OPEN-LABEL FOLLOW-UP STUDY OF THE VIPES STUDY TO EVALUATE LONG-TERM EFFICACY AND SAFETY OF THE VIASKIN® PEANUT (OLFUS-VIPES STUDY)

Test Drug: Viaskin® Peanut (DBV712): Allergen extract of peanut in Viaskin® epicutaneous delivery system

Protocol Number: OLFUS VIPES
Study Phase: Phase II Follow-up
Version and Date: 3.0, Protocol Amendment 3, 25 August 2015, Final (USA only)

Sponsor:
DBV TECHNOLOGIES S.A.
Green Square – Bâtiment D
80/84, rue des Meuniers
92220 Bagneux
FRANCE
Tel: + 33 1 55 42 78 78
Fax:+ 33 1 43 26 10 83
Internet:www.dbv-technologies.com

Clinical Research Organization (CRO):
PRA INTERNATIONAL
500 South Oak Way
Green Park
Reading
Berkshire, RG2 6AD
United Kingdom (UK)
Tel: +44 0118 918 1000
Fax: +44 0118 918 1001
Internet: www.praintl.com

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) as set forth in the International Conference on Harmonisation (ICH) guidelines on GCP (ICH E6), and applicable local regulatory requirements.

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1. SIGNATURES

Representatives of Sponsor

I have read and agree to the OLFUS-VIPES Protocol Version 3.0 (incorporating Protocol Amendment 3), entitled ‘Open-label follow-up study of the VIPES study to evaluate long-term efficacy and safety of the Viaskin® Peanut (OLFUS-VIPES STUDY)’. I am aware of my responsibilities under the guidelines of GCP, local regulations (as applicable) and the study protocol. I agree to conduct the study according to these responsibilities.

Accepted for the Sponsor - DBV Technologies:

Wence AGBOTOUNOU, PhD, MBA

[Signature]

Chief Clinical Trial Officer

26 Aug 2015

Date

Laurent MARTIN, PharmD

[Signature]

Director, Regulatory Affairs & Quality

August 26, 2015

Date

Claude THEBAULT, MD

[Signature]

Director, Medical Affairs

26 Aug 2015

Date
Investigator

I have read and agree to the OLFUS-VIPES Protocol 3.0 (incorporating Protocol Amendment 3), entitled ‘Open-label follow-up study of the VIPES study to evaluate long-term efficacy and safety of the Viaskin® Peanut (OLFUS-VIPES STUDY)’. I am aware of my responsibilities as an Investigator under the guidelines of GCP, local regulations (as applicable) and the study protocol. I agree to conduct the study according to these responsibilities and to appropriately direct and assist the staff under my control, who will be involved in the study.

Clinical Site:

________________________________________________________

Site Principal Investigator:

Print Name  Title

Signature  Date
2. SYNOPSIS

<table>
<thead>
<tr>
<th>NAME OF SPONSOR:</th>
<th>DBV Technologies</th>
<th>PROTOCOL No.: OLFUS-VIPES</th>
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<tbody>
<tr>
<td>NAME OF STUDY TREATMENT:</td>
<td>Viaskin® Peanut (DBV712): Allergen extract of peanut in Viaskin® epicutaneous delivery system</td>
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<tr>
<td>TITLE OF STUDY:</td>
<td>Open-label follow-up study of the VIPES study to evaluate long-term efficacy and safety of the Viaskin® Peanut.</td>
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<tr>
<td>STUDY CENTERS:</td>
<td>This is a multicenter study conducted in Europe and in North America. It is planned to include approximately 20-21 sites in 4 countries. Participating sites will be from those that participated in the VIPES study.</td>
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<td>STUDY PERIOD:</td>
<td>A 24-month treatment period followed by a 2-month period without treatment.</td>
<td>PHASE OF DEVELOPMENT: Phase II follow-up/extension</td>
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<td>PLANNED STUDY DURATION:</td>
<td>Approximately 27 months (allowing for visit windows): 24 months in the treatment period followed by a period of 2 months without treatment.</td>
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<td>OBJECTIVES:</td>
<td>The objectives of this follow-up/extension study of the VIPES study are:</td>
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<td>• To assess the efficacy of Viaskin® Peanut after up to 36 months of Epicutaneous Immunotherapy (EPIT) in peanut-allergic subjects.</td>
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<td>• To evaluate the safety of long-term treatments with Viaskin® Peanut.</td>
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<td>• To evaluate the sustained unresponsiveness to peanut after a period of 2 months without treatment in subjects showing desensitization to peanut after EPIT with Viaskin® Peanut.</td>
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<td>STUDY DESIGN AND METHODOLOGY:</td>
<td>This is an open-label follow-up study or extension study for subjects who previously were randomized and have completed the VIPES study. Subjects will be offered enrollment in this follow-up study to receive an additional 24 months of Viaskin® Peanut treatment followed by a period of 2 months without treatment and a peanut-free diet.</td>
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In Protocol Version 2.0 (incorporating Protocol Amendment 1), all subjects enrolling into the OLFUS-VIPES study after having completed the VIPES study will receive the highest dose of Viaskin® Peanut, i.e. 250 μg peanut protein, regardless of the prior treatment (placebo, 50 μg, 100 μg or 250 μg Viaskin® Peanut) they were receiving in the VIPES study.

Subjects who already enrolled into the OLFUS-VIPES study under the initial protocol design (Protocol Version 1.1 dated 27 May 2013) will all switch to receive the 250 μg dose at their protocol visit at Month 6 (Visit 3) or at Month 12 (Visit 4) after the approval of Protocol Amendment 1 at their sites.

The transition from the VIPES study to the OLFUS-VIPES study or the transition from the initial OLFUS-VIPES design to the amended OLFUS-VIPES design will be performed keeping the blinding in the VIPES study results are obtained. The same Interactive Web Response System (IWRS) used to allocate treatment to subjects in the VIPES study will be used in the OLFUS-VIPES study. Hence, all subjects should receive the 250 μg dose in the OLFUS-VIPES study but none of them will be unblinded until the VIPES study is unblinded.

During the lifetime of the OLFUS-VIPES study, the VIPES study results will be revealed and an optimal clinical dose of Viaskin® Peanut for future studies will be determined. However, in the OLFUS-VIPES study, all subjects would be already treated at the 250 μg dose at that time, and they will remain under the 250 μg dose to the end of the study, whatever the optimal clinical dose is. This will prevent subjects from having to switch to another dose again during the OLFUS-VIPES study.

After the overall 24 months of active treatment with Viaskin® Peanut, a period of 2 months without...
treatment will be considered for those subjects being assessed for sustained unresponsiveness.

Repeated daily application of Viaskin® Peanut will continue as in the VIPES study, i.e. a new patch will be applied every 24 hours on the inner side of both upper arms for adults (≥18 years) and adolescents (12-17 years), or on the inter-scapular area of the back for children (7-11 years). In order not to unblind the treatment arms until the results of the VIPES study are known and to better assure safety in particular for placebo subjects crossing over to receive the active treatment, the duration of application of the Viaskin® Peanut patch will be progressively increased for the first 2 weeks of treatment in all subjects entering the OLFUS-VIPES study (one week shorter than what was done at the start of the VIPES study): patches will be applied for 6 hours every day during the first week, 12 hours every day during the second week, and for the entire 24 hours of daily application from the third week or the 15th day onwards.

Subjects enrolled in the OLFUS-VIPES study before approval of Protocol Amendment 1 and who will switch to the 250 μg dose after Protocol Amendment 1 is approved may apply the new 250 μg patch for the whole 24 hours starting on the very first day. They have been receiving Viaskin® Peanut at one of the three doses for at least 6 months: no safety concerns are expected. However, at the discretion of the Investigator, the 2-week period of progressive increase of time of daily application described above may be repeated.

In this Protocol Version 3.0 (incorporating Protocol Amendment 3), it is offered to subjects reaching their visit at Month 18 (Visit 6) to receive the Viaskin® Peanut patch at 250 μg with a slight change in its design. This patch already includes the polyurethane (PU) breathable adhesive dressing, which will replace the Tegaderm™ dressing that had to be added previously. Of note, the Tegaderm™ dressing is also a polyurethane breathable adhesive dressing. This “integrated Viaskin® Peanut patch” is considered as an improvement of the previous one, with all components of the patch in one. Subjects and/or subjects’ parents will be asked to assess the tolerability, the adhesivity and the comfort of this “integrated Viaskin® Peanut patch” and the tolerability, the adhesivity and the comfort of the “previous patch” with the added Tegaderm™.

Subjects who switch to this “integrated Viaskin® Peanut patch” will continue with this patch until Month 24 (Visit 7).

The first double-blind placebo-controlled food challenge (DBPCFC) in the OLFUS-VIPES study will be conducted after 12 months of treatment up to a cumulative dose of 5,040 mg peanut protein.

The second DBPCFC in the OLFUS study will be conducted after 24 months of treatment for all subjects up to a cumulative dose of 5,040 mg peanut protein.

- Subjects who react objectively below or at a cumulative dose of 1,440 mg of peanut protein during this second DBPCFC at 24 months in the OLFUS-VIPES study will have their last visit at Visit 8 (Month 24 + 1 week).
- Subjects who are unresponsive to the cumulative dose of 1,440 mg of peanut protein or above during this second DBPCFC at 24 months in the OLFUS-VIPES study will continue to a Month 26 visit as described below.

Subjects who are unresponsive at a cumulative dose of 1,440 mg peanut protein or above (unresponsiveness to the DBPCFC is defined as no objective reaction to peanut protein), will be taken off treatment and will continue for an additional 2 months without treatment and will continue their peanut-free diet. This additional period will help to assess the “sustained unresponsiveness” i.e. to study whether the subjects will maintain this level of unresponsiveness to peanut protein even after 2 months without receiving any peanut EPIT treatment.

The third DBPCFC in the study will then be conducted after a period of 2 months without treatment, i.e. at Month 26 (Visit 9 and Visit 10), only for those subjects who were unresponsive to a cumulative dose of
1,440 mg peanut protein or above at Month 24. Visit 10 will be the End of Study Visit for these subjects.

Throughout the OLFUS-VIPES study period, subjects will be instructed to remain on a peanut-free diet. The re-introduction or not of peanut into the subject’s diet at the end of their participation in the study will be left to the Investigator’s decision.
STUDY POPULATION AND MAIN CRITERIA FOR INCLUSION/EXCLUSION:

All subjects (child, adolescent or adult) who completed the VIPES study up to Visit 11 (inclusive) will be eligible for participation in the OLFUS-VIPES study. At Visit 11 in the VIPES study, subjects who decide to enroll in the OLFUS-VIPES study will be rolled-over into the OLFUS-VIPES study, unless in the opinion of the Investigator, it is not in the best interest of the subjects to continue receiving EPIT with Viaskin® Peanut. Visit 1 in the OLFUS-VIPES and Visit 11 in the VIPES study can be conducted concomitantly. Subjects continuing into the OLFUS-VIPES study will not perform Visit 12 in the VIPES study. All subjects will continue with their usual peanut-free diet and label reading of food products to avoid any accidental peanut consumption during the duration of the study.

Inclusion Criteria:
1. Signed informed consent from adult subjects or parent(s)/guardian(s) of children <18 years + children’s assent for children ≥7 years or as per country-specific regulations or laws. This consent should be signed no later than Visit 11 in the VIPES study.
2. Adult and pediatric subjects (≥7 years) who completed the VIPES study, with a mandatory and documented DBPCFC at Month 12 in the VIPES study.
3. Negative pregnancy test for women of childbearing potential at Visit 10 in the VIPES study.
4. Female subject of childbearing potential must use effective methods of contraception to prevent pregnancy and agree to continue to practice an acceptable method of contraception for the duration of participation in the study. Documented sexual abstinence will be accepted as an effective method of contraception for girls below 15 years of age.
5. Subjects and/or parents/guardians willing to comply with all study requirements during their participation in the study.

Exclusion Criteria:
1. Severe reaction during the DBPCFC at Month 12 in the VIPES study, defined as need for intubation, hypotension persisting after epinephrine administration, and/or the need for more than two doses of epinephrine.
2. Pregnancy or lactation.
3. Females of childbearing potential planning a pregnancy in the coming 2 to 3 years.
4. Subjects who became allergic to chocolate or who do not want to consume the chocolate study challenge vehicle anymore.
5. Subjects who developed hypersensitivity to excipients of the Viaskin® patches or of the food challenge formula used during the VIPES study.
6. Inability to discontinue short-acting antihistamines for three days or long-acting antihistamines for five to seven days (depending on half-life) prior to skin prick testing or food challenges.
7. Subjects with asthma that has evolved and now fulfills any of the criteria defined as follows:
   a. uncontrolled persistent asthma by National Asthma Education and Prevention Program Asthma guidelines (2007) or by Global Initiative for Asthma (2011) or being treated with combination therapy of medium dose inhaled corticosteroid with a long acting inhaled β2-agonists.
   b. at least two systemic corticosteroid courses for asthma in the past year or one oral corticosteroid course for asthma in the past three months.
   c. prior intubation for asthma in the past year.
8. Subjects receiving β-blocking agents, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, calcium channel blockers or tricyclic antidepressant therapy.
9. Subjects receiving or planning to receive anti-tumor necrosis factor drugs or anti-IgE drugs (such as omalizumab) or any biologic immunomodulatory therapy.
10. Subjects receiving or planning to receive any type of immunotherapy to any food (e.g. oral immunotherapy, sublingual immunotherapy, specific oral tolerance induction) during their participation in the study.
11. Subjects receiving or planning to receive any aeroallergen immunotherapy during their participation in the study.
12. Allergy or know history of reaction to the Tegaderm™ with no possibilities to use an alternative dressing approved by the Sponsor.
13. Subjects suffering from generalized dermatologic disease (e.g. severe atopic dermatitis, uncontrolled generalized eczema, ichthyosis vulgaris) with no intact zones to apply the Viaskin® patches.

