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STATISTICAL ANALYSIS PLAN
EPOPEX

VERSION: 1.0

DATE OF PLAN:

01-APR-2025

BASED ON:

Protocol V2.0 – 21 Sep 2021 (US only)

Protocol V1.0 – 10 Sep 2018

CRF V10.0 – 17 May 2023

STUDY DRUG:

DBV712 (Viaskin® Peanut), epicutaneous system

PROTOCOL NUMBER:

IND 14366

EU CT Number: 2018-003323-10

STUDY TITLE:

EPITOPE OPEN-LABEL EXTENSION STUDY TO EVALUATE THE LONG-TERM CLINICAL BENEFIT AND SAFETY OF DBV712 IN PEANUT-ALLERGIC CHILDREN

SPONSOR:

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This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

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1. LIST OF ABBREVIATIONS

Sample text is provided in the table below. The list should be tailored to the specific requirements of the protocol and the terminology used in the analysis plan.

Table 1: List of Abbreviations

Abbreviation	Term
AE	Adverse Event
AESI	Adverse Event of Special Interest
ATC	Anatomical Therapeutic Chemical
CI	Confidence Interval
CRD	Cumulative Reactive Dose
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DBPCFC	Double-Blind Placebo-Controlled Food Challenge
ED	Eliciting Dose
EPIT	EPicutaneous Immuno Therapy
FAIM	Food Allergy Independent Measure
FAQLQ	Food Allergy Quality of Life Questionnaire
IgE	Immunoglobulin E
IgG4	Immunoglobulin G4 subtype
IP	Investigational Product
IQR	InterQuartile Range
LLT	Lowest Level Term
(m)LOCF	(modified) Last Observation Carried Forward
LS Mean	Least-Square Mean
MedDRA	Medical Dictionary for Regulatory Activities Terminology
MI	Multiple Imputation
N	Total Sample Size
PD	Protocol Deviation
PT	Preferred Term
Q1, Q3	First, Third Quartile
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

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Abbreviation	Term
SAS	Statistical Analysis System
SCORAD	Scoring Atopic Dermatitis
SD	Standard Deviation
SOC	System Organ Class
SPT	Skin Prick Test
TEAE	Treatment Emergent Adverse Event
TFL	Tables, Listings and Figures
V	Visit
VAS	Visual Analogue Scale
WHO	World Health Organization

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2. INTRODUCTION

The statistical analysis plan (SAP) is based on:

- Study protocol:
  - Version 1.0 (10 September 2018)
  - Version 2.0 (21 September 2021), for US only
- eCRF, Version 10.0 (17 May 2023)
- EPITOPE SAP Version 4.0 (15 March 2022)
- ICH guidelines E4 and E9 (Statistical Principles for Clinical Trials)
- Discussions with the FDA

The purpose of this document is to provide details on study populations and on how the variables will be derived, how missing data will be handled as well as details on statistical methods to be used to analyze the safety and efficacy data collected under the DBV Technologies EPOPEX study.

The document may evolve over time, for example, to reflect the requirements of protocol amendments or regulatory requests. However, the final SAP must be finalized, approved by the Sponsor, and placed on file before database is locked. Deviations from the final approved plan will be noted in the clinical study report.

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3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

The objectives of the EPOPEX follow-up study are:

- To assess the clinical benefit of Viaskin® Peanut after up to 3 years of EPIT to induce/maintain desensitization to peanut in peanut-allergic children;
- To evaluate the safety of long-term treatment with Viaskin® Peanut in peanut-allergic children.

3.2. Study Endpoints

The study endpoints described below will be analyzed. Some are slightly changed from protocol. Details and rationale are described in section Changes in the Analyses from Protocol section 5.3.

3.2.1. Endpoints for the Evaluation of Clinical Benefit

The following endpoints will be explored for the assessment of the sustained clinical benefit of Viaskin® Peanut 250 µg:

- Proportion of subjects reaching an ED ≥1000 mg peanut protein;
- Proportion of treatment responders, using the treatment response definition of the EPITOPE study, i.e. a subject is defined as a treatment responder if:
  - The baseline ED was >10 mg peanut protein and the ED is ≥1000 mg peanut protein at the post-baseline double-blind placebo-controlled food challenges (DBPCFCs) or;
  - The baseline ED was ≤10 mg and the ED is ≥300 mg peanut protein at the post-baseline DBPCFCs.
- Proportion of subjects reaching an ED ≥2000 mg peanut protein;
- Proportion of subjects who tolerate ≥1000 mg peanut protein;
- Proportion of subjects who tolerate ≥2000 mg peanut protein, which is the percentage of subjects who pass the DBPCFC;
- Mean and median TD of peanut protein;
- Mean and median CRD of peanut protein;
- Mean and median ED of peanut protein.

Details of the corresponding statistical analysis are provided in Section 8.

3.2.2. Safety Endpoints

The following safety endpoints will be analyzed:

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- Adverse Events and TEAEs by System Organ Class (SOC) and Preferred Term (PT);
- TEAEs considered related to IP by SOC and PT, and by maximum severity and by maximum duration;
- Serious adverse events (SAEs) by SOC and PTs, maximum severity and relatedness to the IP;
- Treatment-emergent adverse events leading to treatment discontinuation;
- Local AESI (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 IP;
- Incidence, duration and maximum severity of local cutaneous reactions as assessed by the subjects;
- Incidence and severity of local cutaneous reactions as assessed by the Investigators;
- Laboratory data, physical examinations and vital signs;
- Spirometry results and peak expiratory flow (PEF) results.

The following of study procedure safety criteria will also be assessed:

- Symptoms elicited during the DBPCFCs by severity;
- Severity of symptoms score during the DBPCFCs;
- Serious AEs elicited during the DBPCFCs.

Details of the corresponding statistical analysis are provided in Section 9.

3.2.3. Other Exploratory Endpoints

The following other exploratory endpoints will be evaluated:

- Total IgE, peanut-specific IgE and IgG4 levels and levels of IgE and IgG4 specific to peanut protein components (Ara h 1, Ara h 2, Ara h 3);
- Peanut Skin Prick Test (SPT) average wheal diameters;
- Description of the quality of life (QoL) questionnaires (Food Allergy Quality of Life Questionnaires [FAQLQ]/ Food Allergy Independent Measure [FAIM]/EQ-5D-5L) data and QoL scores;
- Enumeration and characterization of reactions triggered by accidental consumption of peanut and analysis of “risk-taking behavior” of subjects (voluntary peanut consumption) during the study;
- Epigenetic modifications of the promoters of some specific genes;
- Sensitization status to other allergens and their evolution over the study period;
- Scoring atopic dermatitis (SCORAD) index evolution over time.

Details of the corresponding statistical analysis are provided in Section 10.

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4. STUDY DESIGN

4.1. Summary of Study Design

4.1.1. Study design

Design: Phase III open-label, follow-up study for subjects who completed the EPITOPE study

Centers: 45 sites in 8 countries

Treatment groups: The EPOPEX study population will consist of 2 groups, based on the treatment received during the EPITOPE study:

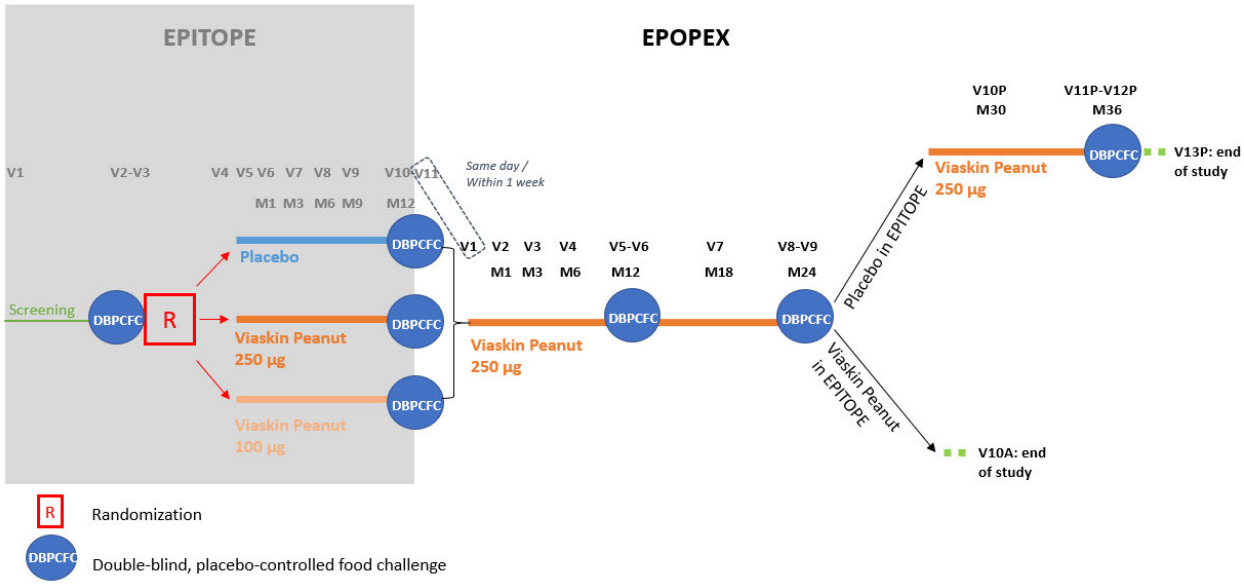
- Subjects who received placebo in the EPITOPE study (**Placebo+VP** group);
- Subjects who received Viaskin® Peanut (any dose) in the EPITOPE study (**VP+VP** group).

Treatment: DBV712 (Viaskin® Peanut) 250 µg system.

