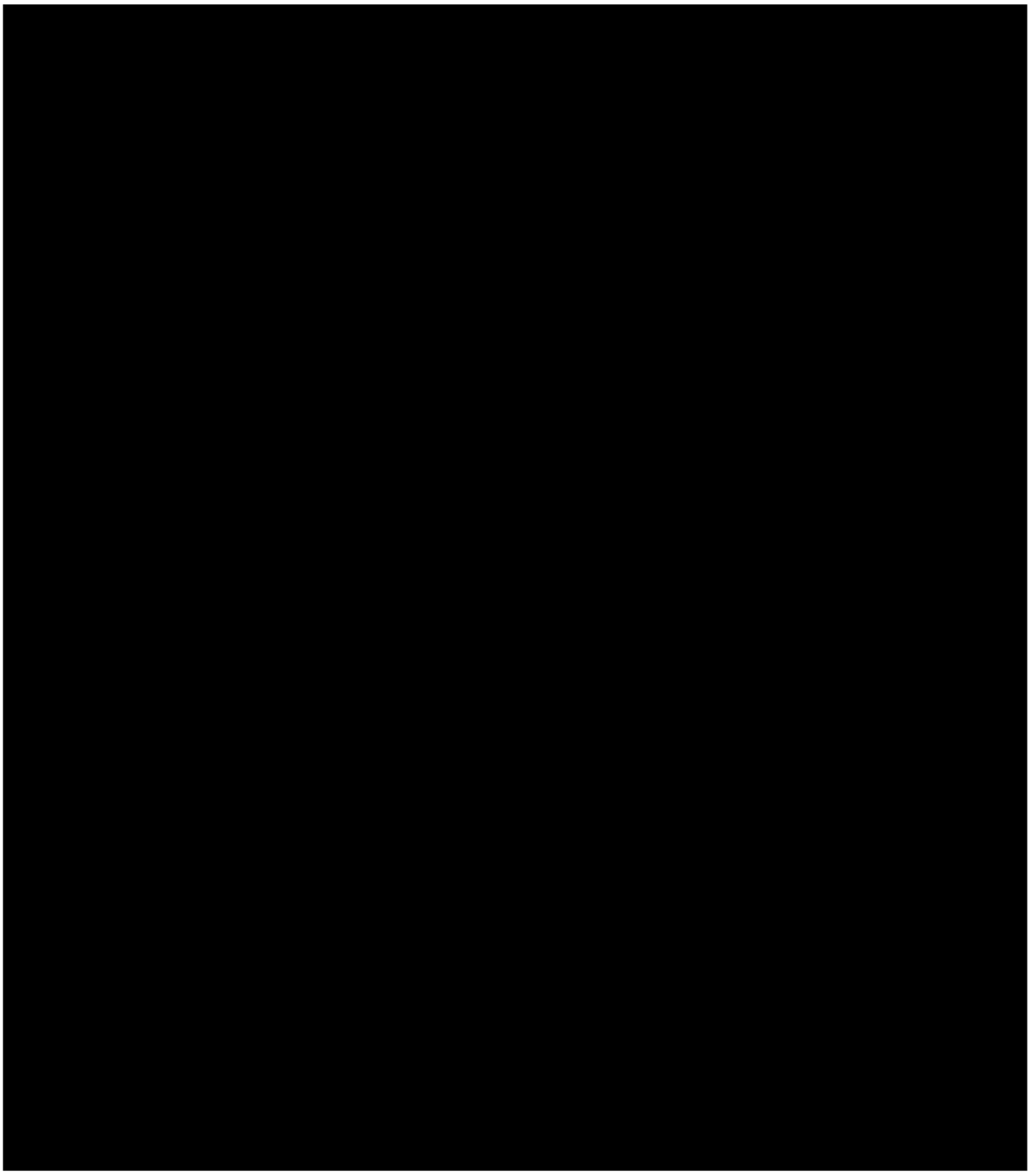
IgE and IgG4 specific to cow’s milk, egg white, house dust mites, and grass pollen will be assessed at Visit 1 (baseline) and Month 12. These will be summarized descriptively as continuous data. Absolute and relative change from baseline at Month 12 will also be presented.