14. Subjects or parent(s)/guardian(s) of subjects with obvious excessive anxiety and unlikely to cope with the conditions of a food challenge.

15. 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 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).

16. Any new disorder in which epinephrine is contraindicated such as coronary artery disease, uncontrolled hypertension, or serious ventricular arrhythmias.

17. A history of drug or alcohol abuse while in the VIPES study.

18. A history of non compliance in the VIPES study. Non compliance is defined as subjects not applying the patch at all for 60 days or more (this can be either consecutive or intermittent non-application of the patches) during the whole VIPES study duration.

19. Subjects unable to follow the protocol requirements.

20. Participation in another clinical intervention study in the past year, other than the VIPES study.

21. Subjects on any experimental drugs in the past year, other than those used in the VIPES study.

| NUMBER OF SUBJECTS: | All subjects who completed the VIPES study will be offered enrollment in this follow-up/extension OLFUS-VIPES study. It is estimated that approximately 220 subjects could be enrolled in the OLFUS-VIPES study. |
| STUDY TREATMENT(S): | Viaskin® Peanut will be administered using the same Viaskin® epicutaneous delivery system as in the VIPES study. Viaskin® Peanut contains a dry deposit of peanut protein extract. The peanut proteins are extracted from the Virginia variety of *Arachis hypogaea* and the extract contains all peanut proteins. The Viaskin® is round-shaped. The inner part of the Viaskin® has a diameter of 18 mm (2.5 cm² surface area). In this inner part, the peanut allergen extract is deposited by electrospraying the liquid peanut protein formulation, which dries instantly. The outer adhesive part of the Viaskin® is composed of a 4 mm wide band of adhesive foam to stick to the skin. The drug product, dose, route and regimen are expected to be exactly the same as in the VIPES study. For the integrated Viaskin® Peanut patch, a breathable adhesive polyurethane dressing is already part of the patch. |

In order not to unblind the treatment arms until the results of the VIPES study are known and to better assure safety for placebo subjects crossing over to receive the active treatment at the 250 μg dose, the duration of application of the Viaskin® Peanut patch will be progressively increased for the first 2 weeks of treatment in all subjects entering the OLFUS-VIPES study (one week shorter than what was done at the start of the VIPES study): patches will be applied for 6 hours every day during the first week, 12 hours every day during the second week, and for the entire 24 hours of daily application from the start of the third week (Day 15) onwards. Once the Viaskin® patch is applied to the skin, the hypoallergenic adhesive film Tegaderm™ or any other alternative dressing allowed by the Sponsor must be used to cover the Viaskin® patch to prevent it from coming off.

At the time of the Month 18 visit (Visit 6), the subjects who have been using the Tegaderm™ as a dressing over the Viaskin® patch so far, will be offered to switch to an integrated Viaskin® Peanut patch containing the same quantity of peanut proteins (250 μg) loaded on the backing of the same patch system but already including the adhesive dressing. For those subjects who will switch to the integrated Viaskin® Peanut patch, the treatment with this patch will continue up to the Month 24 visit (Visit 7).

Repeated daily application of Viaskin® Peanut will continue as in the VIPES study, i.e. a new patch will be applied every 24 hours on the inner aspect of both upper arms for adults (≥18 years) and adolescents (12-17 years), or on the inter-scapular area of the back for children (7-11 years).

Children who turn 12 years of age during the OLFUS-VIPES study may switch from applying the patch to the back to applying it on the arms.
If the Viaskin® comes off, or after removing a Viaskin® patch, it is recommended that the subjects or subject’s parent(s)/guardian(s) wipe off the zone with a disposable napkin or a disposable tissue and wash their hands to prevent accidental transmission of allergenic protein. The next Viaskin® patch should then be applied only at the expected time of the next application. If possible, the subject could take advantage of their shower (or bath) time to change the Viaskin®; the previous Viaskin® should be removed just before the shower (or bath), and the new Viaskin® should be applied a few minutes after the shower (or bath) and drying of the skin. Application of the Viaskin® at a similar time for each daily application (am or pm) is recommended.

The rules for applying the previous patch or for applying the “integrated Viaskin® Peanut patch” remain the same.

**DURATION OF TREATMENT:** Repeated daily application of Viaskin® is planned for 24 months for all OLFUS-VIPES subjects. After 24 months of treatment, the subset of subjects who are unresponsive to a cumulative dose of 1,440 mg peanut protein or above will be followed for an additional period of 2 months without treatment.

**STUDY EVALUATIONS:** The OLFUS-VIPES study will have two treatment groups: Treatment Group 1 will consist of subjects who had received placebo in the VIPES study; Treatment Group 2 will consist of subjects who had received Viaskin® Peanut in the VIPES study.

**Efficacy Endpoints:**
The following efficacy endpoints will be assessed:

- At Month 12 in the OLFUS-VIPES study and by treatment group, the proportion of subjects with a peanut protein eliciting dose equal to or greater than 1,000 mg peanut or with a $\geq 10$-fold increase of the eliciting dose compared to their baseline eliciting dose observed in the VIPES study. Subjects having received active treatment with Viaskin® Peanut for a total of 12 months (Treatment Group 1) and a total of 24 months (Treatment Group 2) will be analyzed separately.

- At Month 24 in the OLFUS-VIPES study and by treatment group 1 or 2, the proportion of subjects with a peanut protein eliciting dose equal to or greater than 1,000 mg peanut or with a $\geq 10$-fold increase of the eliciting dose compared to their baseline eliciting dose observed in the VIPES study. Subjects having received active treatment with Viaskin® Peanut (DBV712) for a total of 24 months and a total of 36 months (since the VIPES study) will be analyzed separately.

- The proportion of subjects unresponsive (i.e. showing no objective symptoms during DBPCFC) to a cumulative dose of 1,440 mg peanut protein or above at Month 12 and Month 24 in the OLFUS-VIPES study.

- The proportion of subjects with a sustained unresponsiveness (i.e. showing no objective symptoms during DBPCFC after a period of 2 months without treatment) to a cumulative dose of 1,440 mg peanut protein or above at Month 26.

- The median and mean cumulative reactive dose of peanut protein at Month 12 and Month 24 by treatment group.

- The change from baseline in peanut-specific IgE and IgG4 at Month 6, Month 12, Month 18 and Month 24 by treatment group.

- The change from baseline in the average wheal diameter during the skin prick testing (undiluted) at Month 6, Month 12, Month 18 and Month 24 by treatment group.

- Change in the Quality of Life (the FAQLQ/FAIM) at Month 12 and Month 24 compared to Day 1 for those countries where the questionnaires were available, globally and by treatment group.
Safety Endpoints:
The following safety endpoints will be assessed:
- Adverse events (AEs) by system organ class, severity and relatedness to Viaskin® Peanut (all subjects and by age strata).
- Serious AEs (SAEs) by system organ class, severity and relatedness to Viaskin® Peanut (all subjects and by age strata).
- Systemic allergic symptoms and relatedness to Viaskin® Peanut (all subjects and by age strata).
- Severity of AEs or SAEs elicited during the study and the DBPCFCs (all subjects).
- Laboratory data, physical examinations and vital signs (all subjects).
- Spirometry or Peak Expiratory Flow (PEF) results (all subjects).

Exploratory Criteria:
- Enumeration and characterization of reactions triggered by accidental consumption of peanut during the follow-up study.
- Analysis of “Risk-taking behavior” of subjects (voluntary peanut consumption) during the follow-up study.
- Analysis of tolerability, adhesivity and comfort of the integrated patch versus the patch with the added Tegaderm™.

STATISTICAL METHODS: In OLFUS-VIPES study Treatment Group 1 will consist of subjects who had received placebo in the VIPES study; Treatment Group 2 will consist of subjects who had received Viaskin® Peanut in the VIPES study.

Demographic, baseline, disposition data will be summarized.

Efficacy Analyses
The number and percentage of responders will be presented by treatment group according to the randomization in the VIPES study. The data will be presented to show the proportion of subjects above or at the eliciting dose of 1,000 mg of peanut protein, or above or at 10-fold their baseline eliciting dose observed in the VIPES study. These data will be assessed at Month 12 and Month 24 in Treatment Group 1 and Group 2 subjects separately. The proportion of treatment responders at Month 12 and Month 24 will also be assessed for those subjects in Treatment Group 2 of the OLFUS-VIPES study, split by those who received 50, 100 and 250 μg during the VIPES study.

The number and percentage of subjects unresponsive to a cumulative dose of 1,440 mg peanut protein or above at Month 12 and Month 24 will also be presented, as well as the number and percentage of subjects showing a sustained unresponsiveness at Month 26 (defined as the proportion of subjects unresponsive to a cumulative dose of 1,440 mg peanut protein or above at Month 24 who remain unresponsive to 1,440 mg or above during DBPCFC after 2 months without treatment).

The median and mean cumulative reactive dose of peanut protein at Month 12 and Month 24 in the OLFUS-VIPES study will be summarized descriptively by treatment group. Changes from baseline (from the VIPES study) will also be presented.

Peanut-specific IgE and peanut-specific IgG4 levels will be summarized descriptively at Month 12 and Month 24 compared to baseline for each subject.

The change in the average wheal diameters of undiluted skin prick testing at 6, 12, 18 and 24 months of treatment and at the Early Termination Visit will be assessed at each time point versus baseline. The number and percentage of subjects per treatment group with an average wheal diameter of SPT equal to 0 mm at Month 6, Month 12, Month 18, Month 24 and Early Termination Visit will be presented.

In addition, summary statistics will be presented for the mean value of SPT average wheal diameter in each treatment group after 6, 12, 18 and 24 months of treatment and at the Early Termination Visit.
The summary statistics for the data from both the FAQLQ and the FAIM will be summarized for each treatment group at Day 1, 12 months and 24 months of treatment. Changes from Day 1 will also be presented at 12 months and 24 months of treatment, globally and by treatment group.

Safety Analyses
For safety analyses, the following data will be summarized for each dose of Viaskin® Peanut during the 12 and 24 months of treatment in the OLFUS-VIPES study:

- Treatment-emergent AEs (TEAEs) since the beginning of OLFUS-VIPES study (distinguished from symptoms/reactions elicited during the DBPCFCs) (incidence, severity and duration).
- Potentially drug-related TEAEs.
- Discontinuations due to TEAEs.
- Laboratory data, physical examinations, vital signs and spirometry results.
- Systemic allergic reactions.
- Potentially drug-related systemic allergic symptoms.
- SAEs.
- Potentially drug-related SAEs.

Besides, TEAEs between 18 and 24 months will be described for the subset of subjects who switched to the integrated patch at the Month 18 visit versus the rest of the population.

Exploratory Analyses
- Frequency of accidental consumption, conditions around the accidental consumption, estimated quantity consumed at each occurrence, and associated reactions and severity of reactions. These AEs will be classified and analyzed separately and specifically.
- Risk-taking behaviors: frequency of deliberate consumption of peanut, conditions around the consumption, estimated quantity consumed at each occurrence and associated reactions with these consumptions. These AEs will be classified and analyzed separately and specifically. Relatedness to the subject’s age will also be analyzed.
- Tolerability, adhesivity and comfort of the integrated patch versus the patch with the added Tegaderm™ for the subset of subjects who switched to the integrated patch at the Month 18 visit (Visit 6).

VERSION AND DATE: Version 3.0 Protocol Amendment 3, 25 August 2015, Final
3. TABLE OF CONTENTS

1. SIGNATURES ........................................................................................................... 2
2. SYNOPSIS .................................................................................................................. 4
3. TABLE OF CONTENTS ........................................................................................ 12
4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS ......................... 17
5. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE ........... 18
6. INTRODUCTION ................................................................................................... 20

6.1 Disease Review, an unmet medical need .......................................................... 20
6.2 Compound Review ............................................................................................... 22
6.2.1 Non-Clinical Studies ........................................................................................ 22
6.2.2 Clinical Studies ................................................................................................. 22
6.3 Clinical Study Rationale ....................................................................................... 24
7. STUDY OBJECTIVES ........................................................................................... 25
8. INVESTIGATIONAL PLAN ................................................................................. 26

8.1 Overall Study Design and Plan .............................................................................. 26
8.2 Discussion of Study Design .................................................................................. 35
8.3 Study Duration ...................................................................................................... 36
8.4 Study Population ................................................................................................... 36
8.4.1 Inclusion Criteria ............................................................................................... 37
8.4.2 Exclusion Criteria .............................................................................................. 37
8.4.3 Withdrawal and Replacement of Subjects ....................................................... 39
8.4.3.1 Criteria for Subject Withdrawal ................................................................. 39
8.4.3.2 Study Stopping Rules .................................................................................. 39
8.4.3.3 Evaluations at Withdrawal .......................................................................... 40
8.4.3.4 Replacement of Subjects ............................................................................. 40
8.5 Treatment ............................................................................................................... 40
8.5.1 Study Treatment Administration ...................................................................... 40
8.5.2 Study Treatment Formulation ......................................................................... 42
8.5.3 Study Treatment Labeling and Packaging ..................................................... 42
8.5.4 Blinding of Study Medication .......................................................................... 43
8.5.5 Study Treatment Storage and Accountability ................................................ 43
8.5.5.1 Study Treatment Storage .......................................................................... 43
8.5.5.2 Study Treatment Accountability ................................................................. 43
8.5.6 Dose Adjustments and Dose Escalation .......................................................... 43
8.5.7 Prior and Concomitant Medications ............................................................... 45
8.5.8 Treatment Compliance ..................................................................................... 45
8.5.9 Assignment to Treatment ............................................................................... 46
8.5.10 Unblinding Procedures ................................................................................... 46
8.6 Efficacy and Safety Variables .............................................................................. 47
8.6.1 Efficacy and Safety Measurements Assessed ............................................... 47
8.6.1.1 Efficacy Measurements .............................................................................. 47
8.6.1.2 Safety Measurements.................................................................................................48
8.6.1.3 Exploratory Criteria.................................................................................................48