Blinding: not applicable (open-label study)

Data collection: electronic Case Report Form (eCRF), central laboratory data and subject e-diaries

4.1.2. Study flowchart



All subjects reaching their V9 (month 24) before the EPITOPE unblinding will continue the treatment for 6 months until V10P
At the time of Visit 10P the treatment allocation will be known:

- Subjects who received Viaskin® Peanut in EPITOPE study will end their treatment at visit 10P which will be followed by the end of treatment visit V11A (same assessments as V10A)
- Subjects who received placebo in EPITOPE study will continue until their visits 11P, 12P and 13P as planned

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4.2. Definition of Study Drugs

The DBV712 epicutaneous system (Viaskin®) (also referred to as 'cutaneous patch' or 'patch' in ex-US countries and in patient-facing materials) is a combination product that includes a CCI consisting of a CCI and a CCI, which is further held in place by an CCI with a CCI. DBV712 is a CCI.

DBV712 contains 250 µg of an unmodified, lyophilized peanut extract CCI

The other components of the IP are inactive excipients: CCI

The IP will be manufactured, labeled, packaged and released for clinical use in accordance with the requirements of Good Manufacturing Practices.

DBV712 is an investigational product that has not been approved for any use in any country.

4.3. Sample Size Considerations

All subjects who completed the EPITOPE study were offered enrollment in the EPOPEX follow-up study, if they were still considered eligible to proceed into the EPOPEX study.

4.4. Randomization

The EPOPEX study is an open-label follow-up study for subjects who have completed the EPITOPE study. Subjects will be offered enrollment in this follow up study to receive either 24 or 36 months of DBV712 250 µg treatment, according to their prior treatment allocation in the EPITOPE study. There will be no randomization in the study.

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5. PLANNED ANALYSES

5.1. Interim Analyses

Two interim analyses will be performed:

- once all subjects from the VP+VP group will have completed the DBPCFC at Year 2.
- once all subjects from the VP+VP group will have completed the DBPCFC at Year 3.

For both interim analyses, no interim report will be produced.

5.2. Final Analyses

The final analysis will be performed after final database lock once all subjects will have completed the study.

5.3. Changes in the Analyses planned in protocol

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

- Endpoints for the evaluation of clinical benefit:
  - The endpoint "*Proportion of subjects reaching a cumulative dose of at least 1444 mg peanut protein at the post-baseline DBPCFCs*" will not be analyzed since reaching a cumulative dose of at least 1444 mg peanut protein is equivalent to reaching an ED ≥ 1000 mg peanut protein, when analyzed in complete case.
  - The endpoint "*Proportion of subjects reaching a cumulative dose of at least 3444 mg peanut protein at the post-baseline DBPCFCs*" will be replaced by the analysis of the proportion of subjects reaching an ED ≥2000 mg peanut protein, which is equivalent, when analyzed in complete case.
  - Analyses of the Tolerated Dose (TD) will be added both as a continuous endpoint and as binary endpoint using thresholds of ≥1,000 mg and ≥2,000 mg.
  - The endpoint "*Proportion of subjects unresponsive (i.e., showing no symptoms leading to stopping the DBPCFC) to the highest dose of peanut protein (i.e. 2000 mg)"* is redefined as the proportion of subjects who tolerate ≥2000 mg peanut protein. The derivation of the endpoint is not impacted, only a title update.
- Endpoints for the evaluation of safety:
  - The endpoint "*Treatment-emergent adverse events by maximum severity and by maximum duration and relatedness to the IP*" will only be analyzed on adverse events considered related to IP by the investigator.
- Baseline definition: The baseline rescheduling rule described in the protocol will not be applied in this statistical analysis plan. The baseline value to be considered is the

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EPITOPE baseline value for all treatment groups (see definition in Section 6.4). Instead, some safety overviews will also be presented by year of active treatment.

- Treatment groups: As stated in the protocol, all analyses will be presented by treatment groups (VP+VP group and Placebo+VP group). In addition, all analyses will also be repeated on the EPITOPE part B subjects by treatment groups.
- Interim Analysis: One additional interim analysis will be performed once all subjects from the VP+VP group will have completed the DBPCFC at Year 2 of active treatment.

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6. GENERAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLING OF DUPLICATE RECORDS

6.1. General Considerations

Unless otherwise specified, all analyses described in this SAP (tables and figures) will be presented by treatment groups (VP+VP group and Placebo+VP group) on the Safety Set. These analyses will also be repeated with EPITOPE part B subjects only, such that 2 outputs, (a) and (b), will be produced for each table or figure:

- (a) EPITOPE part A and B subjects
- (b) EPITOPE part B subjects

Some safety analyses will be repeated on both treatment groups pooled using analysis windows periods for safety analyses by year of active treatment, see Section 6.2.2.2).

Also, the following conventions will be used when presenting summary statistics of the clinical study data:

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.

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. <0.3 kU/L or >100 kU/L) will be considered as equal to that limit/value (e.g. =0.3 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 <0.3 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 0.3 kU/L will be considered as equal to 0.3 kU/L). This conservative approach will ensure that changes from Baseline are consistent.

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For data not normally distributed, depending on the planned analysis, a log10 transformation can be implemented before analysis.

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.

Other considerations:

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".

Whenever appropriate, 95% confidence intervals will be provided by 1 additional decimal place.

Titles for tables and listings produced will specify the analysis set concerned (in parentheses).

Listings will generally include variables: subject identifier, sex and age, treatment group. Data will be sorted by treatment group, site, and subject, and when appropriate by visit or other identifiers for sequence or type of observation. Unless specified otherwise, all listings will be produced on the Enrolled Set.

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 RTF format (one document per output). All report outputs will be also pooled in one single PDF document with bookmarks and a comprehensive table of contents.

6.2. Pooling strategy

All analyses described in this SAP will be based on pooled data collected in both EPITOPE and EPOPEX studies. Details on handling of duplicate records, analysis timepoints and analysis periods mappings are provided hereafter.

6.2.1. Handling of duplicate records

6.2.1.1. Medical History

A pool of medical history collected in EPITOPE and EPOPEX databases will be done with:

- All medical history reported in EPOPEX who started before the treatment initiation in EPITOPE will be used for the analyses described in 7.4 (if start date is partial, month

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and year should clearly indicate that it started before treatment initiation in EPITOPE).

- All medical history reported in EPITOPE database excluding records that meet the following criteria: (1) medical history with ongoing status in EPITOPE or (2) medical history with a stop date entered in EPITOPE for which a corresponding record is found in EPOPEX database ('Corresponding LogLine in EPITOPE' item will be used to identify those records for the second criterion).

6.2.1.2. Medications

A pool of medications collected in EPITOPE and EPOPEX databases will be done with:

- All medications reported in EPOPEX
- All medications reported in EPITOPE excluding records that meet the following criteria: (1) concomitant medication with ongoing status in EPITOPE or (2) concomitant medications with a stop date entered in EPITOPE for which a corresponding record is found in EPOPEX database ('Corresponding LogLine in EPOPEX' item will be used to identify those records for the second criterion).

6.2.1.3. Adverse Events

A pool of AEs collected in EPITOPE and EPOPEX databases will be done with:

- All AEs reported in EPOPEX
- All AEs reported in EPITOPE excluding records that meet the following criteria: (1) AE with ongoing status in EPITOPE or (2) AE with an end date entered in EPITOPE for which a corresponding record is found in EPOPEX database ('Corresponding LogLine in EPITOPE item will be used to identify those records for the second criterion).

6.2.2. Analysis Timepoints and Analysis Windows Mappings

6.2.2.1. Analysis Timepoints for DBPCFC analyses

All the analyses of endpoints for the evaluation of clinical benefit described in section 8 and analyses of the study procedure safety in section 9.8 will be performed using the below table of analysis timepoints, based on DBPCFC visits.

Table 2: Analysis Timepoints for DBPCFC analyses

	VP+VP	Placebo+VP
EPITOPE Baseline	V2 or V3 (EPITOPE)	V2 or V3 (EPITOPE)
Month 12	V10 or V11 (EPITOPE)	V10 or V11 (EPITOPE)
Month 24	V5 or V6 (EPOPEX)	V5 or V6 (EPOPEX)

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	VP+VP	Placebo+VP
Month 36	V8 or V9 (EPOPEX)	V8 or V9 (EPOPEX)
Month 48	-	V11P or V12P (EPOPEX)

Unscheduled visits assessments will be mapped to the previous scheduled visit (e.g. if the unscheduled visit occurred between V8 and V9 EPOPEX, assessments will be mapped to V8).
Only DBPCFC visits where the Peanut Formula was given will be considered.

6.2.2.2. Analysis Periods for Safety analyses

Some analyses of endpoints for the Safety evaluation described in section 9, and analysis of CCI, will be performed by year of treatment or year of active treatment, using the below tables of analysis periods, based on DBPCFC visits.

Table 3: Analysis Periods for Safety analyses by year of treatment

Timepoint	VP+VP	Placebo+VP
Year 1	From V4 (EPITOPE) to V11 (EPITOPE)	From V4 (EPITOPE) to V11 (EPITOPE)
Year 2	From V1 (EPOPEX) to V6 (EPOPEX)	From V1 (EPOPEX) to V6 (EPOPEX)
Year 3	From Max (V5/V6) (EPOPEX) to V9 (EPOPEX)	From Max (V5/V6) (EPOPEX) to V9 (EPOPEX)
Year 4	From Max (V8/V9) (EPOPEX) to V10P (EPOPEX)[1]	From Max (V8/V9) (EPOPEX) to V12P (EPOPEX)

[1]Only for VP+VP subjects who reached their V9 before EPITOPE unblinding
If the subject discontinued within a window, then the end of study date will be used as the end date of the corresponding window.

