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

Sponsor:	DBV TECHNOLOGIES S.A. 177-181 avenue Pierre Brossolette 92120 Montrouge, France Tel: PPD
Clinical Research Organization:	Pharm Research Associates (UK) Ltd 500 South Oak Way, Green Park, Reading RG2 6AD, United Kingdom
Sponsor Protocol No.:	V712-305 (EPOPEX)
IND No.:	14366
EudraCT No.:	2018-003323-10
Investigational Product Name:	DBV712 (Viaskin® Peanut)
Development Phase:	Phase 3 Follow-up
Version and Date of Protocol:	Version 2.0 (including Protocol Amendment 1) 21 September 2021 (for US only) Version 1.0, 10 September 2018

The study will be conducted according to the protocol and in compliance with Good Clinical Practice (GCP), with the Declaration of Helsinki, and with other applicable regulatory requirements.

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SIGNATURE PAGE

Declaration of Sponsor or Responsible Medical Officer

Title: EPITOPE Open-label Extension Study to Evaluate the Long-term Clinical Benefit and Safety of DBV712 in Peanut-Allergic Children (EPOPEX)

This study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational product, as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki, [2013] (APPENDIX 1), and the guidelines on Good Clinical Practice.

Sponsor Signatory:

PPD

PPD

28 September 2021

Chief Medical Officer
DBV Technologies S.A.

Signature

Date

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Declaration of the Investigator

Title: EPITOPE Open-label Extension Study to Evaluate the Long-term Clinical Benefit and Safety of DBV712 in Peanut-Allergic Children (EPOPEX)

I have read and understood and agree to abide by all the conditions and instructions contained in this protocol.

All documentation for this study that is supplied to me and that has not been previously published will be kept in the strictest confidence. This documentation includes this study protocol, Investigator's Brochure, electronic case report form (e-CRF), and other scientific data.

The study will not be commenced without the prior written approval of a properly constituted Institutional Review Board (IRB) or Independent Ethics Committee (IEC). No changes will be made to the study protocol without the prior written approval of the Sponsor and the IRB or IEC, except where necessary to eliminate an immediate hazard to the subjects.

Responsible Investigator of the Local Study Center

_____ _____

Signature Date

_____

Name (block letters)

_____

Title (block letters)

_____

Institution (block letters)

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Phone number

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PROTOCOL SYNOPSIS

Title	EPITOPE Open-label Extension Study to Evaluate the Long-term Clinical Benefit and Safety of DBV712 in Peanut-Allergic Children (EPOPEX)
Sponsor Study No.	V712-305/EPOPEX
Investigational Product	DBV712 250 µg (Viaskin® Peanut)
Phase	3 (Follow-up)
Sponsor	DBV Technologies S.A.
Study Center(s)	This is a multicenter study to be conducted in North America (US and Canada), Europe and Australia. All sites involved in the EPITOPE study are planned to participate in this follow-up study.
Objective(s)	The objectives of this follow-up study of the EPITOPE study are: • To assess the clinical benefit of Viaskin Peanut after up to 3 years of epicutaneous immunotherapy (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.
Design	This is an open-label, follow-up study for subjects who completed the EPITOPE study. Eligible subjects will be offered enrollment in this follow-up study to receive Viaskin Peanut treatment at the dose selected in EPITOPE study (250 µg). Additional treatment duration will be 2 years or 2.5 years dependent upon EPITOPE database lock timelines, if subjects were previously randomized to active treatment in the EPITOPE study, or 3 years if subjects were randomized to placebo in the EPITOPE study. The treatment group during the EPITOPE study will remain blinded until the EPITOPE database is locked and the study results are unblinded. Eligible subjects who decide to participate in the EPOPEX follow-up study will transition into this study during Visit 11 of the EPITOPE study. Subjects continuing into the EPOPEX study will not perform Visit 12 of EPITOPE study. Visit 11 of the EPITOPE study and Visit 1 of the EPOPEX study will be conducted concurrently, as far as possible; however, considering practical aspects for the center and for the subject's family, Visit 1 might be conducted within a week of Visit 11. The EPOPEX study population will consist of 2 sub-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). The overall study duration for each subject is approximately 2 years and 1 month for subjects previously randomized to Viaskin Peanut (any dose) in the EPITOPE study and 3 years and 1 month for subjects previously randomized to placebo in the EPITOPE study (including visit windows). Subjects previously randomized to active treatment in the EPITOPE study who reach their Visit 9 (month 24) before the EPITOPE study unblinding will extend their study duration by 6 months, i.e., up to 30 months treatment in this extension study in total. Double-Blind, Placebo-Controlled Food Challenges (DBPCFCs) will be conducted after 1, 2 and 3 years of EPIT treatment with Viaskin Peanut. As such, subjects in the Placebo+VP group will undergo 3 DBPCFCs in the EPOPEX study, after 1, 2 and 3

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	years of active treatment. Subjects in the VP+VP group will undergo 2 DBPCFCs in the EPOPEX study, after 2 and 3 years of active treatment (the DBPCFC performed at the end of the EPITOPE study corresponds to the DBPCFC after 1 year of active treatment). The starting dose of the challenge will be 1 mg of peanut protein and will escalate up to the highest dose of 2000 mg peanut protein. Key assessments of global safety will include adverse events (AEs), skin observation of the areas of patch application, vital signs, physical examinations, clinical laboratory assessments. In between visits, the occurrence of any AE or local skin reactions and the use of concomitant medications will be recorded by the subject's parent(s)/guardian(s) in a diary. The subject diary will be reviewed by the site medical staff at each visit. When reviewing the diary data, the Investigator will use her/his clinical judgment to validate the AEs and concomitant medications to be reported in the e-CRF. If the diary data entries are not reported in the e-CRF by the Investigator based on her/his clinical judgment, this will be documented in the source documents. The adhesion and the occlusion of the condensation chamber of the patch will be assessed at each site visit by site staff. Additional assessments will include total Immunoglobulin E (IgE), peanut-specific IgE and Immunoglobulin G4 (IgG4), IgE and IgG4 specific to peanut protein components, skin prick tests (SPTs), quality of life (Food Allergy Quality of Life Questionnaire [FAQLQ]/Food Allergy Independent Measure [FAIM]/EQ-5D-5L), IgE specific to other allergens (i.e., cow's milk, egg white, house dust mite, Timothy grass pollen), description of accidental consumption of peanut and risk-taking behavior, epigenetic modifications and assessment of atopic dermatitis using the scoring atopic dermatitis (SCORAD) index. A Data and Safety Monitoring Board (DSMB) composed of independent experts in food allergy will review study safety data at specific intervals during the study and on an ad hoc basis. During their participation in the study, subjects will be instructed to remain on a strict peanut-free diet. Reintroducing peanut into the subject's diet at the end of their participation in the study will be left to the Investigator's decision. This decision will be collected in the electronic case report from (e-CRF).
Treatment	The investigational product (IP), DBV712 (Viaskin Peanut), is an epicutaneous delivery system (Viaskin® patch) containing a solid deposit of a peanut protein extract formulation. CCI [redacted]
Duration of Treatment	Repeated daily application of Viaskin Peanut dosed at 250 µg peanut protein per patch is planned for 2 years or 3 years for subjects randomized to Viaskin Peanut at any dose or to placebo in the EPITOPE study, respectively. Subjects randomized to Viaskin Peanut who reach their Visit 9 before the EPITOPE unblinding will extend their treatment duration by 6 months, i.e., up to 30 months treatment in this extension study in total. A single patch is applied daily on the inter-scapular area of the back of the subjects for 24 hours (± 4 hours of allowance). To enhance the tolerance at treatment initiation, especially for the former placebo subjects crossing over to receive the active treatment, the duration of daily application of the patch will be progressively increased for the first 4 weeks as follows:

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	• 2 hours (± 30 min) per day during the 1st week (from Day 1 through Day 7); • 4 hours (± 30 min) per day during the 2nd week (from Day 8 through Day 14); • 8 hours (± 1 hour) per day during the 3rd week (from Day 15 through Day 21); • 12 hours (± 2 hours) per day during the 4th week (from Day 22 through Day 28). From the 5th week onwards (Day 29), the duration of the daily application will be 24 hours (± 4 hours). However, in case of severe local skin reactions, the daily duration of patch application can be adapted, and the increase of treatment duration can possibly be extended beyond the 4 week-period described above.
Number of Subjects	All eligible subjects who completed the EPITOPE study will be offered enrollment into the EPOPEX study.
Population	All subjects who completed the EPITOPE study up to Visit 11 (inclusive) will be offered enrollment into the EPOPEX study, provided that all selection criteria are met. Subjects will be enrolled in this study only if they meet, among others, the following key inclusion criteria: completion of the EPITOPE study, with a completed and documented DBPCFC at Month 12 (i.e., both Visit 10 and Visit 11 performed). Subjects will not be enrolled, if they meet, among others, the following exclusion criteria: development of severe anaphylactic reaction during the Month 12 DBPCFC (at Visit 10 or Visit 11) in the EPITOPE study requiring a tracheal intubation or leading to a cardiac arrest and/or to coma; other cases of severe anaphylaxis will be considered eligible to enter the EPOPEX study. All subjects will continue with their usual peanut-free diet and label reading of food products to avoid as much as possible any accidental peanut consumption during the duration of the study.
Rescheduling rules	When applicable, the following rescheduling rules between the 2 groups of subjects will be used:

	Time points			
Groups	**Baseline**	**1 year of active treatment**	**2 years of active treatment**	**3 years of active treatment**
VP+VP	EPITOPE Entry	EPOPEX Entry	EPOPEX Year 1	EPOPEX Year 2
Placebo+VP	EPOPEX Entry	EPOPEX Year 1	EPOPEX Year 2	EPOPEX Year 3

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 after 1, 2 and 3 years of treatment in each group (VP+VP group, Placebo+VP group) and overall: • Proportion of subjects reaching an ED ≥1000 mg; • Proportion of treatment responders, using the treatment response definition of the EPITOPE study, i.e., a subject is defined as a treatment responder if: o The baseline ED was >10 mg peanut protein and the ED is ≥1000 mg peanut protein at the post-baseline DBPCFCs or; o The baseline ED was ≤10 mg and the ED is ≥300 mg peanut protein at the post-baseline DBPCFCs. For the VP+VP group, the baseline ED is defined as the ED reached at the EPITOPE study entry.

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	For the Placebo+VP group, the baseline ED is defined as the latest, valid ED in the EPITOPE study (i.e., Month 12). • Proportion of subjects reaching a cumulative dose of at least 1444 mg peanut protein at the post-baseline DBPCFCs; • Proportion of subjects reaching a cumulative dose of at least 3444 mg peanut protein at the post-baseline DBPCFCs; • 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), which is the percentage of subjects who pass the post-baseline DBPCFCs; • Mean and median CRD of peanut protein; • Mean and median ED of peanut protein.
Safety Endpoints	The following safety endpoints will be analyzed: • Adverse Events and Treatment-emergent adverse events (TEAEs) by System Organ Class (SOC) and Preferred Term (PT); • Treatment-emergent adverse events by maximum severity and by maximum duration and relatedness to the IP; • Serious adverse events (SAEs) by SOC and PTs, maximum severity and relatedness to the IP; • Treatment-emergent adverse events leading to treatment discontinuation; • Local adverse events of special interest (AESIs) (i.e., reactions at patch sites potentially leading to skin barrier disruption) and systemic AESIs (i.e., anaphylaxis, or systemic hypersensitivity reactions leading to epinephrine intake), whatever the causal relationship to the 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 Investigator; • Laboratory data, physical examinations and vital signs; The following study procedure safety criteria will be assessed over 3 years of treatment: • Symptoms elicited during the DBPCFCs by severity; • Severity of symptoms score during the DBPCFCs; • Serious AEs elicited during the DBPCFCs. The safety endpoints will be evaluated in the overall Safety population using the rescheduling rules and by treatment group (VP+VP / Placebo+VP).
Other Exploratory Endpoints	The following exploratory endpoints will be evaluated over 3 years of treatment in each group (VP+VP group, Placebo+VP group) and overall using the rescheduling rules: • 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 SPT average wheal diameters; • Description of the quality of life (QoL) questionnaires (FAQLQ/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;

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	• Epigenetic modifications of the promoters of some specific genes; • Sensitization status to other allergens and their evolution over the study period; • Scoring atopic dermatitis index evolution over time.
Statistical Methods	**Safety Population:** The Safety population will consist of all subjects who received at least 1 dose of the IP. This population will be used to assess safety endpoints. **Statistical methods:** Statistical methods will be exhaustively described in the statistical analysis plan (SAP) that will be finalized before the data review meeting and database lock. Categorical variables will be summarized using number of observations and percentages. Continuous variables will be summarized using descriptive statistics (number of observations [n], mean, standard deviation, minimum, first quartile [Q1], third quartile [Q3], median and maximum). Demographic, baseline, and disposition data will be summarized. <u>Analysis of Endpoints for the Evaluation of Clinical Benefit</u> Statistical methods will be detailed in the SAP based on the distribution of variables and missing data. <u>Analysis of Safety Endpoints</u> The safety analyses will be performed on the Safety population. The safety endpoints and the criteria for evaluation of the safety of the study procedure will be summarized using the rescheduling rules, in the overall Safety population and by treatment group, over 3 years of active treatment. For safety analyses, partial or missing data will be imputed according to the most conservative approach. <u>Analysis of Other Exploratory Endpoints</u> Statistical methods for the analysis of other exploratory endpoints will be detailed in the SAP based on the distribution of variables and the level of missing data.
Interim analysis	An interim analysis will be performed once all subjects from the VP+VP group have completed the DBPCFC at Year 3. Details will be provided in the SAP.

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SCHEDULE OF PROCEDURES

All subjects reaching their V9 (month 24) before the EPITOPE unblinding will continue the treatment for 6 months until V10P (see table "Subjects randomized to Placebo in the EPITOPE study (Placebo + VP group)" for more details)

At the time of Visit 10P the treatment allocation will be known:

- Subjects who received the active treatment in the EPITOPE study (VP+VP group) will end their treatment at visit 10P which will be followed by the end of treatment visit V11A (same assessments as V10A) conducted 12 to 16 days after V10P.
- Subjects who received placebo in the EPITOPE study (Placebo + VP group) will continue until their visits 11P, 12P and 13P as planned (see table "Subjects randomized to Placebo in the EPITOPE study (Placebo + VP group)" for more details)

	Subjects randomized to active treatment in the EPITOPE study (VP+VP group)																
		Treatment period													**End of Study**	**Early Term**	**Unsc. Visit**
Visit Number	**V1[1]**	**PC**	**PC**	**V2**	**V3**	**V4**	**PC**	**V5**	**V6**	**PC**	**V7**	**PC**	**V8**	**V9**	**V10A/ V11A**	**ET[2]**	**UV[3]**
Visit Day/Month	**D1**	**D4**	**D22**	**M1**	**M3**	**M6**	**M9**	**M12**	**M12 +7d**	**M15**	**M18**	**M21**	**M24**	**M24 +7d**			
Time Window	Max 1wk after V11 of EPITOPE	±2 d	±2 d	±3 d	±7 d	±7 d	±7 d	±7 d	Max 1 wk after V5	±7 d	±7 d	±7 d	±7 d	Max 1 wk after V8	12-16 ds after V9		
Informed consent[4]	X																
Check eligibility criteria	X																
Disease/Medical history[5]	X																
Demographics	X																
Physical examination[6]	X[7]			X	X	X		X[8]	X[8]		X		X[8]	X[8]	X	X	X
Vital signs[9]	X[7]			X	X	X		X[8]	X[8]		X		X[8]	X[8]	X	X	X
PEF	X[10]			X[10]	X[10]	X[10]		X[8]	X[8]		X[10]		X[8]	X[8]		X	X
Spirometry (FEV_1)	X[10]			X[10]	X[10]	X[10]		X[10]			X[10]		X[10]			X	X
SCORAD	X[11]				X	X		X			X		X			X	
SPT	X[11]				X	X		X			X		X			X	

	Subjects randomized to active treatment in the EPITOPE study (VP+VP group)																
		Treatment period													End of Study	Early Term	Unsc. Visit
Visit Number	**V1[1]**	**PC**	**PC**	**V2**	**V3**	**V4**	**PC**	**V5**	**V6**	**PC**	**V7**	**PC**	**V8**	**V9**	**V10A/ V11A**	**ET[2]**	**UV[3]**
Visit Day/Month	**D1**	**D4**	**D22**	**M1**	**M3**	**M6**	**M9**	**M12**	**M12 +7d**	**M15**	**M18**	**M21**	**M24**	**M24 +7d**			
Time Window	Max 1wk after V11 of EPITOPE	±2 d	±2 d	±3 d	±7 d	±7 d	±7 d	±7 d	Max 1 wk after V5	±7 d	±7 d	±7 d	±7 d	Max 1 wk after V8	12-16 ds after V9		
Immunological markers[12]	X[13]				X	X		X			X		X			X	
Laboratory tests[14]	X[11]				X	X		X			X		X			X	X
FAQLQ/FAIM/EQ-5D-5L[15]	X[16]			X		X		X			X		X			X	
Epigenetic analyses	X[11]				X	X		X					X				
DBPCFC								X	X				X	X			
Adverse events[17]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications[18]	X[19]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Check for any accidental peanut consumption	X[20]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Subject participation card	X																
Dispense/check subject diary	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense subject safety leaflet	X																
Dispense IP (Viaskin Peanut) to the subject	X			X	X	X		X	X		X		X				
Apply first patch at study site	X																
Check used/unused IP dispensed to the subject				X	X	X		X	X		X		X	X		X	X
Check skin reaction under the patch and grading[21]	X			X	X	X		X	X		X		X	X		X	X
CCI [redacted]																	
Photographs of patch application site. Download photos taken by	X			X	X	X		X	X		X		X	X		X	X

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	Subjects randomized to active treatment in the EPITOPE study (VP+VP group)																
		Treatment period													End of Study	Early Term	Unsc. Visit
Visit Number	**V1[1]**	**PC**	**PC**	**V2**	**V3**	**V4**	**PC**	**V5**	**V6**	**PC**	**V7**	**PC**	**V8**	**V9**	**V10A/ V11A**	**ET[2]**	**UV[3]**
Visit Day/Month	**D1**	**D4**	**D22**	**M1**	**M3**	**M6**	**M9**	**M12**	**M12 +7d**	**M15**	**M18**	**M21**	**M24**	**M24 +7d**			
Time Window	Max 1wk after V11 of EPITOPE	±2 d	±2 d	±3 d	±7 d	±7 d	±7 d	±7 d	Max 1 wk after V5	±7 d	±7 d	±7 d	±7 d	Max 1 wk after V8	12-16 ds after V9		
subject's parent(s)/guardian(s) if any																	
Review use of epinephrine auto-injector and Anaphylaxis Emergency Action Plan (if required)[22]	X			X	X	X		X			X		X				
Dispense 1% hydrocortisone ointment[23]	X			X	X	X		X			X		X				
Time under observation before discharge	3 h							3 h	3 h				3 h	3 h			

Abbreviations: d=day; ds=days; DBPCFC=Double-Blind Placebo-Controlled Food Challenge; EOS= End of Study; ET=Early Termination; FAQLQ=Food Allergy Quality of Life Questionnaire; FAIM=Food Allergy Independent Measure; FEV_1=Forced Expiratory Volume in 1 second; IP=Investigational Product; M=Month; PC= Phone Contact; PEF=Peak Expiratory Flow; SCORAD=Scoring Atopic Dermatitis; SPT=Skin Prick Test; UV=Unscheduled Visit; V=Visit; wk=week; wks=weeks.

1. Visit 1 in the EPOPEX study should be conducted on the same day as Visit 11 in the EPITOPE study or within a week of Visit 11. Therefore, the procedures common to both visits only need to be performed once.
2. Early Termination Visit is only for subjects withdrawing prematurely.
3. Procedures during the unscheduled Visit will be performed as deemed necessary by the Investigator.
4. Informed consent must be obtained after completion of Month 12 DBPCFC procedures in EPITOPE study, and before any procedure is started in EPOPEX.
5. New medical history and disease history as compared to the EPITOPE screening visit.
6. Including a complete skin examination, body weight and height.
7. Since Visit 1 in the EPOPEX study is conducted the same day as Visit 11 in the EPITOPE study or within a week of Visit 11, values here are those obtained before starting the food challenge at Visit 11 in the EPITOPE study.
8. These examinations are to be done before the DBPCFC. Additionally, they can be repeated during the DBPCFC procedure on both days anytime if judged necessary by the Investigator.
9. Vital signs measured in a sitting position include heart rate and systolic and diastolic blood pressure.

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10. Pulmonary explorations at these timepoints will be performed only in subjects aged 4 years or older with a diagnosis of asthma. Spirometry is the preferred measurement. However, if the subject is not able to perform spirometry, then PEF should be measured instead.
11. Results obtained at Visit 10 in the EPITOPE study can be used for this visit.
12. Total IgE, peanut-specific IgE, peanut-specific IgG4, IgE and IgG4 specific to peanut protein components: Ara h 1, Ara h 2, Ara h 3. IgE specific to cow's milk, egg white, house dust mites, and grass pollen will be collected at Visit 1, Visit 5, Visit 8 and in case of an early termination Visit.
13. For subjects who were in EPITOPE Part B, total IgE results obtained at Visit 10 in the EPITOPE study can be used for this visit. For subjects who were in EPITOPE Part A, total IgE assessment will be performed at this visit on blood samples drawn at Visit 10 in the EPITOPE study.
14. Laboratory tests performed centrally include hematology (hemoglobin, hematocrit, platelets, red blood cells, white blood cells and differential cell count) and biochemistry (alanine aminotransferase, aspartate aminotransferase, total bilirubin, total protein, blood urea nitrogen, creatinine).
15. For FAQLQ and FAIM, Parental Form will be used. The translated forms of FAQLQ and FAIM will be completed in countries where they are available in local languages. EQ-5D-5L will be completed by the subject's parents/guardians.
16. Results of the FAQLQ/FAIM obtained at Visit 10 in the EPITOPE study can be used for this visit. Results of the EQ-5D-5L obtained at Visit 10 in the EPITOPE study can be used for this visit in subjects who were in EPITOPE Part B. The EQ-5D-5L must be completed at this visit for subjects who were in EPITOPE Part A.
17. All adverse events will be collected at all visits, and during the phone calls, including adverse events/allergic symptoms during the DBPCFC.
18. All concomitant medications will be collected at all visits and during the phone calls, including concomitant medications given to treat allergic symptoms during the DBPCFC.
19. Ongoing concomitant medications from the EPITOPE study will be collected at Visit 1.
20. The information obtained at Visit 11 in the EPITOPE study can be utilized here.
21. Check the reactions of the skin on the back of the subject and grade the severity of the local skin reactions. At Visit 1, grading is to be performed before patch application and 30 min, 1 h, 2 h and 3 h after patch application.
22. The expiry date of the auto-injector dispensed formerly will be checked and a new auto-injector will be provided to the subject prior to the product's expiry date, if needed.
23. Dispense as necessary.

Study Assessments	Subjects randomized to Placebo in the EPITOPE study (Placebo + VP group)																					
		Treatment Period																		End of Study	Early Term.	Unsc. Visit
Visit Number	**V1[1]**	**PC**	**PC**	**V2**	**V3**	**V4**	**PC**	**V5**	**V6**	**PC**	**V7**	**PC**	**V8**	**V9**	**PC**	**V10P**	**PC**	**V11P**	**V12P**	**V13P**	**ET[2]**	**UV[3]**
Visit Day/Month	**D1**	**D4**	**D22**	**M1**	**M3**	**M6**	**M9**	**M12**	**M12 +7d**	**M15**	**M18**	**M21**	**M24**	**M24 +7d**	**M27**	**M30**	**M33**	**M36**	**M36 +7d**			
Time Window	Max 1wk after V11 of EPITOPE	±2 d	±2 d	±3 d	±7 d	±7 d	±7 d	±7 d	Max 1 wk after V5	±7 d	±7 d	±7 d	±7 d	Max 1 wk after V8	±7 d	±7 d	±7 d	±7 d	Max 1 wk after V11P	12-16 ds after V12P		
Informed consent[4]	X																					
Check eligibility criteria	X																					
Disease/Medical history[5]	X																					
Demographics	X																					
Physical examination[6]	X[7]			X	X	X		X[8]	X[8]		X		X[8]	X[8]		X		X[8]	X[8]	X	X	X
Vital signs[9]	X[7]			X	X	X		X[8]	X[8]		X		X[8]	X[8]		X		X[8]	X[8]	X	X	X
PEF	X[10]			X[10]	X[10]	X[10]		X	X		X[10]		X	X		X[10]		X	X		X	X
Spirometry (FEV_1)	X[10]			X[10]	X[10]	X[10]		X[10]			X[10]		X[10]			X[10]		X[10]			X	X
SCORAD	X[11]				X	X		X			X		X			X		X			X	
SPT	X[11]				X	X		X			X		X			X		X			X	
Immunological markers[12]	X[13]				X	X		X			X		X			X		X			X	
Laboratory tests[14]	X[11]				X	X		X			X		X			X		X			X	X
FAQLQ/FAIM/EQ-5D-5L[15]	X[16]			X		X		X			X		X			X		X			X	
Epigenetic analyses	X[11]				X	X		X					X					X				
DBPCFC								X	X				X	X				X	X			
Adverse events[17]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications[18]	X[19]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Check for any accidental peanut consumption	X[20]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Assessments	Subjects randomized to Placebo in the EPITOPE study (Placebo + VP group)																				
		Treatment Period																		End of Study	Early Term.	Unsc. Visit
Visit Number	**V1[1]**	**PC**	**PC**	**V2**	**V3**	**V4**	**PC**	**V5**	**V6**	**PC**	**V7**	**PC**	**V8**	**V9**	**PC**	**V10P**	**PC**	**V11P**	**V12P**	**V13P**	**ET[2]**	**UV[3]**
Visit Day/Month	**D1**	**D4**	**D22**	**M1**	**M3**	**M6**	**M9**	**M12**	**M12 +7d**	**M15**	**M18**	**M21**	**M24**	**M24 +7d**	**M27**	**M30**	**M33**	**M36**	**M36 +7d**			
Time Window	Max 1wk after V11 of EPITOPE	±2 d	±2 d	±3 d	±7 d	±7 d	±7 d	±7 d	Max 1 wk after V5	±7 d	±7 d	±7 d	±7 d	Max 1 wk after V8	±7 d	±7 d	±7 d	±7 d	Max 1 wk after V11P	12-16 ds after V12P		
Subject participation card	X																					
Dispense/check subject diary	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense subject safety leaflet	X																					
Dispense IP (Viaskin Peanut) to the subject	X			X	X	X		X	X		X		X	X		X*		X				
Apply first patch at study site	X																					
Check used/unused IP drug dispensed to the subject				X	X	X		X	X		X		X	X		X		X	X		X	X
Check skin reaction under the patch and grading[21]	X			X	X	X		X	X		X		X	X		X		X	X		X	X
CCI [redacted]																						
Photographs of patch application site. Download photos taken by the subject's parent(s)/guardian(s) if any	X			X	X	X		X	X		X		X	X		X		X	X		X	X

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Study Assessments	Subjects randomized to Placebo in the EPITOPE study (Placebo + VP group)																				
		Treatment Period																	End of Study	Early Term.	Unsc. Visit
Visit Number	**V1[1]**	**PC**	**PC**	**V2**	**V3**	**V4**	**PC**	**V5**	**V6**	**PC**	**V7**	**PC**	**V8**	**V9**	**PC**	**V10P**	**PC**	**V11P**	**V12P**	**V13P**	**ET[2]**	**UV[3]**
Visit Day/Month	**D1**	**D4**	**D22**	**M1**	**M3**	**M6**	**M9**	**M12**	**M12 +7d**	**M15**	**M18**	**M21**	**M24**	**M24 +7d**	**M27**	**M30**	**M33**	**M36**	**M36 +7d**			
Time Window	Max 1wk after V11 of EPITOPE	±2 d	±2 d	±3 d	±7 d	±7 d	±7 d	±7 d	Max 1 wk after V5	±7 d	±7 d	±7 d	±7 d	Max 1 wk after V8	±7 d	±7 d	±7 d	±7 d	Max 1 wk after V11P	12-16 ds after V12P		
Review use of epinephrine auto-injector and Anaphylaxis Emergency Action Plan (if required)[22]	X			X	X	X		X			X		X			X		X				
Dispense 1% hydrocortisone ointment[23]	X			X	X	X		X			X		X			X		X				
Time under observation before discharge	3 h							3 h	3 h				3 h	3 h				3 h	3 h			

Abbreviations: d=day; ds=days; DBPCFC=Double-blind Placebo-Controlled Food Challenge; EOS=End of Study; ET=Early Termination; FAQLQ=Food Allergy Quality of Life Questionnaire; FAIM=Food Allergy Independent Measure; IP=Investigational Product; M=Month; PC= Phone Contact; SCORAD=Scoring Atopic Dermatitis; SPT=Skin Prick Test; UV=Unscheduled Visit; V=Visit; wk=week; wks=weeks.

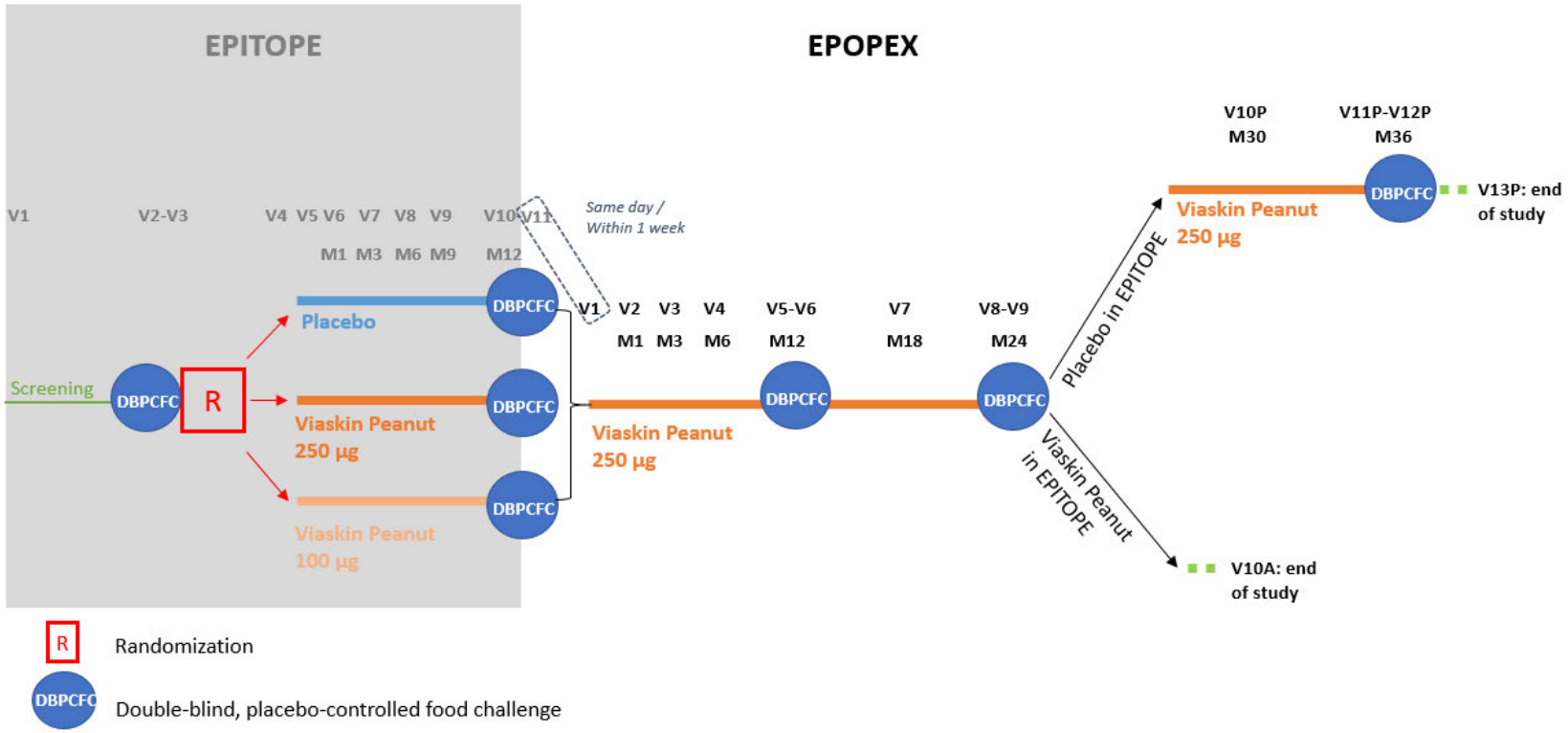
*Not applicable for subjects from the VP + VP group.