9. STUDY EVALUATIONS BY VISIT .........................................................................48
9.1 Visit 1: Day 1.............................................................................................................48
9.2 Visit 2: Month 1 (± 7 days) .......................................................................................49
9.3 Visit 3: Month 6 (± 14 days) ....................................................................................50
9.4 Visit 4: Month 12 (± 14 days) ..................................................................................50
9.5 Visit 5: Month 12; within 7 days of Visit 4 (+ 7 days) ..............................................51
9.6 Phone Contact 1 (PC1) – 2 weeks prior visit 6 (- 7days) ...........................................52
9.7 Visit 6: Month 18 (± 14 days) ...................................................................................52
9.8 Phone Contact 2 (PC2) – 2 weeks after visit 6 (+ 7days) ...........................................53
9.9 Phone Contact 3 (PC3) – 2 weeks prior visit 7 (- 7days) ..........................................54
9.10 Visit 7: Month 24 (± 14 days) ..................................................................................54
9.11 Visit 8: Month 24; within 7 days of Visit 7 (+ 7 days) ..............................................55
9.12 Visit 9: Month 26 (± 14 days) ..................................................................................56
9.13 Visit 10: Month 26; within 7 days of Visit 9 (+7 days) ..............................................56
9.14 Early Termination Visit ............................................................................................57

10. METHODS OF ASSESSMENT ................................................................................58
10.1 Food Allergy Quality of Life Questionnaire/Food Allergy Independent Measure...58
10.2 Pregnancy Test ...........................................................................................................58
10.3 Physical Examination ..............................................................................................58
10.4 Vital Signs, Weight and Height ...............................................................................59
10.5 Spirometry Tests ......................................................................................................59
10.6 Skin Prick Tests ........................................................................................................59
10.7 Immunological Markers .........................................................................................60
10.8 Peanut Components ...............................................................................................60
10.9 Clinical Laboratory Testing.....................................................................................60
10.10 Double-Blind Placebo-Controlled Food Challenge (DBPCFC) to Peanut..........60
10.11 Subject Diary ..........................................................................................................65
10.12 Questionnaires on Patch’s Tolerability, Adhesivity and Comfort .......................65

11. SAFETY MEASUREMENTS AND VARIABLES .................................................65
11.1 Adverse Events...........................................................................................................65
11.2 Serious Adverse Events ...........................................................................................67
11.3 Reporting of Serious Adverse Events.......................................................................68
11.4 Monitoring of Subjects with Adverse Events.........................................................69
11.5 Procedures to be Followed in the Event of Abnormal Laboratory Test Values ......69
11.6 Clinical Laboratory Parameters and Abnormal Laboratory Test Results ...............69
11.7 Abnormal Physical Examination Findings ..............................................................69
11.8 Additional Safety Assessments ................................................................................69
11.9 Treatment of Overdose of Study Medication ..........................................................69
11.10 Procedures in Case of Pregnancy ............................................................................70
11.11 Adverse Events of Special Interest to the Sponsor ................................................70
12. DATA MANAGEMENT AND STATISTICAL ANALYSIS ......................... 71
12.1 Data Management ........................................................................ 71
12.2 Sample Size Estimation ............................................................... 71
12.3 Statistical Analysis Plan ............................................................... 71
12.4 Randomization ................................................................. 72
12.5 Analysis Populations ................................................................. 72
12.5.1 Safety Population ............................................................... 72
12.5.2 Intent-to-treat Population ................................................... 72
12.5.3 Per Protocol Population ....................................................... 72
12.6 Statistical Methods ................................................................. 72
12.6.1 Missing Data ................................................................. 73
12.6.2 Demographic and Baseline Data .......................................... 73
12.6.3 Subject Disposition ........................................................... 73
12.6.4 Efficacy ............................................................................. 74
12.6.4.1 Efficacy Variables ........................................................ 74
12.6.5 Pharmacokinetics .............................................................. 75
12.6.6 Safety ............................................................................... 75
12.6.6.1 Adverse Events ........................................................... 75
12.6.6.2 DBPCFC to Peanut: Symptoms/Reactions ...................... 76
12.6.6.3 Laboratory Assessments ............................................... 77
12.6.6.4 Vital Signs .................................................................... 77
12.6.6.5 Spirometry and Peak Expiratory Flow Results .............. 77
12.6.6.6 Concomitant Medications ............................................. 77
12.6.7 Exploratory Analyses .......................................................... 77
12.6.8 Additional Data .................................................................. 78
12.6.9 Data and Safety Monitoring Board ...................................... 78
13. MONITORING PROCEDURES (QUALITY ASSURANCE) ................. 79
13.1 Routine Monitoring ................................................................... 79
13.2 Inspections and Auditing Procedures ......................................... 79
14. STUDY MANAGEMENT AND MATERIALS ..................................... 80
14.1 Electronic Case Report Forms .................................................... 80
14.2 Data Collection ......................................................................... 80
14.3 Source Documents Maintenance .............................................. 81
14.4 Record Maintenance ................................................................. 81
14.5 Confidentiality ........................................................................ 81
15. ETHICS ..................................................................................... 82
15.1 Ethics Committee ...................................................................... 82
15.2 Ethical Conduct of the Study ..................................................... 82
15.3 Subject Information and Consent ............................................. 83
16. ADMINISTRATION PROCEDURES ............................................. 83
16.1 Regulatory Approval ................................................................. 83
16.2 Protocol Amendments ............................................................. 83
16.3 Protocol Adherence and Deviations ........................................ 84
16.4 Publication Policy ................................................................. 84
16.5 Clinical Study Report .............................................................. 84
16.6 Contractual and Financial Details ........................................... 85
16.7 Insurance, Indemnity and Compensation ................................. 85
16.8 Discontinuation of the Study ................................................ 85
16.9 Study Center File Management .............................................. 85

17. REFERENCE LIST ........................................................................ 87

18. APPENDICES ............................................................................... 90
18.1 Appendix 1: Declaration of Helsinki .......................................... 90
18.2 Appendix 2: Anaphylaxis Staging System ................................. 95
18.3 Appendix 3: Oral Food Challenge Symptom Score Sheet (24) ........ 96
18.4 Appendix 4: Subject Card and Anaphylaxis Emergency Action Plan ... 97
18.5 Appendix 5: Dosages of Inhaled Corticosteroids (from NAEPP 2007) ... 100
18.6 Appendix 6: Food Allergy Quality of Life Questionnaire (FAQLQ), Food Allergy Independent Measure (FAIM) and the Corresponding Parent Forms (25-28) .... 101
LIST OF TABLES AND FIGURES

Figure 1 Study Diagram .................................................................................................................30

Table 1 Study Flow Chart for the OLFUS-VIPES Study (Footnotes are on the next pages)........31
4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>ANCOVA</td>
<td>Analysis of covariance</td>
</tr>
<tr>
<td>ATS</td>
<td>American Thoracic Society</td>
</tr>
<tr>
<td>CFR</td>
<td>Code of Federal Regulations</td>
</tr>
<tr>
<td>CRO</td>
<td>Clinical research organization</td>
</tr>
<tr>
<td>DBPCFC</td>
<td>Double-blind placebo-controlled food challenge</td>
</tr>
<tr>
<td>DSMB</td>
<td>Data and Safety Monitoring Board</td>
</tr>
<tr>
<td>eCRF</td>
<td>Electronic case report form</td>
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<tr>
<td>EPIT</td>
<td>Epicutaneous Immunotherapy</td>
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<tr>
<td>FAIM</td>
<td>Food Allergy Independent Measure</td>
</tr>
<tr>
<td>FAQLQ</td>
<td>Food Allergy Quality of Life Questionnaire</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>FEV₁</td>
<td>Forced expiratory volume in one second</td>
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<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>GMP</td>
<td>Good Manufacturing Practice</td>
</tr>
<tr>
<td>ICF</td>
<td>Informed consent form</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonisation</td>
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<tr>
<td>IgE</td>
<td>Immunoglobulin E</td>
</tr>
<tr>
<td>IgG4</td>
<td>Immunoglobulin G subtype 4</td>
</tr>
<tr>
<td>IEC</td>
<td>Independent Ethics Committee</td>
</tr>
<tr>
<td>IRB</td>
<td>Independent Review Board</td>
</tr>
<tr>
<td>ITT</td>
<td>Intent-to-treat</td>
</tr>
<tr>
<td>i.v.</td>
<td>intravenous</td>
</tr>
<tr>
<td>IWRS</td>
<td>Interactive Web Response System</td>
</tr>
<tr>
<td>MedDRA</td>
<td>Medical Dictionary for Regulatory Activities</td>
</tr>
<tr>
<td>OFC</td>
<td>Oral Food Challenge</td>
</tr>
<tr>
<td>PC</td>
<td>Phone Contact</td>
</tr>
<tr>
<td>PEF</td>
<td>Peak expiratory flow</td>
</tr>
<tr>
<td>PP</td>
<td>Per protocol</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious adverse event</td>
</tr>
<tr>
<td>SAP</td>
<td>Statistical analysis plan</td>
</tr>
<tr>
<td>SPT</td>
<td>Skin Prick Test</td>
</tr>
<tr>
<td>TEAE</td>
<td>Treatment-emergent adverse event</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>US/USA</td>
<td>United States/United States of America</td>
</tr>
<tr>
<td>WhoDRUG</td>
<td>World Health Organization Drug Reference Dictionary</td>
</tr>
<tr>
<td>WMA</td>
<td>World Medical Association</td>
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</tbody>
</table>
5. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

International Coordinating Investigator/Principal Investigator(s):

The following leading Principal Coordinating Investigators are involved in the study:

Professor Christophe Dupont (Europe)
Hôpital Necker
Service des Explorations fonctionnelles digestives
149 rue de Sèvres
75015 Paris - France
Tel: 01 71 19 60 90
Fax: 01 71 19 61 20
E-mail: christophe.dupont@nck.aphp.fr

Professor Hugh Sampson (North America)
Professor of Pediatrics
Dean for Translational Biomedical Sciences
Director, Jaffe Food Allergy Institute
Mount Sinai School of Medicine
One Gustave L Levy Place
New York, NY 10029-6574 – United States of America (USA)
Tel: 212 241 5548
Fax: 212 241 7153
E-mail: hugh.sampson@mssm.edu

Central Laboratories:

Quintiles Limited,
The Alba Campus,
Rosebank, Livingston,
West Lothian, EH54 7EG,
Scotland UK

Clinical Research Organization (CRO):

PRA International
500 South Oak Way
Green Park
Reading
Berkshire, RG2 6AD
UK
Study Medical Monitor:

For DBV TECHNOLOGIES:

Wence AGBOTOUNOU, PhD, MBA
DBV TECHNOLOGIES
Green Square – Bâtiment D
80-84, Rue des Meuniers
92220 Bagneux, France
Tel: + 33 1 55 42 78 74
Mobile: + 33 6 27 57 20 96
E-mail: wence.agbotounou@dbv-technologies.com

Claude THEBAULT, MD
DBV TECHNOLOGIES
Green Square – Bâtiment D
80-84, Rue des Meuniers
92220 Bagneux, France
Tel: + 33 1 84 16 29 07
Mobile: + 33 6 12 63 80 31
E-mail: claude.thebault@dbv-technologies.com
6. INTRODUCTION

6.1 Disease Review, an unmet medical need

Food allergy represents a major health problem that can affect up to 6% of young children and 3-4% of adults and appears to have an increasing prevalence (1, 2). Allergic reactions to food can be due to different immunologic mechanisms including immunoglobulin E (IgE)-mediated reactions (acute onset), non-IgE cell mediated reactions (delayed or chronic onset) or a combination of both. Food allergies lead to a large variety of clinical symptoms that can involve the skin, the gastrointestinal and respiratory tracts, and the cardiovascular system. Some of these symptoms described as anaphylactic shock can be life-threatening and require admission to an emergency room. Food allergy is indeed the leading cause of anaphylaxis treated in hospital emergency departments in Western Europe and in the USA (3).

Peanut allergy is a typical IgE-mediated immune disease (3). National surveys in the USA suggest that 1.1% of Americans are allergic to peanuts, tree nuts or both. In addition, studies of peanut allergy in the USA and UK indicate that the number of children affected has doubled in the past decade, with a prevalence now over 1% (1, 4, 5). Peanut sensitivity is one of the leading causes of fatal food reactions, making peanut allergy a major health concern worldwide, especially in developed countries.

Two recent studies from the US and the UK have shown that the incidence of peanut allergy has doubled in children below five years of age (4, 5). Hence, it is likely that there will be a gradual increase in peanut allergy in the general population as the population ages. The prevalence of peanut allergy in many other Western countries (Canada, France, and Spain) has been determined to be between 0.9% and 1.5% (6, 7, 8). In Sweden, sensitization to peanut as determined by IgE tests was estimated to occur in 3.3% of the population (9). Peanut allergy starts in childhood, and its prevalence in children has doubled in the past five years. Barely 20% of peanut-allergic children will outgrow this allergy and up to 8% of those will recur after apparent remission. To date, the management of peanut allergy has been based on avoidance of peanut and injectable epinephrine after the systemic allergic reactions has started. Immunotherapy methods currently available have shown promise, but are limited by important safety issues. Hence, there is a significant unmet medical need for effective and safe treatments for peanut allergy, particularly because inadvertent ingestion occurs frequently.