Table 4: Analysis Periods for Safety analyses by year of active treatment

Timepoint	VP+VP	Placebo+VP
Year 1	From V4 (EPITOPE) to V11 (EPITOPE)	From V1 (EPOPEX) to V6 (EPOPEX)
Year 2	From V1 (EPOPEX) to V6 (EPOPEX)	From Max (V5/V6) (EPOPEX) to V9 (EPOPEX)
Year 3	From Max (V5/V6) (EPOPEX) to V9 (EPOPEX)	From Max (V8/V9) (EPOPEX) to V12P (EPOPEX)

If the subject discontinued within a window, then the end of study date will be used as the end date of the corresponding window.

6.2.2.3. Analysis Timepoints for visit dependent safety and exploratory analyses

All the other visit dependent safety analyses described in sections 9.4 (Local Skin Reactions assessed by the Investigator), 9.9 (Laboratory Assessments), 9.10 (Vital Signs), 9.11 (Physical

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Examination), 9.12 (Spirometry and Peak Expiratory Flow Results), and all exploratory analyses described in section 10 will be analyzed according to the following table of analysis timepoints, based on months of follow-up from EPITOPE baseline.

Table 5: Analysis Timepoints for visit dependent safety and exploratory analyses

Timepoint	Visit Mapping
Baseline	Last data observed from V1 to V4 (EPITOPE)
Month 1[1]	V6 (EPITOPE)
Month 3[2]	V7 (EPITOPE)
Month 6	V8 (EPITOPE)
Month 12	Last data observed from V10-V11 (EPITOPE) to V1 (EPOPEX)
Month 13	V2 (EPOPEX)
Month 15	V3 (EPOPEX)
Month 18	V4 (EPOPEX)
Month 24	Last data observed from V5 to V6 (EPOPEX)
Month 30	V7 (EPOPEX)
Month 36	Last data observed from V8 to V9 (EPOPEX)
Month 42[3]	V10P
Month 48[4]	Last data observed from V11P to V12P

[1]Only for Local Skin Reaction CCI
[2]Only for Immunological Mar ocal Skin Reaction CCI
[3]Only for Placebo+VP subjects and VP+VP subjects who reached their V9 before EPITOPE unblinding
[4]Only for Placebo+VP subjects

Unscheduled visits assessments will be mapped to the previous scheduled visit (e.g. if the unscheduled visit occurred between V3 and V4 EPOPEX, assessments will be mapped to V3). Early Termination visits assessments will be mapped to the next scheduled visit (e.g. if the early term visit occurred after V3 and V4 EPOPEX, assessments will be mapped to V4).

All assessments that are not mapped to a timepoint will be considered “Not Windowed” but will be kept in the analysis dataset.

The last non-missing assessment by analysis timepoint will be flagged and analyzed.

6.3. Analysis Sets

6.3.1. Enrolled Set

The Enrolled Set will include all subjects who signed the EPOPEX informed consent form. This set will be used for disposition summary and subject individual data listings.

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6.3.2. Safety Set

The Safety set will be comprised of all subjects from the Enrolled Set who have received at least one dose of IP in EPOPEX study. This set will be used for safety evaluation, evaluation of the clinical benefit and other exploratory analyses.

6.4. Baseline Definition

As the EPOPEX study is the follow-up study of the EPITOPE study, the EPITOPE baseline will be considered, and will be the latest, non-missing pre-dose assessment in EPITOPE study.

All data collected before (<) V4 EPITOPE are considered as pre-dose.

At V4 EPITOPE, the 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, SCORAD, SPT)

Other findings will be considered as post-dose and not included in the EPITOPE baseline calculation.

6.5. Derived and Transformed Data

6.5.1. Baseline Age

The baseline age is defined by the documented age (integer value) in the EPITOPE CRF.

6.5.2. Treatment and Active Treatment Start Date

The treatment start date will be defined as the date of the first treatment intake in EPITOPE, i.e. EPITOPE Visit 4 date

The active treatment start date will be defined as the date of the first active treatment intake:

- EPOPEX Visit 1 date for subjects initially randomized to Placebo in EPITOPE study
- EPITOPE Visit 4 date for subjects initially randomized to any active treatment in EPITOPE study

6.5.3. Treatment and Active Treatment Day

Treatment day will be calculated from the first treatment intake date. If the date of interest occurs on or after the date of the first dose, the treatment day will be calculated as (date of interest – date of first dose) + 1. If the date of interest occurs prior to the first dose in the study date, then treatment day will be calculated as (date of interest – date of first dose in the study). There is no treatment day 0.

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Active treatment day will be calculated from the first active treatment intake date. If the date of interest occurs on or after the date of the first active dose, the active treatment day will be calculated as (date of interest – date of first active dose) + 1. If the date of interest occurs prior to the first active dose in the study date, then active treatment day will be calculated as (date of interest – date of first active dose in the study). There is no active treatment day 0.

6.5.4. Change from Baseline

Change from baseline is calculated as (post-baseline result – baseline result).

Percent change from baseline is calculated as (change from baseline/baseline result * 100).

If either the baseline or the post-baseline result is missing, the change from baseline and/or percentage change from baseline is set to missing as well.

6.5.5. Change from Month 12

Change from Month 12 is calculated as (post-month 12 result – month 12 result).

Percent change from month 12 is calculated as (change from month 12 / month 12 result * 100).

If either the month 12 or the post-month 12 result is missing, the change from month 12 and/or percentage change from month 12 is set to missing as well.

6.5.6. Last Ingested Dose

The Last Ingested Dose (LID) will be used in the derivation of some clinical benefit endpoints. For each post-baseline DBPCFC initiated (peanut formula only), the Last Ingested Dose (LID) is defined as follows:

- If the subject fully ingested the last dose administered before stopping the DBPCFC, then the dose to be considered is the last dose administered
- If the dose was partially ingested but the amount consumed exceeds the previous dose, then the dose to be considered is the partial dose
- If the subject partially ingested the last dose and the amount consumed is ≤ to the previous dose, then the dose to be considered is the previous dose administered

Examples: If the last dose being administered is 1,000 mg but only 200 mg is actually ingested, then the LID to consider is 300 mg. If the last dose being administered is 1,000 mg and 700 mg is actually ingested, then the LID to consider is 700 mg.

The modified Last Ingested Dose (mLID) is defined as follows:

- If the subject fully ingested the last dose administered before stopping the DBPCFC, then the dose to be considered is the last dose administered
- If the dose was partially ingested but the amount consumed exceeds the previous dose, then the dose to be considered is the last planned dose to be administered
- If the subject partially ingested the last dose and the amount consumed is ≤ to the previous dose, then the dose to be considered is the previous dose administered

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Examples: If the last dose being administered is 1,000 mg but only 200 mg is actually ingested, then the LID to consider is 300 mg. If the last dose being administered is 1,000 mg and 700 mg is actually ingested, then the LID to consider is 1000 mg.

6.5.7. Tolerated Dose

For each DBPCFC, the Tolerated Dose (TD) is defined as the maximum dose given, in totality, that do not lead to stopping of the DBPCFC (i.e. with no or mild symptoms, which do not meet stopping criteria).

If the first dose led to stopping of the DBPCFC then the TD is set to 0.

6.6. Handling of Missing Data

6.6.1. Missing Endpoints for the Evaluation of Clinical Benefit

6.6.1.1. Missing Endpoints for the Main Analyses

Main analyses of the evaluation of clinical benefit will be performed on complete cases (subjects with non-missing endpoint). For each post-baseline DBPCFC timepoints (see Table 2), different cases leading to missing or non-missing endpoint will be considered:

- If the Eliciting Dose (ED) is documented by the investigator in the eCRF, all binary and continuous endpoints are non-missing.
- If a DBPCFC was not initiated, the ED is not documented by the investigator in the eCRF, hence all binary and continuous endpoints are missing
- If a DBPCFC was initiated but early stopped without showing symptoms leading to stopping the DBPCFC, or the subject took the full 2,000mg dose without showing symptoms leading to stopping the DBPCFC, the ED is also not documented in the eCRF by the investigator. However, the endpoints for the evaluation of clinical benefit can be derived depending on its nature:
  - For binary endpoints based on ED or TD, if the LID is higher than or equal to the threshold defined, then the endpoint could be defined and will be non-missing. For example, if a subject's DBPCFC is early stopped (with no symptom or symptoms not meeting stopping criteria) after completing the 1,000 mg dose, subject would be considered for the analysis of the ED or TD ≥1000 mg endpoint. Conversely, the ED or TD ≥2,000 mg endpoint for this subject would be considered unevaluable and missing since he/she stopped before attempting the final dose.
  - For continuous endpoints, if the subject completed the 2,000 mg dose without symptoms meeting the stopping criteria, then ED and TD will be set to 2,000, and CRD taken from eCRF. Otherwise, ED and TD will remain missing, and CRD will be set to missing.

As a result, the number of subjects analyzed (i.e. with non-missing endpoint) for the main analyses of the endpoints for the evaluation of clinical benefit may vary.

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6.6.1.2. Imputations Strategies for Sensitivity Analyses

For sensitivity analyses of clinical benefit endpoints, different imputation strategies will be applied to the missing endpoints of the main analyses:

Last Observation Carried Forward imputation (LOCF):

For binary endpoints, the missing endpoint at a post-baseline DBPCFC will be imputed with the last non-missing value at previous DBPCFCs.

modified Last Observation Carried Forward imputation (mLOCF):

For continuous endpoints, the missing endpoints at a post-baseline DBPCFC will be imputed using mLOCF defined as follows:

The mLOCF ED value at post-baseline DBPCFC is considered as the maximum between:

- the mLID value at this post-baseline DBPCFC (see derivation details in Section 6.5.6)
- the last non-missing ED value at previous DBPCFCs.

The mLOCF TD value at post-baseline DBPCFC is considered as the maximum between:

- the TD value at this post-baseline DBPCFC (see derivation details in Section 6.5.7)
- the last non-missing TD value at previous DBPCFCs.