1. Visit 1 in the EPOPEX study is conducted on the same day as Visit 11 in the EPITOPE study or within a week of Visit 11. Therefore, the procedures common to both visits only need to be performed once.
2. Early Termination Visit is only for subjects withdrawing prematurely.
3. Procedures during the unscheduled Visit will be performed as deemed necessary by the Investigator.
4. Informed consent must be obtained after completion of Month 12 DBPCFC procedures in EPITOPE study, and before any procedure is started in EPOPEX.
5. New medical history and disease history as compared to the EPITOPE study screening visit.
6. Including a complete skin examination, body weight and height.

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7. Since Visit 1 in EPOPEX study is conducted the same day as Visit 11 in EPITOPE study or within a week of V11, values here are those obtained before starting the food challenge at Visit 11 in EPITOPE study.
8. These examinations are to be done before the DBPCFC. Additionally, they can be repeated during the DBPCFC procedure on both days anytime if judged necessary by the Investigator.
9. Vital signs measured in a sitting position include heart rate and systolic and diastolic blood pressure.
10. Pulmonary explorations will be performed at these timepoints only in subjects aged 4 years or older with a diagnosis of asthma. Spirometry is the preferred measurement. However, if the subject is not able to perform spirometry, then PEF should be measured instead.
11. Results obtained at Visit 10 in EPITOPE study can be used for this visit.
12. Total IgE, peanut-specific IgE, peanut-specific IgG4, IgE and IgG4 specific to peanut protein components: Ara h 1, Ara h 2, Ara h 3. IgE specific to cow's milk, egg white, house dust mites, and grass pollen will be collected at Visit 1, Visit 5, Visit 8, Visit 11P and in case of an early termination Visit.
13. For subjects who were in EPITOPE Part B, total IgE results obtained at Visit 10 in the EPITOPE study can be used for this visit. For subjects who were in EPITOPE Part A, total IgE assessment will be performed at this visit on blood samples drawn at Visit 10 in the EPITOPE study.
14. Laboratory tests performed centrally include hematology (hemoglobin, hematocrit, platelets, red blood cells, white blood cells and differential cell count) and biochemistry (alanine aminotransferase, aspartate aminotransferase, total bilirubin, total protein, blood urea nitrogen, creatinine).
15. For both FAQLQ and FAIM, Parental Form will be used. The translated forms of FAQLQ and FAIM will be completed in countries where they are available in local languages. EQ-5D-5L will be completed by the subject's parents/guardian.
16. Results of the FAQLQ/FAIM obtained at Visit 10 in the EPITOPE study can be used for this visit. Results of the EQ-5D-5L obtained at Visit 10 in the EPITOPE study can be used for this visit in subjects who were in EPITOPE Part B. The EQ-5D-5L must be completed at this visit for subjects who were in EPITOPE Part A.
17. All adverse events will be collected at all visits and during the phone calls, including adverse events/allergic symptoms during the DBPCFC.
18. All concomitant medications will be collected at all visits and during the phone calls, including concomitant medications given to treat allergic symptoms during the DBPCFC.
19. Ongoing concomitant medications from EPITOPE study will also be collected at Visit 1.
20. The information obtained at Visit 11 in EPITOPE study can be utilized here.
21. Check the reactions of the skin on the back of the subject and grade the severity of the local skin reactions. At Visit 1, grading is to be performed before patch application and 30 min, 1 h, 2 h and 3 h after patch application.
22. The expiry date of the auto-injector dispensed formerly will be checked and a new auto-injector will be provided to the subject prior to the product's expiry date, if needed.
23. Dispense as necessary.

STUDY DESIGN



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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LIST OF STUDY PERSONNEL

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Drug Manufacturing Company	CCI
	CCI
Drug Supply/Packaging Company	CCI

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse Event
AESI	Adverse Event of Special Interest
CRD	Cumulative Reactive Dose
CSR	Clinical Study Report
DBPCFC	Double-Blind, Placebo-Controlled Food Challenge
DSMB	Data and Safety Monitoring Board
e-CRF	Electronic Case Report Form
ED	Eliciting Dose
EDC	Electronic Data Capture
EPIT	EPicutaneous ImmunoTherapy
EPITOPE	EPITOPE study
EPOPEX	EPOPEX study
FAIM	Food Allergy Independent Measure
FAQLQ	Food Allergy Quality of Life Questionnaire
FEV_1	Forced Expiratory Volume in 1 second
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization
ICS	Inhaled Corticosteroids
IEC	Independent Ethics Committee
IgE, IgG4	Immunoglobulin E, Immunoglobulin G4 subtype
IND	Investigational New Drug
IP	Investigational Product
IRB	Institutional Review Board
IV	Intravenous
IWRS	Interactive Web Response System
LABA	Long-Acting β2-Agonist
LTRA	Leukotriene Receptor Antagonist

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MedDRA	Medical Dictionary for Regulatory Activities
OFC	Oral Food Challenge
OIT	Oral Immunotherapy
PEF	Peak Expiratory Flow
PT	Preferred Term
Q1, Q3	first quartile, third quartile
QoL	Quality of Life
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCORAD	Scoring atopic dermatitis
SLIT	Sublingual Immunotherapy
SOC	System Organ Class
SPT	Skin Prick Test
TEAE	Treatment-Emergent Adverse Event
US	United States
VP Group	Viaskin® Peanut Group
WHO	World Health Organization

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1 INTRODUCTION

1.1 Background

Food allergies represent a major public health concern, affecting approximately 5% of adults and 8% of children, with accumulating evidence of prevalence worldwide (1, 2).

Peanut allergy is one of the most common food allergies in children (3) and one of the major causes of fatal food-allergic reactions (4, 5). Its prevalence has increased steadily over the past decade, mostly in the Western world (6, 7). Based on published studies, the majority of childhood onset peanut allergy is not outgrown prior to adulthood (8, 9) and may recur in some desensitized individuals, making this allergy a life-long affliction in most cases.

Peanut allergy falls within the immunoglobulin E (IgE)-mediated category of food allergies, with immediate reactions triggered by circulating allergen-specific IgE upon exposure to the allergen (10). IgE-mediated allergic reactions to foods have a rapid onset, usually within a few minutes following exposure to the allergen. IgE-mediated allergic reactions to peanut provoke characteristic responses in the skin, gastrointestinal tract, upper and lower respiratory tract, and cardiovascular system. IgE-mediated reactions to food may also trigger generalized reactions, i.e., anaphylaxis, a severe, potentially fatal, systemic allergic reaction that occurs suddenly after contact with an allergy-causing substance (11).

Currently, there is no cure available for food allergy and specifically for peanut allergy. The mainstays of management remain strict allergen avoidance and management of severe systemic and/or life-threatening reactions/anaphylaxis with emergency medications (12, 13) (14). However, achieving successful avoidance is particularly challenging since peanut is a ubiquitous ingredient in many food products and undeclared contamination of foods with peanut occurs regularly. Accidental ingestion of peanut by peanut-allergic subjects may result in severe reactions and fatal outcomes (4). The dietary restrictions, the constant vigilance, and the anxiety about the risk of experiencing a reaction following inadvertent peanut ingestion, negatively impact the quality of life of peanut allergic subjects and caretakers. Therefore, preventative therapies are urgently needed for peanut allergy, to address the health risk and the associated social burden for peanut allergic subjects.

Various non-specific and food allergen-specific treatment approaches have been under investigation for the treatment of food allergy (15). Non-specific approaches to food allergy include the use of monoclonal anti-IgE antibodies, which might increase the eliciting dose (ED) threshold for the food allergen (16, 17). Food allergen-specific approaches in clinical development include oral immunotherapy (OIT), sublingual immunotherapy (SLIT), and epicutaneous immunotherapy (EPIT) (18). Sublingual immunotherapy and OIT have shown some encouraging efficacy results (clinical desensitization) in early clinical trials with a limited number of selected patients. Oral immunotherapy has shown evidence for inducing desensitization in most subjects, with immunologic changes over time (19–23). These advances are, however, hampered by the significant risk of side effects and occurrence of eosinophilic esophagitis in the context of OIT (24, 25, 25–28). Sublingual immunotherapy for peanut allergy has demonstrated evidence of clinical success, with some subjects showing signs of desensitization with a more satisfactory side effect profile compared to

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OIT and with significant immunologic changes noted during the first year of therapy (20, 29).

Epicutaneous immunotherapy represents an emerging allergen-specific immunotherapy approach acting through a repeated cutaneous administration of allergens, triggering an immunomodulatory effect on the immune system, by targeting especially Langerhans cells in the epidermis.

1.2 Summary of Findings with Viaskin Peanut

The investigational product (IP) DBV712 (Viaskin® Peanut) developed by DBV Technologies, consists of a cutaneous patch containing a solid deposit of a formulated peanut allergen extract. Comprehensive information on the IP is provided in the Investigator's Brochure (IB) (30).

Viaskin Peanut is a ready-to-use and easy-to-administer form of EPIT, particularly well-adapted to the pediatric population. It is intended to induce clinical desensitization/tolerization to peanut in subjects with documented hypersensitivity to peanut, thus reducing the risk of severe systemic reactions in case of accidental exposure.

Once applied onto the skin, the Viaskin® patch forms an occlusive chamber over the skin, and the water generated by the natural transepidermal water loss is kept within the chamber, which becomes water-saturated. This leads to the solubilization of the peanut allergens, enhancing their entry into the outer layers of the skin. Peanut allergens are locally processed by the antigen presenting cells of the outer layers of the skin that can migrate to the draining lymph nodes and activate immune responses and specific cytokine production.

Via the epicutaneous route of administration, Viaskin Peanut is intended to initiate the immunomodulatory processes, while minimizing the potential safety concerns associated with systemic exposure to peanut allergenic proteins.

The efficacy and safety of Viaskin Peanut have been evaluated in several Phase 2 and Phase 3 studies conducted in children and adults (Phase 2 studies only) diagnosed with peanut-allergy.

Details on the efficacy and safety results of individual clinical studies with Viaskin Peanut are provided in the IB (30).

Overall, consistent and robust efficacy results were observed across the clinical development of Viaskin Peanut. The primary efficacy results from the pivotal Phase 3 study (PEPITES/V712-301) demonstrated a statistically significant treatment effect versus placebo. Following 12 months of treatment with Viaskin Peanut 250 µg, 35.3% of children were responders, with a difference from placebo of 21.7% ($p<0.001$). The clinical efficacy of Viaskin Peanut in the pivotal Phase 3 study was further corroborated by higher peanut protein reactivity thresholds during the food challenges, i.e. increased ED and cumulative reactive dose (CRD) as compared to baseline in the active group, but not in the placebo group, and by the immunological changes over the 12-month treatment period. The efficacy results of the pivotal Phase 3 study are consistent with the results of the Phase 2 studies VIPES/V712-202 and CoFAR6/V712-204-E.

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Similar consistency throughout the clinical development program was evident in the safety profile of Viaskin Peanut. The most common adverse events (AEs) were local application reactions at the site of patch application (e.g., pruritus, erythema or edema). Serious treatment-related AEs and AEs of special interest (AESI) were infrequent episodes of mild to moderate anaphylactic reactions and grade 4 local skin reactions, that were managed with standard treatment and rarely led to study discontinuation. Overall subject compliance was high and treatment-related discontinuations were low.

The AEs considered expected with Viaskin Peanut, based on the comparative frequency analysis of AEs in completed placebo-controlled studies, the occurrence in open-labelled completed clinical trials, the pharmacological plausibility and non-clinical data, are provided in the reference safety information within the IB (30).

1.3 Study Rationale

The EPITOPE study was a Phase 3 study in peanut-allergic subjects aged 1-3 years designed for assessing the safety and local tolerance of 2 Viaskin Peanut doses (100 and 250 µg peanut protein) in part A, and for evaluating the efficacy and safety of a 12-month treatment period with Viaskin Peanut at the selected dose (250 µg) in part B.
In the first part of the study (part A), the safety of the 2 tested doses was compared with placebo. The Data and Safety Monitoring Board (DSMB) that evaluated safety data in EPITOPE concluded that the highest tested dose (250 µg) was equally safe as the lowest tested dose (100 µg). Therefore, the dose selected for the second part of EPITOPE (part B) was the 250-µg one, and subjects were randomized to this dose or to placebo.
The EPOPEX study will allow the subjects who completed the EPITOPE study to receive an additional 2 years (for subjects who were randomized to the active treatment in EPITOPE study) or 3 years (for subjects who were randomized to placebo in EPITOPE study) of treatment with Viaskin Peanut 250 µg. The prolonged treatment period aims at assessing a possible long-lasting treatment response. It will also allow to gather information about long-term safety and tolerability of Viaskin Peanut in young children and to increase the size of the global safety database of Viaskin Peanut.

1.4 Risk-Benefit Assessment

The primary safety concern for any allergen specific immunotherapy is related to the risk of inducing systemic, severe or life-threatening allergic reactions. The epicutaneous immunotherapy with Viaskin Peanut was developed with the objective to induce clinical desensitization/tolerization to peanut in peanut allergic subjects while minimizing the potential safety concerns associated with the systemic exposure to peanut allergenic proteins.

Data from completed clinical studies provide evidence of the efficacy and clinical relevance of Viaskin Peanut in the treatment of peanut allergy in children 4-11 years of age with a documented hypersensitivity to peanut.

Safety information from the completed and ongoing Phase 1 to Phase 3 studies have demonstrated a good safety profile for Viaskin Peanut dosed at 100 µg and 250 µg peanut proteins/patch in children aged 4-11 years. The expected local skin reactions triggered by Viaskin Peanut at the site of patch application, which are pruritus, erythema and edema, are

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managed and controlled satisfactorily by the subjects with topical medications containing corticosteroids.

Overall, the available information gathered from several clinical studies support the favorable risk/benefit profile of Viaskin Peanut for the treatment of peanut allergy in children 4-11 years of age. Viaskin Peanut addresses an unmet medical need in a serious/life-threatening disease in a pediatric population.

The EPITOPE study was the first study to evaluate the efficacy and safety of Viaskin Peanut in young subjects aged 1-3 years. During the first 3 months of EPITOPE study (Part A), no severe treatment-emergent adverse event (TEAEs) and no serious TEAEs occurred in any treatment group. After 3 months, 1 subject out of 51 randomized, withdrew from the study due to AE (based on blinded data). The DSMB concluded that there was no safety concern and that both evaluated doses (100 µg and 250 µg) were equally safe. The dose selected for the second part of EPITOPE, study (Part B), and consequently for EPOPEX study, is the 250-µg dose.

2 STUDY OBJECTIVE AND STUDY DESIGN

2.1 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.

2.2 Endpoints

2.2.1 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 after 1, 2 and 3 years of treatment in each group (VP+VP group, Placebo+VP group) and overall:

- 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.

  For the VP+VP group, the baseline ED is defined as the ED reached at the EPITOPE study entry.

For the Placebo+VP group, the baseline ED is the latest, valid ED in the EPITOPE study (i.e., Month 12).

- Proportion of subjects reaching a cumulative dose of at least 1444 mg peanut protein at the post-baseline DBPCFCs;
- Proportion of subjects reaching a cumulative dose of at least 3444 mg peanut protein at the post-baseline DBPCFCs;
- 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), which is the percentage of subjects who pass the post-baseline DBPCFCs;
- Mean and median CRD of peanut protein;
- Mean and median ED of peanut protein.

Details of the assessment of the efficacy endpoints are provided in Section 6.1 and details of the corresponding statistical analysis are provided in Section 8.5.

2.2.2 Safety Endpoints

The following safety endpoints will be analyzed:

- Adverse Events and TEAEs by System Organ Class (SOC) and Preferred Term (PT);
- Treatment-emergent adverse events by maximum severity and by maximum duration and relatedness to the IP;
- 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 be assessed over 3 years of treatment:

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

The safety endpoints will be evaluated in the overall Safety population using the rescheduling rules and by treatment group (VP+VP / Placebo+VP).

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Details of the assessment of the safety endpoints are provided in Section 6.2 and details of the corresponding statistical analysis are provided in Section 8.6.

2.2.3 Other Exploratory Endpoints

The following other exploratory endpoints will be evaluated over 3 years of treatment in each group (VP+VP group, Placebo+VP group) and overall using the rescheduling rules:

- 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 assessment of the exploratory endpoints are provided in Section 6.4 and details of the corresponding statistical analysis are provided in Section 8.7.

3 STUDY DESIGN

3.1 Overall Study Design

This is an open-label, follow-up study for subjects who completed the EPITOPE study.

Eligible subjects will be offered enrollment in this follow-up study to receive Viaskin Peanut at the dose selected during EPITOPE study, i.e., 250 µg, for 2 additional years if they were previously randomized to Viaskin Peanut 100 µg or 250 µg in the EPITOPE study, or for 3 additional years if they were randomized to placebo in the EPITOPE study. The treatment period will be followed by a 2-week follow-up period.

Eligible subjects who decide to participate in the EPOPEX follow-up study will transition into this study during Visit 11 of the EPITOPE study. Subjects continuing into the EPOPEX study will not perform Visit 12 of EPITOPE study. Visit 11 of the EPITOPE study and Visit 1 of the EPOPEX study will be conducted concurrently, as far as possible; however, considering practical aspects for the center and for the subject's family, Visit 1 might be conducted within a week of Visit 11.

The treatment group subjects were randomized to during the EPITOPE study, will remain blinded until EPITOPE database is locked and the EPITOPE study results are unblinded.

As the EPITOPE screening period was longer than initially expected some subjects from the part B will reach their Visit 9 (Month 24 = 2 years of treatment in EPOPEX) before the EPITOPE database lock.

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Without knowing their treatment arm in EPITOPE at the time of their visit 9, there will be no possibility to know if these subjects need an additional year of treatment to reach 3 years of active treatment in total.
All the impacted subjects (having their V9 before the unblinding of the EPITOPE study) will continue their treatment until the visit 10P (Month 30).
At the time of the Visit 10P the treatment allocation will be known:

- Subjects who received active treatment in the EPITOPE study (VP + VP group) will end their treatment at the visit 10P; in total they will receive 42 months of active treatment instead of 36 months.
- Subjects who received the placebo in the EPITOPE study (Placebo + VP group) will then continue until their visits 11P and 12P (Month 36) and will have no impact on their study duration.

Double-blind placebo-controlled food challenges will be conducted after 1, 2 and 3 years of EPIT treatment with Viaskin Peanut. As such, subjects in the Placebo+VP group will undergo 3 DBPCFCs in the EPOPEX study, after 1, 2 and 3 years of active treatment. Subjects in the VP+VP group will undergo 2 DBPCFCs in the EPOPEX study, after 2 and 3 years of active treatment (the DBPCFC performed at the end of the EPITOPE study corresponds to the DBPCFC after 1 year of active treatment).

The overall study duration for each subject is approximately 2 years and 1 month for subjects previously randomized to Viaskin Peanut in the EPITOPE study and 3 years and 1 month for subjects previously randomized to placebo in the EPITOPE study (including visit windows). As described above subjects having their visit 9 before the EPITOPE unblinding who were randomized to Viaskin Peanut in EPITOPE study will extend their participation in EPOPEX to 2 years and 7 months and will receive 42 months of active treatment in total.

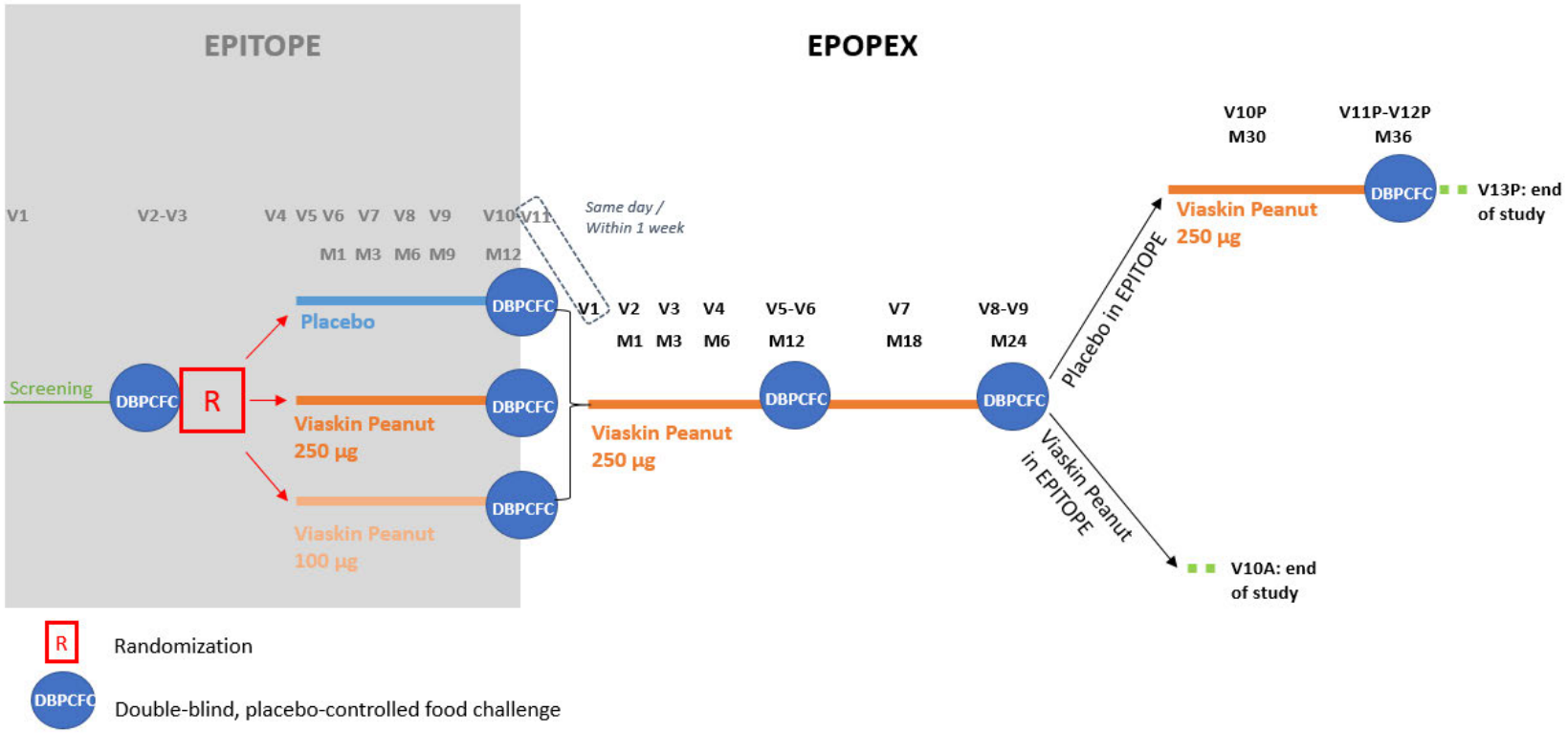
An interim analysis is planned once all subjects from the VP+VP group have completed the DBPCFC at Year 3.

A DSMB composed of independent experts (same DSMB members as in the EPITOPE study) in food allergy will review study safety data at specific intervals during the study and on an *ad hoc* basis.

During their participation in the study, subjects will be instructed to remain on a strict peanut-free diet. Reintroducing peanut into the subject's diet at the end of their participation in the study will be left to the Investigator's decision. This decision, this information will be collected in the electronic case report from (e-CRF).

The overall study design is presented in Figure 1.

Figure 1. Study Design



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

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

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3.2 Discussion of the Study Design

The EPOPEX study is a follow-up for subjects who have completed the EPITOPE study.

The results of the follow-up of a Phase 2 study have suggested that 2 additional years of treatment with Viaskin Peanut 250 µg improved the proportion of treatment responders compared to the proportion reached after 12 months of treatment (30). These results, together with preliminary evidence from literature (31), are in favor of long-term immunotherapy effect for treating peanut-allergic patients. The EPOPEX follow-up study will enable subjects to receive 3 years of active treatment overall and should therefore bring additional insights on the benefit of long-term EPIT treatment.

The DBPCFC has been selected for assessing the treatment response since it is recognized as the "gold standard" for the evaluation of food allergy both by the medical community and by regulatory bodies (1, 32). Subjects participating in the present study already underwent DBPCFCs in the EPITOPE study. A DBPCFC was performed after 12 months of placebo or active treatment in the EPITOPE study and will be repeated every 12 months in the EPOPEX study, until subjects have reached 3 years of treatment with Viaskin Peanut. This sequence of peanut food allergy evaluation should demonstrate the improvement of desensitization to peanut induced by Viaskin Peanut over time.

The EPOPEX study is designed as a single-arm, open-label, uncontrolled study given that long-term placebo treatment beyond 12 months is not appropriate. Hence, subjects who received placebo in the EPITOPE study will switch to active treatment with Viaskin Peanut.

For ensuring the blind of the EPITOPE study data analyses, the subjects entering in the EPOPEX study will remain blinded regarding their treatment group in the EPITOPE study until the database is locked and the results become unblinded. The unblinding is scheduled to occur before the Month 24 visit, so that only subjects in the Placebo+VP group prolong their study treatment by 12 additional months.

As a consequence, a step by step increase of patch application duration will be followed by all subjects, whatever the treatment, active or placebo, they received during the EPITOPE study. This procedure will ensure a good monitoring of the Viaskin Peanut tolerability in the newly treated subjects, without imposing substantial constraints for the subjects who had already initiated Viaskin Peanut treatment in the EPITOPE study.

The study design is compliant with the International Council for Harmonization (ICH) guideline on general considerations for clinical studies (33).

4 STUDY POPULATION

All subjects who completed the EPITOPE study up to Visit 11 (inclusive) will be eligible to participate in the EPOPEX study, if they meet all the inclusion criteria and none of the exclusion criteria listed below. Study participation will require a signed consent from a legally authorized representative.
All subjects and parents/guardians will continue with their usual peanut-free diet and label reading of food products to avoid as much as possible any accidental peanut consumption for the duration of the study.

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4.1 Inclusion Criteria

Subjects will be enrolled into this study only if they meet all the following criteria:

1. Signed informed consent form (ICF) by the subject's parent(s)/guardian(s). This consent should be signed after completion of Month 12 DBPCFC procedures in EPITOPE study, and before any procedure in EPOPEX study is started;
2. Subjects who completed the EPITOPE study, with a completed and documented DBPCFC at Month 12 (Visit 10 and Visit 11);
3. Parents/guardians and subjects willing to comply with all study requirements during the subject's participation in the study.

4.2 Exclusion Criteria

Subjects will be enrolled into this study only if they meet none of the following criteria:

1. Subjects who developed a severe anaphylactic reaction (see APPENDIX 5) during the DBPCFC at Month 12 (Visit 10 or Visit 11) in the EPITOPE study requiring a tracheal intubation or leading to a cardiac arrest and/or to coma. Other cases of severe anaphylaxis will be considered eligible to participate in the EPOPEX study;
2. Any clinically significant disease which in the judgment of the Investigator may preclude safe participation or strict compliance with the protocol procedures;
3. Generalized dermatologic disease (e.g., active atopic dermatitis, uncontrolled generalized active eczema, ichthyosis vulgaris) extending widely on the skin, especially on the back, with no intact zones to apply the patches;
4. Subjects who developed hypersensitivity to materials and/or excipients of the Viaskin® patch;
5. Subjects who developed hypersensitivity to excipients of the food challenge formula (other than peanut proteins) used in the EPITOPE study or confirmed allergy to apple;
6. Subjects who failed to complete the DBPCFC at Month 12 in the EPITOPE study due to any reason, including clear aversion to the food formula matrix;
7. Inability to discontinue short-acting antihistamines or long-acting antihistamines for the minimum wash-out periods required (depending on half-lives, as specified in APPENDIX 4) prior to the SPT or the DBPCFC;
8. Diagnosis of asthma that has evolved and now fulfills any of the criteria defined as follows:
   - Uncontrolled asthma (as per Global Initiative for Asthma [GINA] 2018 guidelines (34); see APPENDIX 3);
   - Asthma requiring controller treatment step 3 or higher (as per GINA 2018 guidelines (34): either moderate [double low dose] of inhaled corticosteroid [ICS], or association of ICS with leukotriene receptor antagonist [LTRA]; see APPENDIX 3);
   - Prior intubation/mechanical ventilation for asthma in the past year.

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Asthmatic subjects with the following treatment options are eligible:

- No controller treatment (GINA step 1);
- Controller treatment monotherapy (GINA step 2): daily or short-term course (intermittent) low dose ICS or LTRA.

9. Presence of more than 3 episodes of wheezing in the past year (each lasting more than 10 consecutive days, apart from colds) or presence of respiratory symptoms (wheezing, cough, heavy breathing) between these episodes, and/or other respiratory symptoms suggesting either undiagnosed asthma or asthma not controlled by asthma treatment (as per GINA 2018 guidelines (34)).
10. Past or current disease(s) which, in the opinion of the Investigator or the Sponsor, may affect the subject's participation in this study, including but not limited to past or active eosinophilic gastrointestinal disorders, autoimmune disorders, immunodeficiency, malignancy, uncontrolled diseases (e.g., hypertension, psychiatric, cardiac), or other disorders (e.g., liver, gastrointestinal, kidney, cardiovascular, pulmonary disease, or blood disorders).
11. Any disease in which epinephrine is contraindicated such as coronary artery disease, uncontrolled hypertension, or serious ventricular arrhythmias.
12. Diagnosis of mast cell disorders including mastocytosis or urticaria pigmentosa as well as hereditary or idiopathic angioedema.
13. Subject receiving β-blocking agents, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, calcium channel blockers or tricyclic antidepressant therapy.
14. Subject who received in the past year or planning to receive anti-tumor necrosis factor drugs or anti-IgE drugs (e.g., omalizumab) any biologic immunomodulatory therapy, cyclosporine or other immunosuppressive drugs within. Topical calcineurin inhibitors are permitted.
15. Subject receiving or planning to receive any other type of immunotherapy to any food (e.g., oral immunotherapy, sublingual immunotherapy, specific oral tolerance induction) or any aeroallergen or venom immunotherapy during their participation in the study.
16. Subjects or parent(s)/guardian(s) with obvious excessive anxiety and unlikely to cope with the food challenge procedures or unable to follow the protocol requirements.
17. A history of high non-compliance during the EPITOPE study (i.e., subjects not applying the patches for 60 or more days in total and not applying the patches 30 or more consecutive days during the EPITOPE study) or subjects unable to perform the DBPCFC.
18. Current participation in another clinical study, other than the EPITOPE study.
19. Subjects being in any personal relationship or dependency with the Sponsor and/or the Investigator or the study staff.