IgE-mediated allergic reactions to foods typically have a rapid onset within a few minutes of exposure to the allergen. IgE-mediated allergic reactions to foods provoke a characteristic clinical syndrome which includes responses in the skin, gastrointestinal tract, and respiratory tract (10). Generalized reactions (i.e., anaphylaxis) may also be triggered in IgE-mediated reactions to food. Generalized reactions may also occur simultaneously with any of the cutaneous, gastrointestinal, and/or respiratory symptoms.

The precise pathogenesis of IgE-mediated food allergy remains unknown. However, it is thought that the development of an IgE-mediated response to an allergen is the result of a series of molecular and cellular interactions involving antigen-presenting cells, T cells, and B cells (3,
Current treatments being investigated for food allergies include allergen-specific immunotherapy, aimed at establishing ‘tolerance’. Allergen-specific immunotherapy consists of administering gradually increasing quantities of an allergen product to an individual with IgE-mediated allergic disease in order to reduce or prevent the symptoms associated with subsequent exposure to the allergen. Immunotherapy induces clinical and immunological tolerance, which may be maintained years after cessation of the treatment. Allergen-specific immunotherapy also attenuates new sensitizations and ultimately improves the quality of life of allergic subjects (12, 13).

To date, the standard of care for management of food allergy is the strict avoidance of the responsible allergen, but peanut is a ubiquitous ingredient in many foods and strict avoidance is difficult to achieve. Consequently, accidental ingestion of peanuts by peanut-allergic subjects is frequent, and could lead to severe and potentially life-threatening reactions. An annual incidence rate of accidental ingestion of 14% was reported (14).

The only available countermeasure in case of severe systemic and/or life-threatening reactions/anaphylaxis to peanuts is injectable epinephrine as recommended by the World Allergy Organization (15). Epinephrine remains a rescue therapeutic agent and is not designed for a routine use. Unfortunately, epinephrine is under-prescribed to subjects with a history of peanut allergy anaphylactic reactions, and subjects may not consistently carry it with them (15, 16), thereby incurring risk if accidental peanut exposure occurs (17).

Developing effective therapies for the treatment of peanut allergy represents a clear unmet medical need since no specific treatment is currently available. Traditional subcutaneous allergen immunotherapy with crude peanut extract has not been feasible for peanut allergy because of the high risk of severe systemic side-effects of the therapy including life-threatening anaphylaxis. Oral immunotherapy represents a potential alternative; however, it also presents safety concerns and is not suitable for all subjects (3).

Epicutaneous Immunotherapy (EPIT), consisting of repeated application of the allergen on intact skin, is a novel innovative method under investigation for the treatment of food allergy.

This clinical trial is designed to assess the efficacy and safety of Viaskin® Peanut after up to 36 months of EPIT in peanut-allergic subjects, as well as to evaluate the proportion of subjects achieving sustained unresponsiveness after a period of 2 months without treatment, in subjects showing desensitization to peanut with Viaskin® Peanut.
6.2 Compound Review

The Investigational New Drug, Viaskin® Peanut, consists of an epicutaneous delivery system (Viaskin® or Viaskin® patch) containing a dry deposit of a formulation of peanut protein extract. The peanut protein allergens are deposited on the backing of an occlusive chamber by electrospraying a liquid formulation of the peanut protein extract. The epicutaneous delivery system (Viaskin® or Viaskin® patch) is made of a titanium/polyethylene terephthalate backing layer comprising a protective liner and functional layers. For the integrated Viaskin® Peanut patch, a breathable adhesive polyurethane dressing is part of the patch.

The drug substance is an unmodified, lyophilized peanut extract produced from the extraction and freeze drying of defatted peanut flour. The drug substance contains the biologically active ingredients, the peanut proteins. This drug substance derives from a natural source material of biological origin: peanut seed, *Arachis hypogaea* (*Fabaceae* family, also called “Legumes”). Refer to the Investigator Brochure for full details (18).

6.2.1 Non-Clinical Studies

DBV Technologies has conducted several non-clinical studies supporting the clinical development of Viaskin® Peanut. These include ISO 10993-compliant biocompatibility studies performed for the device component independent of the drug product, i.e. the Viaskin®, *in vitro* pharmacokinetic/absorption studies, *in vivo* pharmacology (efficacy) studies in a mouse model of peanut allergy, and Good Laboratory Practice-compliant toxicological studies in the rabbit and in a guinea pig model of peanut allergy. Details regarding preclinical studies with Viaskin® Peanut can be found in the Investigator Brochure (18).

6.2.2 Clinical Studies

A completed Phase Ib study (19) with Viaskin® Peanut (PEP01.09 study) evaluated the safety of Viaskin® Peanut administered epicutaneously to adults, adolescents, and children with peanut allergy. No serious adverse events (SAEs) or deaths were reported in this Phase Ib study. There were 100 randomized subjects. There were two subjects receiving Viaskin® Peanut treatment who discontinued due to adverse events (AEs) during the course of this study: one child subject on active treatment (at the dose/regimen of 250 μg Viaskin® patch/48 hours) was discontinued due to treatment-emergent adverse events (TEAEs) of moderate vomiting, mild eye pruritus, mild nasal congestion, and mild throat irritation and one adult subject on active treatment (at the dose/regimen of 100 μg Viaskin® patch/48 hours) was discontinued due to a TEAE reported as moderate anaphylactic reaction (local severe pruritus, erythema, edema, urticaria). Of note, the Data and Safety Monitoring Board (DSMB) upon review of this case considered that it was unlikely that the patient experienced true anaphylaxis. One additional adult subject on placebo treatment was discontinued because of protocol noncompliance following a TEAE of moderate anaphylactic reaction.
There were no significant differences in overall TEAEs in subjects who received Viaskin® Peanut versus subjects who received placebo. However the vast majority of the TEAEs were local skin reactions at the site of patch application and Viaskin® Peanut triggered more local reactions than placebo; the severity profile of the local AEs with Viaskin® Peanut (mostly mild to moderate) was also higher than that with placebo (mostly mild). This was expected to occur with Viaskin® Peanut.

There were no significant differences in overall TEAEs between the 24-hour and the 48-hour regimen in subjects who received Viaskin® Peanut or placebo but a slight better safety profile in the 1 Viaskin® patch/24-hour regimen. There were no statistically significant differences in overall TEAEs (incidence, severity, duration) in nonsevere peanut-allergic subjects versus severe peanut-allergic subjects when treated with Viaskin® Peanut.

AEs of special interest in this study included local skin reactions of Grade 4 as per the modified EAACI-GA²LEN (European Academy of Allergy and Clinical Immunology – Global Allergy and Asthma European Network) position paper from Turjanmaa et al (21) upon application of Viaskin® Peanut. The appearance of any vesicles (skin reactions of Grade 4) or ulcerative skin lesions or any other significant skin lesion that could potentially lead to skin barrier disruption at sites of Viaskin® patch applications were also considered as AEs of special interest. Any occurrence of anaphylaxis or systemic allergic reactions directly related to Viaskin® Peanut or placebo application was also considered an AE of special interest.

There were no TEAEs of special interest due to local skin reactions of Grade 4. Hence, AEs of special interest were limited to systemic allergic reactions related to Viaskin® Peanut or placebo.

Most TEAEs of special interest, i.e. systemic reactions, were mild and transient, none was severe and half of them did not require any countermeasure action, were not treated, and resolved spontaneously.

Overall, after a 2-week treatment period with Viaskin® Peanut, safety was demonstrated in nonsevere peanut-allergic adults and adolescents and in severe peanut-allergic adults up to 500 μg peanut protein/patch, as well as in nonsevere peanut-allergic children up to 250 μg peanut protein/patch.

A pilot Phase II study (the Arachild study) sponsored by the French public institution AP-HP and investigating the efficacy and safety of epicutaneous immunotherapy in children allergic to peanuts is ongoing with Viaskin® Peanut (20). Since the start of the patient randomization in October 2010, and based on the data provided by AP-HP to DBV, twenty one (21) SAEs have been reported so far from the Arachild study. Fourteen SAEs were unrelated to the study conduct and resolved without any complication. Four SAEs were reported during the conduct of the double-blind placebo-controlled food challenges (DBPCFCs) and resolved without any complication. One investigator at one site reported 3 cases of SAEs with a possible relationship to Viaskin® Peanut during the open-label phase of the treatment. One subject of sixteen years of age after 16 months of treatment in the study was hospitalized for 24 hours for a bone abscess of
a pilonidal cyst. The subject was treated with antibiotics. This case resolved without any sequel. The study treatment was not discontinued. The investigator reported this SAE as possibly related to study drug. Five months later, the same subject still under treatment with Viaskin® Peanut (for a total duration of 21 months) reported a life-threatening anaphylactic reaction after having eaten a “kebab” sandwich. The subject was assessed by skin prick testing as being highly reactive to fenugreek. The subject was treated with oral corticosteroids and antihistamines, but no epinephrine. The case resolved within 24 hours. The subject remained under study drug treatment with Viaskin® Peanut during the whole period and study drug was not discontinued. The subject is still under treatment. The investigator reported this SAE as possibly related to study drug.

Another subject at this site of nineteen years of age and treated for 19 months in the study was hospitalized for 4 days because of an episode of gingivostomatitis with difficulties for feeding. This was treated with intravenous aciclovir and resolved. The study drug was not discontinued and the subject is currently still under Viaskin® Peanut treatment. The investigator reported this SAE as possibly related to study drug.

In spite of these 3 cases described above, there have been no discontinuations reported as due to AEs during the course of this study. The most common AEs reported by the subjects in the Arachild study so far were pruritus, eczema, erythema, abdominal cramps, asthma, diarrhea and nausea.

The VIPES study is a currently ongoing Phase IIb dose-finding study investigating the efficacy of Viaskin® Peanut. This study is being conducted in France, the Netherlands, Poland, USA and Canada. The OLFUS-VIPES study is an open-label follow-up study for subjects completing the VIPES study. The objectives of the OLFUS-VIPES study are to evaluate long-term efficacy and safety of Viaskin® Peanut in peanut-allergic subjects treated for a total of up to 36 months. The OLFUS-VIPES study will offer the subjects participating in the VIPES study 24 months of further treatment with Viaskin® Peanut. Participating sites will be from those that participated in the VIPES study. To date (as of the 28th of November 2013), a total of eight (8) SAEs have been experienced by eight (8) subjects. All of these events (five events of moderate anaphylactic reactions, one event of severe anaphylactic reaction, one event of respiratory depression and one event of mental health issues) were considered by the Investigators to be unrelated to the study medication.

6.3 Clinical Study Rationale

The OLFUS-VIPES study will be conducted at sites that participated in the VIPES study and will allow the subjects completing the VIPES study to receive 24 months of treatment with Viaskin® Peanut.
In the initial protocol design (Protocol Version 1.1 dated 27 May 2013), subjects entering the OLFUS-VIPES study who had previously received Viaskin® Peanut at any of the three doses in the VIPES study would continue at the same dose (i.e. 50 μg or 100 μg or 250 μg of peanut protein). Subjects entering the OLFUS-VIPES study who had previously received placebo in the VIPES study would be re-randomized in a 1:1:1 ratio to receive Viaskin® Peanut at one of the three doses, 50 μg or 100 μg or 250 μg of peanut protein. Randomization of former placebo subjects would be stratified by site.

In Protocol Version 2.0 (incorporating Protocol Amendment 1), all subjects enrolling into the OLFUS-VIPES study after having completed the VIPES study will receive the highest dose of Viaskin® Peanut, i.e. 250 μg peanut protein, regardless of dose level in the VIPES study. On the 09th of September 2013, the independent Data and Safety Monitoring Board (DSMB) of the VIPES study has reviewed data of all 221 subjects randomized and treated in the VIPES study. The safety data reviewed by the DSMB members included data of subjects treated for up to 11 months. The DSMB members concluded that there were no safety concerns even at the highest dose of 250 μg in any patient age category. DBV, as the Sponsor of the OLFUS-VIPES study, would like to maximize the chances of subjects’ benefit by treating them in the OLFUS-VIPES study at the highest dose.

DBV consulted again with the DSMB members on the 18th of October 2013 and the DSMB supported this amendment.

In this Protocol Version 3.0 (incorporating Protocol Amendment 3), it is offered to subjects reaching their visit at Month 18 (Visit 6) to receive the Viaskin® Peanut patch at 250 μg with a slight change in its design. This patch already includes the polyurethane (PU) breathable adhesive dressing, which will replace the Tegaderm™ dressing that had to be added previously. Of note, the Tegaderm™ dressing is also a polyurethane breathable adhesive dressing. This “integrated Viaskin® Peanut patch” is considered as an improvement of the previous one, with all components of the patch in one. Subjects and/or subjects’ parents will be asked to assess the tolerability, the adhesivity and the comfort of this “integrated Viaskin® Peanut patch” and the tolerability, the adhesivity and the comfort of the “previous patch” with the added Tegaderm™.

Subjects who switch to this “integrated Viaskin® Peanut patch” will continue with this patch until Month 24 (Visit 7).

7. STUDY OBJECTIVES

The objectives of this follow-up/extension study are:

- To assess the efficacy of Viaskin® Peanut after up to 36 months of EPIT in peanut-allergic subjects.
- To evaluate the safety of long-term treatments with Viaskin® Peanut.
To evaluate sustained unresponsiveness to peanut after a period of 2 months without treatment in subjects showing desensitization to peanut after EPIT with Viaskin® Peanut.

8. INVESTIGATIONAL PLAN
8.1 Overall Study Design and Plan

This is an open-label follow-up study or extension study for subjects who previously were randomized and have completed the VIPES study. Subjects will be offered enrollment in this follow-up study to receive an additional 24 months of Viaskin® Peanut treatment followed by a period of 2 months without treatment while maintaining a peanut-free diet.