The mLOCF CRD value at this post-baseline DBPCFC is considered as the maximum between:

- the cumulative dose value documented in the CRF at this post-baseline DBPCFC
- the last non-missing CRD value at previous DBPCFCs.

Missing=failure:

Missing binary endpoint at a post-baseline DBPCFC will be considered as failure.

Multiple Imputation (MI):

Missing binary endpoint at a post-baseline DBPCFC will be multiply imputed using a logistic regression model with the following covariates: treatment group, age at baseline, log10 peanut-specific IgE at baseline, ED at baseline.

Details of the MI procedure is available in Appendix 11.1.2 .

6.6.2. Missing Start and End Dates for Adverse Events and Concomitant Medications

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

AE/CM end date:

If AE/CM end date is missing AE/CM end date will be imputed based on the date of subject end of study.

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If AE/CM end date is partial:

- If AE/CM end day is missing it will be imputed to month end day, unless month and year are the same as month and year of the EPOPEX study end date then impute to the EPOPEX study end date
- If AE/CM end day/month are missing it will be imputed to "31DEC", unless year is the same as year of the EPOPEX study end date then impute to the EPOPEX study end date

AE/CM start date:

If AE/CM start date is missing:

- If the AE/CM was collected in EPITOPE study, then AE/CM start date will be imputed to EPITOPE first treatment date.
- If the AE/CM was collected in EPOPEX study, then AE/CM start date will be imputed to EPOPEX first treatment date.

If AE/CM start date is partial:

- If derived AE/CM end date is missing or end date is on or after (≥) the EPITOPE treatment start date:
  - If AE/CM start day is missing it will be imputed to "01" unless month and year are the same as month and year of the EPITOPE treatment start date then impute to the EPITOPE treatment start date
  - If AE/CM start day/month are missing, they will be imputed to "01JAN" unless year is the same as year of the EPITOPE treatment start date then impute to the EPITOPE treatment start date
- If derived AE/CM end date is before (<) the EPITOPE treatment start date:
  - Missing day will be imputed to 01 and Missing month will be imputed to "JAN"

6.6.3. Missing severity and causality for Adverse Events

Severity:

TEAEs with missing severity will be considered as "Severe".

Causality:

TEAEs with missing relationship to the IP will be considered as "Drug-related".

6.6.4. Missing Last Date of Patch Application

The date of last patch application of each subject will be taken from the last exposure date from eCRF.

If this date is missing or partially missing, then:

- 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

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- 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, then date of last treatment will be the maximum (i.e., latest date) of the most recent treatment exposure entered in the subject's e-diary and the last date available from the study visits and phone contacts.

6.6.5. Missing date of assessments

For the analyses of visit dependent assessments (e.g. physical exams, laboratory assessments, vital signs…):

- 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 study visit date, then impute to study 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 study visit date, then impute to study visit date.
- If the assessment date (--DTC) is missing, it will be imputed with the study visit date.

6.6.6. Missing Study End Date

The study end date is the study completion date or study discontinuation date, if the subject discontinued the study. If this date is missing or partially missing, then:

- If only the day is missing, it will be imputed to the last day of the month
- If day and month are missing, they will be imputed to the 31st of December
- If the date is missing because the subject was lost to follow-up, then study end date will be the maximum (i.e., latest date) of the most recent treatment exposure entered in the subject's e-diary and the last date available from the study visits and phone contacts

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7. STUDY POPULATION

7.1. Subjects Disposition

A clear accounting of the disposition of all subjects who enter the study will be provided, from enrollment to study completion. Subject disposition will be summarized for all enrolled subjects, overall and by treatment group and will present the following descriptions:

- Number of subjects who completed EPITOPE treatment but did not enroll to EPOPEX
- Number of subjects enrolled in EPOPEX and number of subjects in the Safety Set
- Number and percentage of subjects who completed 3 years of active treatment (up to 2nd day of the active year 3-DBPCFC)
- Number and percentage of subjects who discontinued before 3 years of active treatment and reasons for discontinuation
- Number and percentage of subjects who completed the study
- Number and percentage of subjects who discontinued the study and reasons for discontinuation

An enrolment summary will be presented overall, by region, country and site, showing the number of subjects enrolled in EPOPEX, number of subjects who completed 3 years of active treatment and who completed the study, the first date of consent in EPITOPE and in EPOPEX, the last study visit date, the study duration (in days, calculated as last study visit date – first date of consent in EPITOPE +1).

7.2. 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 the final database lock.

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.

The number and percentage of subjects with major protocol deviations and with deviations related to COVID-19 will be summarized by type of deviation, by treatment group and overall, on the Safety Set. All protocol deviations will also be listed. Major deviations will be listed separately from minor deviations.

7.3. Demographics

Descriptive statistics will be produced for demographic data which include:

- Sex (Male, Female)

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- Age (years) at EPITOPE baseline, continuous and by category (1-year, 2-years, 3-years), as collected in the EPITOPE eCRF
- Race using the following mapping from EPITOPE e-CRF values:
  - White (when = “White”),
  - Black or African American (when = “Black or African American”),
  - Asian (when = ”Asian”),
  - Other (when = “Native Hawaiian or Other Pacific Islander”, “American Indian or Alaska Native” or “Other”),
  - Not collected (when = “Not reported” or missing)

7.4. Medical History

Medical history covers the collections of information on past or current conditions at the time of treatment initiation in EPITOPE study (with the exclusion of peanut allergy) taken from both EPITOPE and EPOPEX database (see details for pooling strategy and handling of duplicate records in Section 6.2.1.1).

Medical history will be coded using the version of the Medical Dictionary for Regulatory Activities (MedDRA) used for EPITOPE (Version 20.1). The summary 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.

A summary table of the following medical history of specific interest ongoing at the time of treatment initiation in EPITOPE study will be presented (using EPITOPE derived dataset flags):

- Any allergy other than peanut
- Any food allergy other than peanut
- Other atopic conditions:
  - Asthma
  - Eczema/Atopic Dermatitis
  - Allergic Rhinitis

7.5. Prior Medications

All medications taken before the EPITOPE 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 data are taken from both EPITOPE and EPOPEX database (see details for handling of duplicate records in Section 6.2.1.2).

Will be considered as prior medication:

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- Any medication taken prior to the date of first application in EPITOPE study, that stopped before this date,
- Any medications with partial start/stop date where there is clear evidence to suggest that the medication stopped before V4 in EPITOPE study.

Prior medications will not be tabulated.

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8. CLINICAL BENEFIT

8.1. Main analyses

At the analysis timepoints for DBPCFC analyses described in Section 6.2.2.1, the following binary endpoints will be analyzed on complete cases (subjects with non-missing endpoint - see details in Section 6.6.1.1):

- Proportion of subjects reaching an ED ≥1,000 mg peanut protein;
- Proportion of treatment responders, using the treatment response definition of the EPITOPE study, i.e. a subject is defined as a treatment responder if:
  - The baseline ED was >10 mg peanut protein and the ED is ≥1000 mg peanut protein at the post-baseline double-blind placebo-controlled food challenges (DBPCFCs) or;
  - The baseline ED was ≤10 mg and the ED is ≥300 mg peanut protein at the post-baseline DBPCFCs.
- Proportion of subjects reaching an ED ≥2,000 mg peanut protein;
- Proportion of subjects who tolerate ≥1,000 mg peanut protein;
- Proportion of subjects who tolerate ≥2,000 mg peanut protein, which is the percentage of subjects who pass the DBPCFC.

For each of the above binary endpoint, at each post-month 12 DBPCFC, the number and proportion of subjects will be provided with a 2-sided Wilson 95% CI.

Also, the proportion difference from month 12 DBPCFC will be computed, and a 95% confidence interval will be calculated using Newcombe's method based on Wilson score intervals with continuity correction for the difference between paired binomial proportion (see Appendix 11.1.3 for more details).

The following continuous endpoints will also be analyzed on complete cases (subjects with non-missing endpoint - see details in Section 6.6.1.1):

- TD of peanut protein: Mean, median and change from Baseline and from Month 12;
- ED of peanut protein: Mean, median and change from Baseline and from Month 12;
- CRD of peanut protein: Mean, median and change from Baseline and from Month 12.

The effect of treatment exposure on the above endpoints will also be assessed with longitudinal models using GLMM for repeated measures for each treatment group, adjusted on the following covariates: age at baseline, log10 peanut-specific IgE at baseline, ED at baseline DBPCFC. The adjusted predicted probabilities (for binary endpoints) or Least Square (LS) Means (for continuous endpoints) and their associated 95% confidence interval at each timepoint will be presented. Predicted probabilities will be obtained via inverse-link transformation of the LS Means estimate of the log odds. Odds-Ratio (for binary endpoints) or Geometric Means Ratio

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(for continuous endpoints) from baseline and from Month 12 and their associated 95% confidence intervals and p-values will also be presented (see Appendix 11.1.1 for details on SAS code to be implemented).

8.2. Sensitivity analyses

The main analyses of binary endpoints described in 8.1 will be repeated using the following imputations strategies for the subjects with missing binary endpoints (see definitions in Section 6.6.1.2):

- missing=failure
- LOCF
- multiple imputation

The main analyses of continuous endpoints described in 8.1 will be repeated on the Safety Set using:

- mLOCF

Per-Protocol analyses will also be performed for each of the endpoints for the evaluation of clinical benefit. At each timepoint, these per-protocol analyses will exclude subjects with major protocol deviations at the timepoint that may affect the analysis of the endpoint.

The longitudinal analyses of endpoints described in 8.1 will be repeated using LOCF (for binary endpoints) or mLOCF (for continuous endpoints).