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4.3 Subject Withdrawal and Replacement

4.3.1 Criteria for Withdrawal from Study Treatment and Study

Subjects **may withdraw** from the study at any time without penalty and for any reason without prejudice to their future medical care.

Subjects **must be withdrawn** from the study treatment under the following circumstances:

- Severe (stage 3) anaphylaxis (see APPENDIX 5) related to Viaskin Peanut application;
- More than 2 epinephrine injections for an AE related to patch application (not occurring during the DBPCFC nor related to an accidental food allergen consumption);
- The subject is unwilling to continue in the study (consent withdrawal);
- The Sponsor, Regulatory Authorities, or Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) for any reason, stop the study.

Subjects **may be required to be withdrawn** from the study treatment or the study after discussion with the Investigator and/or Sponsor for the following reasons:

- Occurrence of AE(s);
- Severe "maculo-papular rash" or severe generalized "atopic dermatitis", outside of patch application area, which failed to be controlled by adequate corrective treatments (including topical corticosteroids) and despite several study treatment interruptions;
- At the discretion of the Investigator, if she/he decides that it is in the subject's best interest to be withdrawn from the study;
- Lack of compliance with protocol requirements, study treatment or procedures;
- The subject fails to return to the clinic for scheduled visits and parents/guardians do not respond to telephone or written attempts at contact (lost to follow-up);

In all cases, the primary reason for withdrawal, must be recorded in the e-CRF.

4.3.2 Data Collection and Follow-up after Withdrawal

If a subject is prematurely withdrawn from the study treatment for any reason before completing all study visits, the Investigator must make every effort to perform the evaluations described for the Early Termination Visit (see Section 7.2.20). The Investigator must furthermore complete all appropriate e-CRF pages, providing the date and explanation for the subject's withdrawal/discontinuation. When indicated, the Investigator must arrange for appropriate follow-up and/or alternative medical care of the discontinued subject.

If the subject fails to attend a scheduled End of Study Visit, there will be at least 2 documented attempts to contact the subject's parents/guardians via telephone and written communication. If these receive no reply, the subject will be considered as lost to follow-up.

4.3.3 Replacement of Withdrawn Subjects

The EPOPEX study is the follow-up of the EPITOPE study. Hence, subjects who withdraw prematurely will not be replaced.

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4.3.4 Study Stopping Rules

The study will be suspended pending an expedited safety review by the DSMB if any of the following occur:

- Any death related to patch dosing;
- More than 1 case of severe (stage 3) anaphylaxis (see APPENDIX 5) related to patch application (not occurring during the DBPCFC);
- More than 3 subjects requiring more than 2 injections of epinephrine for an AE confirmed as related to patch application (not occurring during the DBPCFC nor related to an accidental food allergen consumption).

Upon the DSMB safety review, 1 of the following outcomes will be determined:

- The study may continue without modification;
- The study may continue with modifications as prescribed by the DSMB;
- The study should be discontinued.

The study will be prematurely stopped if the Sponsor, Regulatory Authorities, or IECs/ IRBs for any reason, request to stop the study.

4.4 Planned Sample Size and Number of Study Centers

All eligible subjects who completed the EPITOPE study will be offered enrollment into the EPOPEX study. It is planned that all sites involved in the EPITOPE study will participate in this follow-up study.

4.5 Subject Identification and Randomization

4.5.1 Subject Identification

Subjects in the EPOPEX study will keep the same subject number used in the EPITOPE study.

4.5.2 Randomization Scheme

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 Viaskin Peanut 250 µg treatment, according to their prior treatment allocation in the EPITOPE study. There will be no randomization in the study.

5 INVESTIGATIONAL PRODUCT(S)

5.1 Identity

The IP, DBV712, is a cutaneous patch (Viaskin® patch) containing a solid deposit of a formulation of peanut allergen extract. CCI

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The other components of the IP are inactive excipients: CCI

Viaskin Peanut will be manufactured by CCI or CCI and labeled, packaged and released for clinical use by CCI in accordance with the requirements of Good Manufacturing Practices.

5.2 Packaging, Labeling and Storage

The IP will be packaged and labeled by CCI in accordance with applicable local regulatory requirements. Treatment boxes will be dispensed to subjects at each visit, with enough quantity of Viaskin® patches to cover the period between 2 consecutive visits.

The labeled and packaged study treatment must be stored in accordance with the Sponsor's instructions (below 25°C [77°F] and should not be frozen). Shipments from depots to clinical sites will be performed at temperature controlled with a temperature monitoring device.

Upon receipt of a shipment request via the Interactive Web Response System (IWRS), the IP will be shipped to the clinical site. The site pharmacist or any other staff member designated for this task will receive and store the IP until the time of dispensing. Until dispensed by the Investigator to the subjects, the IP will be stored in a securely locked area, accessible to authorized personnel only. At the end of the study, or at times designated by the Sponsor, and after complete accountability, the site pharmacist or the designated person will be responsible for preparing the return of the IP to the study treatment distributor. Destruction of the IP on-site is not allowed.

5.3 Investigational Product Accountability

The Investigator is responsible for maintaining accurate IP accountability records throughout the study. Each site will have to complete a site IP accountability log and an individual IP accountability log for each subject. These records should include the amounts and dates that IP supplies were received on-site, dispensed to the subject, returned by the subject, and returned to the IP distributor. Any discrepancy must be documented.

Investigational product accountability will be monitored by a site monitor during site monitoring visits and at study completion.

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Each IP dispensing will be performed via the IWRS.

5.4 Blinding and Breaking the Blind

The EPOPEX study is an open label study where all subjects will receive Viaskin Peanut 250 µg. The IWRS will be used to allocate treatment to subjects in the study.

Subjects in the EPOPEX study will keep the same subject number used in the EPITOPE study. The IWRS will allocate the treatment box from the stock of treatment boxes available at site. Each treatment box has its specific treatment kit number. Further instructions will be provided in a separate IWRS Manual.

Of note, the treatment group subjects were randomized to during the EPITOPE study, will remain blinded until EPITOPE database is locked and the EPITOPE study results become unblinded.

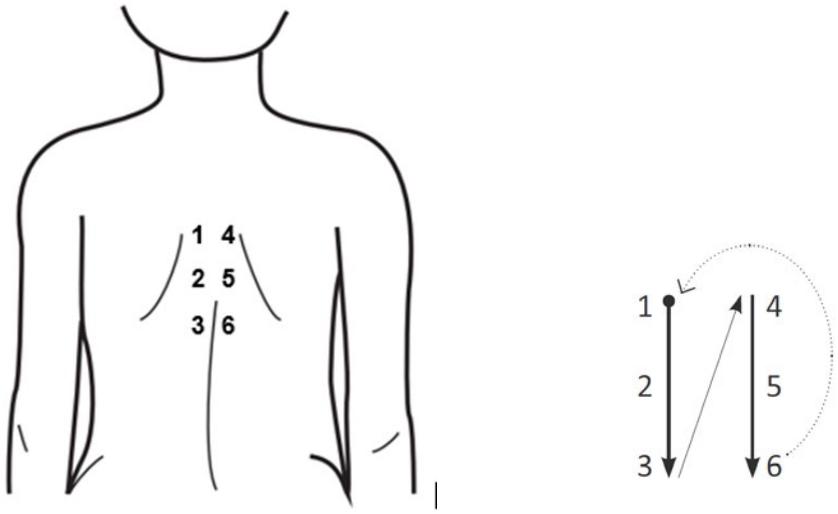
5.5 Administration

During the 24- or 36-month treatment period, except for the first 4 weeks (see below), the Viaskin® patch will be applied on the skin for 24 hours (± 4 hours of allowance) every day and renewed daily (i.e., 1 new patch per day).

The location of patch application is the inter-scapular area of the back. The specific place where the patch is applied will represent a zone. Six zones in total will be used and rotated for application of the patches on the inter-scapular area on the back, 3 on each side of the spine (see Figure 2). The first Viaskin® patch will be applied on zone 1, the second on zone 2 (after removal of the first patch), and so forth until all 6 zones have been used. After zone 6, dosing restarts with zone 1 and continues sequentially.

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Figure 2: Schematic Representation of Viaskin® Patch Application on the Back of the Subjects



To enhance the tolerance at treatment initiation, especially for the former placebo subjects crossing over to receive the active treatment, the duration of daily application of the patch will be progressively increased for the first 4 weeks as follows:

- 2 hours (± 30 min) per day during the 1st week (from Day 1 through Day 7);
- 4 hours (± 30 min) per day during the 2nd week (from Day 8 through Day 14);
- 8 hours (± 1 hour) per day during the 3rd week (from Day 15 through Day 21);
- 12 hours (± 2 hours) per day during the 4th week (from Day 22 through Day 28).

From the 5th week onwards (Day 29), the duration of the daily application will be 24 hours. Any daily duration of patch application of 24 hours ± 4 hours will be allowed

Some subjects may have a higher skin reactivity at treatment initiation, leading to uncomfortable sensations or intense pruritus. Although these local reactions usually decrease over time as far as the treatment continues, some subjects may have difficulties in bearing them. In these subjects, it is recommended to remove the patch as soon as the subject starts complaining, to clean and to wash the skin area and if necessary use topical corticosteroids. The next patch will be applied the following day on the next skin zone, as scheduled.

The daily duration of patch application at treatment initiation can be adapted and possibly extended beyond the 4 week-period described above.

The patch should be applied daily, preferably at approximately the same time every day. Application can be in the morning or in the evening, whatever schedule is the most convenient to the subject and/or parent(s)/guardian(s).

If possible, the subjects could take advantage of their shower (or bath) time to change the patch. The previous patch should be removed before the shower (or bath) and discarded.

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The new patch should be applied a few minutes after the shower (or bath) and after careful drying of the skin. If the subject does not take a shower (or bath) daily, it is recommended that the zone to which the patch will be applied be cleaned with a moist disposable napkin or tissue and dried prior to application.

When removing a patch or in case the patch comes off accidentally, it is recommended that the subject or the subject's parent(s)/guardian(s) thoroughly wipe off the zone with a moist disposable napkin or disposable tissue and wash their hands to prevent any accidental transmission of the allergenic proteins.

A patch that has been removed prematurely or falls off must not be re-applied. A patch that has been removed prematurely for any reason other than safety reasons or has fallen off inadvertently within 2 hours of being applied can be replaced by another patch and applied at the same location, after thorough wiping of the zone with a moist disposable napkin or tissue. However, should the patch be removed or fall off after more than 2 hours of application, another patch will not be applied on the same day and the subject will have to wait for the next time of application the following day to apply the subsequent patch.

The first application of the Viaskin® patch will be performed in a hospital setting at the study site, with appropriate and readily available emergency treatment (epinephrine) and resuscitation equipment. After the first application of the Viaskin® patch at the study site, all subjects will be monitored for 3 hours before being discharged, to check and grade any reactions under or around the patch

On Day 4 and on Day 22, specific phone contacts will be made to the subject's parent(s)/guardian(s) to assess the safety of patch application. If required, the subjects may need to come to the site earlier than planned to be seen and evaluated by the Investigator.

5.5.1 Adjustment of Patch Application in Case of Local or Systemic Reactions

When subjects are unable to apply the patch for the recommended duration because of local intense or severe reactions under or adjacent to the patch site, the patch should be removed immediately, the site of application should be wiped with a moist disposable tissue/napkin and a topical corticosteroid medication might be applied topically to treat the reaction. It is recommended that the parent(s)/guardian(s) take a photo to document these intense or severe reactions.

In the specific case of local intense or severe reactions, it is mandatory to apply the next patch only the following day, on the next zone; no other patch must be applied the same day. In case of re-appearance of the local intense or severe reactions after application of the next patch the following day, the same process is repeated every day. The daily duration of patch application should be adjusted/reduced as necessary, and subjects may need more than 4 weeks before they can apply and tolerate the patch for the full 24 hours daily.

In case of any suspected systemic reactions related to patch application (including cutaneous reactions distant from the sites of patch application), the patch should be removed immediately. A treatment can be administered to treat the systemic or local reactions: topical corticosteroids, antihistamines, oral corticosteroids or other anti-allergic drugs, as deemed necessary by the Investigator. The next patch will only be applied the following day.

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The subject's parent(s)/guardian(s) will be instructed to contact the Investigator in case of systemic or intense or severe local reactions lasting for more than 1 day or any unexpected reactions during the treatment period, particularly in case of appearance of vesicles under the patch or close to the site of patch application. It is recommended that the parent(s)/guardian(s) take a photo to document these intense or severe reactions.

Appearance of any vesicles (grade 4) or ulcerative skin lesions or any other significant skin lesion seen under the patch (while the patch is still applied on the skin or upon removal of the patch) which could potentially lead to skin barrier disruption at sites of patch application, will be cautiously managed and followed-up.

Subject's parent(s)/guardian(s) will be instructed to take a photo in case of appearance of any vesicles or ulcerative skin lesions. In these rare specific cases, subjects should transiently discontinue patch application and return to the site for evaluation and treatment of the wounded area, as well as for the next patch application.

Upon re-application of the new patch, the subject should remain at the site for 1 hour before being discharged. The site must contact the subject's parent(s)/guardian(s) by phone the day after this visit to ensure that no additional local blisters or vesicles developed and to confirm that the treatment can continue normally. The zone with vesicles or ulcerative skin lesions should not be used for patch application until it has completely healed.

In case the subject has experienced allergic reaction(s) after accidental ingestion of peanut containing-food, the new patch application(s) must be skipped until allergic symptoms have resolved.

5.5.2 Safety Precaution Information

A safety leaflet with precautions for using the Viaskin® patch and instructions to follow in case of any safety issue will be given to subject's parent(s)/guardian(s). This safety leaflet will specify at least the following information:

1. Instructions and procedures to apply the patch safely and correctly in the back of the subject;
2. Instruction to call the investigational site staff in case of intense or severe local reactions lasting for more than 1 day or any unexpected reactions during the treatment period, particularly any appearance of vesicles/blisters under the patch or close to the area of patch application and recommendation to take photos of the site of application to document such a situation;
3. Instruction to call the investigational site staff in case of occurrence of chicken pox or measles. In this situation, the patch application is interrupted until recovery;
4. Instructions to follow in case of active eczema extending on the back: stop applying the patch until recovery from the active eczema;
5. Anaphylaxis Emergency Action Plan in case of a suspected anaphylactic reaction and how to administer the epinephrine auto-injector to rapidly treat the reaction;

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5.6 Compliance

It is the Investigator's responsibility to ensure that the subject's parent(s)/guardian(s) are correctly instructed on how to store and apply the IP. The IP should be dispensed by the Investigator, or by a qualified individual under the Investigator's supervision. An up-to-date drug accountability record must be maintained (see Section 5.3). Records of IP used and intervals between visits will be kept during the study. Investigational product accountability will be monitored by a site monitor during site monitoring visits and at study completion. Subject's parent(s)/guardian(s) will be asked to return the unused IP (in their boxes) when they come back for their study visits. All unused IP and used IP (empty boxes) should be returned at the end of the study to the study IP distributor.

At each visit, prior to IP dispensing, the previously dispensed IP will be retrieved by the Investigator and the compliance will be assessed. Compliance at each visit will be calculated taking into account the total number of patches applied since the last visit versus the number of days in that time frame. Subjects exhibiting poor compliance (below 80%) at any specific time point during the treatment period should be counseled on the importance of good compliance to the study dosing regimen.
Subjects who are persistently non-compliant with the study treatment will be withdrawn from the study (see Section 4.3.1).

5.7 Prior and Concomitant Medications

Any medication used in the last 6 months up to the time of transition to the EPOPEX study and stopped prior to Visit 1 is considered a prior medication. Any medication taken by the subject other than the IP (including herbal and other non-traditional remedies) from the study start until the end of the study, is considered a concomitant medication.

Ongoing concomitant medications from the EPITOPE study will be recorded at entry into the EPOPEX study. At each subsequent study visit, subjects will be asked which concomitant medications they are currently taking. All concomitant and prior medications must be recorded in the e-CRF. Of note, prior or concomitant medication prescribed to a subject but not actually taken or administered should not be reported in the e-CRF (e.g., the epinephrine auto-injector prescribed for use in case of anaphylaxis but never injected).

5.7.1 Permitted Concomitant Medication

- Application of a topical corticosteroid and topical calcineurin inhibitors to treat any local condition (eczematous lesions, pruritus, edema, etc.) is allowed and should be recorded as concomitant medication.
- A topical medication (ointment, gel, cream) with 1% hydrocortisone or equivalent will be distributed to each subject at Day 1 and at subsequent visits, if necessary, for treatment of local reactions to the Viaskin® patch, especially if the previous given one has expired or has been entirely utilized. In case the 1% hydrocortisone topical medication is not sufficient to treat the local reaction, a topical medication containing a more potent corticosteroid can be prescribed and locally applied in accordance to the local approved indication of each product for the subject age class.

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- Oral antihistamines or oral corticosteroids are allowed to treat conditions determined as being allergic reactions and should be recorded as concomitant medications. These treatments should be limited in duration and stopped as soon as the condition has resolved. The Investigator will determine the best choice of treatment, the dose and the regimen according to the subject's age, and the type and the degree of severity of the reactions. Cetirizine is recommended as the oral antihistamine of choice.
- The subject's parent(s)/guardian(s) will keep the intramuscularly injectable epinephrine auto-injector (EpiPen® or any other brand name available in the different countries at the right dosages) they had been provided with during the EPITOPE study to be used in case of symptoms of anaphylaxis. The expiry date of the subject's intramuscularly injectable epinephrine auto-injector will be checked at each study visit up to the subject's final DBPCFC, and a new epinephrine auto-injector will be provided to the subject's parent(s)/guardian(s) prior to product expiry. The epinephrine auto-injector will also be replaced if used. The Investigator will remind the subject's parent(s)/guardian(s) when and how to inject epinephrine according to the Anaphylaxis Emergency Action Plan. Any use of injectable epinephrine should be recorded as a concomitant medication.

All other treatments prescribed by the Investigator or any other physician to treat any conditions are also permitted. Medications that are not noted in Section 5.7.2 are also permitted.

5.7.2 Prohibited Prior and Concomitant Medication

Prohibited prior and concomitant are the following:

- Asthma treatment:
  - For children aged 5 years or younger, the following are prohibited:
    - Moderate daily dose of ICS or higher (i.e., ≥2 times "low dose"; see APPENDIX 3);
    - Combination therapy of ICS with LTRA;
    - Combination therapy of ICS with a long-acting inhaled β2-agonist (LABA). Note that the use of LABA is not recommended in children below the age of 5 years as per GINA 2018 guidelines (34).

    Daily low dose of ICS and short course of ICS indicated for treating either asthma or acute bronchitis are permitted.
  - For children above the age of 5 years, the following are prohibited:
    - Medium daily dose of ICS (see APPENDIX 3);
    - Combination therapy of ICS with LABA;
    - Other treatment regimens corresponding to step 4 or step 5 for controlling asthma.
- β-blocking agents, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, calcium channel blockers or tricyclic antidepressant therapy, during study participation;

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- Anti-tumor necrosis factor drugs or anti-IgE drugs (such as omalizumab) or any biologic immunomodulatory therapy are prohibited if taken within 1 year prior to Visit 1, or during study participation;
- Cyclosporine or other immunosuppressive agents are prohibited if used within 1 year prior to Visit 1, or during the study participation. Topical calcineurin inhibitors are permitted;
- Systemic corticosteroids used for more than 4 weeks are not permitted during the study. If this situation is encountered, the asthma control status should be checked or if the corticosteroid need is related to another disease, the continuation of the subject in the study should be re-assessed;
- Any immunotherapy to any food (for example EPIT or OIT or SLIT or specific oral tolerance induction) is not permitted during the study;
- Aeroallergen immunotherapies are not permitted during study participation.

Before the first day of the DBPCFC:

The minimal washout period for short and long acting antihistamines (refer to APPENDIX 4) and long-acting β2-agonists (36 hours prior to the DBPCFC) will have to be respected.

Regarding systemic corticosteroids, the following minimal wash-out period will be applied:

- Subjects should not have received any course of systemic short-acting/intermediate-acting corticosteroids of more than 3 days within 2 weeks of the DBPCFC, or any course of systemic long-acting corticosteroids within 2 weeks of the DBPCFC. In this case, the DBPCFC should be delayed, to allow for 2 weeks of corticosteroid wash-out.
- In case the subject has received a systemic long-acting corticosteroid for asthma before the DBPCFC, the food challenge should be delayed, to allow for 4 weeks of wash-out.
- If a subject has a reaction during the first day of the DBPCFC that requires treatment with systemic corticosteroids, the subject has to wait at least 3 days before performing the second day of the DBPCFC.

6 VARIABLES AND METHODS OF ASSESSMENT

The timepoints of the planned study assessments are summarized in the schedule of procedures (see page 9).

6.1 Efficacy Variable: Double-Blind, Placebo-Controlled Food Challenge to Peanut

6.1.1 General Principles for Conducting Double-Blind, Placebo-Controlled Food Challenges

Double-blind, placebo-controlled food challenges to peanut will be conducted after 1, 2 and 3 years of active treatment. Thus, subjects in the Placebo+VP group will undergo 3 DBPCFCs and subjects in the VP+VP group will undergo 2 DBPCFCs in the EPOPEX study (the DBPCFC performed at the end of the EPITOPE study corresponds to the DBPCFC after 1 year of active treatment in these subjects).

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The DBPCFC to peanut will be performed to assess the following endpoints: proportion of subjects reaching an ED ≥1000 mg, proportion of treatment responders, proportion of subjects reaching a cumulative dose ≥ 1444 mg peanut protein, ≥ 3444 mg peanut protein, proportion of subjects unresponsive to the highest dose of peanut protein, mean and median ED and CRD of peanut protein.

The food challenges will occur over 2 days, up to 7 days apart. The subject will be gradually fed with increasing amounts of standardized blinded oral formulas containing either peanut protein or without any peanut protein. The child will receive one of the two formulas on the first day, and the other formula on the second day, according to the random order of the challenges. Challenges must take place under direct medical supervision in a hospital/clinic setting with resuscitation equipment and emergency medications and staff immediately available. An intravenous (IV) line can be established prior to the challenge when judged necessary by the Investigator. In that case, a local anesthetic cream can be used for placing the IV line. If a site prefers to have the subjects come to the hospital the day before the conduct of the DBPCFC, to get them ready for the following day, or have the subjects stay at hospital after the DBPCFC for practical reasons, this is allowed and will not be considered an SAE.

If the subject is experiencing a concomitant disease such as a rhinitis, bronchitis, gastrointestinal infection or acute asthma flare-up, which temporarily contra-indicates the performance of the DBPCFC, the test will be postponed until at least 7 days following recovery.

Subjects should wash out any antihistamines for the minimum period of time specified in the table in APPENDIX 4 prior to performing the DBPCFC.

Subjects will not be allowed to use long-acting β2-agonists within 36 hours prior to the DBPCFC. Subjects who received more than a 3-day course of systemic short/intermediate-acting corticosteroids within 2 weeks of the DBPCFC or any course of systemic long-acting corticosteroids within 2 weeks of the DBPCFC should have the DBPCFC delayed to allow for 2 weeks of corticosteroid wash-out (in case the subject has received a systemic long-acting corticosteroid for asthma before the DBPCFC, the food challenge should be delayed to allow for 4 weeks of wash-out). If a subject has a reaction during the first day of the DBPCFC that requires treatment with systemic corticosteroids on the first day, the subject has to wait at least 3 days before performing the second day of the DBPCFC.

The subject may have a light breakfast and drink water at home at least 2 hours before starting the DBPCFC at the site. During the conduct of the challenge, drinking a sip of water to help swallow the formulas is allowed. Apple sauce will be given to the subjects during the challenge after the third dose (10 mg) and onwards to improve the acceptability of the food challenge formulas and prevent discomfort due to hunger, considering the prolonged fasting required by the procedure in these young children. A defined apple sauce formulation will be used by all the centers and the amount of apple sauce administered will be standardized and limited so that it does not interfere with the subject's willingness to ingest the food challenge formula. After the last dose of the challenge formula is administered, the medical staff should wait at least 1 hour before feeding the subject with any other food and/or water. This first feeding should be light.

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A detailed and study-specific Manual of Procedures for the conduct of the DBPCFC will be provided to the Investigators, the site staff and the unblinded study-trained person responsible for reconstituting the food challenge formulas. Of note, the amounts of apple sauce to be administered are specified in the Manual of Procedures. When needed, updated versions will be made available. An outline of the procedures is specified below.

6.1.2 Preparation of Peanut and Placebo Formulas

Standardized formulas, centrally produced by CCI [redacted], and packed and released by CCI [redacted] will be distributed to all participating centers for the DBPCFC. One of the formulas will be peanut protein-free (placebo) and the other one will contain peanut proteins. An unblinded person identified at each site by the investigator, specifically trained to reconstitute the formulas in the study and not involved in the challenge itself will be responsible for the preparation, adequate labeling and blinding of the pots containing the prepared/hydrated formulas. The blinded pots will then be handed to the medical team to perform the challenge.

6.1.3 Time Interval and Doses

The order of the formulas to be consumed during the first and the second day of the DBPCFC will be pre-determined at random. The randomization will be performed via the eCRF. The site staff (for example the Investigator, study coordinators, and study nurses), the subject/parents/guardians will remain blinded to the order of consumption until the end of the second day of the DBPCFC.
Up to 7 days (1 week) between the 2 days of the DBPCFC will be permitted. The 2 days of the DBPCFC may be 2 consecutive days, but not the same day.

The challenge will consist in giving doses of peanut protein or placebo in gradually increasing doses at 20-minute intervals.
The starting dose of the challenge is 1 mg and the maximum dose is 2000 mg. The dose increments are the following: 1 mg, 3 mg, 10 mg, 30 mg, 100 mg, 300 mg, 1000 mg and 2000 mg.

6.1.4 Procedure for Double-Blind Placebo-Controlled Food Challenge to Peanut

All DBPCFCs will be conducted following the same procedure. Subjects will receive one formula (placebo or peanut) on the first day and the other formula (peanut or placebo) on the second day, as randomly determined. All subjects will undergo both days of the DBPCFC. At the end of the second day of challenge, the sequence of the two formulas will be unblinded and revealed to the medical staff.

The second day of a challenge might be not performed if the subject experienced severe reaction(s) during the first day of the challenge, leaving no doubt about the nature of the formula administered, which is peanut (i.e. need for intubation, hypotension persisting after epinephrine administration, and/or the need for ≥3 doses of epinephrine). In this rare case and in this case only, the second day of the DBPCFC could not be performed. The formula will be unblinded to confirm that the subject received the peanut formula.

The challenge will be continued up to the dose of 2000 mg peanut protein or until reactions leading to stopping the DBPCFC occur.

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Objective symptoms and/or:

- **Moderate abdominal pain with decreased activity associated with other objective symptoms,**
- **Severe and/or persistent abdominal pain with significant change in behavior**

requiring treatment will be considered to stop the challenge and to determine the ED (highest dose given during the challenge) as well as the CRD of peanut protein. **Other subjective symptoms will be graded but will not count in the stopping rules of the challenge.**

The Oral Food Challenge (OFC) Symptom Score Sheet (see APPENDIX 6) will be used to score the severity of each pre-specified objective and subjective symptoms. This scoring is classified under the 5 categories:

I Skin (Pruritus, Urticaria, Angioedema, Erythematous Rash),
II Upper respiratory/Ocular (Sneezing/Itching, Nasal Congestion, Rhinorrhea, Laryngeal, Conjunctivitis),
III Lower Respiratory (Wheezing),
IV Gastrointestinal (Subjective Complains, Objective Complains),
V Cardiovascular/Neurologic (hypotension/collapse/unconsciousness).

More specifically, the food challenge must be stopped if:

Only 1 out of 5 categories has increased its grading symptom score

≥ 1-point rise for at least 1 following symptom (i.e. mild, moderate or severe)		**≥ 2-point rise for at least 1 following symptom (i.e. moderate or severe)**		**3-point rise for at least 1 following symptom (i.e. severe)**
○ Laryngeal* ○ Wheezing ○ Objective Gastrointestinal** ○ Cardiovascular/neurological***	**OR**	○ Urticaria ○ Angioedema ○ Rash	**OR**	○ Pruritus ○ Sneezing /Itching ○ Nasal Congestion ○ Rhinorrhea ○ Conjunctivitis ○ Abdominal complaints

Or 2 categories (or more) have increased their grading symptom scores

≥ 1-point rise for at least 1 following symptom (i.e. mild, moderate or severe)		**≥ 2-point rise for at least 1 following symptom (i.e. moderate or severe)**
○ Urticaria ○ Angioedema ○ Rash	**AND**	○ Sneezing/Itching ○ Nasal Congestion ○ Rhinorrhea ○ Conjunctivitis

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		○ Abdominal complaints
OR		
≥ 2-point rise (i.e. moderate or severe)	**AND**	**≥ 2-point rise for at least 1 following symptom (i.e. moderate or severe)**
○ Pruritus		○ Sneezing/Itching ○ Nasal Congestion ○ Rhinorrhea ○ Conjunctivitis ○ Abdominal complaints
OR		
≥ 2-point rise (i.e. moderate or severe)	**AND**	**≥ 2-point rise for at least 1 following symptom (i.e. moderate or severe)**
○ Abdominal complaints		○ Sneezing/Itching ○ Nasal Congestion ○ Rhinorrhea ○ Conjunctivitis ○ Pruritus

*"Laryngeal" refers to laryngeal edema symptoms and must be differentiated from other causes of cough such as transient pharyngeal irritation or lower respiratory symptom (e.g., cough due to bronchospasm). Causes of cough other than laryngeal edema symptoms will be documented as "other symptom" in the e-CRF and specified in the free textbox. Transient laryngeal irritation will not be considered as an objective OFC symptom and will not be considered in the stopping rules.

**For emesis/vomiting, the symptoms may result from 2 different situations: vomiting/spitting-up during the feeding, resulting from subjective intolerance to the food formula or vomiting/emesis resulting from a gastrointestinal allergic reaction to the peanut allergen, usually delayed from the feeding. Only the second situation will be considered as an objective OFC symptom and will be considered for the stopping rules.

***Cardiovascular symptoms: hypotension or cardiovascular failure directly related to the systemic allergic reaction. These symptoms have to be differentiated from similar symptoms related to another cause, such as a dizziness induced by vomiting. Objective measures of blood pressure and hemoglobin saturation should be recorded for documenting these symptoms.

For each peanut protein dose step, the consumption must be carried out as fast as possible, not exceeding 30 minutes between the start and end of dose ingestion. The evaluation of prespecified challenge stopping criteria must be carried out imperatively within a 20-minutes period after the dose has been completely ingested (i.e., 20-minute period starting from the end of dose ingestion):

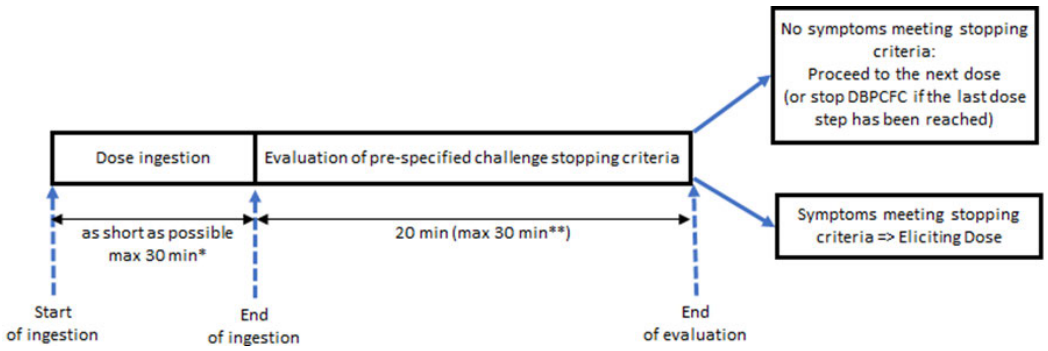
- If no symptoms meeting the stopping criteria are observed within this 20-minute period, the Investigator must proceed immediately to the administration of the next ascending dose (or stop the DBPCFC if the last dose step has been reached);
- If there is a doubt on a possible development of symptoms meeting stopping criteria at the end of the 20-minute period, the Investigator may exercise his/her clinical judgement and extend the evaluation period to an additional 10 minutes (not exceeding 30-minute evaluation period overall, starting from the end of dose ingestion). If the emerging symptoms have not met the stopping criteria at the end of the additional evaluation period, the Investigator must proceed to the administration

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of the next ascending dose (or stop the DPBCFC if the last dose step has been reached). However, the administration of the next dose may be administered more slowly, not exceeding 30-minute between the start and end of dose ingestion.