All analyses will be performed on the FAS using observed data, with no imputation of missing data.

CCI

All data will be included in a listing for the FAS.

CCI



5.7.5 SCORAD evolution over time

The SCORAD index score at baseline (V1), Month 3, Month 6, Month 12 and absolute change from baseline at each post-baseline visit will be summarized descriptively as continuous data.

The summaries will be provided by treatment group based on the FAS using observed data. No imputation of missing data will be performed.

SCORAD data will be listed for the FAS set.

5.7.6 Quality of Life using EQ-5D-5L

The questionnaire will be completed for subjects' parents/guardians, randomized in Part B only. Data from this endpoint will be included in a listing for the FAS.

If the questionnaire was incorrectly answered on behalf of the child, rather than the parent, a footnote will be included in any tabulations or listings presenting this data to indicate that some parents incorrectly filled out this questionnaire, leading to some unexpected results.

5.7.7 Basophil Activation Test (BAT)

BAT data will be analysed in US eligible sites only. Details on analyses will be formulated in a dedicated SAP.

5.8 Sample Size Determination

5.9 Planned Analyses

Analysis will be performed after study database lock.

5.10 Data Safety Monitoring Board (DSMB)

A DSMB composed of experts in Peanut Allergy and in the methodology of clinical studies will review study safety data at specific intervals during the study and on an *ad hoc* basis.

A specific SAP for DSMB meeting was prepared in addition to the present document. Details on the occurrence and content of DSMB meetings are described in the DSMB charter.

5.11 Changes in the Analyses planned in protocol

The following changes have been done compared to the analyses described in the protocol:

- Farrington-Manning 95% confidence interval (CI) method is used instead of Newcombe method for the difference in response rates, to allow multiple imputation. This change has no impact on the study power.
- Intercurrent events have been detailed for primary and secondary analyses.
- Additional sensitivity, other efficacy and subgroup analyses have been added.
- Safety will also be assessed by subgroups.
- Additional analysis on DBPCFC symptoms have been added.
- AESI identification has been updated.