8.3. Baseline Prognostic Characteristics Analyses

To further support the clinical benefit analysis, the prognostic effect of the following EPITOPE baseline characteristics, on subjects who tolerate ≥2,000 mg peanut protein, will be analyzed in the VP+VP group using logistic regression at each of the analysis timepoints for DBPCFC analyses described in Section 6.2.2.1. These analyses will be repeated on complete cases and LOCF imputation, and results will be presented in forest plots.

- ED group (ED ≤10 mg, ED >10 mg)
- Age group (1-year, 2-years, 3-years)
- Peanut-Specific IgE (continuous log-transformed)
- Peanut-Specific IgG4 (continuous log-transformed)
- Peanut Skin Prick Test (continuous)
- Region (Australia, Europe, North America)
- Gender (Male, Female)

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- 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 (Yes/No)
- Ongoing Medical history of allergy other than peanut (Yes/No)
- Ongoing Medical history of food allergy other than peanut (Yes/No)
- Ongoing Medical history of eczema/atopic dermatitis (Yes/No)
- Ongoing Medical history of rhinitis allergic (Yes/No)

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9. SAFETY AND TOLERABILITY

9.1. Study Duration, Treatment Exposure and Compliance

9.1.1. Study Duration

The EPOPEX study duration for each subject will be calculated in days as:

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

The overall study duration for each subject will be calculated in days as:

End of EPOPEX study date - Date of EPITOPE informed consent +1

9.1.2. Treatment Exposure

The EPOPEX exposure duration (in days, regardless of treatment interruption), will be calculated over the whole study period as:

Date of last patch application in EPOPEX – Date of first patch application in EPOPEX +1

The overall treatment exposure duration (in days, regardless of treatment interruption), will be calculated over EPITOPE and EPOPEX studies periods as:

Date of last patch application in EPOPEX– Date of first patch application in EPITOPE +1

The overall active treatment exposure duration (in days, regardless of treatment interruption), will be calculated over EPITOPE and EPOPEX studies periods as:

Date of last active patch application – Date of first active patch application +1

The total dose of peanut protein (in mg) received via the patch during the study, will be calculated over the whole active treatment period as:

Active Treatment Exposure duration (in days) * Actual treatment dosage / 1,000

9.1.3. Treatment Compliance

The treatment compliance will be calculated over EPITOPE and EPOPEX studies periods as:

$$\frac{100 \times (\text{Number of patches dispensed} - \text{Number of patches returned})}{\text{Overall treatment exposure duration in days}}$$

Treatment compliance will be summarized using frequency tables (<80%, ≥80%) 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 number 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.

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9.2. Adverse Events

9.2.1. General Considerations

AEs collected in EPITOPE study will be pooled with AEs collected in EPOPEX study (see Section 6.2.1.3 for pooling strategy and handling of duplicates from EPITOPE and EPOPEX).

AEs will be coded using the same version of the MedDRA dictionary as the one used in the EPITOPE study (MedDRA version 20.1).

The following AEs will be excluded from analyses (unless otherwise specified) and presented separately:

- AEs related to accidental peanut consumption (see Section 9.7).
- SAEs elicited during DBPCFC (see Section 9.8.1).

For each summary presented by SOC and PT:

- Tables will be ordered in terms of decreasing frequency for SOC, and PT within SOC, in the VP+VP group, and then similarly by decreasing frequency in the Placebo+VP, and then alphabetically for SOC, and PT within SOC.
- 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.

9.2.2. Definitions

9.2.2.1. Treatment-emergent AEs

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

Active treatment-emergent AEs will be defined as any AEs, regardless of relationship to IP, reported during or after the application of the first active patch (see Section 6.5.2 for definition of active treatment start date).

When dates are missing or partially missing, see Section 6.6.2.

9.2.2.2. Concomitant Medication use of interest

Following concomitant medication use of interest will be defined:

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- **Epinephrine use** will be identified by a standard medication name that contains "EPINEPHRINE" and (ATC level 1 = "CARDIOVASCULAR SYSTEM" or ATC level 1 = "RESPIRATORY 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) or "R03BA" (Glucocorticoids)
- **Topical corticosteroid use** will be identified by ATC code starting with "D07" (Corticosteroids, Dermatological preparations)

9.2.2.3. Adverse Event of Special Interest (AESI)

AESI are defined as any of the following:

- **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** will be 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 IP, and occurring outside the DBPCFCs. This includes:
  - Anaphylactic reaction
  - 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") leading to an epinephrine intake. Epinephrine use will be retrieved using Standard medication name containing

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"EPINEPHRINE" and (ATC level 1 = "CARDIOVASCULAR SYSTEM" or ATC level 1 = “RESPIRATORY SYSTEM”)

9.2.2.4. TEAEs Considered Related to Treatment

TEAEs considered related to treatment are those reported by the investigator as related, probably, or possibly related to the IP.

9.2.2.5. IP-induced Local TEAEs

IP-induced Local TEAEs are defined as TEAEs considered as related to IP with a High-Level Term equal to “Application and instillation site reactions”.

9.2.3. Analyses

9.2.3.1. Overview of TEAEs

An overall overview table of TEAEs will be provided showing the number and percentage of subjects who experienced at least one event and the number of events for the following categories of TEAEs:

- TEAEs,
  - Mild TEAEs,
  - Moderate TEAEs,
  - Severe TEAEs,
- Serious TEAEs,
- TEAEs leading to death,
- TEAEs considered related to IP:
  - reported as related,
  - reported as probably related,
  - reported as possibly related,
- Severe TEAEs considered related to IP,
- Serious TEAEs considered related to IP,
- TEAEs leading to permanent study treatment discontinuation,
- TEAEs leading to temporary study treatment discontinuation,
- IP-induced Local TEAEs,
- Severe IP-induced Local TEAEs,
- Treatment-emergent local AESI,
- Treatment-emergent systemic AESI
  - Reported as Anaphylactic reaction

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  - Reported as Systemic hypersensitivity reaction leading to epinephrine intake
- Treatment-emergent systemic AESI considered related to IP:
  - Reported as Anaphylactic reaction
  - Reported as Systemic hypersensitivity reaction leading to epinephrine intake
- TEAEs leading to epinephrine intake
- TEAEs leading to epinephrine intake considered related to IP
- TEAEs leading to systemic or inhaled corticosteroid use
- TEAEs leading to topical corticosteroid use

The overview of TEAEs table will be provided:

1. Overall and by year of treatment, and by treatment group (without total column)
2. Overall and by year of active treatment, by treatment group and treatment groups pooled (with total column)
3. Overall active treatment period incidence rates, by treatment group and treatment group pooled (with total column). Incidence rates are calculated as the number of events divided by the duration of follow-up for all subjects, expressed in subject-years, multiplied by 100. The follow-up duration is calculated as: End of EPOPEX study date – Date of first active patch application +1.

9.2.3.2. TEAEs by SOC and PT

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

- TEAEs,
- TEAEs considered related to IP,
- Serious TEAEs,
- Serious TEAEs considered related to IP,
- TEAEs leading to permanent study treatment discontinuation,
- TEAEs leading to temporary study treatment discontinuation,
- Treatment-emergent AESI,
- Treatment-emergent AESI considered related to IP,
- TEAEs leading to epinephrine intake,
- TEAEs leading to epinephrine intake considered related to IP,
- TEAEs leading to systemic or inhaled corticosteroid use,

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- TEAEs leading to topical corticosteroids use

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

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

- 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 90 Days, 91 to 180 Days, 181 to 365 Days, >365 Days).

9.2.3.3. AE listings

A by-subject listing of all adverse events will be provided including: treatment group, subject identifier, age at EPITOPE baseline, sex, adverse event (SOC, PT, and verbatim term), date/time of onset (and corresponding time since start of active treatment in days), date/time of resolution, duration, severity, treatment required, relationship to IP, relationship to an accidental peanut consumption, relationship to DBPCFC, AESI flag, epinephrine use flag, action taken with the IP, outcome, and whether the event is classified as serious or not. The listing will be provided in XLS format.

Adverse events leading to permanent discontinuation will also be listed separately with the same data as the listing of all adverse events, but in RTF format.

Finally, SAEs will also be listed separately with the same data as the listing of all adverse events, with additional seriousness criteria, in RTF format.

9.3. Deaths

A detailed listing will be created showing the subjects who experienced SAE leading to Death.

9.4. Local Skin Reaction assessed by the Investigator

The Investigators will assess the severity of local skin reactions under the patch and any of the previous sites of patch application at each study visit.

Examination will be performed by the investigator at several visits:

- At Visit 4 of the EPITOPE study and Visit 1 of the EPOPEX study, the assessment will specifically be performed before patch application, 30 minutes, and 1 hour post-application.
- At each visit, the skin reaction will be graded by the Investigators on a scale of Grade 0 (negative) to Grade 4 (erythema, vesicles), see details in Table 6.

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Table 6: Local Skin Reaction Grading System by the Investigators

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

The number and percentage of subjects with each grade will be presented by analysis timepoints for visit dependent safety analyses described in Section 6.2.2.3, plus timepoint within visit for visit 4 EPITOPE and visit 1 EPOPEX.

Additionally, the highest grade of skin reaction (all previous patch sites not including current patch site) will be summarized as the number and percentage of subjects in each grade category.

9.5. Local Skin Reaction assessed by the Subject

The severity of local skin reactions will be assessed on a daily basis by the parents/guardians during the whole treatment duration in e-diaries for Part B subjects only. The following proportions derived from the subject's diaries will be summarized for Part B only overall and by year of treatment (see analysis periods in Section 6.2.2.2) for itching, redness, swelling and any local reaction (itching, redness, swelling).

- Proportion of days with no reaction (Grade 0);
- Proportion of days with a reaction reported Grade ≥ 1 / Grade ≥ 2 / Grade 3

The proportion of days with a blistering or sores will also be summarized overall and by year of treatment.