- The repetition of a same dose step will not be allowed during DBPCFC. If there are no symptoms meeting the stopping criteria after a maximum of 30-minute evaluation, the Investigator must proceed to the next ascending dose, or must stop the Food Challenge if the last dose step has been reached.

The procedure is schematized below:



* A slower administration (not exceeding 30 minutes) may be possible if emerging symptoms (not meeting stopping criteria) occurred at the end of the evaluation period of the previous dose.

** In case of emerging symptoms at the end of the 20-minute period, evaluation can be extended to an additional 10 minutes (not exceeding 30 minutes overall).

Further details are provided in the study-specific Manual of Procedures for the DBPCFC that will be provided to the sites.

The dose that triggers objective symptoms and/or abdominal complaints as defined by the stopping rules will be considered as the ED.

As a safety precaution, the symptoms leading to the DBPCFC stop will be treated. The Investigator and medical staff will use their own clinical judgment for the selection of appropriate treatments considering the subject's age, the type of allergic reactions and their severity. Also refer to the recommendations made by Sampson et al. for treating anaphylaxis (35). Suggested treatments for the different symptoms are detailed in the study-specific Manual of Procedures for the DBPCFC provided to the sites.

Should epinephrine need to be administered, it should be injected intramuscularly in the anterolateral thigh using auto-injectors commercially available in each specific site/country or using weight-adjusted doses of epinephrine in a standard syringe. Weight-adjusted doses of epinephrine in a standard syringe should be used in children who weigh less than 15 kg. Intravenous epinephrine should NOT be considered at the investigative sites to treat the allergic reactions.

Subjects will be kept under observation for an additional 3 hours after the ingestion of the last dose of the challenge formula. Based on the Investigator's judgment, the observation period could be extended beyond the first 3 hours to ensure that all symptoms have subsided before the subject is discharged. For instance, an overnight stay may be considered necessary

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by the Investigator if the symptoms have not completely resolved within the 3 hours or if the symptoms have been severe or serious and require longer observation periods.

Complete information for all reactions will be reported first in source documents then in the e-CRF, along with DBPCFC doses given, symptoms observed and their highest grades reached after each dose, time of appearance of the symptoms and Investigator's assessment of the ED.

Food challenges to other food allergens (besides peanut) may be conducted during the study if medically justified, and only if performed in the context of a diagnosis or for confirming a desensitization. Whether the subject's medical condition is still compatible with their participation in the study should be assessed by the Investigator and the Sponsor's medical monitor, before the food challenge is performed. If not compatible, the Sponsor may decide to discontinue the subject from the study. Importantly, the initiation of immunotherapy to any food allergen remains prohibited during the participation in the study (See Section 5.7.2). The patch should not be applied on the day of a food challenge and until all procedures are completed.

6.2 Safety Variables

6.2.1 Adverse Events

Coding of AEs will be performed as described in Section 9.5.

6.2.1.1 Collection of Adverse Events

It is responsibility of the Investigator to collect all AEs (both serious and non-serious) derived by spontaneous, unsolicited reports of subjects, by observation and by routine open questionings, for example, "How have you felt since I last saw you?"

The following application site reactions and systemic events of a potential allergic nature (regardless of causal relationship with the study treatment) will be specifically solicited at each study visit and phone contact, and reported as AEs in the eCRF:

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Table 1: List of solicited adverse events

Application site reactions	Systemic events of a potential allergic nature
• Pruritus • Erythema • Edema • Urticaria • Hyperpigmentation • Eczema • Excoriation (erosion) • Ulceration • Blister (vesicles) • Grade 4 patch site reactions (erythema with vesicles) • Pain under the patch	• Asthma aggravation/exacerbation • Hives • Eyelid edema • Allergic contact conjunctivitis • Lip swelling • Angioedema

6.2.1.2 Definitions

An AE is any untoward medical occurrence in a subject participating in a clinical investigation and administered a pharmaceutical product, and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the product.

All AEs, including intercurrent illnesses, occurring during the study will be documented in the e-CRF. Concomitant illnesses, which existed before entry into the study, will not be considered AEs unless they worsen during the treatment period. All AEs, regardless of the source of identification (for example physical examination, laboratory assessment, electrocardiogram, reported by subject), must be documented.

Adverse events will be recorded in the EPOPEX study only from Visit 1 onwards. Adverse events/SAEs occurring after written informed consent for the EPOPEX study has been signed but before Visit 1 will be recorded in the EPITOPE study only.

Adverse events still ongoing at the time of the End of Study Visit will be followed until they either resolve or stabilize, or for an additional 30 days.

A TEAE will be defined as an AE that begins or that worsens in severity after at least 1 dose of study treatment has been administered.

Adverse events and TEAEs due to DBPCFC will also be recorded in the e-CRF but will be analyzed separately.

6.2.1.3 Assessment of Adverse Events

Each AE will be assessed by the Investigator with regard to the following categories.

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6.2.1.3.1 Seriousness

An SAE is defined as any untoward medical occurrence that at any dose:

- Results in death;
- Is life-threatening: this means that the subject is at risk of death at the time of the event; it does not mean that the event hypothetically might have caused death if it was more severe

  Note: Whereas a systemic anaphylactic reaction is generally considered potentially life-threatening, not all anaphylaxes put the subjects at immediate risk of death, if for example appropriate treatments lead to symptoms reduction or disappearance. As per the Anaphylaxis Staging System (APPENDIX 5), an anaphylaxis assessed as mild or moderate should not be classified as life-threatening;

- Requires hospitalization (at least overnight stay or inpatient hospital admission) or prolongation of existing hospitalization;

  Events associated with **hospitalization** for the following reasons will **not** be considered as an SAE:

  1. Evaluation or treatment of a pre-existing (before informed consent signature) and non-exacerbating condition:
     a. The condition existed prior to the subject's entry into the study and has been recorded in the subject's disease/medical history and the e-CRF *AND*
     b. The condition has not worsened in severity or frequency during the subject's exposure to the study treatment *AND*
     c. The condition has not required a change in treatment management during the subject's exposure to the study treatment;
  2. Hospitalization the day prior to or after the day of DBPCFC for practical reasons and without fulfilling any other seriousness criterion.

- Results in persistent or significant disability or incapacity (an AE is incapacitating or disabling if it results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions);
- Is a congenital anomaly or birth defect;
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but that may jeopardize the subject or require intervention to prevent one of the above outcomes. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.
  - An anaphylactic reaction classified as severe using the Anaphylaxis Staging System in APPENDIX 5 (i.e., anaphylactic reaction with cyanosis or SpO2 ≤92%, hypotension with >20% drop in blood pressure, confusion, collapse, loss of consciousness) or requiring 3 or more epinephrine intakes

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should be reported at least with the seriousness criterion "important medical event";

- In the context of the DBPCFC, in addition to the severe anaphylaxis, the occurrence of:
  - Bronchospasm/audible wheezing with use of accessory muscles,
  - Severe angioedema
  - Admission in Intensive Care Unit and/or requirement of oxygen therapy
  - Intake of 3 or more doses of epinephrine

should be considered as meeting the seriousness criterion of "important medical event".

Medical and scientific judgment should be exercised in deciding whether a case is serious and whether expedited reporting is appropriate.

6.2.1.3.2 Severity

The severity of each AE must be assessed by the Investigator using 1 of the following categories, and recorded in the e-CRF:

- Mild: The AE was transient and easily tolerated by the subject;
- Moderate: The AE caused discomfort and interference with the subject's general condition;
- Severe: The AE caused considerable interference with the subject's general condition and may have been incapacitating.

The anaphylaxis (including those reported as part of Medical History) will be graded in accordance to the Anaphylaxis Staging System (APPENDIX 5).

6.2.1.3.3 Causality

The Investigator will assess the causality/relationship between the study treatment and the AE and record that assessment in the source documents and in the e-CRF.

The most likely cause of an AE/SAE (for example disease under treatment, concomitant disease, concomitant medication, other) will be indicated in the e-CRF with details of the concomitant disease or medication or other cause.

The causal relationship of the AE to study treatment will be described in terms of:

- Related: the AE:
  - Follows a clear temporal sequence from administration of the study treatment.
  - Has no other possible explanations, such as the subject's clinical state, environmental or toxic factors or other therapies administered to the subject.
  - Disappears or decreases on cessation or reduction in dose of the study treatment.
  - Follows a clear pattern of response to the study treatment.

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- Reappears or worsens upon rechallenge.

- Probable: the AE:
  - Follows a reasonable temporal sequence from administration of the study treatment.
  - Could not be reasonably explained by the subject's clinical state, environmental or toxic factors or other therapies administrated to the subject.
  - Disappears or decreases on cessation or reduction in dose of the study treatment.
  - Follows a known pattern of response to the study treatment.
  - Reappears or worsens upon rechallenge.
- Possible: the AE:
  - Follows a reasonable temporal sequence from administration of the study treatment.
  - Could be reasonably explained by the subject's clinical state, environmental or toxic factors or other therapies administrated to the subject.
  - Follows a known pattern of response to the study treatment.
- Unlikely: the AE
  - Does not follow a reasonable temporal sequence from administration of the study treatment.
  - Could be reasonably explained by the subject's clinical state, environmental or toxic factors or other therapies administrated to the subject.
  - Does not follow a known pattern of response to the study treatment.
  - Does not reappear or worsen upon rechallenge.
- Not related:
  - The AE does not meet the above criteria.
  - There is sufficient information that the etiology of the AE is not related to the study treatment.

All SAEs assessed as related, probably related, and possibly related will be considered as related for expedited reporting (see Section 6.2.1.5).

The study conduct relatedness for SAEs will also be assessed and documented.

6.2.1.3.4 Local Skin Reactions

The Investigator will assess the severity of local skin reactions induced by the study patches at each site visit during the physical examination and photos should be taken during the site visits by the medical staff to document these local skin reactions (see Sections 6.2.3 and 6.2.7).

In addition, the collection of pre-specified application site reactions will be solicited at each study visit and phone contact (see Section 6.2.1.1).

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6.2.1.3.5 Adverse Events of Special Interest

Adverse Events of Special Interest to the Sponsor are defined as follows:

Local AESI: Any reaction at patch application site which could potentially lead to a skin barrier disruption, such as but not limited to, blister, vesicle, ulcerative skin lesion, bleeding or any Grade 4 patch site reaction.

Skin reactions will be examined at the time points specified in the Schedule of Procedures according to grading in Table 2 (Section 6.2.8). Subject's parents/guardians will be instructed to take a photo in case of appearance of any vesicles or ulcerative skin lesions. In these rare specific cases, subjects should transiently discontinue patch application and return to the site for evaluation and treatment of the wounded area, as well as for the next patch application and adequate evaluation and treatment of the wounded zone.

Upon re-application of the new patch, the subject should remain at the site for 1 hour before being discharged. The site must contact the subject's parents/guardians by phone the day after this visit to ensure that no additional local blisters or vesicles developed and to confirm that the treatment can continue normally. The zone with vesicles or severe lesions should not be used for patch application until it has completely healed.

However, **local AESI should NOT be reported on the specific AESI form of the e-CRF**. This specific AESI form is only to be used for systemic AESI (see below).

Systemic AESI: Any acute systemic immediate allergic reaction (rapid onset) after exposure to a known or suspected allergen regardless of the causal relationship to the study treatment, and occurring outside the DBPCFCs:

1. Anaphylactic reaction:
    - Any AE diagnosed by physician as an anaphylactic reaction, regardless of the severity and causal relationship to the study treatment.
    - Anaphylactic reaction defined as the occurrence of the following allergic symptoms (35):
        - Major acute allergic reaction (associated or not with other symptoms): acute hypotension (>20% drop in blood pressure) or associated cardiovascular symptoms (hypotonia, confusion, loss of consciousness, collapse, syncope),
        - 2 or more concomitant acute allergic symptoms from at least 2 different organ systems such as, but not limited to:
            - Upper airway or respiratory symptoms (dyspnea, wheeze-bronchospasm, stridor, hypoxemia, decreased SaO2)
            - Acute and persistent gastro-intestinal symptoms (abdominal pain, cramps, vomiting)
            - Acute skin or mucosal tissue symptoms (angioedema, urticaria, pruritus, flush, swollen lips-tongue-uvula)
            - Acute cardiovascular symptoms (hypotonia, reduced blood pressure)
2. Any systemic hypersensitivity reaction leading to epinephrine intake

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Any AE meeting the definition of a systemic AESI must be ticked as an AESI in the AE form of the e-CRF. In addition, it must be documented and reported in the specific form by the Investigator on an ongoing basis (guidance and precisions will be given in the e-CRF Completion Guidelines). The AESI forms must be sent by the Investigator within 24 hours of the site becoming aware of the event.

Potential systemic AESIs will be identified by dedicated Standardized MedDRA Queries (SMQ). Cases retrieved by the SMQs will then be confirmed by medical review.

6.2.1.3.6 Symptoms During the Double-Blind, Placebo-Controlled Food Challenge

The severity of the objective and subjective symptoms elicited during the DBPCFCs will be assessed by the Investigator. They will not be reported as single independent AEs in the AE pages of the e-CRF. Complete information for all these symptoms will be reported in the DBPCFC pages of the e-CRF, along with all peanut protein doses given, the symptoms observed, the time of appearance of the symptoms and their specific grades, the time of grade change of each symptom, the doses of epinephrine given, the doses of corticosteroids and antihistamines given and the Investigator's assessment of the peanut ED as well as the peanut cumulative dose. If, as per the Investigator's judgment, the combination of all these symptoms resulted in an anaphylaxis requiring a prolonged (minimally overnight) hospitalization, then this will be considered an SAE. Any such SAE with its specific verbatim (e.g. 'during food challenge' or 'due to food challenge') must be reported in the AE pages of the e-CRF.

6.2.1.4 Recording Adverse Events

Adverse events occurring between signing the ICF for EPOPEX study and Visit 1 will be recorded in the EPITOPE study only. Adverse event reporting for the EPOPEX study will start at Visit 1 and end after the 2-week follow-up period (End of Study Visit). Adverse events occurring after the end of the study should be reported to the Sponsor by the Investigator if the Investigator considers that there is a causal relationship with the IP.

Adverse events still ongoing at the time of the End of Study Visit will be followed up for an additional 30 days, or until they resolve or stabilize, whichever comes first.

All AEs occurring on or after the day of the first dose of IP in the EPOPEX study, regardless of the relationship to the IP, will be recorded in the e-CRF.

All AE reports in the e-CRF should contain the following information of the event: date and time of onset, date and time of resolution, severity, treatment required, relationship to study treatment, action taken with the study treatment, outcome, and whether the event is classified as serious or not.

6.2.1.5 Reporting Serious Adverse Events

All initial or follow-up information regarding SAEs must be reported immediately and within a maximum of 24 hours of the site becoming aware of the event by filling in the SAE pages in the e-CRF. In case of technical issues with the e-CRF, the reporting can be done by e-mailing a completed SAE Report Form to the DBV Technologies safety department at: pharmacovigilance@dbv-technologies.com. After the technical issue is resolved, the SAE information must be reported in the e-CRF.

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The minimum information required for an initial report is:

- Name of person sending the report (that is name and address of Investigator);
- Subject identification (screening number, NOT the subject's name);
- Protocol number;
- Description of the SAE including a comprehensive verbatim term;
- Causality assessment, if possible.

However, as far as possible all requested information in the SAE pages in the e-CRF (or on the SAE Report Form, in case of technical issues with the e-CRF) should be reported in the initial report. If an SAE occurs during the DBPCFC, the verbatim of the SAE must specify "during the DBPCFC" or "due to the DBPCFC" both on the SAE Report Form and in the SAE pages of the e-CRF.

Systemic AESIs, regardless of their causal relationship to the IP, must also be reported within 24 hours of the site becoming aware of the event, by filling the AESI specific report form in the e-CRF. In case a systemic allergic reaction is associated with a seriousness criterion, an SAE report form must be completed instead.

The Sponsor will either directly or through contracted service providers submit expedited and periodic reports to both Competent Authorities, Ethics Committees and Investigators as per regulations and procedures in force, taking into account local specific requirements.

Serious AEs that are both related (according to the sponsor and/or the Investigator) to the IP and unexpected (according to Sponsor and based on the IP Reference Safety Information [RSI] in use) will usually be assessed as reportable by the Sponsor to Competent Authorities.

Waiver to expedited reporting:

In case an anaphylactic reaction is experienced during the DBPCFC and assessed as serious by the Investigator, this event should be reported immediately and within a maximum of 24 hours of awareness by the investigational site as for other SAEs. Allergic reactions are voluntarily triggered by an "allergen" protein matrix (placebo matrix or "allergen" protein matrix) during the DBPCFC procedures, therefore anaphylaxis are elicited events. These anaphylactic reactions will be considered as expected, if not leading to death (see APPENDIX 10 for the RSI related to DBPCFC peanut protein matrix). Serious anaphylactic reactions assessed as related to the DBPCFC will not be subject to expedited reporting, unless they lead to death.

Serious unexpected suspected adverse reactions which are subject to expedited reporting will be submitted by the Sponsor or its representative to the Regulatory Authorities.

6.2.1.6 Follow-up of Adverse Events

All AEs experienced by a subject, irrespective of the suspected causality, will be monitored until the AE has resolved, any abnormal laboratory values have returned to baseline or stabilized at a level acceptable to the Investigator and Medical Monitor, until there is a satisfactory explanation for the changes observed, until the subject is lost to follow-up, or until the subject has died.

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6.2.1.7 Treatment of Overdose of Study treatment

Overdose is defined as the concomitant application of 2 Viaskin Peanut patches or more on the skin of the subject, whatever the duration of the concomitance of the multiple patch application.

The case when one patch applied the same day after the previous patch was removed or has fallen off is NOT an overdose.

There has been no experience of overdosing with Viaskin Peanut patches so far. No specific treatment for overdosing is known. The first action will be to remove any additional patch from the skin, leaving only 1 patch on the skin. Treatment given to a subject in case of overdosing should be symptomatic and supportive.

All cases of overdose should be tracked in the subject's eCRF according to the eCRF completion guidelines. Any AEs associated with the overdose should be reported in the relevant AE/SAE sections in the e-CRF. Any SAE associated with the overdose should be reported the same way as other SAEs (see Section 6.2.1.5).

6.2.2 Laboratory Variables

Laboratory assessments will be performed by a central laboratory, as identified in the List of Study Personnel.

Venous blood samples will be taken for hematology and biochemistry testing.

The following laboratory variables will be determined in accordance with the Schedule of Procedures:

- Hematology: hemoglobin, hematocrit, platelets, red blood cells, white blood cells with differential cell count;
- Biochemistry: alanine aminotransferase, aspartate aminotransferase, total bilirubin, total protein, blood urea nitrogen, creatinine;

Details of the procedures to be followed for sample collection, storage, and shipment will be documented in the Laboratory Manual.

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

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

The maximal blood volume drawn for blood analyses (hematology, biochemistry, immunological markers and epigenetic analyses) at a single study visit will be approximately 7.5 mL. The total blood volume drawn during the study will be approximately up to 43 mL over 2 years in the VP+VP group and 56 mL over 3 years in the Placebo+VP group.

Additional and repeat laboratory safety testing outside the study may be performed at the discretion of the Investigator.

6.2.3 Physical Examinations

Physical examinations will be performed in accordance with the Schedule of Procedures.

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Physical examinations will be performed by a physician or a master level clinician qualified for performing physical examinations and will include examination of the following:

- General appearance;
- Head, ears, eyes, nose and throat;
- Neck;
- Complete skin examination;
- Cardiovascular system;
- Respiratory system;
- Abdominal system;
- Nervous system;
- Body weight (kg);
- Height (cm).

Body weight will be measured without shoes, jacket or diaper and per Schedule of Procedures and as frequently as necessary.

Height will be measured without shoes and per Schedule of Procedures and as frequently as necessary for this population of subjects in active growth.

For each body system, an assessment of normal or abnormal will be recorded in the e-CRF at study entry (baseline measurement will be the one collected before the DBPCFC at Visit 11 in the EPITOPE study) and the abnormality will be documented. Besides, the skin aspect will be graded for the sites of patch application (see Section 6.2.8).

Physical examinations must be performed before the DBPCFC. Additional assessments can be repeated during the DBPCFC procedure on both days at any time judged necessary by the Investigator.

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

6.2.4 Vital Signs

The following vital signs will be assessed in accordance with the Schedule of Procedures:

- Blood pressure (systolic and diastolic; mmHg),
- Heart rate (beats per minute).

Systolic blood pressure and diastolic blood pressure will be measured in sitting position on the same arm after the subject has been resting.

Heart rate will be recorded simultaneously with blood pressure measurements, followed by respiratory rate.

During the study, the measurement of vital signs may be repeated at the discretion of the Investigator for safety reasons. Clinically relevant abnormal findings will be reported as AEs.

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Vital signs must be assessed before the DBPCFC. Additional assessments can be repeated during the DBPCFC procedure on both days at any time if judged necessary by the Investigator.

6.2.5 Peak Expiratory Flow

For subjects ≥ 4 years of age with a diagnosis of asthma and unable to perform the spirometry test, PEF will be measured at all visits. At least 3 acceptable measures will be obtained from the peak flow meter and the highest of the 3 attempts will be reported in the e-CRF. The PEF will not be derived from the spirometer measurement. On the days where a challenge is performed, PEF will be measured both in asthmatic and non-asthmatic subjects. On these days, the PEF assessment must be performed just before the DBPCFC. This can be repeated during the DBPCFC if needed.

6.2.6 Spirometry Test

For subjects ≥ 4 years of age with a diagnosis of asthma, and capable of performing a spirometry test, forced expiratory volume in 1 second (FEV_1) will be measured on a standardized calibrated spirometer following the American Thoracic Society guidelines. At least 3 acceptable FEV_1 maneuvers will be obtained and the highest of the 3 attempts will be recorded in the e-CRF. The test will be performed at all visits except the second day of the DBPCFC.

6.2.7 Subject Diaries

Subject diaries will be dispensed to subject' parents/guardians in order to report specific information between visits. Only the subject's number will be recorded, and subjects will not be identified by name.
Subject's parents/guardians will be instructed to use the diaries as reminder tools and to report any local skin reactions or other medical events and any concomitant medication or treatment taken.
All data entered in the subject diary will be reviewed by the site medical staff at each visit. When reviewing the diary data, the Investigator will use her/his clinical judgment to validate the AEs and concomitant medications to be reported in the e-CRF. If the diary data entries are not reported in the e-CRF by the Investigator based on her/his clinical judgment, this will be documented in the source documents.
Subject's parents/guardians must bring the diary to the Investigator at each visit and the Investigator must check the diary for completeness and accuracy It is the Investigator's responsibility to instruct the subject's parents/guardians about the use of the diary, and to ensure that the diary is accurately completed. Any problems with completing the diary will be addressed with the subject's parents/guardians. At each site visit, the completed pages of the diary will be collected and kept by the Investigators. The remaining blank pages of the diary will be given back to the subjects' parents/guardians at each visit before discharge. All diaries must be returned to the site at completion of the study or if the subject discontinues.

6.2.8 Skin Reaction and Photography

Local skin reactions under the Viaskin® patch or on any of the previous sites of patch application will be graded by the Investigator as a whole at each visit according to the

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recommendations of the European Academy of Allergology and Clinical Immunology and the Global Allergy and Asthma European Network (36), and modified as follows:

Table 2: Skin Reaction Grading System by the Investigator

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

Additional information for grading local skin reactions can be found in the leaflet provided to the Investigators.

The Viaskin® patch is transparent thus the degree of local reactions can be easily seen through the patch. Grading of the local skin reactions on the back will start being recorded at Visit 1 right after the Viaskin® patch has been applied and while the subject is kept at site under observation. Grading will subsequently be recorded when subjects return at site for their visits.

During Visit 1, the first Viaskin® patch will be applied at the study site for 2 hours. The patch will then be removed after 2 hours and all subjects will be observed for 1 additional hour before being discharged. The reactions under or around the patch will be checked and graded: before application, at 30 min, 1 hour, 2 hours during patch application and then 1 hour after the patch removal, before subject discharge. Photos will be taken at each grading time point.

At any time during the study, appearance of any vesicles (grade 4), ulcerative skin lesions or any other significant skin lesion which could potentially lead to skin barrier disruption seen under the patch while the patch is still applied on the skin or upon removal of the patch will be cautiously assessed, managed and followed-up.

Subject's parents or guardians will be instructed to take a photo of the patch skin area at home in case of appearance of any vesicles or ulcerative skin lesions. In these rare cases, subjects should transiently discontinue the patch applications and return to the site for evaluation and treatment of the wounded area, as well as for the next patch application and adequate evaluation and treatment of the wounded zone.

Upon re-application of the new patch, the subject should remain at the site for 1 hour before being discharged. The application duration may be temporarily adapted if deemed necessary. The site must contact the subject's parents/guardians by phone the day after this visit to ensure that no additional local blisters or vesicles developed and to confirm that the treatment can continue normally. The zone with vesicles or severe lesions should not be used for patch application until it has completely healed.

Photographic records of the application sites of the Viaskin® patch will be taken and documented as medical records or source documents. The subject's face will not, at any

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time, be captured in the photo. Camera and photography acquisition guidelines will be provided to the sites, so that photo process can be standardized as much as possible. All photos will be downloaded by the site staff onto a dedicated secured server with a restrictive access to the site staff members, the Sponsor members and Sponsor representatives.

Photographic records will be made available to the DSMB members upon request.

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6.3 Demographics and Baseline Characteristics

Demographics and baseline characteristics consist of those variables that are assessed before treatment during Visit 1, or previously recorded during the EPITOPE study.

6.3.1 Subject Demography

Subject demography will be available from the EPITOPE study data. Only age and sex will be recorded at Visit 1 as subject identification.

6.3.2 Disease History and Medical History

Any relevant disease history and medical history from the screening examination of the EPITOPE study will be reported to the EPOPEX e-CRF.

For coding of medical history, see Section 9.5.

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6.3.3 Previous and Concomitant Medications

Previous and concomitant medication will be documented as described in Section 5.7.

6.4 Exploratory Variables

6.4.1 Immunological Markers

Venous blood samples will be drawn to assess total IgE, peanut-specific IgE and IgG4 and IgE and IgG4 specific to peanut protein components (Ara h 1, Ara h 2 and Ara h 3) at the visits specified in the Schedule of Procedures.

IgE specific to cow's milk, egg, house dust mites, and grass pollen will be assessed at visits V1, V5, V8 and V11P, and in case of an early termination visit.

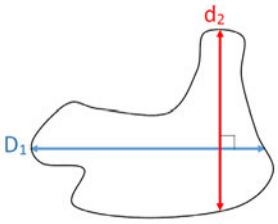
Analysis of samples will be conducted by Q^2 Solutions Laboratory and the results will be blinded until the EPITOPE study data are unblinded. Remaining serums will be kept in a serum bank for after the end of the study. Further details of the procedures to be followed for sample collection, storage, and shipment will be documented in the Laboratory Manual.

6.4.2 Skin Prick Test

Peanut extract plus negative saline control and positive histamine control will be used for SPTs. All materials (SoluPrick® solutions and ancillary materials, CE marked, ALK, Denmark) will be provided free of charge centrally to all sites by the Sponsor, including a detailed procedure for conducting the SPTs.

The subjects should wash out any oral antihistamines for the minimum period of time (specified in the table in APPENDIX 4) prior to performing the test. Briefly, a skin Duotip II® is pressed through a small drop of the commercial extract of peanut or positive and negative controls into the epidermis of the volar surface of the forearm. After 15 minutes the area will be measured by the longest wheal diameter (D1) and the longest perpendicular diameter (d2). The Average wheal diameter = (D1 + d2) / 2.

e.g.



D1: size of the longest diameter in mm

d2: size of the longest perpendicular diameter to D1 in mm

A tracing should be obtained by using a fine ballpoint pen. The tracing will be performed at the demarcation line for the wheal as the skin drops back to flush. Scotch or a clear transparent tape should be used to lift the tracing; the tape tracing should be placed on the appropriate SPT Form and filed as part of the subject's source documentation.

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6.4.3 Quality of Life Questionnaires

6.4.3.1 Food Allergy Quality of Life Questionnaires /Food Allergy Independent Measure

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 (37). The FAIM questionnaires capture the subject's expectation of something happening because of her/his food allergy (38). FAQLQ and FAIM will be completed in the countries where they are available in local languages.

Parents/guardians will complete the Parent Forms of the questionnaires (FAQLQ-PF, FAIM-PF) at the time points specified in the Schedule of procedure.

The FAQLQ and FAIM must be completed prior to starting any procedures of the visits mentioned. In order to maintain an unbiased assessment, the Investigator or study site personnel must not influence the subject's parent(s)/guardians(s) whilst they are completing the forms.

The template questionnaires are provided in APPENDIX 7.

6.4.3.2 Generic Quality of Life Questionnaire: EQ-5D-5L

Parents/guardians will complete the EQ-5D-5L questionnaire at the time points specified in the Schedule of procedure. The template questionnaire is provided in APPENDIX 8.

6.4.4 Accidental Consumption of Peanut-containing Food

Specific reactions triggered by suspected accidental consumption of peanut-containing food and the conditions around that consumption will be collected with as much detailed information as possible, in particular with regard to the nature of the food and the quantity consumed. The subjects' parents/guardians will be asked to clarify whether any peanut consumption was accidental or not. The AEs induced by the consumption will be classified and analyzed separately.

As far as possible, a sample of the food having triggered the reactions will be collected and sent for analysis of its allergen content to a specialized laboratory. A specific procedure to organize the collection and the shipment of these samples will be provided to the centers and the subjects' parents/guardians.

6.4.5 Epigenetic Analyses

Venous blood samples (approximately 2 mL) will be drawn to assess the epigenetic modifications induced by the EPIT treatment with Viaskin Peanut on the promoter regions of key genes coding for several allergy-specific proteins. The tests will be managed centrally, and the results will be blinded until the EPITOPE study data are unblinded. Detailed procedures to be followed for sample collection, storage and shipment will be documented in a specific manual provided to the sites.

6.4.6 Scoring of Atopic Dermatitis

The SCORAD, a scoring index of atopic dermatitis developed by the European Task Force on Atopic Dermatitis (39) will be assessed as specified in the Schedule of Procedures by a physician or a master level clinician qualified for performing this procedure.

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Sections A and B must be assessed and completed by the Investigator, while Section C is assessed by the subject's parents/guardians.

The SCORAD is provided in APPENDIX 9.

7 STUDY CONDUCT

7.1 Schedule of Procedures

The Schedule of Procedures is presented on page 9.