All subjects enrolling into the OLFUS-VIPES study after having completed the VIPES study will receive the highest dose of Viaskin® Peanut, i.e. 250 μg peanut protein, regardless of dose level in the VIPES study.

Subjects who already entered the OLFUS-VIPES study under the initial protocol design (Protocol Version 1.1 dated 27 May 2013) will all switch to receive the 250 μg dose at their protocol visit at Month 6 (Visit 3) or at Month 12 (Visit 4) after the approval of Protocol 2.0 (incorporating Protocol Amendment 1) at their sites.

The transition from the VIPES study to the OLFUS-VIPES study or the transition from the initial OLFUS-VIPES design to the amended OLFUS-VIPES design will be performed keeping the blinding in the VIPES study until the VIPES study results are obtained. The same Interactive Web Response System (IWRS) used to allocate treatment to subjects and to maintain the blinding in the VIPES study will be used in the OLFUS-VIPES study, but the transition does not require any unblinding in the VIPES study. Hence, all subjects should receive the 250 μg dose in the OLFUS-VIPES study but none of them will be unblinded until the VIPES study is unblinded.

The subjects in the OLFUS-VIPES already treated at the 250 μg dose will remain under the 250 μg dose to the end of the study, whatever the optimal clinical dose determined in the VIPES study is. This will prevent subjects from having to switch to another dose again during the OLFUS-VIPES study.

After the overall 24 months of active treatment with Viaskin® Peanut, a period of 2 months without treatment will be considered for those subjects being assessed for sustained unresponsiveness.

Repeated daily application of Viaskin® Peanut will continue as in the VIPES study, i.e. a new patch will be applied every 24 hours on the inner side of both upper arms for adults (≥18 years) and adolescents (12-17 years), or on the inter-scapular area of the back for children (7-11 years).
In order not to unblind the treatment arms until the results of the VIPES study are known and to also guarantee safety in particular for placebo subjects crossing over to receive the 250 μg dose of Viaskin® Peanut, the duration of application of the Viaskin® Peanut patch will be progressively increased for the first 2 weeks of treatment in all subjects entering the OLFUS-VIPES study (one week shorter than what was done at the start of the VIPES study): patches will be applied for 6 hours every day during the first week, 12 hours every day during the second week, and for the entire 24 hours of daily application from the third week or the 15th day onwards.

Subjects enrolled in the OLFUS-VIPES study before approval of Protocol Amendment 1 and switching to the 250 μg dose after Protocol Amendment 1 is approved may apply the new 250 μg patch for the whole 24 hours starting on the very first day. They have been receiving Viaskin® Peanut at one of the three doses for at least 6 months: no safety concerns are expected. However, at the discretion of the Investigator, the 2-week period of progressive increase of time of daily application described above may be repeated.

In this Protocol Version 3.0 (incorporating Protocol Amendment 3), at the time of the Month 18 visit (Visit 6), the subjects who have been using the Tegaderm™ as a dressing over the Viaskin® patch so far, will be proposed to switch to an integrated Viaskin® Peanut patch containing the same quantity of peanut proteins (250 μg) loaded on the backing of the same patch system but already integrating the adhesive dressing. These subjects who switch to the integrated Viaskin® Peanut patch, will continue to receive this patch up to the Month 24 visit (Visit 7).

The first DBPCFC in the OLFUS-VIPES study will be conducted after 12 months of treatment up to a cumulative dose of 5,040 mg peanut protein.

The second DBPCFC in the OLFUS-VIPES study will be conducted after 24 months of treatment up to a cumulative dose of 5,040 mg peanut protein.
- Subjects who react objectively below or at a cumulative dose of 1,440 mg of peanut protein during this second DBPCFC at 24 months in the OLFUS-VIPES study will have their last visit at Visit 8 (Month 24 + 1 week).
- Subjects who are unresponsive to the cumulative dose of 1,440 mg of peanut protein or above during this second DBPCFC at 24 months in the OLFUS-VIPES study will continue to a Month 26 visit as described below.

Subjects who are unresponsive to the cumulative dose of 1,440 mg peanut protein or above (unresponsiveness to the DBPCFC is defined as no objective reaction to peanut protein), will be taken off treatment and will continue for an additional 2 months without treatment and following their peanut-free diet. This additional period will help to assess the “sustained unresponsiveness” i.e. to study whether the subjects will maintain this level of unresponsiveness to peanut protein even after 2 months without receiving any peanut EPIT treatment.
The third DBPCFC in the study will then be conducted after a period of 2 months without treatment, i.e. at Month 26 (Visit 9 and Visit 10), only for those subjects who were unresponsiveness to a cumulative dose of 1,440 mg peanut protein or above at Month 24. Visit 10 will be the End of Study Visit for these subjects.

Throughout the OLFUS-VIPES study period, subjects will be instructed to remain on a peanut-free diet. The re-introduction or not of peanut into the subject’s diet at the end of their participation in the study will be left to the Investigator’s decision.

In summary, treatment will be comprised of daily applications of Viaskin® Peanut for 24 months. Each subject will undergo two DBPCFCs: one at Month 12 and one at Month 24. A third DBPCFC will be conducted at Month 26 after 2 months without treatment only for those subjects who were unresponsive to a cumulative dose of 1,440 mg of peanut protein or above at Month 24.

In total, subjects will attend overall 10 or 11 study visits as follows:

- **24-Month Treatment Period:**
  - Visit 1, Day 1 (this visit is either held the same day as Visit 11 in the VIPES study, or can be held within 1 week from Visit 11 of the VIPES study).
  - Visit 2, Month 1
  - Visit 3, Month 6
  - Visit 4, Month 12
  - Visit 5, within 1 week from Visit 4
  - Visit 6, Month 18
  - Visit 7, Month 24
  - Visit 8, within 1 week from Visit 7. Last Visit for subjects reacting objectively below or at a cumulative dose of 1,440 mg peanut protein.

- **Two-Month Follow-up Period Without Treatment:**
  - Visit 9, Month 26 – Visit 9 will be performed only by subjects who are unresponsive to a cumulative dose of 1,440 mg peanut protein or above at Month 24 DBPCFC (i.e. responsive to treatment).
  - Visit 10, within 1 week from Visit 9 – End of Study Visit for subjects who completed all study visits.

- **Early Termination:**
  - Early Termination Visit is for subjects withdrawing prematurely.

With the Protocol Version 3.0 (incorporating Protocol Amendment 3), in addition to the regular study visits, the study personnel will contact the subjects/subjects’ parents/guardians:

- 2-3 weeks prior to the Month 18 visit (Phone Contact 1).
- 2-3 weeks after the Month 18 visit (Phone Contact 2).
- 2-3 weeks prior to the Month 24 visit (Phone Contact 3).
Between the visits, investigators and their staff members can also contact any subject by phone at their discretion.
A schematic diagram of the trial design is provided below in Figure 1.

A schedule outlining study assessments and times of assessments is shown in Table 1. Study assessments are described in Section 9.

Subject participation will be approximately 27 months (allowing for visit windows): 24 months in the treatment period followed by a period of 2 months without treatment.
Figure 1 Study Diagram

Switch to the integrated Viaskin® Peanut patch

<table>
<thead>
<tr>
<th>Visits in OLFUS-VIPES</th>
<th>D1</th>
<th>M1</th>
<th>M6</th>
<th>M12</th>
<th>M18</th>
<th>M24</th>
<th>M26 (subjects unresponsive to 1,440 mg peanut protein or above at M24 DBPCFC)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 1 Study Flow Chart for the OLFUS-VIPES Study (Footnotes are on the next pages)

<table>
<thead>
<tr>
<th>Visit Number</th>
<th>V1</th>
<th>V2</th>
<th>V3</th>
<th>V4</th>
<th>V5</th>
<th>PC1</th>
<th>V6</th>
<th>PC2</th>
<th>PC3</th>
<th>V7</th>
<th>V8</th>
<th>V9</th>
<th>V10</th>
<th>Early Termination Visit1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit Day/ Month (Allowance days)</td>
<td>D1</td>
<td>M1 (±7)</td>
<td>M6 (±14)</td>
<td>M12 (±14)</td>
<td>M12 + 7 days (+7 days)</td>
<td>M18 (±14)</td>
<td>2 weeks prior V6 (±7 days)</td>
<td>M24 (±14)</td>
<td>M24 + 7 days (-7 days)</td>
<td>M26 (±14)</td>
<td>M26 + 7 days (+7 days)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Study Assessments:

1. Informed consent/assent
2. Medical History (including ongoing AEs from the VIPES study)
3. Demography
4. Check eligibility criteria
5. Physical examination
6. Vital signs
7. FAQLQ/FAIM
8. Spirometry (FEV1)
9. PEF
10. Immunological markers
11. Peanut components
12. Laboratory tests
13. Urine pregnancy test
14. DPICCLS
15. Adverse events
16. Concomitant medications
17. Dispense Diary Cards/Check any information reported in it (medical event(s)/peanut consumption)
18. Dispense IP to subject

Footnotes:

1. +7 days after V6 (±7 days)
Table 1 Study Flow Chart for the OLFUS-VIPES Study (Footnotes are on the next pages)

<table>
<thead>
<tr>
<th>Visit Number</th>
<th>24 Months Treatment</th>
<th>2 Months Without Treatment</th>
<th>Early Termination Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>V1</td>
<td>V2</td>
<td>V3</td>
</tr>
<tr>
<td>Visit Day/Month (Allowance days)</td>
<td>M1 (±7)</td>
<td>M6 (±14)</td>
<td>M12 (±14)</td>
</tr>
<tr>
<td></td>
<td>D1</td>
<td>M1 (±7)</td>
<td>M6 (±14)</td>
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<tr>
<td></td>
<td>D1</td>
<td>M1 (±7)</td>
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<td></td>
<td>D1</td>
<td>M1 (±7)</td>
<td>M6 (±14)</td>
</tr>
<tr>
<td></td>
<td>D1</td>
<td>M1 (±7)</td>
<td>M6 (±14)</td>
</tr>
</tbody>
</table>

Study Assessments:
- Collect the previous treatment box dispensed to subject and check the used/unused IP
- Check expiry date of the epinephrine auto-injector
- Discussion by phone about the availability of the integrated patch
- Collect the signed ICF/assent addendum for amendment 3
- Questionnaire on the tolerability, adhesivity and comfort of the current patch with the added Tegaderm™ (last 2 weeks of application prior visit 6)
- Questionnaire on the tolerability, adhesivity and comfort of the integrated patch (first 2 weeks of application after visit 6)
Table 1 Study Flow Chart for the OLFUS-VIPES Study (Footnotes are on the next pages)

<table>
<thead>
<tr>
<th>Visit Number</th>
<th>V1</th>
<th>V2</th>
<th>V3</th>
<th>V4*</th>
<th>V5*+</th>
<th>PC1</th>
<th>V6</th>
<th>PC2</th>
<th>PC3</th>
<th>V7*+</th>
<th>V8*</th>
<th>V9*</th>
<th>V10*+</th>
<th>Early Termination Visit*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit Day/ Month (Allowance days)</td>
<td>D1</td>
<td>M1</td>
<td>M6</td>
<td>M12</td>
<td>M12+7 days</td>
<td>M12+7 days</td>
<td>M18</td>
<td>M18+7 days</td>
<td>M24</td>
<td>M24+7 days</td>
<td>M26</td>
<td>M26+7 days</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Study Assessments:

- Questionnaire on the tolerability, adhesivity and comfort of the integrated patch (last 2 weeks of application prior visit 7)
- X

Duration of observation:

- 3 hrs
- 3 hrs
- 3 hrs
- 3 hrs
- 3 hrs
- 3 hrs
Abbreviations: V=Visit, D=Day; M=Month; FAQLQ=Food Allergy Quality of Life Questionnaire; FAIM=Food Allergy Independent Measure; FEV1=Forced Expiratory Volume in one second; PC=Phone Contact; PEF=Peak Expiratory Flow; SPT=Skin Prick Test; DBPCFC=Double-Blind Placebo-Controlled Food Challenge; IP=Investigational Product.

1. Visit 1 in the OLFUS-VIPES study is also Visit 11 in the VIPES study or can be conducted within a week from Visit 11 of the VIPES study. If Visit 1 in the OLFUS-VIPES study is conducted on the same day as Visit 11 in the VIPES study, the common procedures will be performed only once.

2. Visit 8 will be the end of study visit for subjects who react objectively below or at a cumulative dose of 1,440 mg of peanut protein.

3. Visit 9 and Visit 10 will be performed only by subjects who are unresponsive (i.e. showing no objective symptoms) to a cumulative dose of 1,440 mg of peanut protein or above at Month 24 DBPCFC.

4. Visit 10 will be the end of study visit for subjects unresponsive (i.e. showing no objective symptoms to a cumulative dose of 1,440 mg peanut protein or above at Month 24 DBPCFC).

5. Early Termination Visit is only for subjects withdrawing prematurely.

6. Including weight (kg) and height (cm).

7. Including a complete skin examination.

8. Vital signs measured in a sitting position include heart rate, systolic and diastolic blood pressure, respiratory rate and temperature.

9. For both FAQLQ and FAIM, use the form corresponding to the subject’s age range (child, adolescent or adult). Parent(s)/guardian(s) of children and adolescents will also have to complete the Parent Forms specific to children or adolescents. The specific forms of FAQLQ and FAIM will be completed in the countries where they are available in local languages. FAQLQ/FAIM must be completed prior to starting the DBPCFC at Visit 11 in the VIPES study and after the OLFUS-VIPES informed consent form is signed by subject.


11. Specific IgE for Ara h 1, h 2, h 3, h 8 and h 9.

12. Laboratory tests include Hematology: hemoglobin, hematocrit, platelets, red blood cells, white blood cells; Biochemistry: aspartate aminotransferase, alanine aminotransferase, total bilirubin, total protein, blood urea nitrogen and creatinine.