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

(Number of days with a reaction reported) / (Number of days with a patch assessed)

The number of days with a reaction reported and number of days with patches assessed will be calculated based on available application dates in the local skin reaction diary.

9.6. Medications

Medications collected in EPITOPE study will be pooled with medications collected in EPOPEX study (see Section 6.2.1.2 for pooling strategy and handling of duplicates from EPITOPE and EPOPEX).

All medications will be coded using the World Health Organization (WHO) Drug Dictionary (Sept. 2017).

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Medications will be classified either as “Prior only” (P), “Both Prior and Concomitant” (PC) or “Concomitant only” (C), using medication start/end dates compared to date of first treatment intake in EPITOPE.

- Will be considered “Prior only” (P):
  - Any medications with start and end dates before the first dose of treatment intake,
  - Any medications with partial start/end date where there is clear evidence to suggest that the medication ended prior to the first dose of treatment intake.
- Will be considered “Both Prior and Concomitant” (PC):
  - Any medications with start date before the first dose of treatment intake and end date on or after the first dose of treatment intake,
  - Any medications with partial start/end date where there is clear evidence to suggest that the medication started prior to the first dose of treatment intake (no evidence for the stop date).
- Will be considered “Concomitant only” (C):
  - Any medications with a start date on or after the first dose of treatment intake,
  - Any medications with partial start/end date where there is clear evidence to suggest that the medication started after the first dose of treatment intake,
  - Any medications with partial or complete end date where there is clear evidence to suggest that the medication ended after the first dose of treatment intake (no evidence for the start date),
  - All other medications with partial start/end date where there is no clear evidence to suggest that the medication started or ended before or after the first dose of treatment intake.

The following concomitant medications analyses described below, will be presented overall and by year of treatment, per ATC class (level 3) and preferred drug name:

- Concomitant medications (other than the ones taken for the post-baseline food challenges 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;
- Non-drug therapies and surgical procedures;
- Concomitant medications taken due to peanut consumption.

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

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9.7. Accidental Peanut Consumption

In case of potential 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 analyses will be provided overall and by year of treatment:

- Number and percentage of subjects with any peanut consumption (from APC form) overall and by number of consumptions (1, 2, 3, >3),
  - confirmed as accidental,
  - leading to an allergic reaction
  - not leading to an allergic reaction
- Overview table of TEAEs induced by APC (from AE form) will be provided showing the number and percentage of subjects having:
  - Any TEAE induced by APC (Mild/Moderate/Severe),
  - Any Serious TEAEs induced by APC,
  - Any TEAE induced by APC leading to Death
  - Any TEAE induced by APC leading to permanent study treatment discontinuation
  - 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 TEAEs induced by APC leading to Epinephrine intake (Epinephrine use will be retrieved using Standard medication name containing “EPINEPHRINE” and ATC level 1 = “CARDIOVASCULAR SYSTEM”).

The overview of TEAEs induced by APC table will be provided:

1. Overall and by year of treatment, and by treatment group (without total column)
2. Overall and by year of active treatment, by treatment group and treatment groups pooled (with total column)
3. Overall active treatment period incidence rates, by treatment group and treatment group pooled (with total column). Incidence rates are calculated as the number of events divided by the duration of follow-up for all subjects, expressed in subject-years, multiplied by 100. The follow-up duration is calculated as: End of EPOPEX study date – Date of first active patch application in EPITOPE +1.

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9.8. Study Procedure Safety

9.8.1. Serious Adverse Events Elicited during DBPCFCs

All SAEs elicited during the entry/screening DBPCFC and each post-baseline DBPCFC will be tabulated by SOC/PT by analysis timepoints for DBPCFC analyses described in Section 6.2.2.1. It will be discriminated between Peanut and Placebo Formula.

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

9.8.2. Symptomatic Reactions during DBPCFCs

The objective symptoms collected during the DBPCFC are the following:

- Skin:
  - Rash
  - Erythematous rash (and % of rash area concerned)
  - Pruritus
  - Urticaria/ angioedema
- 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 during the DBPCFC are the following:

- Itchy mouth
- Itchy throat
- Nausea

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- 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.

The reactions appearing during a DBPCFC will be summarized by analysis timepoints for DBPCFC analyses described in Section 6.2.2.1 and by formula (peanut, placebo), showing:

- The number and percentage of subjects with objective symptoms (by severity) at Baseline and at each post-baseline DBPCFC (overall and by type of symptom)
- The number and percentage of subjects with subjective symptoms (by severity) at Baseline and at each post-baseline DBPCFC (overall and by type of symptom)

9.8.3. Severity of Symptoms score during DBPCFCs

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 actual value and change from baseline of the total symptom score will be summarized by analysis timepoints for DBPCFC analyses described in Section 6.2.2.1.

9.8.4. Medications taken during DBPCFCs

Medications taken for food challenges (collected in the CM page of the eCRF) will be described by showing number and percent of subjects overall and per ATC class (level 3) and preferred drug name, by analysis timepoints for DBPCFC analyses described in Section 6.2.2.1, and formula (Peanut or Placebo).

Number of antihistamine and number of epinephrine administrations during food challenges (taken from specific CRF pages, not from the CM page) will also be tabulated by analysis timepoints for DBPCFC analyses, and formula (Peanut or Placebo) as follows: Any Antihistamine/Epinephrine, 1 dose, 2 doses, 3 doses or more.

9.9. Laboratory Assessments

Laboratory assessments will include the following:

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- 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

The following results will be tabulated for hematology and biochemistry tests (in SI units) at each analysis timepoints for visit dependent safety analyses described in Section 6.2.2.3:

- Continuous descriptive statistics of actual values and change from Baseline and from Month 12 of each laboratory test result.
- Common Toxicity Criteria for Adverse Events (CTCAE version 4.03) grade. CTCAE grades for hematology and biochemistry measures will be derived according to Appendix 11.2 .
- Number and percentage of subjects with laboratory test abnormalities (Low, Within normal range, High).

9.10. Vital Signs

Vital signs parameters will include the following:

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

The following vital signs results will be tabulated by analysis timepoints for visit dependent safety analyses described in Section 6.2.2.3:

- Continuous descriptive statistics of actual values and change from Baseline and from Month 12 of each vital sign

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- Number and percentage of subjects with vital signs abnormalities for heart rate, systolic blood pressure and diastolic blood pressure classified using the criteria defined in Table 7.

Table 7: Criteria to Determine Clinically Relevant Abnormalities in Vital Signs

	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

9.11. Physical Examination

Complete physical examination will include examination of the following:

- Weight (kg),
- Height (cm),
- 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 by analysis timepoints for visit dependent safety analyses described in Section 6.2.2.3:

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- Continuous descriptive statistics of actual values of weight and height
- Number and percentage of subjects with normal / abnormal (not clinically significant (NCS) and clinically significant (CS) / not done) physical examination for each of the system examined.

9.12. Spirometry and Peak Expiratory Flow Results

The Spirometry (FEV1) and Peak Expiratory Flow (PEF) will be assessed for subjects ≥ 4 years (at EPOPEX Visit 1) by analysis timepoints for visit dependent safety analyses described in Section 6.2.2.3.

Continuous descriptive analyses of actual values will be provided for both FEV1 and PEF.

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10. OTHER EXPLORATORY ANALYSES

10.1. Maximum Severity of DBPCFC symptoms

The subject's maximum severity (absent, mild, moderate or severe) of objective symptoms elicited during DBPCFC will be tabulated by analysis timepoints for DBPCFC analyses described in Section 6.2.2.1. At each analysis timepoint, only subjects who completed the DBPCFC will be considered (i.e. subjects showing symptoms leading to stopping the DBPCFC, or subjects who took the full 2,000 mg dose without showing symptoms leading to stopping the DBPCFC)

The effect of treatment exposure on the severity of DBPCFC symptoms will also be assessed with longitudinal models using GLMM for repeated measures of the ordinal endpoint for each treatment group, adjusted on the following covariates: age at baseline, log10 peanut-specific IgE at baseline, ED at baseline DBPCFC. Odds-ratio from baseline and from Month 12 and their associated 95% confidence intervals and p-values will also be presented (see Appendix 11.1.1 for details on SAS code to be implemented).

10.2. Immunological Markers

10.2.1. Peanut-Specific IgE and IgG4

Descriptive summaries of peanut-specific IgE and IgG4, and components (Ara h 1, Ara h 2, and Ara h 3), and sIgE to sIgG4 ratio will include actual values, absolute and relative changes from Baseline and from Month 12 and will be described by analysis timepoints for visit dependent exploratory analyses described in Section 6.2.2.3.

Actual values Median (±IQR), over time in peanut-specific IgE and IgG4 will be presented graphically, by treatment group.

10.2.2. Total IgE, and IgE and IgG4 Specific to Other Allergens

Total IgE, and IgE and IgG4 specific to cow's milk, egg white, house dust mites, and grass pollen will be described by analysis timepoints for visit dependent exploratory analyses described in Section 6.2.2.3. Absolute and relative change from baseline and from Month 12 will also be presented.

10.3. Skin Prick Test

Descriptive summaries of SPT mean wheal diameter (for undiluted peanut extract) will include actual values and absolute change from Baseline and from Month 12 and will be described by analysis timepoints for visit dependent exploratory analyses described in Section 6.2.2.3 will be provided.

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10.4. Quality of Life

10.4.1. 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.

The template of the questionnaire is provided in Appendix 7 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 in EPITOPE 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 absolute value and change from baseline and from Month 12 of the FAQLQ-PF total score and each domain score will be summarized by analysis timepoints for visit dependent exploratory analyses described in Section 6.2.2.3.

10.4.2. 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.

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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.

Absolute value and change from baseline and from Month 12 of the FAIM-PF scores will be summarized overall and for each type of questionnaire, by analysis timepoints for visit dependent exploratory analyses described in Section 6.2.2.3.