7.2 Procedures by Visit

Visits should occur within the time windows indicated in the Schedule of Procedures.

7.2.1 Visit 1

Visit 1 in the EPOPEX study will be conducted on the same day as Visit 11 in the EPITOPE study, as far as possible, but Visit 1 might be conducted within a week of Visit 11, considering some practical aspects for the center and for the subject's family. The procedures that are common to both visits only need to be performed once.

All subjects for whom a written informed consent has been obtained and only subjects who fulfill all inclusion criteria and none of the exclusion criteria will be eligible to be enrolled into the EPOPEX study. The ICF for the EPOPEX study should be signed after all procedures of Month 12 DBPCFC in EPITOPE study have been completed, and before any procedure is started in EPOPEX. All eligibility assessments must be completed before effective enrollment into the EPOPEX study. As such, enrollment in the EPOPEX study can occur after completing Visit 11 of the EPITOPE study.

At Visit 1 (Day 1), the following assessments/procedures will be performed:

- Written informed consent (before the challenge at Visit 11 in the EPITOPE study);
- Check and confirm eligibility before enrolling the subject (can use results from Visit 10 in the EPITOPE study);
- New medical history and disease history as compared to the EPITOPE inclusion visit;
- Demographics;
- FAQLQ/FAIM and EQ-5D-5L (see Section 6.4.3). Results of the FAQLQ/FAIM obtained at Visit 10 in the EPITOPE study can be utilized here. Results of the EQ-5D-5L obtained at Visit 10 in the EPITOPE study can be utilized here for subjects who were in EPITOPE Part B. The EQ-5D-5L must be completed at this visit for subjects who were in EPITOPE Part A;
- Physical examination (including a complete skin examination) and measurement of height and weight (see Section 6.2.3). The physical examination findings obtained before the challenge at Visit 11 in the EPITOPE study can be utilized here;
- Vital signs (see Section 6.2.4). The vital signs results obtained before the challenge at Visit 11 in the EPITOPE study can be utilized here;

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- Spirometry (FEV_1) (See Section 6.2.5) (preferred test) or PEF (see Section 6.2.6) for subjects aged ≥ 4 years and with a diagnosis of asthma;
- SCORAD (see Section 6.4.6). SCORAD results obtained at Visit 10 in the EPITOPE study can be utilized here;
- SPT (see Section 6.4.2). Skin prick test results obtained at Visit 10 in the EPITOPE study can be utilized here;
- Immunological markers (see Section 6.4.1) including specific IgE to cow's milk, egg white, house dust mites, and grass. The results obtained at Visit 10 in the EPITOPE study can be utilized here. For subjects who were in EPITOPE Part B, total IgE results obtained at Visit 10 in the EPITOPE study can be used for this visit. For subjects who were in EPITOPE Part A, total IgE assessment will be performed at this visit on blood samples drawn at Visit 10 in the EPITOPE study;
- Laboratory tests (see Section 6.2.2). The results obtained at Visit 10 in the EPITOPE study can be utilized here. If applicable, subjects with abnormal laboratory assessments due to a concomitant transient disease (flu, viral illness, etc.) can repeat their laboratory assessments or be rescheduled for laboratory assessment at the discretion of the Investigator;
- AE recording (see Section 6.2.1);
- Collect blood sample for epigenetic analyses (see Section 6.4.5). The results obtained at Visit 10 in the EPITOPE study can be utilized here;
- Record all concomitant medications (including ongoing concomitant medications from the EPITOPE study) (see Section 5.7);
- Check for any accidental peanut consumption (see Section 6.4.4). The information obtained at Visit 11 in the EPITOPE study can be utilized here;
- Dispense the subject diary (give reminders to subject/parents/guardians on its use) (see Section 6.2.7);
- Dispense the subject safety leaflet and the subject participation card;
- Dispense the first box of study treatment to the subject's parents/guardians (give reminders on the proper application, timing and storage);
- Apply the first Viaskin® patch to the subject's back for 2 hours;
- Keep under observation on-site for 3 hours after the patch has been applied;
- Check skin reaction under or around the patch without removing it and grade severity. Take photos of the application site before and 30 minutes, 1 hour, 2 hours and 3 hours after application (see Table 2, Section 6.2.8);

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- The expiry date of the auto-injector will be checked and a new auto-injector will be provided to the subject prior to product expiry, if needed. Review the use of the auto-injector of epinephrine and the Anaphylaxis Emergency Action Plan;
- Dispense 1% hydrocortisone ointment;

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- Schedule Day 4 and Day 22 phone contacts and Visit 2.

After the first application of the Viaskin® patch at the study site, all subjects will be observed for 3 hours before being discharged with the patch still applied on the skin and the reactions under and around the patch will be checked and graded before discharge.

7.2.2 Phone Contacts (Day 4±2 days, Day 22±2 days)

The parents/guardians of the subject will be called between two consecutive visits, to assess the subject's condition since the previous visit.

At Day 4 after the patch was applied for 2 hours daily for 3 days, and at Day 22 (Week 3 of treatment), 1 week after the patch was applied for 8 hours daily, specific phone contacts will be made to the parents/guardians to assess the safety/tolerability of patch applications on the back.

During the phone contacts, the site staff could ask to be provided with photos of the application site to assess the local skin reactions. If required, the subjects may be seen earlier by the Investigator.

The following assessments will be performed during the phone contacts:

- AE recording (including solicited AEs and AESIs) (see Section 6.2.1);
- Concomitant medications (see Section 5.7);
- Check for any accidental peanut consumption (see Section 6.4.4);
- Check with the subject's parents/guardians to ensure that the diary has been completed accurately and that the subject's parents/guardians are comfortable with using the diary;
- Remind of next Visit.

7.2.3 Visit 2 (Month 1±3 days)

At this visit the following assessments/procedures will be performed:

- FAQLQ/FAIM and EQ-5D-5L (see Section 6.4.3) before any other procedure is performed;
- Physical examination (including a complete skin examination) and measurement of height and weight (see Section 6.2.3);
- Vital signs (see Section 6.2.4);
- Spirometry (FEV_1) (See Section 6.2.5) (preferred test) or PEF (see Section 6.2.6) for asthmatic subjects aged ≥4 years;
- AE recording (including solicited AEs and AESIs) (see Section 6.2.1);
- Concomitant medications (see Section 5.7);
- Check for any accidental peanut consumption (see Section 6.4.4);
- Check with the subject's parents/guardians to ensure that the diary has been completed accurately and that the subject's parents/guardians are comfortable with using the diary;

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- Collect the treatment box dispensed at the previous visit, check the unused medication and assess medication compliance;
- Dispense new boxes of study treatment (re-instruct subject/parents/guardians on the proper application, timing and storage conditions, if necessary);
- Check skin reactions under or around the current patch (if the patch is still worn by the subject at the time of the visit but without removing it) and all other zones of application and grade severity of the skin reactions. Take photos of the application site if required (see Table 2, Section 6.2.8);

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- Review the use of the auto-injector of epinephrine and the Anaphylaxis Emergency Action Plan;
- Dispense 1% hydrocortisone ointment as necessary;
- Schedule Visit 3.

There is no requirement for subject observation before discharge at Visit 2.

7.2.4 Visit 3 (Month 3±7 days)

At this visit, the following assessments/procedures will be performed:

- Physical examination (including a complete skin examination) and measurement of height and weight (see Section 6.2.3);
- Vital signs (see Section 6.2.4);
- Spirometry (FEV_1) (See Section 6.2.5) (preferred test) or PEF (see Section 6.2.6) for subjects aged ≥ 4 years and with a diagnosis of asthma;
- SCORAD (see Section 6.4.6);
- SPT (see Section 6.4.2);
- Immunological markers (see Section 6.4.1);
- Laboratory tests (see Section 6.2.2);
- Collect blood sample for epigenetic analyses (see Section 6.4.5);
- AE recording (including solicited AEs and AESIs) (see Section 6.2.1);
- Concomitant medications (see Section 5.7);
- Check for any accidental peanut consumption (see Section 6.4.4);
- Check with the subject's parents/guardians to ensure that the diary has been completed accurately and that the subject's parents/guardians are comfortable with using the diary;
- Collect the treatment boxes dispensed at the previous visit, check the unused medication and assess medication compliance;

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- Dispense new boxes of study treatment (re-instruct on the proper application, timing and storage conditions, if necessary);
- Check skin reactions under or around the current patch (if the patch is still worn by the subject at the time of the visit but without removing it) and all other zones of application and grade severity of the skin reactions. Take photos of the application site if required (see Table 2, Section 6.2.8);

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- Review the use of the auto-injector of epinephrine and the Anaphylaxis Emergency Action Plan;
- Dispense 1% hydrocortisone ointment as necessary;
- Schedule Visit 4.

There is no requirement for subject observation before discharge at this visit.

7.2.5 Visit 4 (Month 6±7 days)

At this visit, the following assessments/procedures will be performed:

- FAQLQ/FAIM and EQ-5D-5L (see Section 6.4.3) before any other procedure is performed;
- Physical examination (including a complete skin examination) and measurement of height and weight (see Section 6.2.3);
- Vital signs (see Section 6.2.4);
- Spirometry (FEV_1) (See Section 6.2.5) (preferred test) or PEF (see Section 6.2.6) for subjects aged ≥ 4 years and with a diagnosis of asthma;
- SCORAD (see Section 6.4.6);
- SPT (see Section 6.4.2);
- Immunological markers (see Section 6.4.1);
- Laboratory tests (see Section 6.2.2);
- AE recording (including solicited AEs and AESIs) (see Section 6.2.1);
- Collect blood sample for epigenetic analyses (see Section 6.4.5);
- Concomitant medications (see Section 5.7);
- Check for any accidental peanut consumption (see Section 6.4.4);
- Check with the subject's parents/guardians to ensure that the diary has been completed accurately and that the subject's parents/guardians are comfortable with using the diary;
- Collect the treatment boxes dispensed at the previous visit, check the unused medication and assess medication compliance;

- Dispense new boxes of study treatment (re-instruct on the proper application, timing and storage conditions, if necessary);
- Check skin reactions under or around the current patch (if the patch is still worn by the subject at the time of the visit but without removing it) and all other zones of application and grade severity of the skin reactions. Take photos of the application site if required (see Table 2, Section 6.2.8);

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- Review the use of the auto-injector of epinephrine and the Anaphylaxis Emergency Action Plan;
- Dispense 1% hydrocortisone ointment as necessary;
- Schedule Visit 7.

There is no requirement for subject observation before discharge at this visit.

7.2.6 Phone Contact (Month 9±7 days)

The parents/guardians of the subject will be called between Visit 6 and Visit 7, to assess the subject's condition since the previous visit.

During the phone contacts, the site staff could ask to be provided with photos of the application site to assess the local skin reactions. If required, the subjects may be seen earlier by the Investigator.

The following assessments will be performed during the phone contacts:

- AE recording (including solicited AEs and AESIs) (see Section 6.2.1);
- Concomitant medications (see Section 5.7);
- Check for any accidental peanut consumption (see Section 6.4.4);
- Check with the subject's parents/guardians to ensure that the diary has been completed accurately and that the subject's parents/guardians are comfortable with using the diary;
- Remind of next Visit.

7.2.7 Visit 5 (Month 12±7 days), First Day of Food Challenge

This Visit corresponds to the first day of the post-treatment DBPCFC. If the subject is wearing a patch at the time of the visit, it must be removed before starting the DBPCFC procedures. A new patch can be applied only after all procedures have been completed, or the next day, depending if the patch has been applied for less or more than 2 hours at the time of the visit.

The following assessments/procedures will be performed:

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- FAQLQ/FAIM and EQ-5D-5L (see Section 6.4.3) before any other procedure is performed;
- Physical examination (including a complete skin examination) and measurement of height and weight (see Section 6.2.3);
- Vital signs (see Section 6.2.4);
- Spirometry (FEV_1) (See Section 6.2.5) (preferred test) or PEF (see Section 6.2.6) for subjects aged ≥ 4 years and with a diagnosis of asthma;
- SCORAD (see Section 6.4.6);
- SPT (see Section 6.4.2);
- Immunological markers (see Section 6.4.1);
- Laboratory tests (see Section 6.2.2);
- AE recording (including solicited AEs and AESIs) (see Section 6.2.1);
- Collect blood sample for epigenetic analyses (see Section 6.4.5);

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- First day of DBPCFC (see Section 6.1);
- Concomitant medications (see Section 5.7);
- Check for any accidental peanut consumption (see Section 6.4.4);
- Check with the subject's parents/guardians to ensure that the diary has been completed accurately and that the subject's parents/guardians are comfortable with using the diary;
- Collect the treatment boxes dispensed at the previous visit, check the unused medication and assess medication compliance;
- Dispense new box of study treatment for application until the 2nd day of the challenge (re-instruct on the proper application, timing and storage conditions, if necessary);
- Check skin reactions at zones of application and grade severity of the skin reactions. Take photos of the application site if required (see Table 2, Section 6.2.8);
- Review the use of the auto-injector of epinephrine and the Anaphylaxis Emergency Action Plan;
- Dispense 1% hydrocortisone ointment as necessary;
- Schedule Visit 6 within the next 7 days.

Physical examinations, assessment of vital signs and PEF measurements are to be done before the DBPCFC but can be repeated during the DBPCFC as deemed necessary by the Investigator.

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The subject may be discharged after a minimum observation period of 3 hours after the last dose of the challenge formula is ingested. The observation period can be extended beyond 3 hours if deemed necessary by the Investigator.

7.2.8 Visit 6 (Month 12+7 days), Second Day of Food Challenge

The second day of the annual DBPCFC takes place at this visit, within 7 days of the first day of the DBPCFC. If the subject is wearing a patch at the time of the visit, it must be removed before starting the DBPCFC procedures. A new patch can be applied only after all procedures have been completed or the next day, depending if the patch has been applied for less or more than 2 hours at the time of the visit.

The following assessments/procedures will be performed:

- Physical examination (including a complete skin examination) and measurement of height and weight (see Section 6.2.3);
- Vital signs (see Section 6.2.4);
- PEF (see Section 6.2.6);
- AE recording (including solicited AEs and AESIs) (see Section 6.2.1);

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- Second day of DBPCFC (see Section 6.1);
- Concomitant medications (including any medications given to treat allergic symptoms) (see Section 5.7);
- Check for any accidental peanut consumption (see Section 6.4.4);
- Check with the subject's parents/guardians to ensure that the diary has been completed accurately and that the subject's parents/guardians are comfortable with using the diary;
- Collect the treatment box dispensed at the previous visit, check the unused medication and assess medication compliance;
- Dispense new boxes of study treatment (re-instruct on the proper application, timing and storage conditions, if necessary);
- Check skin reactions at zones of application and grade severity of the skin reactions. Take photos of the application site if required (see Table 2, Section 6.2.8);
- Schedule Visit 7.

Physical examinations, assessment of vital signs and PEF measurements are to be done before the DBPCFC but can be repeated during the DBPCFC as deemed necessary by the Investigator.

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The subject may be discharged after a minimum observation period of 3 hours after the last dose of the challenge formula is ingested. The observation period can be extended beyond 3 hours if deemed necessary by the Investigator.

7.2.9 Phone Contact (Month 15±7 days)

The parents/guardians of the subject will be called between Visit 4 and Visit 5, to assess the subject's condition since the previous visit.

During the phone contacts, the site staff could ask to be provided with photos of the application site to assess the local skin reactions. If required, the subjects may be seen earlier by the Investigator.

The following assessments will be performed during the phone contacts:

- AE recording (including solicited AEs and AESIs) (see Section 6.2.1);
- Concomitant medications (see Section 5.7);
- Check for any accidental peanut consumption (see Section 6.4.4);
- Check with the subject's parents/guardians to ensure that the diary has been completed accurately and that the subject's parents/guardians are comfortable with using the diary;
- Remind of next Visit.

7.2.10 Visit 7 (Month 18±7 days)

At this visit, the following assessments/procedures will be performed:

- FAQLQ/FAIM and EQ-5D-5L (see Section 6.4.3) before any other procedure is performed;
- Physical examination (including a complete skin examination) and measurement of height and weight (see Section 6.2.3);
- Vital signs (see Section 6.2.4);
- Spirometry (FEV_1) (See Section 6.2.5) (preferred test) or PEF (see Section 6.2.6) for subjects aged ≥ 4 years and with a diagnosis of asthma;
- SCORAD (see Section 6.4.6);
- SPT (see Section 6.4.2);
- Immunological markers (see Section 6.4.1);
- Laboratory tests (see Section 6.2.2);
- AE recording (including solicited AEs and AESIs) (see Section 6.2.1);
- Concomitant medications (see Section 5.7);
- Check for any accidental peanut consumption (see Section 6.4.4);
- Check with the subject's parents/guardians to ensure that the diary has been completed accurately and that the subject's parents/guardians are comfortable with using the diary;

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- Collect the treatment boxes dispensed at the previous visit, check the unused medication and assess medication compliance;
- Dispense new boxes of study treatment (re-instruct on the proper application, timing and storage conditions, if necessary);
- Check skin reactions under or around the current patch (if the patch is still worn by the subject at the time of the visit but without removing it) and all other zones of application and grade severity of the skin reactions. Take photos of the application site if required (see Table 2, Section 6.2.8);

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Review the use of the auto-injector of epinephrine and the Anaphylaxis Emergency Action Plan;

- Dispense 1% hydrocortisone ointment as necessary;
- Schedule Visit 8.

There is no requirement for subject observation before discharge at this visit.

7.2.11 Phone Contact (Month 21±7 days)

The parents/guardians of the subject will be called between Visit 7 and Visit 8, to assess the subject's condition since the previous visit.

During the phone contacts, the site staff could ask to be provided with photos of the application site to assess the local skin reactions. If required, the subjects may be seen earlier by the Investigator.

The following assessments will be performed during the phone contacts:

- AE recording (including solicited AEs and AESIs) (see Section 6.2.1);
- Concomitant medications (see Section 5.7);
- Check for any accidental peanut consumption (see Section 6.4.4);
- Check with the subject's parents/guardians to ensure that the diary has been completed accurately and that the subject's parents/guardians are comfortable with using the diary;
- Remind of next Visit.

7.2.12 Visit 8 (Month 24±7 days), First Day of Food Challenge

This Visit corresponds to the first day of the post-treatment DBPCFC. If the subject is wearing a patch at the time of the visit, it must be removed before starting the DBPCFC procedures. A new patch can be applied only after all procedures have been completed or the next day, depending if the patch has been applied for less or more than 2 hours at the time of the visit.

The following assessments/procedures will be performed:

- FAQLQ/FAIM and EQ-5D-5L (see Section 6.4.3) before any other procedure is performed;
- Physical examination (including a complete skin examination) and measurement of height and weight (see Section 6.2.3);
- Vital signs (see Section 6.2.4);
- Spirometry (FEV_1) (See Section 6.2.5) (preferred test) or PEF (see Section 6.2.6) for subjects aged ≥ 4 years and with a diagnosis of asthma;
- SCORAD (see Section 6.4.6);
- SPT (see Section 6.4.2);
- Immunological markers (see Section 6.4.1);
- Laboratory tests (see Section 6.2.2);
- AE recording (including solicited AEs and AESIs) (see Section 6.2.1);
- Collect blood sample for epigenetic analyses (see Section 6.4.5);

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- First day of DBPCFC (see Section 6.1);
- Concomitant medications (see Section 5.7);
- Check for any accidental peanut consumption (see Section 6.4.4);
- Check with the subject's parents/guardians to ensure that the diary has been completed accurately and that the subject's parents/guardians are comfortable with using the diary;
- Collect the treatment boxes dispensed at the previous visit, check the unused medication and assess medication compliance;
- Dispense new box of study treatment for application until the 2nd day of the challenge (re-instruct on the proper application, timing and storage conditions, if necessary);
- Check skin reactions at zones of application and grade severity of the skin reactions. Take photos of the application site if required (see Table 2, Section 6.2.8);
- Review the use of the auto-injector of epinephrine and the Anaphylaxis Emergency Action Plan;
- Dispense 1% hydrocortisone ointment as necessary;
- Schedule Visit 9 within the next 7 days.

Physical examinations, assessment of vital signs and PEF measurements are to be done before the DBPCFC but can be repeated during the DBPCFC as deemed necessary by the Investigator.

The subject may be discharged after a minimum observation period of 3 hours after the last dose of the challenge formula is ingested. The observation period can be extended beyond 3 hours if deemed necessary by the Investigator.

7.2.13 Visit 9 (Month 24+7 days), Second Day of Food Challenge

The second day of the annual DBPCFC takes place at this visit, within 7 days of the first day of the DBPCFC. If the subject is wearing a patch at the time of the visit, it must be removed before starting the DBPCFC procedures. A new patch can be applied only after all procedures have been completed or the next day, depending if the patch has been applied for less or more than 2 hours at the time of the visit.

The following assessments/procedures will be performed:

- Physical examination (including a complete skin examination) and measurement of height and weight (see Section 6.2.3);
- Vital signs (see Section 6.2.4);
- PEF (see Section 6.2.6);
- AE recording (including solicited AEs and AESIs) (see Section 6.2.1);

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- Second day of DBPCFC (see Section 6.1);
- Concomitant medications (including any medications given to treat allergic symptoms) (see Section 5.7);
- Check for any accidental peanut consumption (see Section 6.4.4);
- Check with the subject's parents/guardians to ensure that the diary has been completed accurately and that the subject's parents/guardians are comfortable with using the diary;
- Collect the treatment box dispensed at the previous visit, check the unused medication and assess medication compliance;
- Dispense new boxes of study treatment (re-instruct on the proper application, timing and storage conditions, if necessary)
    - for subjects in the Placebo+VP group;
    - for subjects who reached their visit 9 before the EPITOPE unblinding
- Check skin reactions at zones of application and grade severity of the skin reactions. Take photos of the application site if required (see Table 2, Section 6.2.8);
- Schedule End-of-Study visit (Visit 10A) for subjects in the VP+VP group (i.e., these subjects are to receive 24 months of treatment in the EPOPEX study).
- Schedule a Visit 10P

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- for subjects in the Placebo+VP group (i.e., these subjects are to receive 36 months of treatment in the EPOPEX study).
- for subjects who reached their visit 9 before the EPITOPE unblinding.

Physical examinations, assessment of vital signs and PEF measurements are to be done before the DBPCFC but can be repeated during the DBPCFC as deemed necessary by the Investigator.

The subject may be discharged after a minimum observation period of 3 hours after the last dose of the challenge formula is ingested. The observation period can be extended beyond 3 hours if deemed necessary by the Investigator.

7.2.14 Phone Contact (Month 27±7 days)

This phone contact will be performed for subjects in the Placebo+VP group and for subjects who reached their visit 9 before the EPITOPE unblinding.

The parents/guardians of the subject will be called between Visit 9 and Visit 10P, to assess the subject's condition since the previous visit.

During the phone contacts, the site staff could ask to be provided with photos of the application site to assess the local skin reactions. If required, the subjects may be seen earlier by the Investigator.

The following assessments will be performed during the phone contacts:

- AE recording (including solicited AEs and AESIs) (see Section 6.2.1);
- Concomitant medications (see Section 5.7);
- Check for any accidental peanut consumption (see Section 6.4.4);
- Check with the subject's parents/guardians to ensure that the diary has been completed accurately and that the subject's parents/guardians are comfortable with using the diary;
- Remind of next Visit.

7.2.15 Visit 10P (Month 30±7 days)

This visit will be performed in all subjects in the Placebo+VP group and for subjects in the VP+VP group who reached their visit 9 before the EPITOPE unblinding.

For subjects in the VP+VP group and who reached their visit 9 before the EPITOPE unblinding, this visit 10P will also be the end of treatment visit.

At this visit, the following assessments/procedures will be performed:

- FAQLQ/FAIM and EQ-5D-5L (see Section 6.4.3) before any other procedure is performed;
- Physical examination (including a complete skin examination) and measurement of height and weight (see Section 6.2.3);
- Vital signs (see Section 6.2.4);

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- Spirometry (FEV_1) (See Section 6.2.5) (preferred test) or PEF (see Section 6.2.6) for subjects aged ≥ 4 years and with a diagnosis of asthma;
- SCORAD (see Section 6.4.6);
- SPT (see Section 6.4.2);
- Immunological markers (see Section 6.4.1);
- Laboratory tests (see Section 6.2.2);
- AE recording (including solicited AEs and AESIs) (see Section 6.2.1);
- Concomitant medications (see Section 5.7);
- Check for any accidental peanut consumption (see Section 6.4.4);
- Check with the subject's parents/guardians to ensure that the diary has been completed accurately and that the subject's parents/guardians are comfortable with using the diary;
- Collect the treatment boxes dispensed at the previous visit, check the unused medication and assess medication compliance;
- Dispense new boxes of study treatment for subjects in Placebo +VP group (re-instruct on the proper application, timing and storage conditions, if necessary); Not applicable for subjects from the VP + VP group.
- Check skin reactions under or around the current patch (if the patch is still worn by the subject at the time of the visit but without removing it) and all other zones of application and grade severity of the skin reactions. Take photos of the application site if required (see Table 2, Section 6.2.8);

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- Review the use of the auto-injector of epinephrine and the Anaphylaxis Emergency Action Plan;
- Dispense 1% hydrocortisone ointment as necessary;
- Schedule Visit 11P for subjects from the Placebo + VP group
- Schedule Visit 11A (End of Study visit) for subjects from the VP + VP group who reached their visit 9 before the EPITOPE unblinding

There is no requirement for subject observation before discharge at this visit.

7.2.16 Phone Contact (Month 33±7 days)

This phone contact will be performed only in subjects in the Placebo+VP group.

The parents/guardians of the subject will be called between Visit 10P and Visit 11P, to assess the subject's condition since the previous visit.

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During the phone contacts, the site staff could ask to be provided with photos of the application site to assess the local skin reactions. If required, the subjects may be seen earlier by the Investigator.

The following assessments will be performed during the phone contacts:

- AE recording (including solicited AEs and AESIs) (see Section 6.2.1);
- Concomitant medications (see Section 5.7);
- Check for any accidental peanut consumption (see Section 6.4.4);
- Check with the subject's parents/guardians to ensure that the diary has been completed accurately and that the subject's parents/guardians are comfortable with using the diary;
- Remind of next Visit.

7.2.17 Visit 11P (Month 36±7 days), First Day of Food Challenge

This Visit corresponds to the first day of the post-treatment DBPCFC for subjects in the Placebo+VP group. If the subject is wearing a patch at the time of the visit, it must be removed before starting the DBPCFC procedures. A new patch can be applied only after all procedures have been completed or the next day, depending if the patch has been applied for less or more than 2 hours at the time of the visit.

The following assessments/procedures will be performed:

- FAQLQ/FAIM and EQ-5D-5L (see Section 6.4.3) before any other procedure is performed;
- Physical examination (including a complete skin examination) and measurement of height and weight (see Section 6.2.3);
- Vital signs (see Section 6.2.4);
- Spirometry (FEV_1) (See Section 6.2.5) (preferred test) or PEF (see Section 6.2.6) for subjects aged ≥ 4 years and with a diagnosis of asthma;
- SCORAD (see Section 6.4.6);
- SPT (see Section 6.4.2);
- Immunological markers (see Section 6.4.1);
- Laboratory tests (see Section 6.2.2);
- AE recording (including solicited AEs and AESIs) (see Section 6.2.1);
- Collect blood sample for epigenetic analyses (see Section 6.4.5);

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- First day of DBPCFC (see Section 6.1);

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- Concomitant medications (see Section 5.7);
- Check for any accidental peanut consumption (see Section 6.4.4);
- Check with the subject's parents/guardians to ensure that the diary has been completed accurately and that the subject's parents/guardians are comfortable with using the diary;
- Collect the treatment boxes dispensed at the previous visit, check the unused medication and assess medication compliance;
- Dispense new box of study treatment for application until the 2nd day of the challenge (re-instruct on the proper application, timing and storage conditions, if necessary);
- Check skin reactions at zones of application and grade severity of the skin reactions. Take photos of the application site if required (see Table 2, Section 6.2.8);
- Review the use of the auto-injector of epinephrine and the Anaphylaxis Emergency Action Plan;
- Dispense 1% hydrocortisone ointment as necessary;
- Schedule Visit 12P within the next 7 days.

Physical examinations, assessment of vital signs and PEF measurements are to be done before the DBPCFC but can be repeated during the DBPCFC as deemed necessary by the Investigator.

The subject may be discharged after a minimum observation period of 3 hours after the last dose of the challenge formula is ingested. The observation period can be extended beyond 3 hours if deemed necessary by the Investigator.

7.2.18 Visit 12P (Month 36+7 days), Second Day of Food Challenge

The second day of the annual DBPCFC takes place at this visit for subjects in the Placebo+VP group, within 7 days of the first day of the DBPCFC. If the subject is wearing a patch at the time of the visit, it must be removed before starting the DBPCFC procedures. A new patch can be applied only after all procedures have been completed or the next day, depending if the patch has been applied for less or more than 2 hours at the time of the visit.

The following assessments/procedures will be performed:

- Physical examination (including a complete skin examination) and measurement of height and weight (see Section 6.2.3);
- Vital signs (see Section 6.2.4);
- PEF (see Section 6.2.6);
- AE recording (including solicited AEs and AESIs) (see Section 6.2.1);

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- Second day of DBPCFC (see Section 6.1);

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- Concomitant medications (including any medications given to treat allergic symptoms) (see Section 5.7);
- Check for any accidental peanut consumption (see Section 6.4.4);
- Check with the subject's parents/guardians to ensure that the diary has been completed accurately and that the subject's parents/guardians are comfortable with using the diary;
- Collect the treatment box dispensed at the previous visit, check the unused medication and assess medication compliance;
- Check skin reactions at zones of application and grade severity of the skin reactions. Take photos of the application site if required (see Table 2, Section 6.2.8);
- Schedule End-of-Study visit (Visit 13P).

Physical examinations, assessment of vital signs and PEF measurements are to be done before the DBPCFC but can be repeated during the DBPCFC as deemed necessary by the Investigator.

The subject may be discharged after a minimum observation period of 3 hours after the last dose of the challenge formula is ingested. The observation period can be extended beyond 3 hours if deemed necessary by the Investigator.

7.2.19 End-of-Study Visit: Visit 10A (12-16 days after Visit 9) or Visit 13P (12-16 days after Visit 12P) or Visit 11 A (12-16 days after Visit 10P)

This visit takes place 12-16 days after the end of treatment (after Visit 9 for subjects in the VP+VP group, after Visit 12P for subjects in the Placebo+VP group and after Visit 10P for subjects from the VP+VP group who reached their Visit 9 before the EPITOPE unblinding).

The following assessments/procedures will be performed at this visit:

- Physical examination (including a complete skin examination; see Section 6.2.3);
- Vital signs (see Section 6.2.4);
- AE recording (including solicited AEs and AESIs) (see Section 6.2.1);
- Concomitant medications (see Section 5.7);
- Check for any accidental peanut consumption (see Section 6.4.4);
- Check with the subject's parents/guardians to ensure that the diary has been completed accurately and collect the diary.

7.2.20 Early Termination Visit

Subjects who discontinue early from the study should, if possible, have an Early Termination Visit. This visit should take place as soon as possible after the subject stops taking the study treatment (see also Section 4.3).