13. Urine pregnancy test to be performed only for childbearing potential females subjects. Pregnancy testing may be repeated during the study at the discretion of the Investigator.

14. If Visit 1 in the OLFUS-VIPES study is conducted the same day as Visit 11 in the VIPES study, values here are those obtained before starting the challenge at Visit 11 in the VIPES study.

15. All AEs will be collected at all visits including AEs/allergic symptoms during the DBPCFC.

16. All concomitant medications will be collected at all visits including concomitant medications given to treat allergic symptoms during the DBPCFC. Ongoing concomitant medications from the VIPES study will also be collected at Visit 1.

17. The expiry date of the auto-injector dispensed formerly will be checked if needed and a new auto-injector will be provided to the subject prior to product expiry.

18. EPIT Treatment should continue between Visits 4 and 5, i.e. between the 2 days of the DBPCFC at Month 12.

19. EPIT Treatment is permanently discontinued at Visit 7, i.e. at the 1st day of the challenge at Month 24.
8.2 Discussion of Study Design

The OLFUS-VIPES study is a follow-up study or extension study for subjects who have completed the VIPES study. Participating sites will be from those that participated in the VIPES study.

In the initial protocol design (Protocol Version 1.1 dated 27 May 2013), subjects entering the OLFUS-VIPES study who had previously received Viaskin® Peanut at any of the three doses in the VIPES study would continue at the same dose (i.e. 50 μg or 100 μg or 250 μg of peanut protein). Subjects entering the OLFUS-VIPES study who had previously received placebo in the VIPES study would be re-randomized in a 1:1:1 ratio to receive Viaskin® Peanut at one of the three doses, 50 μg or 100 μg or 250 μg of peanut protein. Randomization of former placebo subjects would be stratified by site.

In Protocol 2.0 (incorporating Protocol Amendment 1), all subjects enrolling into the OLFUS-VIPES study after having completed the VIPES study will receive the highest dose of Viaskin® Peanut, i.e. 250 μg peanut protein, regardless of dose level in the VIPES study. Thus, the study will be fully open-label earlier than originally planned. The 250 μg dose of the VIPES study dose did not present any safety concerns as evaluated by the independent DSMB, and may maximize the chances of the subjects to be desensitized to peanut.

Subjects already enrolled in the OLFUS-VIPES study under the initial protocol design (Protocol Version 1.1 dated 27 May 2013) will all switch to receive the 250 μg dose at Visit 3 (Month 6) or at Month 12 (Visit 4) after the approval of Protocol Amendment 1 at their sites.

The subjects in the OLFUS-VIPES study already treated at the 250 μg dose will remain under the 250 μg dose to the end of the study, whatever the optimal clinical dose determined in the VIPES study is. This will prevent subjects from having to switch to another dose again during the OLFUS-VIPES study.

All subjects completing the OLFUS-VIPES follow-up/extension study should receive overall 24 months of active treatment followed by a period of 2 months without treatment for those subjects being assessed for sustained unresponsiveness.

General safety will be monitored using physical examinations, vital signs, laboratory testing, peak expiratory flow, forced expiratory volume in one second, AE and SAE assessments. Cutaneous local reactions at the site of patch application in the back or the arms such as pruritus, erythema, edema or urticaria (rash) are expected and are considered AEs; it is expected that the intensity of these AEs would decrease over time on EPIT. Less frequently, AEs distant from the site of patch application, i.e. systemic events of a potential allergic nature, may occur such as eczema, generalized or distant rash, atopic dermatitis, pallor, hives, eyelid edema, facial flushing, nausea, nasal congestion, coughing, sneezing, throat pruritus, watery eyes, vomiting, and/or dyspnea. Based on the available data, the majority of these systemic AEs are expected to be mild and to resolve quickly with or without treatment. In case of local intolerable skin reactions, or in case of systemic allergic reactions, subjects are instructed to remove the Viaskin® Peanut patch immediately and cleanse the area. This should allow the reaction to quickly subside. Application of a topical corticosteroid such as 1% hydrocortisone ointment or equivalent to treat any local AEs
(eczematous lesions, pruritus, edema, etc.) is allowed. If required, a more potent corticosteroid ointment might be prescribed and applied topically. Oral antihistamine or oral corticosteroids are also allowed to treat AE(s) determined to be allergic reactions. Each subject will continue to have their epinephrine auto-injector (EpiPen®, Twinject®, AnaPen® or any other trade name commercially available in a country) to be used and injected intra-muscularly in case of symptoms of anaphylaxis. All subjects will continue with their usual peanut-free diet and label reading of food products to avoid any accidental peanut consumption during the duration of the study.

8.3 Study Duration

The planned duration of the clinical study is approximately 27 months (allowing for visit windows): 24 months in the treatment period followed by a period of 2 months without treatment.

8.4 Study Population

All subjects (child, adolescent or adult) who completed the VIPES study up to Visit 11 (inclusive) could be eligible for participation in the OLFUS-VIPES study. At Visit 11 in the VIPES study, subjects who decide to enroll in the OLFUS-VIPES study will be rolled-over into the OLFUS-VIPES study, unless in the opinion of the Investigator, it is not in the best interest of the subjects to continue receiving EPIT with Viaskin® Peanut. The choice is left for the subject and the investigative site to decide whether the subject will roll-over from VIPES to OLFUS-VIPES the same day of Visit 11 of VIPES or within a week from Visit 11 of VIPES.

If the decision is made to roll-over to OLFUS the same day, Visit 1 in the OLFUS-VIPES can be conducted on the same day as Visit 11 in the VIPES study. In which case the subject should sign the Informed consent form for the OLFUS study prior to starting the challenge of Visit 11 and some procedures are conducted prior to the challenge.

If the decision is made to continue in the OLFUS-VIPES but the majority of the procedures of Visit 1 are to be held within a week, the subject should still sign the Informed consent form and the quality of Life questionnaires are completed for the OLFUS study prior to starting the challenge of Visit 11.

Subjects continuing into the OLFUS-VIPES study will not perform Visit 12 in the VIPES study. All subjects will continue with their usual peanut-free diet and label reading of food products to avoid any accidental peanut consumption during the duration of the study.
8.4.1 **Inclusion Criteria**

Subjects **MUST** satisfy all of the following entry criteria:

1. Signed informed consent from adult subjects or parent(s)/guardian(s) of children <18 years old, children’s assent for children ≥7 years or as per country-specific regulations or laws. This consent should be signed no later than at Visit 11 in the VIPES study.
2. Adult and pediatric subjects (≥7 years) who completed the VIPES study, with a mandatory and documented DBPCFC at Month 12 in the VIPES study.
3. Negative pregnancy test for women of childbearing potential at Visit 10 in the VIPES study.
4. Female subject of childbearing potential must use effective methods of contraception to prevent pregnancy and agree to continue to practice an acceptable method of contraception for the duration of participation in the study. Sexual abstinence will be accepted as an effective method of contraception for girls below 15 years of age.
5. Subjects and/or parents/guardians willing to comply with all study requirements during their participation in the study.

8.4.2 **Exclusion Criteria**

If any of the following apply, the subject **MUST NOT** enter the study:

1. Severe reaction during the DBPCFC at Month 12 in the VIPES study (at Visit 10 or 11), defined as need for intubation, hypotension persisting after epinephrine administration, and/or the need for more than two doses of epinephrine.
2. Pregnancy or lactation.
3. Females of childbearing potential planning a pregnancy in the coming 27 months.
4. Subjects who became allergic to chocolate or who do not want to consume the chocolate study challenge vehicle anymore (the chocolate mousse).
5. Subjects who developed hypersensitivity to excipients of the Viaskin® patches or of the food challenge formula used during the VIPES study.
6. Inability to discontinue short-acting antihistamines for three days or long-acting antihistamines for five to seven days (depending on half-life) prior to skin prick testing or food challenges.
7. Subjects with asthma that has evolved and now fulfills any of the criteria defined as follows:
   a. uncontrolled persistent asthma by National Asthma Education and Prevention Program Asthma guidelines (2007) or by Global Initiative for Asthma (2011) or being treated with combination therapy of medium dose inhaled corticosteroid with a long acting inhaled β2-agonists.
   b. at least two systemic corticosteroid courses for asthma in the past year or one oral corticosteroid course for asthma in the past three months.
   c. prior intubation for asthma in the past year.
8. Subjects receiving β-blocking agents, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, calcium channel blockers or tricyclic antidepressant therapy.
9. Subjects receiving or planning to receive anti-tumor necrosis factor drugs or anti-IgE drugs (such as omalizumab) or any biologic immunomodulatory therapy.
10. Subjects receiving or planning to receive any type of immunotherapy to any food (e.g. oral immunotherapy, sublingual immunotherapy, specific oral tolerance induction) during their participation in the study.
11. Subjects receiving or planning to receive any aeroallergen immunotherapy during their participation in the study.
12. Allergy or known history of reaction to the Tegaderm™ with no possibilities to use an alternative dressing approved by the Sponsor.
13. Subjects suffering from generalized dermatologic disease (e.g. severe atopic dermatitis, uncontrolled generalized eczema, ichthyosis vulgaris) with no intact zones to apply the Viaskin® patches.
14. Subjects or parent(s)/guardian(s) of subjects with obvious excessive anxiety and unlikely to cope with the conditions of a food challenge.
15. 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).
16. Any new disorder in which epinephrine is contraindicated such as coronary artery disease, uncontrolled hypertension, or serious ventricular arrhythmias.
17. A history of drug or alcohol abuse while in the VIPES study.
18. A history of non-compliance in the VIPES study. Non-compliance is defined as subjects not applying the patch at all for 60 days or more (this can be either consecutive or intermittent non-application of the patches) during the whole VIPES study duration.
19. Subjects unable to follow the protocol requirements.
20. Participation in another clinical intervention study in the past year, other than the VIPES study.
21. Subjects on any experimental drugs in the past year, other than those used in the VIPES study.
8.4.3 Withdrawal and Replacement of Subjects

8.4.3.1 Criteria for Subject Withdrawal

In accordance with the Declaration of Helsinki (Appendix 1) and other applicable regulations, a subject has the right to withdraw from the study at any time for any reason without prejudice to his or her future medical care by the physician or at the institution.

Subjects may withdraw from the study/schedule of assessments for any of the following reasons:

- AE.
- The Investigator decides that it is the subject’s best interest to be withdrawn from the study. The Sponsor or Sponsor designee is to be notified immediately.
- The subject is unwilling to continue in the study (consent withdrawal).
- Lack of compliance with protocol requirements and procedures.
- The Sponsor or Regulatory Authorities, for any reason, stop(s) the study.
- The subject fails to return to the clinic for scheduled visits and does not respond to telephone or written attempts at contact (lost to follow-up).
- Severe anaphylaxis (Appendix 2) related to Viaskin® application.
- In the case of death.

The reason for withdrawal will be recorded in the clinical records and the electronic Case Report Form (eCRF). All subjects who are withdrawn from the trial during the 24-month treatment period will undergo the procedures planned for the Early Termination Visit (see Section 9). All subjects who are withdrawn or discontinue should be provided with alternative medical care, if applicable.

8.4.3.2 Study Stopping Rules

Study enrollment will be suspended pending an expedited safety review by an independent DSMB if any of the following occur:

1. Any death related to Viaskin® dosing.
2. More than one Stage 3 anaphylaxis (See Appendix 2, Anaphylaxis Staging System) related to Viaskin® application (not occurring during DBPCFC).
3. More than three subjects requiring more than one injection of epinephrine related to Viaskin® application (and not occurring during the DBPBFC).

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

- Accrual to the study may continue without modification.
- Accrual to the study may continue with modifications as prescribed by the DSMB.
- Accrual to the study should be discontinued.
8.4.3.3 Evaluations at Withdrawal

For any subject who is withdrawn before completing all study visits, the Investigator should:

- Perform an end of study visit: all subjects who are withdrawn early from the trial will undergo the procedures planned for Early Termination Visit (see Section 9) wherever possible.
- Check the subject Diary and Complete all appropriate eCRF pages, providing the date and explanation for the subject’s withdrawal/discontinuation.
- When indicated, arrange for appropriate follow-up and/or alternative medical care of the discontinued subject.

If the subject fails to attend for a scheduled end of study visit, there will be at least two attempts to contact the subject via telephone and written communication. If these receive no reply, the subject will be considered lost to follow-up.

8.4.3.4 Replacement of Subjects

As the OLFUS-VIPES study is an extension of the VIPES study, replacement of subjects is not planned.

8.5 Treatment

8.5.1 Study Treatment Administration

The Investigator must ensure that the investigational product will be used only in accordance with the protocol.

Subjects enrolling into the OLFUS-VIPES study after having completed the VIPES study will receive the highest dose of Viaskin® Peanut, i.e. 250 μg peanut protein, regardless of dose level in the VIPES study. Subjects who entered the OLFUS-VIPES study under the initial protocol design (Protocol Version 1.1 dated 27 May 2013) prior to approval of Protocol Amendment 1, will switch to receive the 250 μg dose at their protocol visit at Month 6 (Visit 3) or at Month 12 (Visit 4) after the approval of Protocol Amendment 1 at their sites.

The subjects in the OLFUS-VIPES study as they are treated at the 250 μg dose will remain under the 250 μg dose to the end of the study, whatever the optimal clinical dose determined in the VIPES study is. This will prevent subjects from having to switch to another dose again during the OLFUS-VIPES study.

All subjects entering the OLFUS-VIPES extension study should receive overall 24 months of active treatment followed by a period of 2 months without treatment for those subjects being assessed for sustained unresponsiveness.