10.4.3. EQ-5D-5L

The questionnaire will be completed for subjects' parents/guardians, randomized in Part B only. only if none of the items is missing. In both scores question 4 will be reverse scored.

Absolute value and change from baseline and from Month 12 of the EQ-5D-5L scores will be summarized for each domain, by analysis timepoints for visit dependent exploratory analyses described in Section 6.2.2.3.

10.5. Epigenetic Analyses

Epigenetic analysis will be performed to assess the epigenetic modifications induced by the EPIT treatment with DBV712 on the promoter regions of key genes coding for several allergy-specific proteins.

Absolute value and change from baseline of the epigenetic modifications of specific genes will be summarized by analysis timepoints for visit dependent exploratory analyses described in Section 6.2.2.3.

Note: Epigenetic data will not be available at time of database lock and corresponding final outputs will be created only after receipt of the final data.

10.6. Scoring of Atopic Dermatitis

Absolute value and change from baseline of the SCORAD index score will be summarized by analysis timepoints for visit dependent exploratory analyses described in Section 6.2.2.3.

If the answer to the question 'Did subject have any areas of atopic dermatitis?' is 'No' then the SCORAD index score will be imputed to 0.

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11. APPENDIX

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11.2. Common Terminology Criteria for Adverse Events (CTCAE) grades

Haematology	**G1**	**G2**	**G3**	**G4**
Red blood cells (x10e12 /L)	No grading according to CTCAE			
Hematocrit (V/V)	No grading according to CTCAE			
Hemoglobin (g/L) - low	[100;LLN[	[80;100[	<80	
Hemoglobin (g/L) - high	]ULN;ULN+20]	]ULN+20;ULN+40]	>ULN+40	
Platelets (x10e9 /L) - low	[75;LLN [	[50;75[	[25;50[	<25
Leucocytes (x10e9 /L) - low	[3;LLN[	[2;3[	[1;2[	<1
Neutrophils (x10e9 /L) - low	[1.5;LLN[	[1;1.5[	[0.5;1[	<0.5
Eosinophils (x10e9 /L)	No grading according to CTCAE			
Basophils (x10e9 /L)	No grading according to CTCAE			
Lymphocytes (x10e9 /L) - low	[0.8;LLN[	[0.5;0.8[	[0.2;0.5[	<0.2
Monocytes (x10e9 /L)	No grading according to CTCAE			

Biochemistry	**G1**	**G2**	**G3**	**G4**
BUN/urea (mmol/L)	No grading according to CTCAE			
Total protein (g/L)	No grading according to CTCAE			
Total bilirubin (µmol/L) – high	]ULN; ULN*1.5]	]ULN*1.5; ULN*3]	]ULN*3;ULN*10]	>ULN*10
AST (U/L) - high	]ULN; ULN*3]	]ULN*3; ULN*5]	]ULN*5;ULN*20]	>ULN*20
ALT (U/L) - high	]ULN; ULN*3]	]ULN*3; ULN*5]	]ULN*5;ULN*20]	>ULN*20
Creatinine (µmol/L) - high	]ULN; ULN*1.5]	]ULN*1.5; ULN*3]	]ULN*3;ULN*6]	>ULN*6

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11.3. List of Tables, Figures and Listings

Tables and Figures

Note: All the below Tables and Figures will be repeated as described in Section 6.1. Output number will end either with "a" or "b".

Number	Title	Set	Unique/ Repeated
Study Population Section			
14.1.1.1	Subject Disposition	Enrolled	Unique
14.1.1.2	Enrollment Summary by Region, Country and Site	Enrolled	Unique
14.1.2	Major Protocol Deviations	Safety	Unique
14.1.3	Demographic Characteristics	Safety	Unique
14.1.4.1	Medical History by SOC/PT	Safety	Unique
14.1.4.2	Medical History of Specific Interest	Safety	Unique
Clinical Benefit Section			
14.2.1.1	Proportion of subjects reaching an ED ≥1,000 mg peanut protein (Complete Case Analysis)	Safety	Unique
14.2.1.2	Proportion of subjects reaching an ED ≥1,000 mg peanut protein (Sensitivity Analyses)	Safety	Unique
14.2.1.3	Longitudinal analysis of proportion of subjects reaching an ED ≥1,000 mg peanut protein (Complete Case Analysis)	Safety	Unique
14.2.1.4	Longitudinal analysis of proportion of subjects reaching an ED ≥1,000 mg peanut protein (LOCF Analysis)	Safety	Repeated
14.2.2.1	Proportion of subjects treatment responders, using EPITOPE definition (Complete Case Analysis)	Safety	Repeated
14.2.2.2	Proportion of subjects treatment responders, using EPITOPE definition (Sensitivity Analyses)	Safety	Repeated
14.2.2.3	Longitudinal analysis of proportion of subjects treatment responders subjects, using EPITOPE definition (Complete Case Analysis)	Safety	Repeated
14.2.2.4	Longitudinal analysis of proportion of subjects treatment responders subjects, using EPITOPE definition (LOCF Analysis)	Safety	Repeated
14.2.3.1	Proportion of subjects reaching an ED ≥2,000 mg peanut protein (Complete Case Analysis)	Safety	Repeated
14.2.3.2	Proportion of subjects reaching an ED ≥2,000 mg peanut protein (Sensitivity Analyses)	Safety	Repeated
14.2.3.3	Longitudinal analysis of proportion of subjects reaching an ED ≥2,000 mg peanut protein (Complete Case Analysis)	Safety	Repeated
14.2.3.4	Longitudinal analysis of proportion of subjects reaching an ED ≥2,000 mg peanut protein (LOCF Analysis)	Safety	Repeated

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Number	Title	Set	Unique/ Repeated
14.2.4.1	Proportion of subjects who tolerate ≥1,000 mg peanut protein (Complete Case Analysis)	Safety	Repeated
14.2.4.2	Proportion of subjects who tolerate ≥1,000 mg peanut protein (Sensitivity Analyses)	Safety	Repeated
14.2.4.3	Longitudinal analysis of proportion of subjects who tolerate ≥1,000 mg peanut protein (Complete Case Analysis)	Safety	Repeated
14.2.4.4	Longitudinal analysis of proportion of subjects who tolerate ≥1,000 mg peanut protein (LOCF Analysis)	Safety	Repeated
14.2.5.1	Proportion of subjects who tolerate ≥2,000 mg peanut protein (Complete Case Analysis)	Safety	Repeated
14.2.5.2	Proportion of subjects who tolerate ≥2,000 mg peanut protein (Sensitivity Analyses)	Safety	Repeated
14.2.5.3	Longitudinal analysis of proportion of subjects who tolerate ≥2,000 mg peanut protein (Complete Case Analysis)	Safety	Repeated
14.2.5.4	Longitudinal analysis of proportion of subjects who tolerate ≥2,000 mg peanut protein (LOCF Analysis)	Safety	Repeated
14.2.5.5	Analysis of Baseline Characteristics Prognostic of who tolerate ≥2,000 mg peanut protein	Safety	Unique
14.2.6.1	Tolerated Dose of peanut protein (Complete Case Analysis)	Safety	Unique
14.2.6.2	Tolerated Dose of peanut protein (Sensitivity Analysis)	Safety	Unique
14.2.6.3	Longitudinal analysis of Tolerated Dose of peanut protein (Complete Case Analysis)	Safety	Unique
14.2.6.4	Longitudinal analysis of Tolerated Dose of peanut protein (mLOCF Analysis)	Safety	Repeated
14.2.7.1	Eliciting Dose of peanut protein (Complete Case Analysis)	Safety	Repeated
14.2.7.2	Eliciting Dose of peanut protein (Sensitivity Analysis)	Safety	Repeated
14.2.7.3	Longitudinal analysis of Eliciting Dose of peanut protein (Complete Case Analysis)	Safety	Repeated
14.2.7.4	Longitudinal analysis of Eliciting Dose of peanut protein (mLOCF Analysis)	Safety	Repeated
14.2.8.1	Cumulative Reactive Dose of peanut protein (Complete Case Analysis)	Safety	Repeated
14.2.8.2	Cumulative Reactive Dose of peanut protein (Sensitivity Analysis)	Safety	Repeated
14.2.8.3	Longitudinal analysis of Cumulative Reactive Dose of peanut protein (Complete Case Analysis)	Safety	Repeated
14.2.8.4	Longitudinal analysis of Cumulative Reactive Dose of peanut protein (mLOCF Analysis)	Safety	Repeated
Safety Section			
14.3.1.1	Study Duration	Safety	Unique