The following assessments will be performed at this visit:

- FAQLQ/FAIM and EQ-5D-5L (see Section 6.4.3) before any other procedure is performed;
- Physical examination (including a complete skin examination; see Section 6.2.3);

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- Vital signs (see Section 6.2.4);
- Spirometry (FEV_1) (see Section 6.2.5) (preferred test) or PEF (see Section 6.2.6) for subjects aged ≥ 4 years and with a diagnosis of asthma;
- SCORAD (see Section 6.4.6);
- SPT (see Section 6.4.2);
- Immunological markers (see Section 6.4.1) including specific IgE to cow's milk, egg white, house dust mites, and grass;
- Laboratory tests (see Section 6.2.2);
- AE recording (including solicited AEs and AESIs) (see Section 6.2.1);
- Concomitant medications (see Section 5.7);
- Check for any accidental peanut consumption (see Section 6.4.4);
- Check with the subject's parents/guardians to ensure that the diary has been completed accurately and collect the diary.
- Check unused medication and assess medication compliance;

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- Check skin reactions under or around the current patch (if the patch is still worn by the subject at the time of the visit but without removing it) and all other zones of application and grade severity of the skin reactions. Take photos of the application site if required (see Table 2, Section 6.2.8).

7.2.21 Unscheduled Visit

Subjects may come to the site for visits outside of the scheduled visits in case of AEs, Viaskin® patch adhesion problems, etc.

The following assessments will be performed at these visits, at the discretion of the Investigator:

- Physical examination (including a complete skin examination; see Section 6.2.3);
- Vital signs (see Section 6.2.4);
- Spirometry (FEV_1) (see Section 6.2.5) (preferred test) or PEF (see Section 6.2.6) for subjects aged ≥ 4 years and with a diagnosis of asthma;
- Laboratory tests (see Section 6.2.2);
- AE recording (including solicited AEs and AESIs) (see Section 6.2.1);
- Concomitant medications (see Section 5.7);
- Check for any accidental peanut consumption (see Section 6.4.4);

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- Check with the subject's parents/guardians to ensure that the diary has been completed accurately and that the subject's parents/guardians are comfortable with using the diary;
- Check unused medication and assess medication compliance;

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- Check skin reactions under or around the current patch (if the patch is still worn by the subject at the time of the visit but without removing it) and all other zones of application and grade severity of the skin reactions. Take photos of the application site if required (see Table 2, Section 6.2.8).

8 STATISTICAL METHODS

The statistical considerations summarized in this section outline the plan for data analysis of this study.

A separate detailed statistical analysis plan (SAP) providing detailed methods for the analyses outlined below will be prepared after the final protocol and finalized before database lock to preserve the integrity of the statistical analysis and study conclusions.

Any deviations from the planned analyses will be described and justified in the final integrated study report.

8.1 Study Subjects

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

- **Placebo+VP group** will consist of subjects who had received placebo in the EPITOPE study and who will receive Viaskin Peanut 250 µg for up to 36 months in this follow-up study.
- **VP+VP group** will consist of subjects who had received Viaskin Peanut 100 µg or 250 µg in the EPITOPE study and who will receive Viaskin Peanut 250 µg for up to 24 months in this follow-up study (36 months in total). Some subjects from the VP+VP group reaching their Visit 9 (24 months) before the EPITOPE unblinding will extend their treatment duration by 6 months, i.e., up to 30 months in this extension study (42 months active treatment in total).

8.1.1 Disposition of Subjects

The number and percentage of subjects enrolled, subjects in each study population, and subjects who completed the treatment period, who discontinued the treatment period, and the primary reason for discontinuation from the treatment period, will be tabulated by treatment group and overall.

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An enrollment summary will be presented overall and by site, showing the first date of consent, and the last study visit exit date among enrolled subjects, duration (in days) which is calculated as last study visit exit date – first date of consent +1, and number of subjects enrolled and completed. The number and percentage of subjects enrolled in total and by site will be summarized for each treatment group and overall.

8.1.2 Protocol Deviations

Deviations from the protocol including violations of inclusion/exclusion criteria will be assessed as "minor" or "major" in cooperation with the Sponsor.

8.1.3 Analysis Sets

All analysis populations will be defined in the SAP.

The Safety population will be comprised of all subjects who have received at least 1 dose of study treatment. This population will be used to assess safety endpoints.

8.2 General Considerations

8.2.1 Statistical Methods

The statistical analyses for the entire study as further outlined in the SAP will be included in the Clinical Study Report (CSR). The SAP will give a detailed description of the summaries and analyses that will be performed and clearly describe when these analyses will take place. The SAP will be prepared after the final protocol and ahead of the database lock to preserve the integrity of the statistical analysis and study conclusions.

All pre-defined statistical analyses will be performed after the database is locked. Statistical analyses will be performed using SAS® Version 9.3 or higher (SAS Institute, Cary, NC, USA).

Categorical variables will be summarized using number of observations and percentages. The denominator for percentages will be the number of subjects in the population with data available unless otherwise stated. Continuous variables will be summarized using descriptive statistics (number of observations [n], mean, standard deviation, minimum, first quartile [Q1], third quartile [Q3], median and maximum).

8.2.2 Analysis and Data Conventions

8.2.2.1 Definition of Baseline

For the Placebo+VP group, the baseline assessment is the latest valid assessment in the EPITOPE study and for the VP+VP group, it is the latest, valid pre-dose assessment in the EPITOPE study.

Depending on the variable to be analyzed and the treatment group, baseline values will be taken either:

- From data collected at Visit 11 or Visit 10 (DBPCFC) in the EPITOPE study/ Visit 1 in the EPOPEX study or
- From the screening data values from Visit 1 up to Visit 3 (screening period) in the EPITOPE study.

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8.2.2.2 Visit Windows

Assessments outside of protocol allowable windows will be taken into account in the analysis according to the visit in which the data are entered.

8.2.2.3 Unscheduled Assessments

Extra assessments (laboratory data or vital signs associated with non-protocol clinical visits or obtained in the course of investigating or managing AEs) will be included in listings, but not summaries. If more than 1 laboratory value is available for a given visit, the first valid observation will be used in summaries and all observations will be presented in listings. It is noted that invalid laboratory data may not be used (from hemolyzed samples, mishandled samples, quantity not sufficient, or other conditions that would render values invalid).

8.2.2.4 Missing Data Conventions

Best efforts should be made by the Investigator to provide complete data.

For safety analyses, partial or missing data will be imputed according to the most conservative approach and described in the SAP.

The conventions for handling missing data for the analysis of endpoints pertaining to the evaluation of clinical benefit of Viaskin Peanut and for the analysis of other exploratory endpoints will be described in the SAP.

8.3 Demographics, Medical History, Baseline Characteristics, and Concomitant Medications

Descriptive statistics will be produced for continuous demographic and baseline characteristics (including age, height, weight, body mass index, FEV_1, PEF, and peanut-specific IgE) for each treatment group and overall. The number and percent of subjects in each group of the categorical demographic and baseline characteristics (including race, medical history, and SPT) will be tabulated by treatment group and overall.

Concomitant medications will be coded using the latest available version of the World Health Organization (WHO) Drug Dictionary. A summary of concomitant medications will be produced by preferred drug name and treatment group. All concomitant medications will be listed.

Medical history will be reported by SOC and PT and coded using the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Disease history will also be described.

All individual subject demographic and baseline characteristic data will be listed.

8.4 Treatment Compliance and Exposure

Treatment compliance (see Section 5.6), extent of exposure and the total dose of peanut protein received during the study will be summarized for each treatment group by means of descriptive statistics (n, mean, SD, median, Q1, minimum, Q3, and maximum) and/or frequency tables (compliance < or ≥80%).

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8.5 Analysis of Endpoints for the Evaluation of Clinical Benefit

The following endpoints will be analyzed after 1, 2 and 3 years of treatment in each group (VP+VP group, Placebo+VP group) and overall:

- 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 DBPCFCs or;
  - The baseline ED was ≤10 mg and the ED is ≥300 mg peanut protein at the post-baseline DBPCFCs.

  For the VP+VP group, the baseline ED is defined as the ED reached at the EPITOPE study entry.

  For the Placebo+VP group, the baseline ED is defined as the latest, valid ED in the EPITOPE study (i.e. Month 12).
- Proportion of subjects reaching a cumulative dose of at least 1444 mg peanut protein at the post-baseline DBPCFCs;
- Proportion of subjects reaching a cumulative dose of at least 3444 mg peanut protein at the post-baseline DBPCFCs;
- 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), which is the percentage of subjects who pass the post-baseline DBPCFCs;
- Mean and median CRD of peanut protein;
- Mean and median ED of peanut protein.

When applicable, the following rescheduling rules will be applied:

Table 3. Rescheduling rules

	Time points			
Groups	**Baseline**	**1 year of active treatment**	**2 years of active treatment**	**3 years of active treatment**
VP+VP	EPITOPE Entry	EPOPEX Entry	EPOPEX Year 1	EPOPEX Year 2
Placebo+VP	EPOPEX Entry	EPOPEX Year 1	EPOPEX Year 2	EPOPEX Year 3

Statistical methods will be detailed in the SAP based on the distribution of variables and missing data.

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8.6 Safety Analyses

8.6.1 Evaluation of Study treatment Safety

The safety analysis will be performed on the Safety population (all subjects who received at least 1 dose of study treatment).

The safety endpoints will be summarized in the overall Safety population and by treatment group over the 3 years of active treatment using the rescheduling rules described in Table 3.

Treatment-emergent AEs will be defined as any AEs, regardless of relationship to study treatment, which occur during or after the initial Viaskin® patch application or any event already present that worsens in either severity or relationship to study treatment following exposure to Viaskin® patches.

All AEs will be reported by SOC and PT as detailed in Section 9.5 and coded using the latest available version of the MedDRA dictionary.

An overall summary of TEAEs will be provided showing the number and percentage of subjects in each treatment group with any TEAEs, any potentially drug-related TEAEs, any severe TEAEs, any severe potentially drug-related TEAEs, any serious TEAEs, any TEAEs leading to discontinuation, and any TEAEs leading to death. The number of events will also be presented.

The number of AEs as well as the number and percentage of subjects who experienced at least 1 AE will be summarized by SOC, PT and treatment group. The incidence of the following events will be summarized:

- TEAEs (distinguished from symptoms/reactions elicited during the DBPCFCs) by maximum severity, relatedness to Viaskin Peanut and maximum duration;
- TEAEs leading to Study Treatment discontinuation;
- SAEs and by SOC and PTs and relatedness to Viaskin Peanut;
- AESIs (including local AESI at patch application site and systemic allergic AESI whatever the causal relationship to Viaskin Peanut).

All AEs will be listed.

8.6.2 Evaluation of Study Procedure Safety

The safety criteria for evaluation of the safety of the study procedure will be summarized using the rescheduling rules, in the overall Safety population and by treatment group, over 3 years of active treatment.

The following DBPCFC data will be tabulated in the overall Safety population as well as by treatment group (VP+VP / Placebo+VP):

- Objective/subjective symptoms by severity elicited during the DBPCFCs;
- Change in objective/subjective symptoms severity;
- Serious adverse events elicited during the DBPCFCs.

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8.6.3 Laboratory Assessments

Descriptive statistics will be calculated for clinical laboratory tests (hematology and biochemistry) performed over the 3-year treatment period. Categorical variables will be summarized by frequency and percentages of subjects.

Changes in laboratory data from baseline will also be presented. In addition, summaries of laboratory values categorized based on Common Terminology Criteria for Adverse Events grade will be presented.

Shift tables of test abnormalities will be generated to compare baseline values to the values collected at other time points.

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

8.6.4 Vital Signs

Observed vital sign values and changes from baseline will be descriptively summarized by visit and treatment group. All vital signs data will be listed.

The analysis of vital signs will focus on abnormalities assessed as clinically relevant. The number of subjects evaluated and the number and percentage of subjects with clinically relevant post-baseline abnormalities at each visit will be presented. The criteria of potentially clinically relevant post-baseline abnormalities are shown in Table 4.

Table 4: Criteria of Potentially Clinically Relevant Abnormalities in Vital Signs

Vital Sign Criteria for Abnormalities	Criteria for Abnormalities
Pulse	>130 beats per minute or an increase from pre-dosing of >20 beats per minute, or <60 beats per minute or a decrease from pre-dosing of >20 beats per minute
Systolic blood pressure	>130 mmHg or an increase from pre-dosing of >40 mmHg, or <70 mmHg or a decrease from pre-dosing of >30 mmHg
Diastolic blood pressure	>85 mmHg or an increase from pre-dosing of >30 mmHg, or <45 mmHg or a decrease from pre-dosing of >20 mmHg

8.6.5 Physical Examination

Physical examination data will be summarized by visit and treatment group and listed.

Changes in physical examination data from baseline will be presented.

Skin reactions observed during the physical examinations will also be reported and the corresponding data will be tabulated separately (see Section 8.6.7).

8.6.6 Spirometry and Peak Expiratory Flow Results

Percent predicted values for FEV_1 and PEF and changes from baseline will be descriptively summarized separately by visit and treatment group. All FEV_1 and PEF data will be listed.

8.6.7 Skin Reactions

Viaskin® patch site examination data will be summarized where appropriate and listed.

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Examination of the skin at the site of patch application will be graded by the Investigators on a scale of Grade 0 (negative) to Grade 4 (erythema, vesicles). Localization of the skin reaction (under the patch/beyond the patch) will also be collected. These results will be summarized using descriptive statistics and presented by visit and treatment group. The worst grade reported will also be tabulated.

8.7 Other Exploratory Analyses

The following exploratory endpoints will be evaluated over 3 years of treatment in each group (VP+VP group, Placebo+VP group) and overall using the rescheduling rules described in Table 3:

- 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 SPT average wheal diameters;
- Description of the QoL questionnaires (FAQLQ/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 index evolution over time

8.7.1 Immunological Markers

Actual values and change from baseline in total IgE, peanut specific IgE and IgG4 and IgE and IgG4 specific to peanut protein components will be tabulated at each time point. Besides, other allergen-specific IgE analyzed (i.e. IgE specific to cow's milk, egg, house dust mites, and grass pollen) will be summarized at the different available timepoints.

8.7.2 Skin Prick Test

Actual values and change from baseline in wheal diameters of undiluted skin prick will be tabulated at the different timepoints.

8.7.3 Quality of Life: Food Allergy Quality of Life Questionnaire /Food Allergy Independent Measure/EQ-5D-5L

The FAQLQ Quality of life scores and changes from baseline will be derived and summarized at the different timepoints. The FAQLQ data will also be listed.
Data collected from the FAIM questionnaires will help validating the different forms of FAQLQs and will be listed. Quality of life assessed with EQ-5D-5L will also be analyzed.

8.7.4 Accidental Consumption of Peanut-containing Food

Frequency of peanut-containing food consumption, conditions around the consumption: accidental consumption, estimated quantity consumed at each occurrence, and associated reactions and severity of reactions will be analyzed specifically. These AEs will be classified

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and analyzed separately and specifically. Risk-taking behaviors will be assessed using the frequency of consumption of peanut reported as deliberate consumptions.

8.7.5 Epigenetic Analyses

Descriptive analyses of epigenetic modifications of specific genes, using observed data will be presented.

8.7.6 Scoring of Atopic Dermatitis

The SCORAD actual value and change from baseline at the different timepoints will be presented using observed data.

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8.9 Interim Analyses

All analyses will be described in the SAP. An interim analysis will be performed once all subjects from the VP+VP group will have completed the DBPCFC at Year 3.

8.10 Determination of Sample Size

All subjects who completed the EPITOPE study will be offered enrollment in the EPOPEX follow-up study.

9 ETHICAL, LEGAL, AND ADMINISTRATIVE ASPECTS

9.1 Informed Consent

The Investigator is responsible for and will obtain a signed ICF from each subject's parent/guardian, before each subject is admitted to the study, in accordance with the ICH-GCP Guidelines, the Declaration of Helsinki, and applicable regulatory requirements.

This consent form must be dated and signed. The original copy must be retained by the Investigator as part of the study records. The Investigator will not undertake any investigation specifically required only for the clinical study until valid consent has been obtained. The terms of the consent and when it was obtained must be documented in the subject's medical records and the e-CRF.

Subjects/parents/guardians will be informed of the nature of the study, its aim, its possible risks and restrictions, its duration, and the compensation that they might receive. The protocol will be explained during a meeting prior to study enrollment, and each subject/parent/guardian must be informed that participation in the study is voluntary and that the subject may withdraw from the study at any time. The parents/guardians should read the ICF before signing and dating it and a copy of the signed document should be given to the parents/guardians. No subject can enter the study before informed consent has been obtained from her/his parents/guardians.

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The explicit wish of a minor, who is capable of forming an opinion and assessing the study information, to refuse participation in or to be withdrawn from the study at any time will be respected by the Investigator.

If a protocol amendment is required, the ICF may need to be revised to reflect the changes to the protocol. If the consent form is revised, it must be reviewed and approved by the appropriate IEC/IRB and signed by the parents/guardians of all subjects subsequently enrolled in the study as well as those currently enrolled in the study.

The Investigator should inform the subject's primary physician about participation in the clinical study wherever required.

9.2 Data Quality Assurance

The Sponsor or Sponsor's designee will conduct a site visit or a site phone contact to verify the qualifications of each Investigator, inspect the site facilities, and inform the Investigator of her/his responsibilities and the required procedures for ensuring adequate site selection and correct documentation.

All data generated by the site personnel will be captured electronically at each study center using e-CRFs. Data from external sources (such as laboratory data) will be imported into the database.

Once clinical data are entered and validated in the e-CRF, they are transmitted and recorded by the central server in the central database. Computerized edit-checks will be developed in addition to manual review to detect any discrepancies and to ensure consistency of the data. The appropriate staff at the study site will answer queries sent to the Investigator. The reason for changes, the name of the person who performed the changes, together with the time and date will be automatically recorded by the Electronic Data Capture (EDC). An electronic audit trail system will be used to track all data changes in the database subsequent to the first data entry.

If additional corrections are needed, the responsible monitor or data manager or the Sponsor will raise a query in the EDC application. Appropriate feedback to the study staff or other corrective measures will be undertaken if any missing data, inconsistent data, outlier data and potential protocol deviations are identified during routine remote data review.

Once all source data verification is complete and all queries are closed, the monitor will freeze the e-CRF page.

9.3 Case Report Forms and Source Documentation

All data obtained during this study should be entered in the e-CRFs promptly. All source documents from which e-CRF entries are derived should be placed in the subject's medical records. Measurements for which source documents are usually available include laboratory assessments, spirometry, PEF and immunological markers.

Data that will be entered directly into the e-CRF (those for which there is no prior written or electronic record of data) are considered to be source data.

The original e-CRF entries for each subject may be checked against source documents at the study site by the PRA site monitor.

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After review by the PRA site monitor, completed e-CRF entries will be uploaded and forwarded to PRA. Instances of missing or uninterpretable data will be discussed with the Investigator for resolution.

The specific procedures to be used for data entry and query resolution using the e-CRF/ EDC system will be provided to study sites in a training manual. In addition, site personnel will receive training on the e-CRF.

The Investigators (and appropriately authorized staff) will be given access to an online web-based EDC system which is 21 CFR Part 11 compliant. This system is specifically designed for the collection of the clinical data in electronic format. Access and rights to the EDC system will be carefully controlled and configured according to each individual's role throughout the study. In general, only the Investigator and authorized staff will be able to enter data and make corrections in the e-CRFs.

The e-CRF should be completed for each subject for whom the study specific ICF was obtained and should reflect the latest observations on the subject participating in the study. Therefore, the e-CRFs are to be completed as soon as possible during or immediately after the subject's visit or assessment. The Investigator must verify that all data entries in the e-CRF are accurate and correct. If some assessments cannot be done, or if certain information is unavailable, not applicable or unknown, the Investigator should indicate this in the e-CRF.

Computerized data-check programs and manual checks will identify any clinical data discrepancies for resolution. Corresponding queries will be loaded into the system and the site will be informed about new issues to be resolved on-line. All discrepancies will be solved on-line directly by the Investigator or by authorized staff within 7 days of query issue. Off-line edit checks will be done to examine relationships over time and across panels to facilitate quality data.

After completion, the Investigator will be required to validate and electronically sign-off the clinical data recorded in each e-CRF.

Information concerning study treatment dispensation to the subject will be tracked in the e-CRF.

9.4 Access to Source Data

9.4.1 Routine Monitoring

During the study, a site monitor from PRA will conduct site visits to review protocol compliance, compare e-CRF entries and individual subject's medical records, assess treatment accountability, and ensure that the study is being conducted according to ethical and pertinent regulatory requirements. The e-CRF entries will be verified against source documentation. The review of medical records will be performed in a manner to ensure that subject confidentiality is maintained.

Checking of the e-CRF entries for completeness and clarity, and cross-checking with source documents, will be required to monitor the progress of the study. Direct access to source data will be required for the monitoring activities.

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9.4.2 Inspections and Auditing Procedures

The Sponsor or its representative may conduct audits at the investigative sites including, but not limited to, treatment supply, presence of required documents, the informed consent process, and comparison of e-CRFs with source documents. All medical records (progress notes) must be available for audit. The Investigator agrees to participate in audits conducted at a convenient time in a reasonable manner.

Moreover, local or foreign Regulatory Authorities of certain countries may wish to carry out such source data checks and/or on-site inspections. Direct access to source data will be required for these inspections; they will be carried out giving due consideration to data protection and medical confidentiality.

9.5 Data Processing

All data will be entered by site personnel into the e-CRF (as detailed in Section 9.3).

The data-review and data-handling document, to be developed during the initiation phase of the study, will include specifications for consistency and plausibility checks on data and will also include data-handling rules for obvious data errors. Queries/inconsistencies will be sent to the study Investigators and monitors for resolution. The database will be updated on the basis of validated/signed corrections.

Previous and concomitant medications will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Disease and Medical histories/current medical conditions and AEs will be coded using the MedDRA terminology.

The versions of the coding dictionaries will be provided in the CSR.

9.6 Archiving Study Records

All data derived from the study will remain the property of the Sponsor. Records must be retained in accordance with the current ICH Guidelines on GCP. All essential study documents including records of subjects, source documents, e-CRFs and study treatment inventory must be kept in a study specific file.

Trial documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or planned marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the product.

For this study, the Investigator site files records must be retained by the Investigator at least 15 years after the completion of the trial, or longer if required by their national regulation.

Subjects' medical records must be kept for the maximum period permitted by the hospital, institution or private practice.

The Investigator will not discard any relevant records to this study without prior written permission from the Sponsor. The Investigator shall notify the Sponsor in writing of their intent to destroy all such material. The Sponsor shall have 30 days to respond to the Investigator's notice and the Sponsor shall have a further opportunity to retain such materials at the Sponsor's expense.

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The Investigator shall take responsibility for maintaining adequate and accurate hard copy source documents of all observations and data generated during this study. Such documentation is subject to inspection by the Sponsor, its representatives and Regulatory Authorities. If an Investigator moves, withdraws from the study or retires, the responsibility for maintaining the records may be transferred to another person who will accept responsibility. Notice of transfer must be made to and agreed by the Sponsor.

9.7 Good Clinical Practice

The procedures set out in this study protocol are designed to ensure that the Sponsor and Investigator abide by the principles of the ICH-GCP Guidelines, and of the Declaration of Helsinki (APPENDIX 1). The study will be carried out in keeping with local legal requirements.

9.8 Protocol Approval and Amendment

Before the start of the study, the study protocol and/or other relevant documents will be reviewed and approved by the IEC/IRB/Regulatory Authorities, in accordance with local legal requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first subject is enrolled in the study.

This protocol is to be followed exactly. Any change to the protocol must be handled as a protocol amendment. Any potential amendment must be approved by the Sponsor. A written amendment must be submitted to the appropriate Regulatory Authorities and to the IRB/IECs assuming this responsibility. The Investigator must await IRB/IEC approval of protocol amendments before implementing the changes, except where necessary to eliminate apparent immediate hazard to subjects.

All substantial amendments to the protocol must be approved in writing by both the appropriate Regulatory Authorities and the IRB/IEC, except for administrative amendments, which require notification but not written approval. Once approved, the protocol amendment will be distributed to all recipients of the original protocol, with instructions to append the amendment to the protocol. If, in the judgment of the local IRB/IEC, the Investigator and/or Sponsor, the protocol amendment alters the study design, procedures and/or increases the potential risk to the subject, the currently approved written ICF will require modifications. The modified ICF must also be reviewed and approved by the Sponsor, appropriate Regulatory Authorities, and the IRB/IEC. In such cases, repeat informed consent must be obtained from the enrolled subjects' parents/guardians before participation continues.

9.9 Data and Safety Monitoring Board

A DSMB composed of independent experts in food allergy and in the methodology of clinical studies (same DSMB members as in the EPITOPE study) will be established in due time for the first data review. This DSMB will be independent of the Sponsor and will review safety data from the study at specified intervals during the study and on an *ad hoc* basis as deemed necessary by the DSMB Chair person or when conveyed by the Sponsor.

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During these review meetings, the DSMB will assess whether the nature, frequency, and severity of the AEs associated with the study treatment warrant any recommendations or corrective actions in the best interest of the subjects.

The roles, responsibilities, constitution, and operations of the DSMB will be described in the DSMB Charter, which will be reviewed and signed by each member before the first subject is randomized and treated.

9.10 Duration of the Study

For an individual subject, the maximum duration of study participation will be up to 2 years and 1 month for subjects previously randomized to Viaskin Peanut 100 µg or 250 µg in the EPITOPE study and 3 years and 1 month for subjects previously randomized to placebo in the EPITOPE study (including visit windows). The planned study duration is around 60 months. The study will close when all subjects have completed the final End of Study Visit.

Subjects randomized to the active treatment arm and who will reach their Visit 9 (month 24) before the EPITOPE study unblinding will extend their EPOPEX study participation up to 2 years and 7 months.

9.11 Premature Termination of the Study

If the Investigator, the Sponsor, or the Medical Monitor becomes aware of conditions or events that suggest a possible hazard to subjects if the study continues, the study may be terminated after appropriate consultation between the relevant parties. The study may also be terminated early at the Sponsor's discretion in the absence of such a finding.

Conditions that may warrant termination include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the subjects enrolled in the study;
- Failure to enroll subjects at an acceptable rate;
- A decision on the part of the Sponsor to suspend or discontinue development of the drug;
- A decision from the Regulatory Authorities to suspend or discontinue the study.

In terminating the study, the Sponsor and the Investigators will ensure that adequate consideration is given to the protection of the subjects' interests.

9.12 Confidentiality

All information, including skin photos, obtained during the conduct of the study with respect to the subject's state of health will be regarded as confidential. For disclosure of any such information, an agreement will be obtained in writing. The Investigator must ensure that each subject's anonymity is maintained. On e-CRFs, e-diaries and other documents transmitted to the Sponsor or its representatives, subjects must not be identified by name. Instead, subjects will only be known by the unique subject number allocated to them in order to ensure confidentiality on all study documentation. Subjects will retain this unique number throughout the study. The Investigator will keep a separate log of these codes.

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In order to comply with government regulatory guidelines and to ensure subject safety, it may be necessary for the Sponsor and its representative, the IEC/IRB or Regulatory Authorities to review subjects' medical records as they relate to this study. Only the subject's unique number in the e-CRFs will identify her/him, but their full names may be made known to a Regulatory Authority or other authorized government or health care officials, if necessary, and to personnel designated by the Sponsor.

Documents that are not for submission to the Sponsor (for example consent forms) will be maintained by the Investigator in strict confidence, except to the extent necessary to allow monitoring and auditing by the Sponsor and inspection by Regulatory Authorities. No documents identifying subjects by name will leave the investigative site and subject identity will remain confidential in all publications related to the study.

9.13 Contractual and Financial Details

The Investigator (and/or, as appropriate, the hospital administrative representative) and the Sponsor will sign a clinical study agreement prior to the start of the study, outlining overall Sponsor and Investigator responsibilities in relation to the study. The contract should describe whether costs for pharmacy, laboratory and other protocol-required services are being paid directly or indirectly.

Financial Disclosure Statements will need to be completed, as requested by FDA CFR 21 part 54.

9.14 Liability and Insurance

The Sponsor will take out reasonable third-party liability insurance cover in accordance with all local legal requirements. The civil liability of the Investigator, the persons instructed by her/him and the hospital, practice, or institute in which they are employed and the liability of the Sponsor with respect to financial loss due to personal injury and other damage that may arise as a result of the carrying out of this study are governed by the applicable law.

Deviations from the study protocol, especially the prescription of a dose other than that scheduled in the study protocol, other modes of administration, other indications, and longer treatment periods, are not permitted and shall not be covered by the statutory subject insurance scheme.

The Sponsor will arrange for subjects participating in this study to be insured against financial loss due to personal injury caused by the pharmaceutical products being tested or by medical steps taken in the course of the study.

9.15 Publication Policy

By signing the study protocol, the Investigator agrees with the use of results of the study for the purposes of national and international registration, publication and information for medical and pharmaceutical professionals. If necessary, Regulatory Authorities will be notified of the Investigator's name, address, qualifications and extent of involvement.

The Investigator shall not publish any data (poster, abstract, paper, etc.) without having consulted with the Sponsor in advance and having received a written approval for such a publication. Details are provided in a separate document.

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9.16 Critical Documents

Before the Investigator starts the trial, the following documents must be made available to DBV Technologies:

- Regulatory approval;
- Curricula vitae of Investigator and Sub-investigator(s) (current, dated and signed);
- Favourable opinion from IRB/IEC clearly identifying the documents reviewed: the protocol, any substantial amendments, subject information/informed consent form and any other written information to be provided to the subject, subject recruitment procedures;
- List of IRB/IEC members/constitution;
- Signed and dated agreement on the final protocol;
- Signed and dated agreement on any substantial amendment(s), if applicable;
- Copy of IRB/IEC approved subject information/informed consent form/any other written information/advertisement;
- Signed receipt of IB by Investigator;
- Laboratory certification and normal ranges;
- Financial agreement(s);
- FDA financial disclosure form (as the trial is conducted under an Investigational New Drug Application (IND)).

9.17 Clinical Study Report

Two clinical study reports will be prepared for the EPOPEX study:

- An interim CSR will be prepared after all subjects in the VP+VP group have terminated the study, i.e. after they have completed Visit 10A;
- A final CSR will be prepared at the end of the study.

The CSRs will be prepared according to the ICH guideline on Structure and Contents of Clinical Study Reports. A final clinical study report will be prepared regardless of whether the study is completed or prematurely terminated. The Sponsor will provide each Investigator with a copy of the final report or synopsis for retention.

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LITERATURE CITED

1. Sicherer SH, Sampson HA. Food allergy: epidemiology, pathogenesis, diagnosis, and treatment. J. Allergy Clin. Immunol. 2014; 133(2):291–307.

2. Jackson KD, Howie LD, Akinbami LJ. Trends in allergic conditions among children: United States, 1997-2011. NCHS Data Brief 2013; (121):1–8.

3. McGowan EC, Keet CA. Prevalence of self-reported food allergy in the National Health and Nutrition Examination Survey (NHANES) 2007-2010. J. Allergy Clin. Immunol. 2013; 132(5):1216–9.

4. Bock SA, Munoz-Furlong A, Sampson HA. Fatalities due to anaphylactic reactions to foods. J. Allergy Clin. Immunol. 2001; 107(1):191–3.

5. Bock SA, Munoz-Furlong A, Sampson HA. Further fatalities caused by anaphylactic reactions to food, 2001-2006. J. Allergy Clin. Immunol. 2007; 119(4):1016–8.

6. Sicherer SH, Muñoz-Furlong A, Godbold JH, Sampson HA. US prevalence of self-reported peanut, tree nut, and sesame allergy: 11-year follow-up. J Allergy Clin Immunol 2010; 125(6):1322–6.

7. Grundy J, Matthews S, Bateman B, Dean T, Arshad SH. Rising prevalence of allergy to peanut in children: Data from 2 sequential cohorts. J Allergy Clin Immunol 2002; 110(5):784–9.