6 REFERENCES

Not applicable

7 MODIFICATION HISTORY

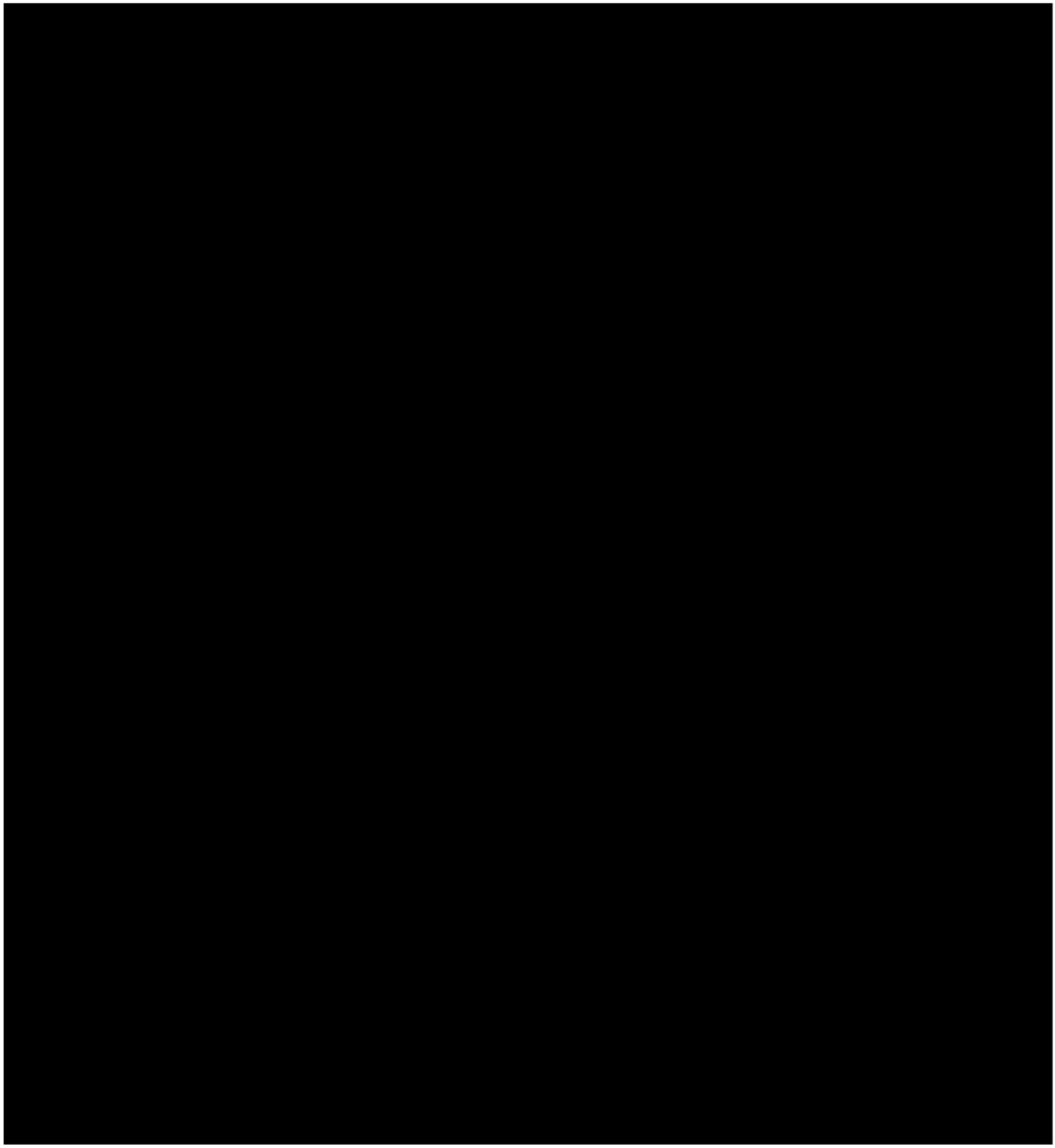
The modification history provides an overview of the status of the current document. It provides the cumulative accounting of changes including rationale and key details for major changes.

SAP Version	Date	Significant changes from the previous version	Author
1.0	02JUL2021	Creation	PPD
2.0	03SEP2021	Updates in: - Time-window at Month 12 - Confidence interval method changed for response rate difference in primary endpoint (Newcombe to Farrington-Manning)	PPD
3.0	10NOV2021	Updates in: - Lower bound of the 95% CI of the difference between the selected active treatment and placebo response rates changed from 15% to 10%	PPD

		- Clarification of intercurrent events handling and multiple imputation inferences for primary and secondary analyses - The 2-sided 95% CIs of individual response rate corrected from Wald to Wilson. - Details on imputation for incomplete date of birth added - Safety overview table of TEAEs (analysis in subperiod of treatment post 4 years old added, overview repeated including APC) - Anaphylactic reaction analyzed by LLT - Modification in SAS® code lines for multiple imputation - [redacted] - Modification in peanut-specific IgE and IgG4 analyses - Modification in local skin tolerance analyses (based on application dates) - Specification of MedDRA version 20.1 used	
4.0	15MAR2022	Per FDA's 3-Feb-2022 Information Request: - Lower bound for success criteria updated to 15%. - Success criteria is based on the lower bound of the 95% CI of the difference between group. - Clarification of intercurrent events Due to the Covid-19 pandemic, some sites have been temporarily closed and study visits were postponed. Therefore, analysis windows were extended. All data (within or outside of Analysis windows) will be presented in Listings. Handling of unreturned kits for the compliance calculation will be discussed on a case by case basis during the Data Review Meeting. Clarification added for aberrant duration of patch application. Subjective symptom abdominal pain grade 2 or 3 was added for calculation of FC total symptom score. An analysis looking at the relationship between FAQLQ-PF scores and treatment response (which was planned in the Protocol) has been added. Clarification added on the algorithm to identify serious AESI.	PPD

8 APPENDICES

CCI



CCI

CCI

[redacted]

[redacted]

[redacted]

CCI

[redacted]

[redacted]

[redacted]