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Number	Title	Set	Unique/ Repeated
14.3.1.2	Treatment Exposure	Safety	Unique
14.3.1.3	Treatment Compliance	Safety	Unique
14.3.2.1	Overview of TEAEs, overall and by year of treatment	Safety	Unique
14.3.2.2	Overview of TEAEs, overall and by year of active treatment	Safety	Unique
14.3.2.3	Overview of TEAEs, Incidence Rates by 100 Subject-Years of active treatment	Safety	Unique
14.3.3.1	TEAEs by SOC/PT, overall and by year of treatment	Safety	Unique
14.3.3.2	TEAEs considered related by SOC/PT, overall and by year of treatment	Safety	Repeated
14.3.3.3	Serious TEAEs by SOC/PT, overall and by year of treatment	Safety	Repeated
14.3.3.4	Serious TEAEs considered related by SOC/PT, overall and by year of treatment	Safety	Repeated
14.3.3.5	TEAEs leading to permanent study treatment discontinuation by SOC/PT, overall and by year of treatment	Safety	Repeated
14.3.3.6	TEAEs leading to temporary study treatment discontinuation by SOC/PT, overall and by year of treatment	Safety	Repeated
14.3.3.7	Treatment-Emergent AESI by SOC/PT, overall and by year of treatment	Safety	Repeated
14.3.3.8	Treatment-Emergent AESI considered related by SOC/PT, overall and by year of treatment	Safety	Repeated
14.3.3.9	TEAEs leading to epinephrine intake by SOC/PT, overall and by year of treatment	Safety	Repeated
14.3.3.10	TEAEs considered related leading to epinephrine intake by SOC/PT, overall and by year of treatment	Safety	Repeated
14.3.3.11	TEAEs leading to systemic or inhaled corticosteroid use by SOC/PT, overall and by year of treatment	Safety	Repeated
14.3.3.12	TEAEs leading to topical corticosteroid use by SOC/PT, overall and by year of treatment	Safety	Repeated
14.3.3.13	Most frequent TEAEs (>5%) by SOC/PT, overall and by year of treatment	Safety	Repeated
14.3.3.14	TEAEs considered Related by SOC/PT and maximum severity, overall and by year of treatment	Safety	Unique
14.3.3.15	TEAEs considered Related by SOC/PT and maximum duration, overall and by year of treatment	Safety	Repeated
14.3.4.1	Listing of Deaths	Safety	Unique
14.3.4.2	Listing of Serious Adverse Events	Safety	Repeated
14.3.4.3	Listing of Adverse Events Leading to Permanent Discontinuation	Safety	Repeated
14.3.5	Local Skin Reaction assessed by the Investigator	Safety	Unique

Docusign Envelope ID: CCI [redacted]

Number	Title	Set	Unique/ Repeated
14.3.6	Local Skin Reaction assessed by the Subject, overall and by year of treatment	Safety	Unique
14.3.7.1	Concomitant Medications by ATC Class Level 3 and Preferred Name, overall and by year of treatment	Safety	Unique
14.3.7.2	Medications taken for peanut consumption by ATC Class Level 3 and Preferred Name, overall and by year of treatment	Safety	Repeated
14.3.7.3	Non-drug therapies and surgical procedures by SOC/PT, overall and by year of treatment	Safety	Repeated
14.3.8.1	Number of Peanut Consumptions, overall and by year of treatment	Safety	Unique
14.3.8.2.1	Overview of TEAEs due to APC, overall and by year of treatment	Safety	Repeated
14.3.8.2.2	Overview of TEAEs due to APC, overall and by year of active treatment	Safety	Repeated
14.3.8.2.3	Overview of TEAEs due to APC, Incidence Rates by 100 Subject-Years of active treatment	Safety	Repeated
14.3.9.1	SAEs elicited during DBPCPCs by SOC/PT and by Timepoint and Formula	Safety	Unique
14.3.9.2.1	DBPCFC Objective Symptoms by Severity, and Severity Score, by Timepoint and Formula	Safety	Unique
14.3.9.2.2	DBPCFC Subjective Symptoms by Severity and by Timepoint and Formula	Safety	Unique
14.3.9.3.1	Medications taken for DBPCFC by Timepoint and Formula, and by ATC Class Level 3 and Preferred Name	Safety	Unique
14.3.9.3.2	Antihistamine and Epinephrine Intakes during DBPCFCs	Safety	Unique
14.3.10.1	Laboratory Results – Hematology - Actual Values, Change from Baseline and Month 12, CTCAE Grades and Abnormalities	Safety	Unique
14.3.10.2	Laboratory Results – Biochemistry - Actual Values, Change from Baseline and Month 12, CTCAE Grades and Abnormalities	Safety	Repeated
14.3.11.1	Vital Signs - Actual Values, Change from Baseline and Month 12, and abnormalities	Safety	Unique
14.3.11.2	Physical Examination – Weight, Height and Abnormalities	Safety	Unique
14.3.13	Spirometry and Peak Expiratory Flow - Actual Values and Change from Month 12	Safety	Unique
Other Exploratory			
14.4.1.1	Maximum Severity of DBPCFC symptoms	Safety	Unique
14.4.1.2	Longitudinal Analysis of Maximum Severity of DBPCFC symptoms	Safety	Unique
14.4.2.1.1	Peanut Specific IgE and Components - Actual Values, Change from Baseline and Month 12	Safety	Unique
14.4.2.1.2	Figure – Median (Q1, Q3) of Actual Values of Peanut Specific IgE and Components Overtime	Safety	Unique

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Number	Title	Set	Unique/ Repeated
14.4.2.2.1	Peanut Specific IgG4 and Components - Actual Values, Change from Baseline and Month 12	Safety	Repeated
14.4.2.2.2	Figure – Median (Q1, Q3) of Actual Values of Peanut Specific IgG4 and Components Overtime	Safety	Repeated
14.4.2.3.1	Peanut Specific IgE to IgG4 ratio - Actual Values, Change from Baseline and Month 12	Safety	Repeated
14.4.2.3.2	Figure – Median (Q1, Q3) of Actual Values of Peanut Specific IgE to IgG4 Ratio and Components Overtime	Safety	Repeated
14.4.2.4	IgE and IgG4 Specific to Other Allergens	Safety	Repeated
14.4.3.1	Skin Prick Test – Mean Wheal Diameter (Undiluted Peanut Extract) - Actual Values, Change from Baseline and Month 12	Safety	Repeated
14.4.3.2	Figure – Median (Q1, Q3) of Actual Values of Skin Prick Test – Mean Wheal Diameter Overtime	Safety	Repeated
14.4.4.1	FAQLQ-PF - Actual Values, Change from Baseline and Month 12	Safety	Unique
14.4.4.2	FAIM-PF - Actual Values, Change from Baseline and Month 12	Safety	Repeated
14.4.4.3	EQ-5D-5L - Actual Values, Change from Baseline and Month 12	Safety	Repeated
14.4.5	Epigenetic Analyses - Actual Values, Change from Baseline and Month 12	Safety	Repeated
14.4.6	SCORAD - Actual Values, Change from Baseline and Month 12	Safety	Unique
14.4.7.1	CCI	Safety	Unique
14.4.7.2	Assessments of Ease of Removal, Pain and Skin Injury at Removal	Safety	Unique
14.4.7.3	CCI	Safety	Unique

Listings

Number	Title	Set	Comment
16.2.1	Disposition of Subjects	Safety	Unique
16.2.2	Protocol Deviations	Safety	Unique
16.2.3	Clinical Benefit Endpoints	Safety	Unique
16.2.4	Treatment-Emergent Adverse Events	Safety	Unique

Docusign Envelope ID: CCI

11.4. Table, Figure and Listing Shells

Will be provided in a separate document.

Certificat de réalisation

Identifiant d'enveloppe: PPD

État: Complétée

Objet: Complete with Docusign: Statistical Analysis Plan_EPOPEX v1.0.pdf

Enveloppe source:

PPD

Nombre de pages du document: 60

Signatures: 3

Nombre de pages du certificat: 5

Paraphe: 0

Signature dirigée: Activé

Horodatage de l'enveloppe: Activé

Fuseau horaire: (UTC+01:00) Bruxelles, Copenhague, Madrid, Paris

Suivi du dossier

État: Original

24/04/2025 18:12:58

PPD

Emplacement: DocuSign

Événements de signataire	Signature	Horodatage
PPD	PPD Sélection d'une signature : Style présélectionné ID de signature: PPD En utilisant l'adresse IP: PPD Avec l'authentification de signature par mot de passe Docusign Avec motifs de signature (sur chaque onglet): I approve this document	Envoyée: 24/04/2025 18:23:56 Consultée: 25/04/2025 19:21:07 Signée: 25/04/2025 19:21:42
Divulgation relative aux Signatures et aux Dossiers électroniques: Accepté: 07/11/2022 02:00:43 ID: 2699fad5-a7ba-4414-b655-c2638769cab1		
PPD	PPD Sélection d'une signature : Style présélectionné ID de signature: PPD En utilisant l'adresse IP: PPD Avec l'authentification de signature par mot de passe Docusign Avec motifs de signature (sur chaque onglet): J'approuve ce document	Envoyée: 24/04/2025 18:23:55 Consultée: 25/04/2025 15:45:03 Signée: 25/04/2025 15:46:56
Divulgation relative aux Signatures et aux Dossiers électroniques: Accepté: 12/10/2022 18:51:26 ID: 48276943-b8ed-4553-9775-36e75e9b948b		

Événements de signataire	Signature	Horodatage
PPD	PPD	Envoyée: 24/04/2025 18:23:55 Consultée: 24/04/2025 18:24:30 Signée: 24/04/2025 18:25:36
	Sélection d'une signature : Style présélectionné ID de signature: PPD En utilisant l'adresse IP:PPD Avec l'authentification de signature par mot de passe Docusign Avec motifs de signature (sur chaque onglet): I am the author of this document	

Divulgation relative aux Signatures et aux Dossiers électroniques:
Accepté: 14/11/2022 17:16:21
ID: 0700f3cc-ce79-4fad-b88a-4d7d8c4a22b3

Événements de signataire en personne	Signature	Horodatage
Événements de livraison à l'éditeur	**État**	**Horodatage**
Événements de livraison à l'agent	**État**	**Horodatage**
Événements de livraison intermédiaire	**État**	**Horodatage**
Événements de livraison certifiée	**État**	**Horodatage**
Événements de copie carbone	**État**	**Horodatage**
Événements de témoins	**Signature**	**Horodatage**
Événements notariaux	**Signature**	**Horodatage**

Récapitulatif des événements de l'enveloppe	État	Horodatages
Enveloppe envoyée	Haché/crypté	24/04/2025 18:23:56
Livraison certifiée	Sécurité vérifiée	24/04/2025 18:24:30
Signature complétée	Sécurité vérifiée	24/04/2025 18:25:36
Complétée	Sécurité vérifiée	25/04/2025 19:21:42

Événements de paiement	État	Horodatages

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