Repeated daily application of Viaskin® Peanut will be continued as in the VIPES study, i.e. a new patch will be applied every 24 hours on the inner aspect of both upper arms for adults (≥18 years) and adolescents (12-17 years), or on the inter-scapular area of the back for children (7-11 years). In
order not to unblind the treatment arms until the results of the VIPES study are known and to better assure safety in particular for placebo subjects crossing over to receive the active treatment, the duration of application of the Viaskin® Peanut patch will be progressively increased for the first 2 weeks of treatment in all subjects entering the OLFUS-VIPES study (one week shorter than what was done at the start of the VIPES study): patches will be applied for 6 hours every day during the first week (Day 1 to Day 7), then the duration of application will be 12 hours every day during the second week of treatment (from Day 8 to Day 14). From the 15th day of treatment onwards (the beginning of the third week), the duration of application will be an entire 24 hours for each Viaskin® applied daily until Month 24. This paradigm is similar to that followed in the VIPES study, with the only change that the 3-hour duration of application is removed. Once the Viaskin® patch is applied to the skin, the hypoallergenic adhesive film Tegaderm™ or any other alternative dressing allowed by the Sponsor must be used to cover the Viaskin® patch to prevent it from coming off.

At the time of the Month 18 visit (Visit 6), the subjects who have been using the Tegaderm™ as a dressing over the Viaskin® patch so far, will be offered to switch to an integrated Viaskin® Peanut patch containing the same quantity of peanut proteins (250 μg) loaded on the backing of the same patch system but already including the adhesive dressing. For those subjects who will switch to the integrated Viaskin® Peanut patch, the treatment with this patch will continue up to the Month 24 visit (Visit 7). During this period of treatment with the integrated patch, no additional dressing should be used to cover the patch.

For adults and adolescents, both upper arms will be used for applying the Viaskin®. The specific place where one Viaskin® is administered will represent a “Zone”. In total, six zones will be used in each subject to apply the Viaskin®. The first Viaskin® will be applied on zone 1, the second Viaskin® on zone 2 (after removal of Viaskin® 1), etc, until all six zones have been used, and the dosing will continue with zone 1, zone 2 etc.

For adults and adolescents, zones 1, 2, and 3 are on one arm, while zones 4, 5 and 6 are on the other arm. For children, zones 1, 2, and 3 are on one side of the spine in the inter-scapular area, while zones 4, 5 and 6 are on the other side of the spine. Children who turn 12 years of age during the OLFUS-VIPES study may switch from applying the patch to the back to applying it on the arms.
If the Viaskin® comes off, or after removing a Viaskin® patch, it is recommended that the subjects or subject’s parent(s) wipe off the zone with a disposable napkin or a disposable tissue and wash their hands to prevent accidental transmission of allergenic protein. The next Viaskin® patch should then be applied only at the expected time of the next application. If possible, the subject could take advantage of their shower (or bath) time to change the Viaskin®, the previous Viaskin® should be removed just before the shower (or bath), and the new Viaskin® should be applied a few minutes after the shower (or bath) and after drying of the skin.

Application of the Viaskin® at a similar time of the day (am or pm) is recommended.
The rules for applying the previous patch or for applying the “integrated Viaskin® Peanut patch” remain the same.

8.5.2 Study Treatment Formulation

Viaskin® Peanut will be administered using the Viaskin® epicutaneous delivery system. Viaskin® Peanut contains a dry deposit of peanut protein extract. The peanut proteins are extracted from the Virginia variety of *Arachis hypogaea* (supplied from Greer Laboratories (Lenoir, NC, USA)) and the extract contains all peanut proteins. The other components of the Investigational Medicinal Product are inactive excipients: ethanol, surfactant (Polyoxyl 20 oleyl ether), and buffering agents (trometamol and histidine). The Viaskin® is round-shaped. The inner part of the Viaskin® has a diameter of 18 mm (2.5 cm² surface area). In this inner part, the peanut allergen extract is deposited by electrospraying the liquid peanut protein formulation, which dries instantly. The outer adhesive part of the Viaskin® is composed of a 4 mm wide band of adhesive foam to stick to the skin. For the integrated Viaskin® Peanut patch, a breathable adhesive polyurethane dressing is already part of the patch.

AMATSI, Montpellier, France, will manufacture all doses of Viaskin® Peanut in accordance with the requirements of Good Manufacturing Practice (GMP) and will perform the primary packaging activities (i.e. place one Viaskin® Peanut patch per pouch).

8.5.3 Study Treatment Labeling and Packaging

The secondary packaging and pharmaceutical release activities will be performed either by AMATSI, Montpellier, France or by CREAPHARM, Le Haillan, France.
These manufacturers will label and package the investigational product: the containing boxes as well as each pouch will be labeled. The labeled pouches will be placed in treatment boxes to be delivered to subjects at each visit, with enough quantity of Viaskin® Peanut patches to cover the period between two consecutive visits. The labeled and packaged investigational product will be stored according to the GMP requirements under the storage conditions established by stability studies performed with Viaskin® Peanut.

Upon receipt of a shipment request, the study drug will be shipped to the clinical site. The pharmacist or any other staff member designed for this task will receive and store the study drug until the time of dispensing to the Investigators. At the end of the study or at times specified by the Sponsor, the pharmacist or designed person will be responsible for destroying any unused investigational product and will provide a corresponding certificate of destruction.
8.5.4 Blinding of Study Medication

Blinding of the OLFUS-VIPES study is not relevant as all subjects shall be receiving the 250 μg dose. The same IWRS used to allocate treatment to subjects in the VIPES study will be used in OLFUS-VIPES study.

Subjects in OLFUS-VIPES will keep the same screening number. IWRS will allocate the treatment box from the stock of treatment boxes available at site. Each treatment box has its specific treatment kit number. The 250 μg dose should be made available immediately to any site for whom Protocol Amendment 1 is approved. All previous treatment boxes should be discarded at the site.

Further instructions will be provided in a separate IWRS Manual.

Of note, subjects in OLFUS-VIPES study will not be unblinded for their previous treatment in the VIPES study as long as the VIPES study has not been unblinded and the results are revealed.

8.5.5 Study Treatment Storage and Accountability

It is forbidden to use the investigational drug material for purposes other than as defined in this protocol.

8.5.5.1 Study Treatment Storage

The investigational product will be stored between 2°C to 8°C ([36°F to 46.4°F]; see USP Controlled Room Temperature) until time of dispensing. However, transportation at ambient temperature is permitted.

8.5.5.2 Study Treatment Accountability

All supplies of Viaskin® will be accounted for in accordance with GCP. There will be an individual study drug accountability record for each subject and the Investigator should maintain accurate records of the disposition of all trial medication supplies received during the study. These records should include the amounts and dates that clinical drug supplies were received, dispensed to the subject, returned by the subject, and returned to the Sponsor or destroyed on site. Copies of the study medication accountability records will be provided by each Investigator for inclusion in the final trial master file.

8.5.6 Dose Adjustments and Dose Escalation

Dose Adjustment

In case of local unbearable skin reactions, or in case of systemic allergic reactions potentially related to Viaskin® Peanut, the Viaskin® patch should be removed immediately. This will allow the reactions to subside rapidly. The next patch would be re-applied only the following day at the expected time and the reactions will be observed. If or when the local severe reactions recur, the patch can be
removed at that time. This process can be repeated the followings days until the time the subject can bear the patch for 24 hours a day.

**Dose Escalation**
There will be two situations with a dose escalation in Protocol 2.0 (incorporating Protocol Amendment 1) design:

- Subjects enrolling into the OLFUS-VIPES study after approval of this Protocol Amendment 1, will all receive the 250 μg dose at Visit 1; a progressive extension of the time of daily application to limit any safety issues especially for the former placebo subjects will be implemented at that time for all subjects in a blinded manner, i.e. 6 hours of daily application the first week, 12 hours of daily application the second week before reaching 24 hours of application from the 15th day onwards.

- Subjects enrolled into the initial OLFUS-VIPES design (Protocol Version 1.1 dated 27 May 2013) will not require a progressive extension of the time of application over 2 weeks. These subjects will apply the 250 μg patches for the whole 24 hours starting on the very first day of their switch. Nevertheless, at the discretion of the Investigator, the progressive extension of the time of application could be considered.
8.5.7 Prior and Concomitant Medications

Prohibited prior and concomitant medications are outlined in the exclusion criteria Section 8.4.2. Ongoing concomitant medications from the VIPES study will be recorded at entry into the OLFUS-VIPES study.

Application of a topical corticosteroid to treat any local AE (eczematous lesions, pruritus, edema, etc.) is allowed and should be recorded as concomitant medication. An ointment with 1% hydrocortisone or equivalent will be distributed to subjects enrolled in OLFUS-VIPES at discharge on Day 1 if necessary, especially if the one given for the VIPES study has expired or has been entirely utilized. In case the 1% hydrocortisone ointment or equivalent is not sufficient to treat the local reaction, an ointment containing a more potent corticosteroid can be prescribed and topically applied.

Oral antihistamine or oral corticosteroids are allowed to treat AE(s) determined as being allergic reactions and should be recorded as concomitant medication. These treatments should be limited in duration and stopped as soon as the AE(s) has (have) resolved. The Investigator will determine the best choice of treatment(s), the dose and the regimen according to the subject’s age, and the type and the degree of severity of the reaction. Cetirizine is recommended as the oral antihistamine.

Subjects will keep the intramuscularly injectable epinephrine auto-injector (EpiPen®, Twinject®, AnaPen® or any other brand name available in the countries at the right dosages) that was given to them in the VIPES study and use it in the OLFUS-VIPES study in case of symptoms of anaphylaxis and until time of its expiry. The Investigator will remind the subject when and how to (self) inject the epinephrine according to the Anaphylaxis Emergency Action Plan (Appendix 4) which will also be given to the subject. The expiry date on the subject’s intramuscularly injectable epinephrine auto-injector will be checked at each study visit up to Visit 9 (Month 26), and a new epinephrine auto-injector will be provided to the subject prior to product expiry. The epinephrine auto-injector will also be replaced if used. Only the effective use of epinephrine injector should be recorded as concomitant medication.

All other treatments prescribed by the Investigator or any other physician to treat an AE are also permitted. Administration of any concomitant medications must be reported in the appropriate section of the eCRF along with dosage information, dates of administration, and reasons for use. Generic names for concomitant medication should be used. Trade names are also acceptable, especially in case of combined molecules. The dose should be specified.

8.5.8 Treatment Compliance

It is the Investigators’ responsibility to ensure that subjects are correctly instructed on how to store and administer their study medication. Records of study medication used and intervals between visits will be kept during the study. Drug accountability will be noted by the field monitor during site visits and at the completion of the trial. Subjects will be asked to return their unused medication when they come back for their study visits. All unused medication should be returned at the end of the study. The study drug should be dispensed by the Investigator, or by a qualified individual under the Investigator’s supervision. An up-to-date treatment inventory/dispensing record must be maintained (see Section 8.5.5.2).
At each visit, prior to dispensing a new treatment box, the previously dispensed treatment box will be retrieved by the Investigator and compliance will be assessed. A compliance of >80% over the treatment period is sought.

Compliance is defined as the total number of patches applied each day in a certain period of time versus the number of days in that period of time. It is to be re-calculated at each visit taking into account the historical compliance and the last compliance since the previous visit. Subjects exhibiting poor compliance (below 80%) should be counseled on the importance of good compliance to the study dosing regimen with regards to efficacy.

8.5.9 Assignment to Treatment

Treatment boxes at the 250 μg dose will be distributed and made available at all sites upon approval of Protocol Amendment 1 locally. The IWRS system will be updated on a site by site basis and will accordingly assign an appropriate treatment kit number to each subject switching to the OLFUS-VIPES study. The IWRS system will also be updated for Protocol Amendment 3, in order to assign a specific treatment kit (with integrated Viaskin® Peanut patch including the adhesive dressing) at Month 18 visit, to the subjects who decide to switch to the integrated patch.

8.5.10 Unblinding Procedures

With Protocol Amendment 1, the OLFUS-VIPES study will be an open-label study much earlier. The subjects will all be receiving the dose of 250 μg to the end of the study. There are no specific unblinding procedures under Protocol Amendment 1 and subsequent Amendments.

Unblinding would be eventually relevant only for subjects still under the initial OLFUS-VIPES design (Protocol Version 1.1 dated 27 May 2013) and before they also switch to the 250 μg dose. An Emergency Code Break procedure will be available to Investigators via IWRS to allow for unblinding of a subject, i.e., informing the Investigator of the exact dose of Viaskin® Peanut to which the subject has been assigned. This procedure should be utilized in emergency situations only and when the exact dose of Viaskin® Peanut received by the subject must be known by the Investigator in order to provide appropriate medical treatment. Before a subject is unblinded, if ever possible, please call the Chief Clinical Trial Officer at DBV Technologies/Medical Monitor (contact information is in Section 5). Reasons for unblinding must be clearly explained and justified in the eCRF, along with the date on which the subject was unblinded.
8.6 Efficacy and Safety Variables

8.6.1 Efficacy and Safety Measurements Assessed

8.6.1.1 Efficacy Measurements

The following efficacy endpoints will be assessed:

- At Month 12 in the OLFUS-VIPES study and by treatment group, the proportion of subjects with a peanut protein eliciting dose equal to or greater than 1,000 mg peanut or with a $\geq 10$-fold increase of the eliciting dose compared to their baseline eliciting dose observed in the VIPES study. Subjects having received active treatment with Viaskin\textsuperscript{®} Peanut for a total of 12 months (Treatment Group 1) and a total of 24 months (Treatment Group 2) will be analyzed separately.