8. Fleischer DM, Conover-Walker MK, Christie L, Burks AW, Wood RA. The natural progression of peanut allergy: Resolution and the possibility of recurrence. J Allergy Clin Immunol 2003; 112(1):183–9.

9. Peters RL, Allen KJ, Dharmage SC, Koplin JJ, Dang T, Tilbrook KP et al. Natural history of peanut allergy and predictors of resolution in the first 4 years of life: A population-based assessment. J Allergy Clin Immunol 2015; 135(5):1257-66.e1-2.

10. Eigenmann PA, Beyer K, Wesley Burks A, Lack G, Liacouras CA, Hourihane JO et al. New visions for food allergy: an iPAC summary and future trends. Pediatr Allergy Immunol 2008; 19 Suppl 19:26–39.

11. Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson, N.F., Jr., Bock SA, Branum A et al. Second symposium on the definition and management of anaphylaxis: summary report-Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J. Allergy Clin. Immunol. 2006; 117(2):391–7.

12. Muraro A, Werfel T, Hoffmann-Sommergruber K, Roberts G, Beyer K, Bindslev-Jensen C et al. EAACI Food allergy and Anaphylaxis Guidelines: diagnosis and management of food allergy. Allergy 2014; 69(8):1008–25.

13. Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, Wood RA et al. Guidelines for the diagnosis and management of food allergy in the United States: Summary of the NIAID-Sponsored Expert Panel Report. J. Allergy Clin. Immunol. 2010; 126(6 Suppl):S1-58.

DocuSign Envelope ID: CCI

14. Burks AW, Sampson HA, Plaut M, Lack G, Akdis CA. Treatment for food allergy. J Allergy Clin Immunol 2018; 141(1):1–9.

15. Albin S, Nowak-Wegrzyn A. Potential treatments for food allergy. Immunol. Allergy Clin. North Am. 2015; 35(1):77–100.

16. Leung DY, Sampson HA, Yunginger JW, Burks, A.W., Jr., Schneider LC, Wortel CH et al. Effect of anti-IgE therapy in patients with peanut allergy. N. Engl. J. Med. 2003; 348(11):986–93.

17. Sampson HA, Leung DYM, Burks AW, Lack G, Bahna SL, Jones SM et al. A phase II, randomized, double‐blind, parallel‐group, placebo‐controlled oral food challenge trial of Xolair (omalizumab) in peanut allergy. J Allergy Clin Immunol 2011; 127(5):1309-10.e1.

18. Jones SM, Burks AW, Dupont C. State of the art on food allergen immunotherapy: oral, sublingual, and epicutaneous. J Allergy Clin Immunol 2014; 133(2):318–23.

19. Jones SM, Pons L, Roberts JL, Scurlock AM, Perry TT, Kulis M et al. Clinical efficacy and immune regulation with peanut oral immunotherapy. J Allergy Clin Immunol 2009; 124(2):292-300, 300.e1-97.

20. Kim EH, Bird JA, Kulis M, Laubach S, Pons L, Shreffler W et al. Sublingual immunotherapy for peanut allergy: clinical and immunologic evidence of desensitization. J Allergy Clin Immunol 2011; 127(3):640-6.e1.

21. Varshney P, Jones SM, Scurlock AM, Perry TT, Kemper A, Steele P et al. A randomized controlled study of peanut oral immunotherapy (OIT): clinical desensitization and modulation of the allergic response. J. Allergy Clin. Immunol. 2011; 127(3):654–60.

22. Anagnostou K, Islam S, King Y, Foley L, Pasea L, Bond S et al. Assessing the efficacy of oral immunotherapy for the desensitisation of peanut allergy in children (STOP II): a phase 2 randomised controlled trial. Lancet 2014; 383(9925):1297–304.

23. Blumchen K, Ulbricht H, Staden U, Dobberstein K, Beschorner J, Oliveira LC de et al. Oral peanut immunotherapy in children with peanut anaphylaxis. J. Allergy Clin. Immunol. 2010; 126(1):83–91.

24. Vickery BP, Scurlock AM, Steele P, Kamilaris J, Hiegel AM, Carlisle SK et al. Early and Persistent Gastrointestinal Side Effects Predict Withdrawal from Peanut Oral Immunotherapy (OIT). J. Allergy Clin. Immunol. 2011; 127(2):AB26.

25. Wasserman RL, Sugerman RW, Mireku-Akomeah N, Gallucci AR, Pence DM, Long NA. Peanut oral immunotherapy (OIT) of food allergy (FA) carries a significant risk of eosinophilic esophagitis (EoE). J. Allergy Clin. Immunol. 2011; 127(2):AB28.

26. Wasserman RL, Factor JM, Baker JW, Mansfield LE, Katz Y, Hague AR et al. Oral immunotherapy for peanut allergy: multipractice experience with epinephrine-treated reactions. J. Allergy Clin. Immunol. Pract. 2014; 2(1):91–6.

27. Hsieh FH. Oral food immunotherapy and iatrogenic eosinophilic esophagitis: an acceptable level of risk? Ann Allergy Asthma Immunol 2014; 113(6):581–2.

DocuSign Envelope ID: CCI

28. Lucendo AJ, Arias A, Tenias JM. Relation between eosinophilic esophagitis and oral immunotherapy for food allergy: a systematic review with meta-analysis. Ann. Allergy Asthma Immunol. 2014; 113(6):624–9.

29. Fleischer DM, Burks AW, Vickery BP, Scurlock AM, Wood RA, Jones SM et al. Sublingual immunotherapy for peanut allergy: a randomized, double-blind, placebo-controlled multicenter trial. J. Allergy Clin. Immunol. 2013; 131(1):119–27.

30. Investigator's Brochure Viaskin Peanut (DBV712): current version.

31. Vickery BP, Scurlock AM, Kulis M, Steele PH, Kamilaris J, Berglund JP et al. Sustained unresponsiveness to peanut in subjects who have completed peanut oral immunotherapy. J. Allergy Clin. Immunol. 2014; 133(2):468–75.

32. EMA C. Guideline on the Clinical Development of Products for Specific Immunotherapy for the Treatment of Allergic Diseases; 2008 [cited 15th May 2018]. Available from: URL: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003605.pdf.

33. ICH Expert Working Group. ICH Harmonised Tripartite Guideline: General Considerations for Clinical Trials – E8. Version dated [17 July] 1997. Available from: URL: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E8/Step4/E8_Guideline.pdf.

34. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. Available from: URL: http://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention/.

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

36. Turjanmaa K, Darsow U, Niggemann B, Rancé F, Vanto T, Werfel T. EAACI/GA2LEN position paper: present status of the atopy patch test. Allergy 2006; 61(12):1377–84.

37. Goossens NJ, Flokstra-de Blok, Bertine M J, van der Meulen, Gerbrich N, Arnlind MH, Asero R, Barreales L et al. Health-related quality of life in food-allergic adults from eight European countries. Ann Allergy Asthma Immunol 2014; 113(1):63-68.e1.

38. van der Velde JL, Flokstra-de Blok BM, Vlieg-Boerstra BJ, Oude Elberink JN, DunnGalvin A, Hourihane JO et al. Development, validity and reliability of the food allergy independent measure (FAIM). Allergy 2010; 65(5):630–5.

39. Kunz B, Oranje AP, Labreze L, Stalder JF, Ring J, Taieb A. Clinical validation and guidelines for the SCORAD index: consensus report of the European Task Force on Atopic Dermatitis. Dermatology (Basel) 1997; 195(1):10–9.

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10 APPENDICES

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APPENDIX 1

Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be

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evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

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17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

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23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may

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consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

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and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

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APPENDIX 2

Activity of Corticosteroids

CORTICOSTEROID	*ACTIVITY*	*RELATIVE POTENCY*	*EQUIVALENT DOSE (mg)*
Dexamethasone	**Long-acting**	**25**	**0.75**
Prednisone	**Intermediate-acting**	**4**	**5.0**
Methylprednisolone	**Intermediate -acting**	**5**	**4.0**
Hydrocortisone	**Short-acting**	**1.0**	**20.0**

Information from Drug facts and comparisons. St Louis: Facts and Comparisons, 1997:122-23.

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APPENDIX 3

Management of asthma in children as per Global Initiative for Asthma (GINA) 2018

Children aged 5 years and younger

A. Stepwise approach to long-term management of asthma in children 5 years and younger

	Controller		Reliever
	Preferred option	**Other options**	
Step 1 As-needed inhaled SABA	-	-	As-needed inhaled SABA
Step 2 Initial controlled treatment + as-needed SABA	Daily low dose ICS	LTRA Intermittent ICS	
Step 3 Additional controller treatment + as-needed SABA	Moderate dose (i.e., double 'low dose" ICS)	Low dose ICS + LTRA	
Step 4	Continue controller & refer to specialist assessment	Add LTRA Increase ICS frequency Add intermittent ICS	
ICS: Inhaled corticosteroid; LTRA: Leukotriene receptor antagonist; SABA: Short-acting beta$_2$-agonist.			

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B. Low daily doses of inhaled corticosteroids for children 5 years and younger

Drug	**Low daily dose (mcg)** (age-group with adequate safety and effectiveness data)
Beclomethasone dipropionate (HFA)	100 (ages ≥5 year)
Budesonide nebulized	500 (ages ≥1 year)
Fluticasone propionate (HFA)	100 (ages ≥4 years)
Mometasone furoate	110 (ages ≥4 years)
Budesonide pMDI + spacer	Not sufficiently studied in this age group
Ciclesonide	Not sufficiently studied in this age group
Triamcinolone acetonide	Not sufficiently studied in this age group
HFA: hydrofluoralkane propellant; pMDI; pressurized metered dose inhaler This is not a table of clinical equivalence. A low daily dose is defined as the lowest approved dose for which safety and effectiveness have been adequately studied in this age group.	

In the absence of recommendations on ICS doses for toddlers, the thresholds provided for children 6-11 years is to be applied.

C. Definition of uncontrolled asthma in children 5 years and younger

In the past 4 weeks, the child had 3-4 episodes of:

- Daytime asthma symptoms for more than a few minutes, more than once a week;
- Activity limitation due to asthma;
- Need of reliever medication more than once a week;
- Night waking or night coughing due to asthma.

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Children above the age of 5 years

A. Stepwise approach to long-term management of asthma in children aged 6-11 years

	Controller		Reliever
	Preferred option	**Other options**	
Step 1 As-needed inhaled SABA	-	-	As-needed inhaled SABA
Step 2 Low dose controller plus as-needed SABA	Regular low dose ICS	LTRA	
Step 3 1 or 2 controllers + as-needed SABA	Medium dose ICS	ICS + LABA	As-needed inhaled SABA or ICS/formoterol*
Step 4	Refer for expert assessment and advice		
Step 5			
ICS: Inhaled corticosteroid; LABA: Long-acting beta$_2$-agonist; LTRA: Leukotriene receptor antagonist; SABA: Short-acting beta$_2$-agonist.*Low dose ICS/formoterol is the reliever medication for patients prescribed low dose budesonide/formoterol or low dose beclomethasone/formoterol maintenance and reliever therapy			

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B. Daily doses of inhaled corticosteroids for children aged 6-11 years

Drug	Low Daily Dose	Medium Daily Dose	High Daily Dose
Beclomethasone dipropionate CFC	100-200 mcg	>200-400 mcg	>400 mcg
Beclomethasone dipropionate HFA	50–100 mcg	>100–200 mcg	>200 mcg
Budesonide DPI	100–200 mcg	>200–400 mcg	>400 mcg
Budesonide nebules	250-500 mcg	>500-1000 mcg	>1000 mcg
Ciclesonide	80 mcg	>80-160 mcg	>160 mcg
Fluticasone propionate DPI	100–200 mcg	>200–400 mcg	>400 mcg
Fluticasone propionate HFA	100–200 mcg	>200–500 mcg	>500 mcg
Mometasone furoate	110 mcg	220-<440 mcg	≥440 mcg
Triamcinolone acetonide	400–800 mcg	>800-1200 mcg	>1200 mcg

CFC: chlorofluorocarbon propellant; DPI: Dry powder inhaler; HFA: hydrofluoroalkane propellant
This is not a table of clinical equivalence, but of estimated clinical comparability.

C. Definition of uncontrolled asthma in children aged 6-11 years

In the past 4 weeks, the child had 3-4 episodes of:

- Daytime asthma symptoms more than twice a week;
- Activity limitation due to asthma;
- Need of reliever medication more than twice a week;
- Night waking due to asthma.

Source: Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2018. Available from: www.ginasthma.org

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APPENDIX 4

Wash-out Periods for Short-Acting and Long-Acting Antihistamines Based on Terminal Elimination Half-Lives

Short-acting antihistamines	Terminal elimination half-life (h)	Minimum wash-out period prior to skin prick tests or oral food challenges (days)
Oral		
acrivastine[1]	2-4	1[3] or ideally 3
cetirizine[1]	6.2 - 10	Must be 5[4]
cimetidine[1]	1.4	1[3] or ideally 3
diphenhydramine[1]	2-8	1[3] or ideally 3
famotidine[1]	0.8-5.8	1[3] or ideally 3
fexofenadine[1]	14.4	3
hydroxyzine[1]	4.8-9.4	Must be 5[4]
levocetirizine[1]	6	3
nizatadine[1]	1-2	1[3] or ideally 3
mizolastine[2]	12.9	3
ranitidine[1]	2.5-3	1[3] or ideally 3
rupatadine[2]	13	3
Intranasal/Ophthalmic (optional wash-out prior to SPT)		
emedastine[1]	3-4	1[3] or ideally 3
epinastine[1]	12	3
olopatadine[1]	8-12	3

Long-acting antihistamines	Terminal elimination half-life (h)	Minimum wash-out period prior to skin prick tests or oral food challenges (days)
Oral		
desloratadine[1]	27	7
ebastine[2]	19.3	5
chlorpheniramine[1]	6.3-23.1	6
ketotifen[1]	21	5
loratadine[1]	28	7
Intranasal/Ophthalmic (optional wash-out prior to SPT)		
azelastine[1]	22-25	6
ketotifen[1]	21	5
levocabastine[1]	35-40	7

[1] *Lexicomp Online®, In: UpToDate, Waltham, MA. (Accessed on November 17, 2015.)*
[2] Derived from: *Allergy: Principles and Practice* (Middleton, 7th Edition) in the form of Table 87.4 (authored by FER Simons and C Akdis).
[3] If the antihistamine is used the day prior to an oral food challenge, a Skin Prick Test must be performed before the initiation of the challenge and the result must be positive, i.e. a genuine wheal with the histamine positive control must be obtained before the challenge is effectively initiated. If not, postpone the challenge.
[4] Wash-out period extended beyond 3 days based on actual clinical experience.

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APPENDIX 5

Anaphylaxis Staging System

Anaphylaxis is a generalized allergic reaction that is rapid in onset and may progress to death (Adapted from [1]).

Staging System of Severity of Anaphylaxis	
Stage	**Defined by**
1 Mild skin & subcutaneous tissues, GI, &/or mild respiratory	Flushing, urticaria, periorbital or facial angioedema; mild dyspnea, wheeze or upper respiratory symptoms; mild abdominal pain and/or emesis
2 Moderate mild symptoms + features suggesting moderate respiratory, cardiovascular or GI symptoms	Marked dysphagia, hoarseness, and/or stridor; shortness of breath, wheezing & retractions; crampy abdominal pain, recurrent vomiting and/or diarrhea; and/or mild dizziness
3 Severe hypoxia, hypotension (more than 20% drop in blood pressure) or neurological compromise	Cyanosis or SpO2 ≤ 92% at any stage, confusion, cardiovascular collapse, loss of consciousness, bradycardia, cardiac arrest.

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

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APPENDIX 6

Oral Food Challenge Symptom Score Sheet

I. SKIN

	Stopping rules: # of grade increase	
	Alone	**Associated**
A. Pruritus	**+3**	**+2**
0 = Absent		
1 = Mild: occasional scratching		
2 = Moderate: scratching continuously for >2 minutes at a time		
3 = Severe: hard continuous scratching excoriations		
B. Urticaria	**+2**	**+1**
0 = Absent		
1 = Mild: ≤3 hives		
2 = Moderate: <10 hives but >3		
3 = Severe: generalized involvement		
C. Angioedema	**+2**	**+1**
0 = Absent		
1 = Mild: mild lip edema		
2 = Moderate: significant lip or face edema		
3 = Severe: generalized involvement		
D. Erythematous Rash	**+2**	**+1**
0 = Absent		
1 = Mild: few areas of faint erythema		
2 = Moderate: areas of erythema (>20% and <50%), macular and raised rash		
3 = Severe: generalized marked erythema (>50%), extensive raised lesions (>25%)		
Erythematous Rash % area involved (see below):	/_____/____/%	

	1-4 years old	5-8 years old
Head	17%	16%
Neck	2%	2%
Anterior trunk	16%	14%
Posterior trunk	16%	18%
Leg (1)	15%	15%
Arm (1)	9.5%	10%

Adapted from Lund CC, Browder NC (1944) The estimation of areas of burns. Surg Gynecol Obstet 79: 352–8

II. UPPER RESPIRATORY/OCCULAR

	Stopping rules: minimal # of grade increase	
	Alone	**Associated**
A. Sneezing/Itching	**+3**	**+2**
0 = Absent		
1 = Mild: rare bursts		
2 = Moderate: bursts <10, intermittent rubbing of nose / eyes / external ear canals		
3 = Severe: continuous rubbing of nose / eyes, periocular swelling and/or long bursts of sneezing		
B. Nasal Congestion	**+3**	**+2**
0 = Absent		
1 = Mild: some hindrance to breathing		
2 = Moderate: nostrils feel blocked, breathing through mouth most of time		
3 = Severe: nostrils occluded		
C. Rhinorrhea	**+3**	**+2**
0 = Absent		
1 = Mild: occasional sniffling		
2 = Moderate: frequent sniffling, requires tissues		
3 = Severe: nose runs freely despite sniffling and tissues		
D. Laryngeal (only symptoms due to laryngeal edema are to be considered)	**+2**	**+1**
0 = Absent		
1 = Mild: throat clearing, occasional cough		
2 = Moderate: hoarseness, frequent dry cough		
3 = Severe: inspiratory stridor		
E. Conjunctivitis (see example below)	**+3**	**+2**
0 = Absent		
1 = Mild:		
2 = Moderate:		
3 = Severe:		



Grade 1 Grade 2 Grade 3

III. LOWER RESPIRATORY

	Stopping rules: minimal # of grade increase	
	Alone	**Associated**
A. Wheezing (with or without cough due to bronchospasm)	**+1**	**+1**
0 = Absent		
1 = Mild: expiratory wheezing to auscultation		
2 = Moderate: dyspnea, inspiratory and expiratory wheezing		
3 = Severe: dyspnea, use of accessory muscles, audible wheezing		

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IV. GASTROINTESTINAL

	Stopping rules: minimal # of grade increase	
	Alone	**Associated**
A. Subjective Complaints		
A.1 Abdominal Complaints	**+3**	**+2**
0 = Absent		
1 = Mild: mild abdominal pain with no change in activity		
2 = Moderate: moderate abdominal pain associated with decreased activity		
3 = Severe: severe and/or persistent abdominal pain associated with significant change in behaviour		
A.2 Other Subjective Complaints	**NA**	**NA**
0 = Absent		
1 = Mild: itchy mouth/throat, c/o nausea		
2 = Moderate: frequent c/o nausea		
3 = Severe: patient in bed; crying		
B. Objective Complaints	**+1**	**+1**
0 = Absent		
1 = Mild: 1 episode of emesis* or diarrhea		
2 = Moderate: 2-3 episodes of emesis* or diarrhea or 1 of each		
3 = Severe: >3 episodes of emesis* or diarrhea or 2 of each		

* Emesis to be differentiated from “spitting-up” due to food intolerance while feeding.

V. CARDIOVASCULAR/NEUROLOGIC

	Stopping rules: minimal # of grade increase	
	Alone	**Associated**
Cardiovascular/neurologic	**+1**	**+1**
0 = Normal: heart rate or BP for age/baseline		
1 = Mild: color change, subjective response (weak, dizzy), or tachycardia, mental status change, mild hypotension (weak rapid pulse and/or 10-20% drop in blood pressure from baseline)		
2 = Moderate: drop in blood pressure >20% from baseline, significant change in mental status, light-headedness, feeling of “pending doom”		
3 = Severe: cardiovascular collapse, signs of impaired circulation, unconsciousness, bradycardia, cardiac arrest.		

References:

Nowak-Węgrzyn AH, Assa'ad AH, Bahna SL, Bock SA, Sicherer SH, Teuber SS. Work Group report: oral food challenge testing. J. Allergy Clin. Immunol. 2009; 123(6 Suppl):S365-S383.

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

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APPENDIX 7

FAQLQ/FAIM Parent Questionnaires

FAQLQ-PF

Food Allergy Quality of Life Questionnaire – Parent Form (0-12 years)

This questionnaire is part of the EuroPrevall project, a European multidisciplinary study of the prevalence, costs and basis of food allergy in Europe.

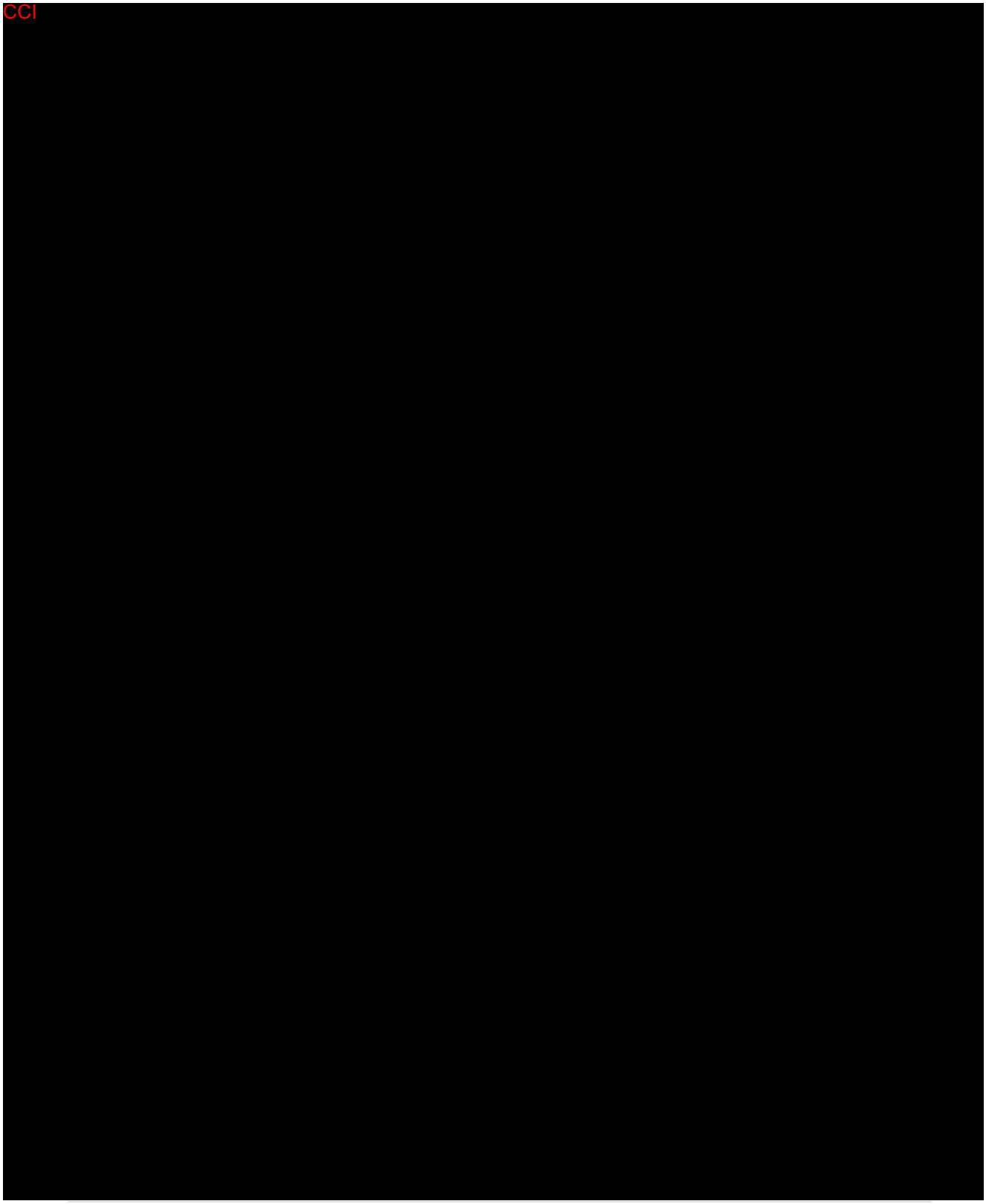
Food Allergy Quality of Life Questionnaire-Parent Form

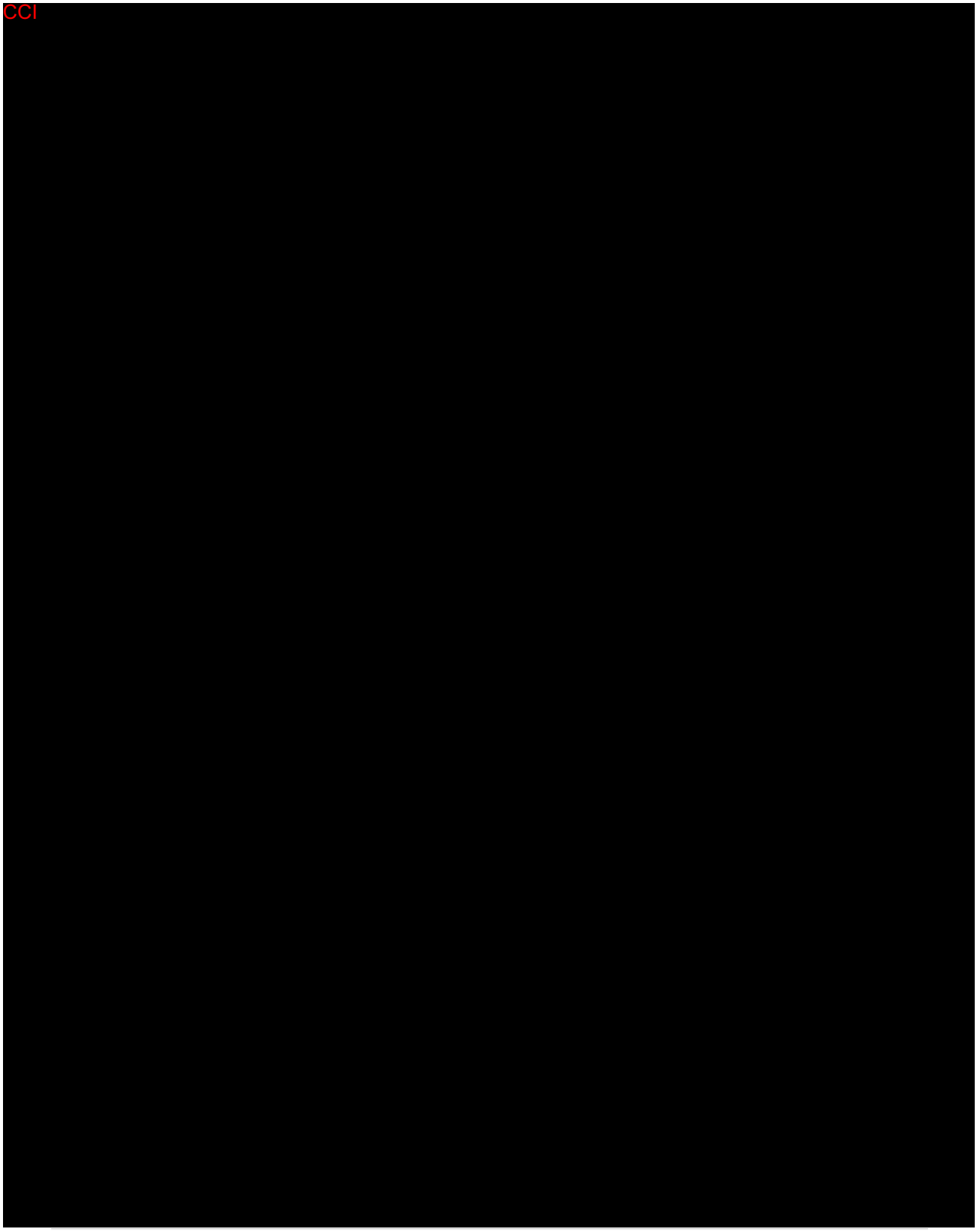
(FAQLQ-PF)

Children aged 0-12 years

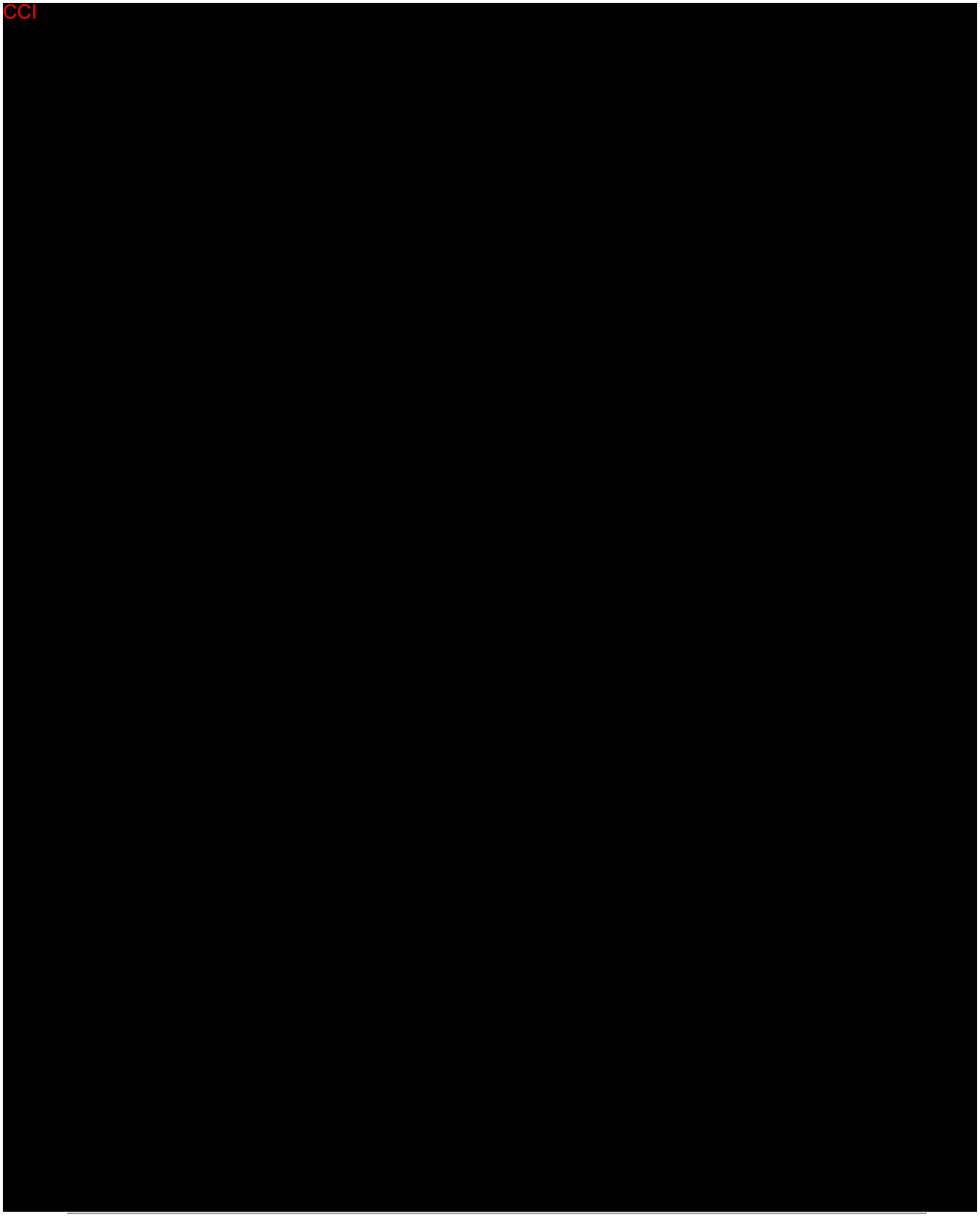
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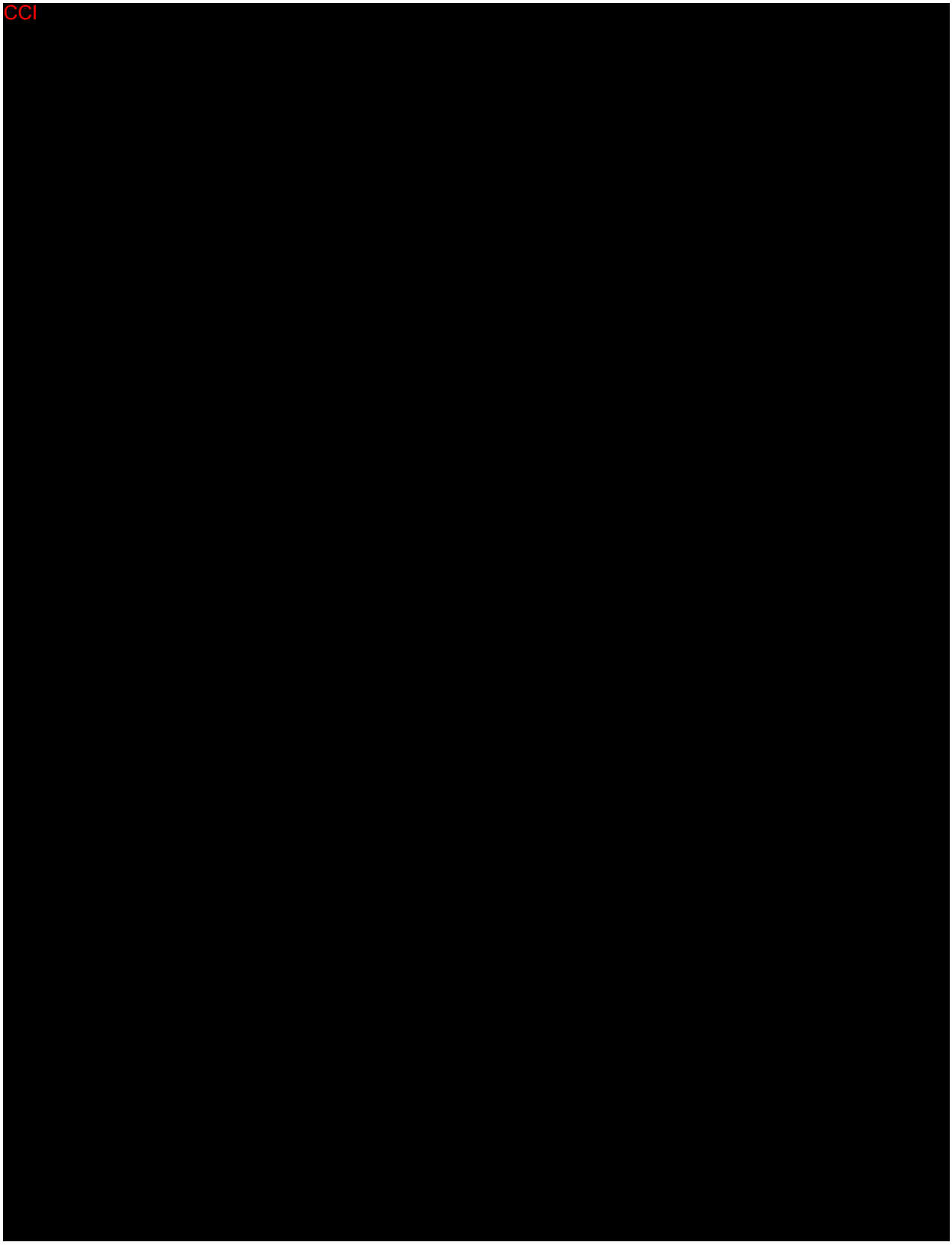


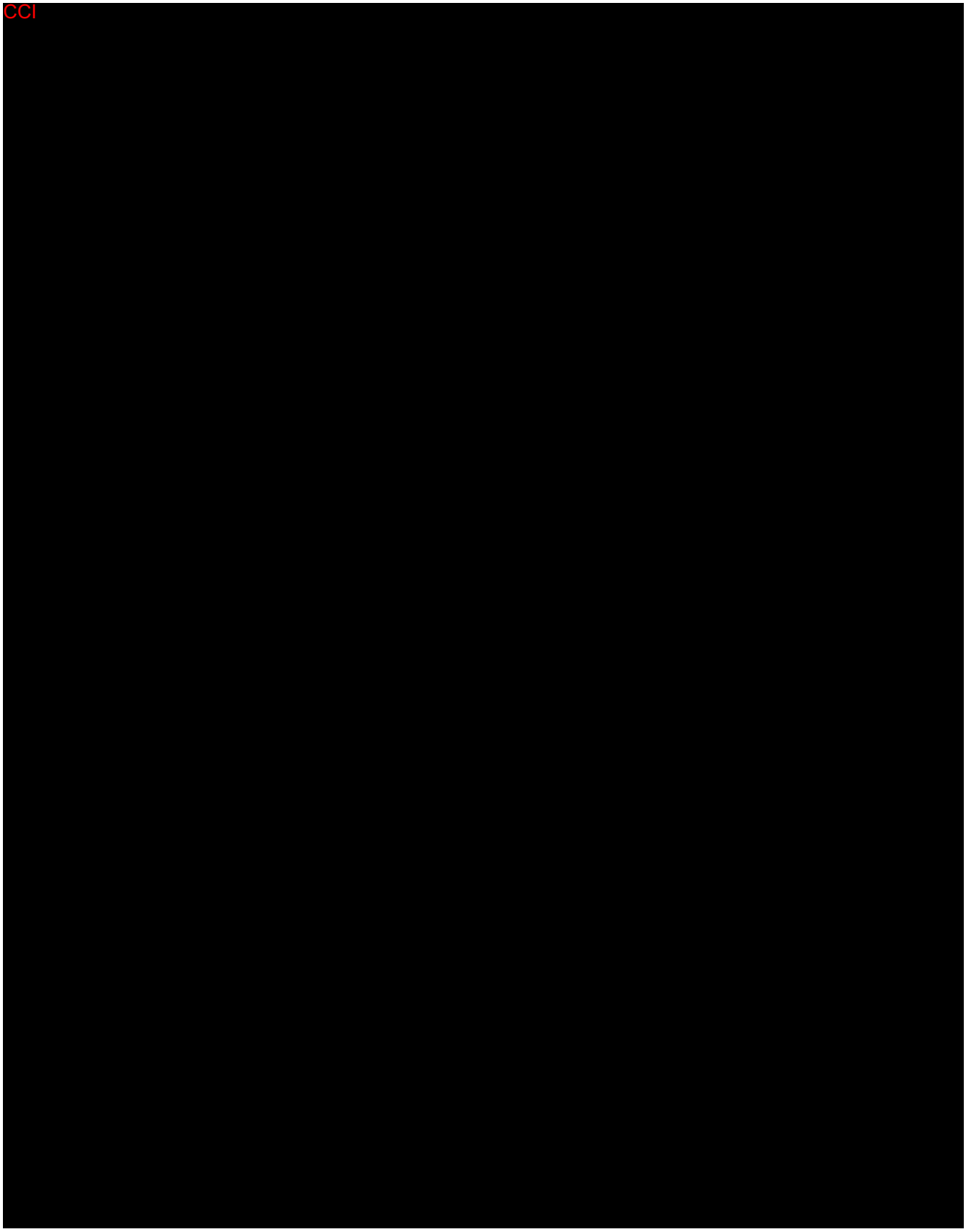

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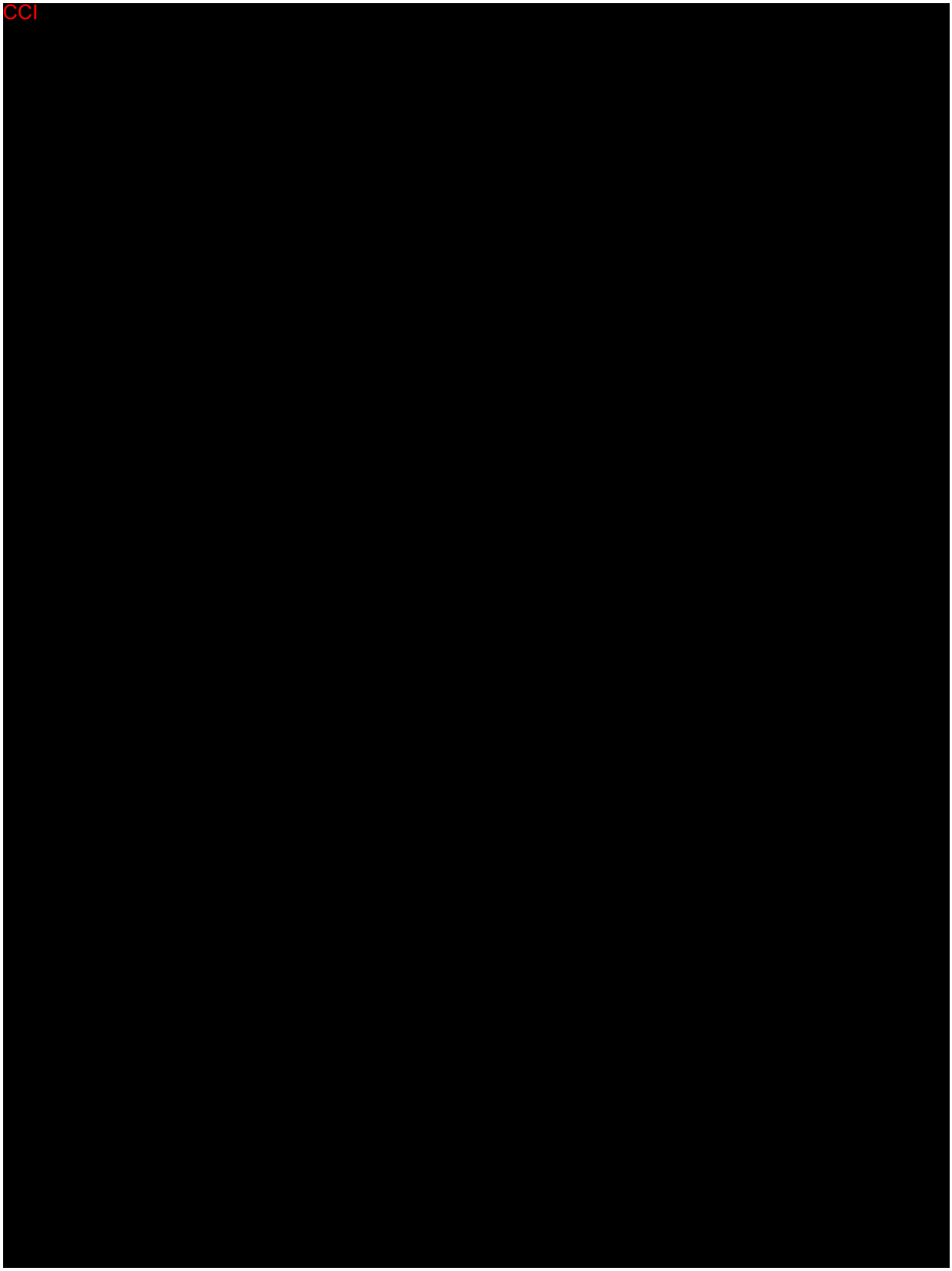


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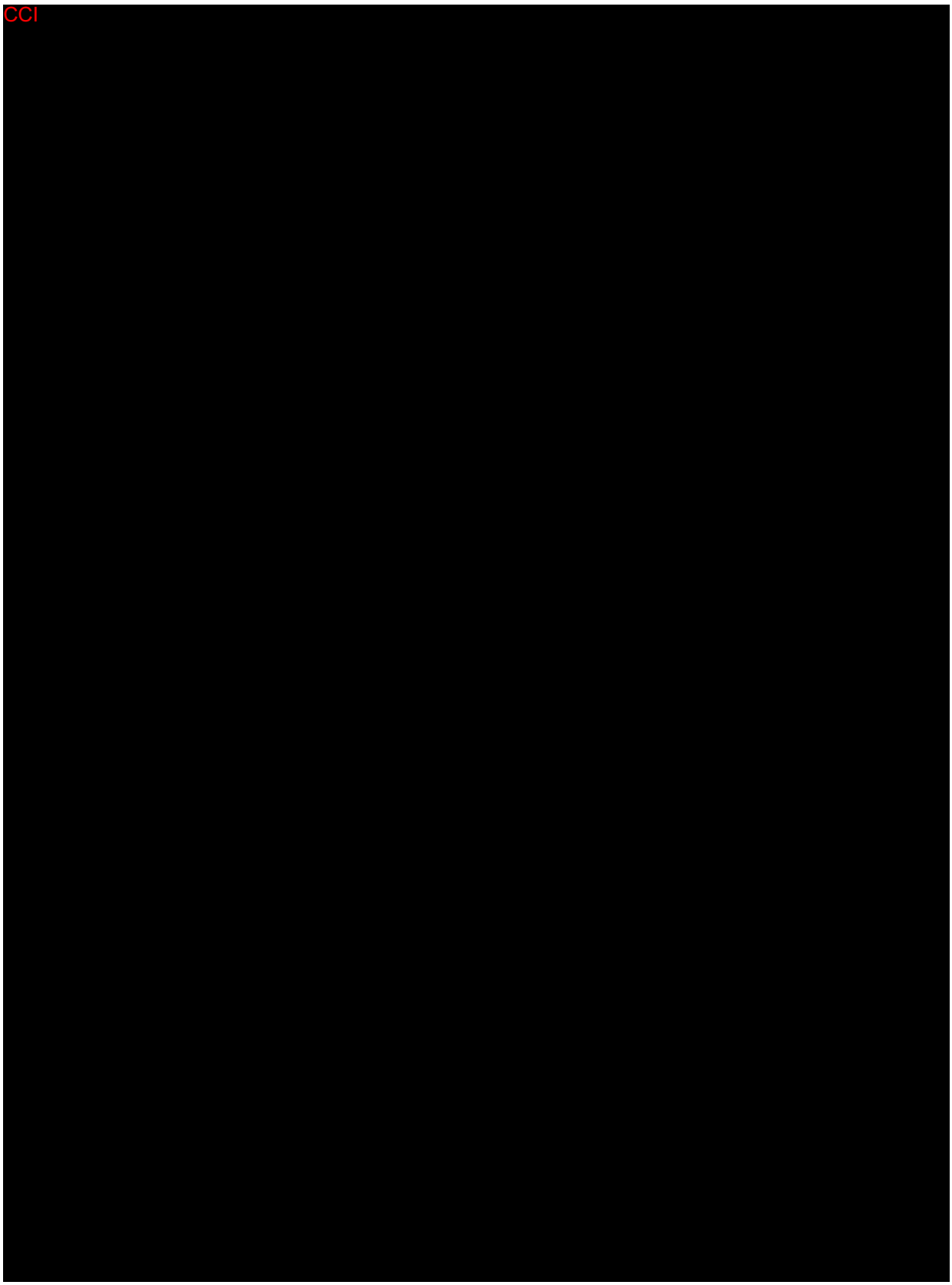



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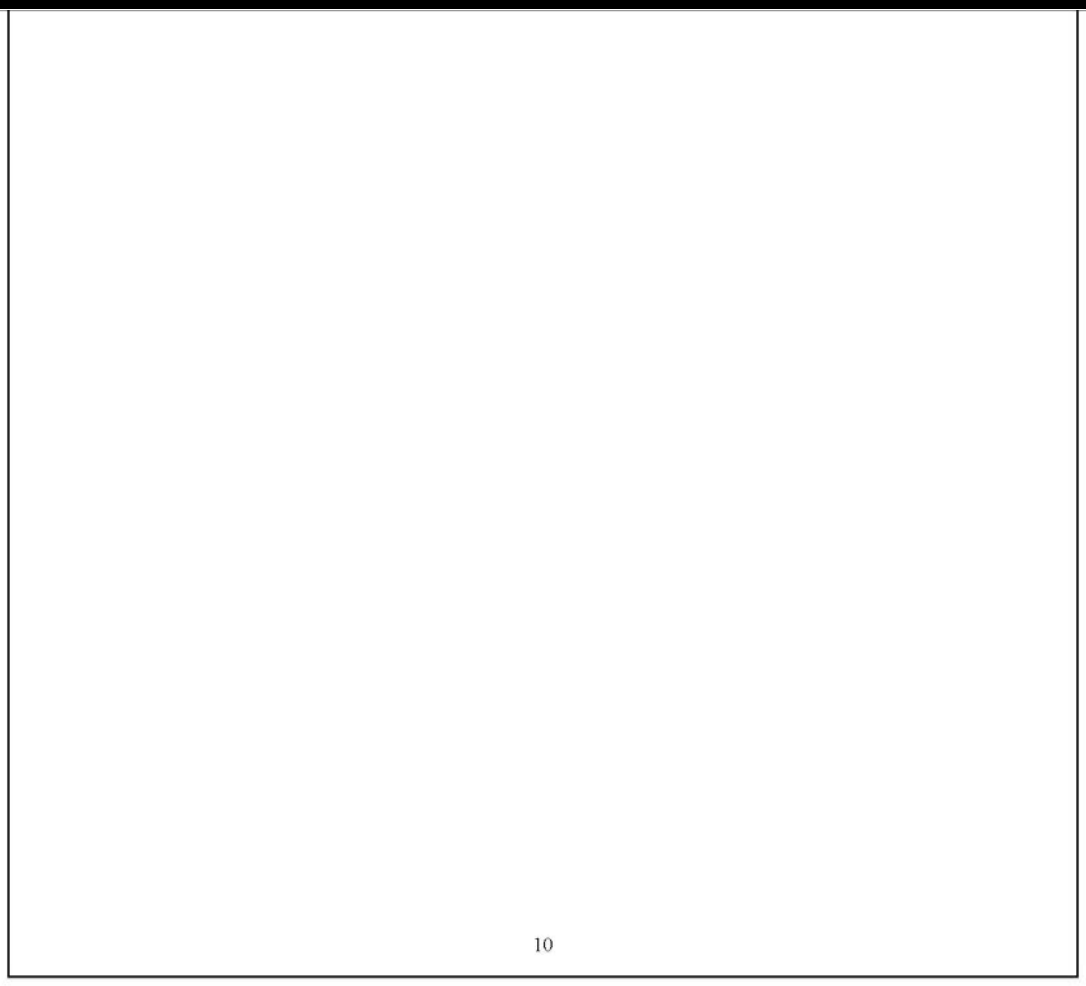


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APPENDIX 8

EQ-5D-5L Questionnaire

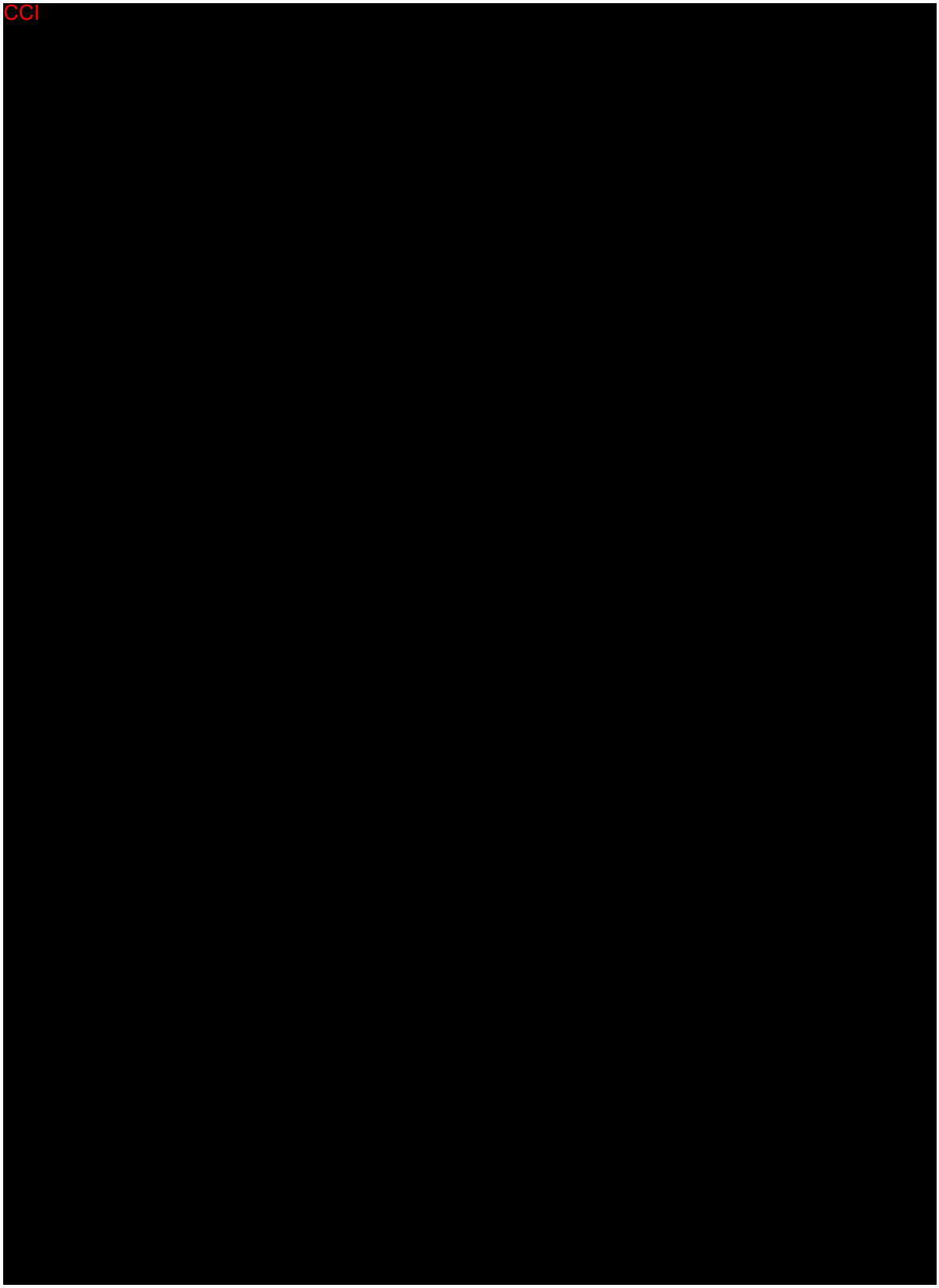


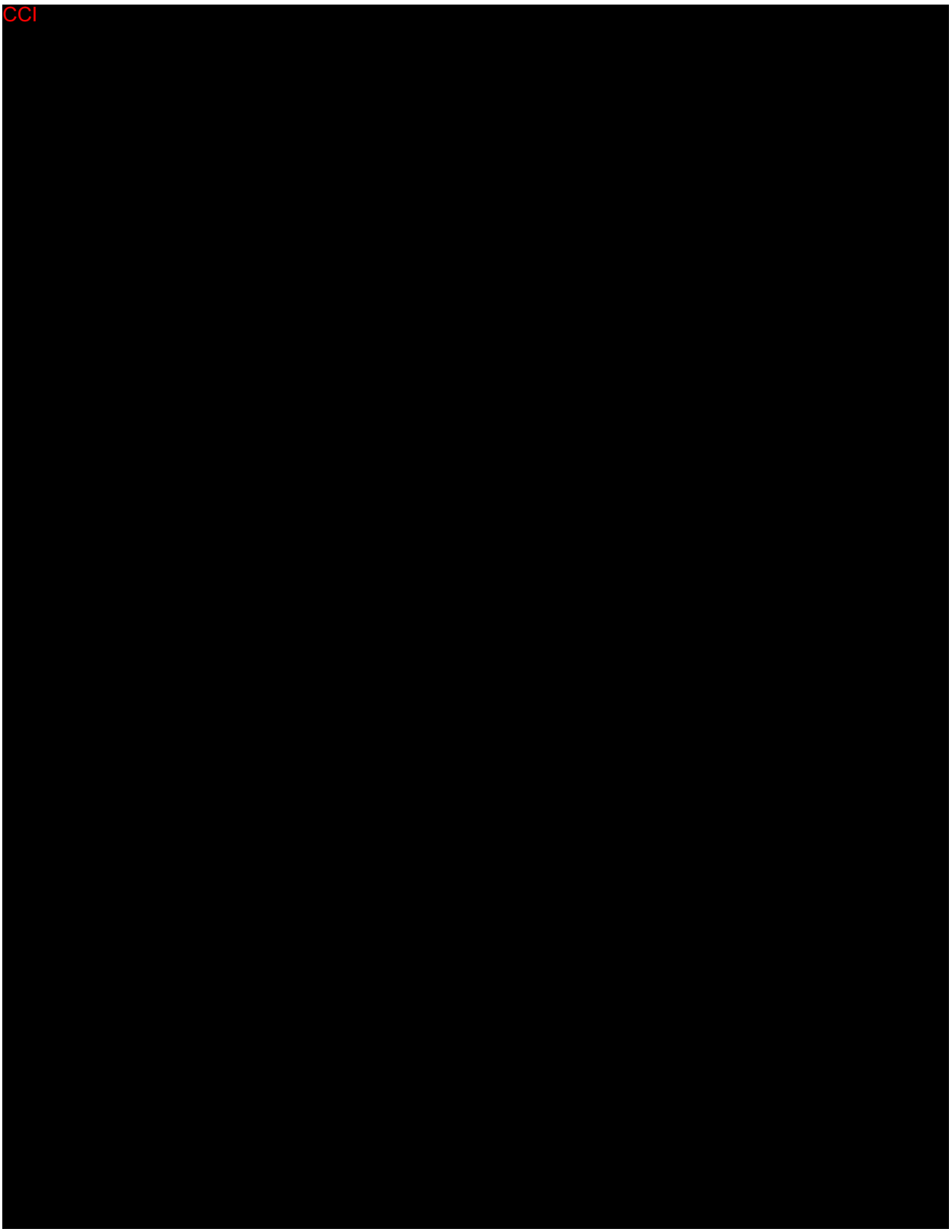
Health Questionnaire

English version for the USA

Sample

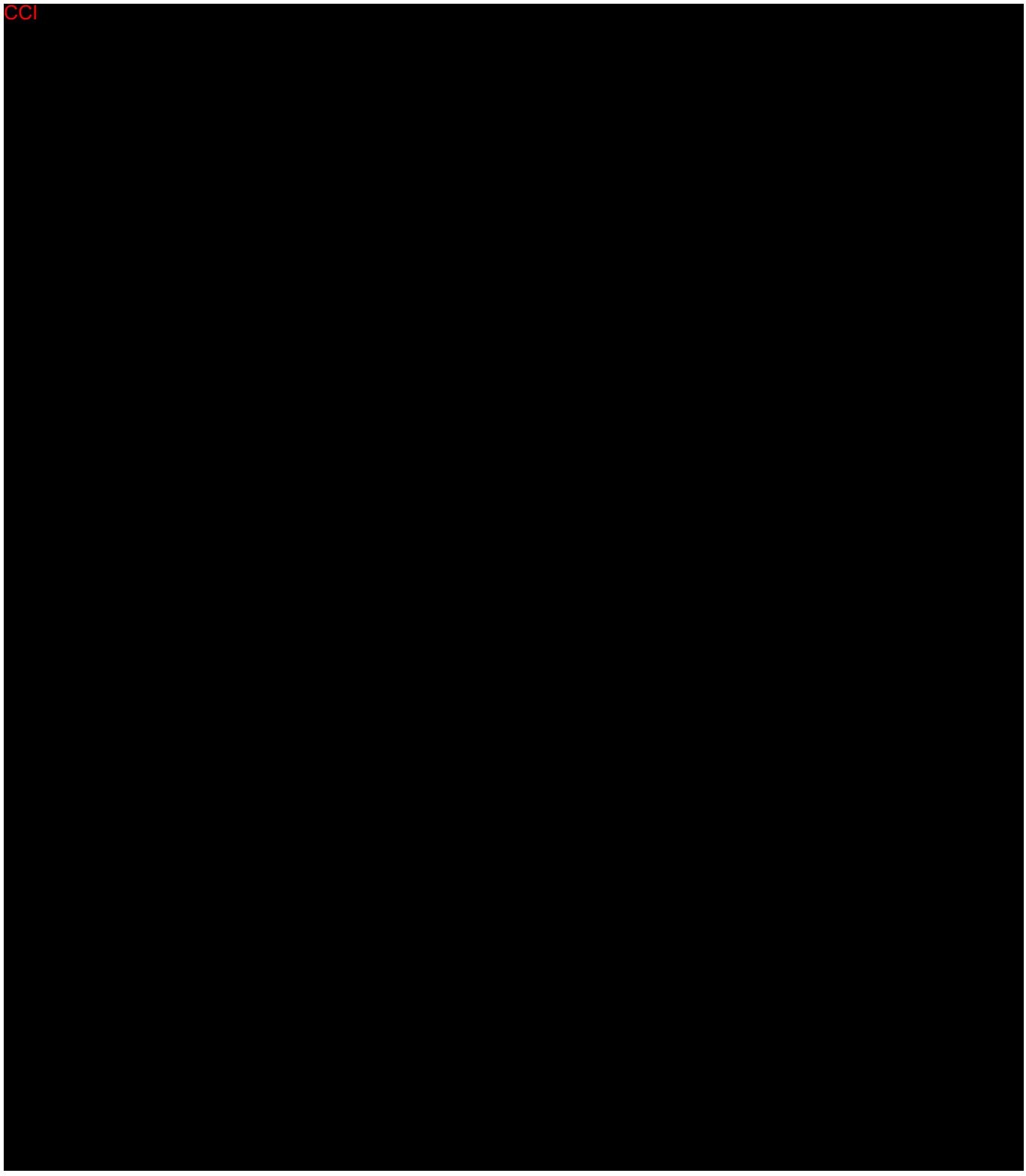
USA (English) © 2009 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group


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APPENDIX 9



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APPENDIX 10

Reference Safety Information for Peanut Food Challenge

In the context of Viaskin Peanut clinical development, a formulated recipe of food challenge has been developed by DBV Technologies for the conduct of the Double-Blind Placebo-Controlled Food Challenge (DBPCFC) procedure in clinical trials.

The food challenge kits, containing the low and high dose of peanut protein and placebo formulas, are provided to all sites participating in the Viaskin Peanut clinical studies where DBPCFCs procedures are conducted according to a specific Manual of Procedure.

The Food Challenge is a non-authorized product used to produce a physiological response that is relevant to the design of the clinical trial.

All serious adverse events (SAEs), including anaphylactic reactions and allergic symptoms, that occur during the Food Challenge procedure are elicited events to either diagnose the food allergy or to assess the efficacy of the corresponding Investigational Medicinal Product (Viaskin Peanut). Therefore, they are considered as expected by definition.

Only Death occurring within the context of the DBPCFC procedure or any SAE with the outcome “Death” related to Food Challenge will be considered as unexpected and considered as a suspected unexpected serious adverse event for expedited reporting purpose.