- At Month 24 in the OLFUS-VIPES study and by treatment group 1 or 2, the proportion of subjects with a peanut protein eliciting dose equal to or greater than 1,000 mg peanut or with a $\geq 10$-fold increase of the eliciting dose compared to their baseline eliciting dose observed in the VIPES study. Subjects having received active treatment with Viaskin\textsuperscript{®} Peanut (DBV712) for a total of 24 months and a total of 36 months (since the VIPES study) will be analyzed separately.

- The proportion of subjects unresponsive (i.e. showing no objective symptoms during DBPCFC) to a cumulative dose of 1,440 mg peanut protein or above at Month 12 and Month 24 in the OLFUS-VIPES study.

- The proportion of subjects with a sustained unresponsiveness (i.e. showing no objective symptoms during DBPCFC after a period of 2 months without treatment) to a cumulative dose of 1,440 mg peanut protein or above at Month 26.

- The median and mean cumulative reactive dose of peanut protein at Month 12 and Month 24 by treatment group.

- The change from baseline in peanut-specific IgE and IgG4 at Month 6, Month 12, Month 18 and Month 24 by treatment group.

- The change from baseline in the average wheal diameter during the skin prick testing (undiluted) at Month 6, Month 12, Month 18 and Month 24 by treatment group.

- Change in the Quality of Life (the FAQLQ/FAIM) at Month 12 and Month 24 compared to Day 1 for those countries where the questionnaires were available, globally and by treatment group.
8.6.1.2 Safety Measurements

The following safety endpoints will be assessed:

- AEs by system organ class, severity and relatedness to Viaskin® Peanut (all subjects and by age strata).
- SAEs by system organ class, severity and relatedness to Viaskin® Peanut (all subjects and by age strata).
- Systemic allergic symptoms and relatedness to Viaskin® Peanut (all subjects and by age strata).
- Severity of AEs or SAEs elicited during the study and during DBPCFCs (all subjects).
- Laboratory data, physical examinations and vital signs (all subjects).
- Spirometry or PEF results (all subjects).

8.6.1.3 Exploratory Criteria

The following exploratory criteria will be assessed:

- Enumeration and characterization of reactions triggered by accidental consumption of peanut during the follow-up study.
- Analysis of “Risk-taking behavior” (voluntary peanut consumption) of subjects during the follow-up study.
- Analysis of tolerability, adhesivity and comfort of the integrated patch versus the patch with the added Tegaderm™.

9. STUDY EVALUATIONS BY VISIT

9.1 Visit 1: Day 1

Visit 1 in the OLFUS-VIPES study can be conducted on the same day as Visit 11 in the VIPES study in which case some procedures will be common to both visits. Visit 1 can also be held within a week from VIPES Visit 11 for those subjects deciding to roll-over in the OLFUS-VIPES Study.

All subjects for whom a written informed consent has been obtained and only subjects who fulfill all eligibility criteria will be eligible to be enrolled into the OLFUS-VIPES study. The ICF for the OLFUS-VIPES study should be signed no later than Visit 11 in the VIPES study. All eligibility assessments must be completed before effective enrollment into the OLFUS-VIPES study. As such effective enrollment in OLFUS-VIPES can occur after completing Visit 11 of VIPES. 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.
At Visit 1 (Day 1), the following assessments/procedures will be performed:

- Written informed consent/assent (before the challenge at Visit 11 in VIPES).
- Medical History (also includes ongoing AEs from the VIPES study).
- Check and confirm eligibility before enrolling the subject.
- Demographics (including weight and height).
- Physical examination (including a complete skin examination). The physical examination findings obtained before the challenge at Visit 11 in the VIPES study will be utilized here.
- Vital signs will be measured in a sitting position (including heart rate, systolic and diastolic blood pressure, respiratory rate, and temperature). The vital sign results obtained before the challenge at Visit 11 in the VIPES study will be utilized here.
- Food Allergy Quality of Life Questionnaire (FAQLQ)/Food Allergy Independent Measure (FAIM). For both FAQLQ and FAIM, the form corresponding to the subject’s age range (child, adolescent or adult) will be used. Parent(s)/guardian(s) of children and adolescents will also have to complete the Parent Forms specific to children or adolescents. FAQLQ and FAIM will be completed in the countries where they are available in local languages. In all cases, they should be filled out before the challenge at Visit 11 in the VIPES study but after signature of the OLFUS-VIPES’ informed consent form. If other procedures of Visit 1 are postponed from Visit 11 in VIPES, the FAQLQL/FAIM must still be filled out before the challenge of Visit 11 in VIPES.
- Peak expiratory flow (PEF). The PEF results obtained before the challenge at Visit 11 in the VIPES study will be utilized here.
- Record all AEs.
- Record all concomitant medications (also includes ongoing concomitant medications from the VIPES study).
- Dispense diary cards.
- Go to IWRS to get the treatment kit number and dispense the first box of trial medication to the subject.
- Check the auto-injector of epinephrine if needed. 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.

9.2 Visit 2: Month 1 (± 7 days)

The following assessments/procedures will be performed:

- Physical examination (including a complete skin examination).
- Vital signs will be measured in a sitting position.
- PEF.
- Record all AEs.
- Record all concomitant medications.
Check if there was any significant information reported by the subject in the diary card and discuss this with the subject: medical event(s), any peanut consumption.

Dispense diary cards (re-instruct subject on use if necessary).

Collect the previous treatment box dispensed to the subject, check used/unused medication and assess medication compliance.

Dispense the new treatment box to subject (no need to go to IWRS at this visit).

Check the expiry date of the epinephrine auto-injector. A new auto-injector should be provided to the subject prior to product expiry.

9.3 Visit 3: Month 6 (± 14 days)

The following assessments/procedures will be performed:

- Physical examination (including a complete skin examination).
- Vital signs will be measured in a sitting position.
- Spirometry (FEV$_1$).
- PEF.
- SPT to peanut.
- Blood collection for immunological markers and laboratory tests.
- Record all AEs.
- Record all concomitant medications.
- Check if there was any significant information reported by the subject in the diary card and discuss this with the subject: medical event(s), any peanut consumption.
- Dispense diary cards (re-instruct subject on use if necessary).
- Collect the previous treatment box dispensed to the subject, check used/unused medication and assess medication compliance.
- Go to IWRS to get the treatment kit number and dispense the new treatment box to subject.
- Check the expiry date of the epinephrine auto-injector. A new auto-injector should be provided to the subject prior to product expiry.

9.4 Visit 4: Month 12 (± 14 days)

This visit corresponds to the first day of the DBPCFC after 12 months (i.e. first day of the first DBPCFC) of treatment in the OLFUS-VIPES study (see Section 10.10).

The following assessments/procedures will be performed:

- FAQLQ/FAIM to be filled out prior to starting any other procedures.
- Physical examination (including a complete skin examination).
- Vital signs will be measured in a sitting position.
- Spirometry (FEV$_1$), PEF.
• SPT to peanut.
• Blood collection for immunological markers, peanut components, and laboratory tests.
• Urine pregnancy test for females of childbearing potential. Pregnancy testing may be repeated during the study at the discretion of the Investigator.
• Record all AEs.
• Record all concomitant medications.
• DBPCFC to peanut or placebo (see Section 10.10).
• Record all AEs/allergic symptom(s) (subjective or objective) (volunteered or in response to an open question) and grade them following the OFC Symptom Score Sheet (Appendix 3).
• Record all concomitant medication(s) to treat allergic symptoms during the challenge.
• Check if there was any significant information reported by the subject in the diary card and discuss this with the subject: medical event(s), any peanut consumption.
• Dispense diary cards (re-instruct subject on use if necessary).
• Collect the previous treatment box dispensed to the subject, check used/unused medication and assess medication compliance.
• Go to IWRS to get the treatment kit number and dispense the new treatment box to subject. Apply the patch daily between the 2 days of the challenge.
• Check the expiry date of the epinephrine auto-injector. A new auto-injector should be provided to the subject prior to product expiry.

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

9.5 Visit 5: Month 12; within 7 days of Visit 4 (+ 7 days)

This visit corresponds to the second day of the DBPCFC after 12 months of treatment (i.e. second day of the first DBPCFC) in the OLFUS-VIPES study (see Section 10.10).

The following assessments/procedures will be performed:

• Physical examination (including a complete skin examination).
• Vital signs will be measured in a sitting position.
• Record PEF values prior to starting the challenge
• Record all AEs.
• Record all concomitant medications.
• DBPCFC to peanut or placebo (see Section 10.10).
• Record all AEs/allergic symptom(s) (subjective or objective) (volunteered or in response to an open question) and grade them following the OFC Symptom Score Sheet (Appendix 3).
• Record all concomitant medication(s) to treat allergic symptoms.
• Check if there was any significant information reported by the subject in the diary card and discuss this with the subject: medical event(s), any peanut consumption.
• Dispense diary cards (re-instruct subject on use if necessary).
• Check the expiry date of the epinephrine auto-injector. A new auto-injector should be provided to the subject prior to product expiry.

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

9.6 Phone Contact 1 (PC1) – 2 weeks prior visit 6 (-7 days)

In addition to the regular study visits at site, the study personnel will contact the subjects/subjects’ parents/guardians by phone for those subjects who can switch to the integrated Viaskin® Peanut patch at the time of their Month 18 visit (visit 6). This first phone contact (PC1) will be held 2 weeks prior to Month 18 visit (Visit 6), with a permitted window of -7 days. During this PC1 the study personnel will discuss with the subject about the availability of the integrated Viaskin® Peanut patch already including the adhesive dressing. The subjects who have been using the Tegaderm™ as a dressing over the Viaskin® patch so far will be offered to switch to the integrated Viaskin® Peanut patch at Month 18 visit if they wish. The subjects who agree to switch to the integrated Viaskin® Peanut patch will be told about the short questionnaire they will be asked to complete at site during the Month 18 visit on the tolerability, the adhesivity and the comfort of the current patch with the added Tegaderm™. The subjects will be explained that the questionnaire will ask them an assessment covering the 2 weeks before the Month 18 visit (visit 6) at site. Subjects who express their interest to switch to the integrated patch will be sent by mail, e-mail or else a copy of the addendum to the informed consent/assent prior to their Month 18 visit.

9.7 Visit 6: Month 18 (± 14 days)

The following assessments/procedures will be performed:

• Physical examination (including a complete skin examination).
• Vital signs will be measured in a sitting position.
• Spirometry (FEV₁). PEF.
• SPT to peanut.
• Blood collection for immunological markers and laboratory tests.
• Record all AEs.
• Record all concomitant medications.
- Check if there was any significant information reported by the subject in the diary card and discuss this with the subject: medical event(s), any peanut consumption.
- Dispense diary cards (re-instruct subject on use if necessary).
- Collect the previous treatment box dispensed to the subject, check used/unused medication and assess medication compliance.
- Collect the signed written informed consent/assent Addendum for those subjects who decide to switch to the integrated patch.
- Complete and record the questionnaire on the tolerability, adhesivity and comfort of the current patch with the added Tegaderm™ for the last 2 weeks before Month 18 visit (visit 6); only for those subjects who signed the informed consent/assent Addendum above.
- Go to IWRS to get the treatment kit number (kit containing the integrated patches only for those subjects who switch to the integrated patch) and dispense the new treatment box to subject.
- Check the expiry date of the epinephrine auto-injector. A new auto-injector should be provided to the subject prior to product expiry.

During the visit 6 (Month 18) the subjects and/or parents/guardians who decided to switch to the integrated patch:
- Will be trained for applying the integrated patch on the skin. If possible, the first integrated patch will be applied on site.
- Will be reminded that they will have to complete the same type of questionnaire to assess the tolerability, the adhesivity and the comfort of the integrated patch during a Phone Contact which will be held 2-3 weeks after visit 6.
- Will be reminded that the same questionnaire will be completed also during the Month 24 visit (visit 7) to assess the tolerability, the adhesivity and the comfort of the integrated patch during the last 2 weeks prior to visit 7.

9.8 Phone Contact 2 (PC2) – 2 weeks after visit 6 (+7 days)

In addition to the regular study visits at site, the study personnel will contact the subjects/subjects’ guardians or parents by phone for those subjects who decided to switch to the integrated Viaskin® Peanut patch including the adhesive dressing.

This second phone contact (PC2) will be held 2 weeks after the Month 18 visit (Visit 6), with a permitted window of +7 days. This PC2 will permit to complete and record the questionnaire on the tolerability, adhesivity and comfort of the integrated Viaskin® Peanut patch, over a 2-week period after the Month 18 visit (Visit 6).
9.9 Phone Contact 3 (PC3) – 2 weeks prior visit 7 (-7 days)

In addition to the regular study visits at site, the study personnel will contact the subjects/subjects’ guardians or parents by phone for those subjects who decided to switch to the integrated Viaskin® Peanut patch including the adhesive dressing.

This third phone contact (PC3) will be held 2 weeks prior to Month 24 visit (Visit 7), with a permitted window of -7 days. During this PC3, the subject will be reminded that he/she will be asked to complete the same questionnaire at Month 24 visit (visit 7) to assess the tolerability, the adhesivity and the comfort of the integrated patch for the last 2 weeks period before the Month 24 visit (visit 7).

9.10 Visit 7: Month 24 (± 14 days)

This visit corresponds to the first day of the DBPCFC after 24 months of treatment (i.e. first day of the second DBPCFC) in the OLFUS-VIPES study (see Section 10.10).

The following assessments/procedures will be performed:

- Physical examination (including a complete skin examination).
- Vital signs will be measured in a sitting position.
- FAQLQ/FAIM to be filled out prior to starting the DBPCFC.
- Spirometry (FEV₁), PEF.
- SPT to peanut.
- Blood collection for immunological markers, peanut and laboratory tests.
- Urine pregnancy test for females of childbearing potential. Pregnancy testing may be repeated during the study at the discretion of the Investigator.
- Record all AEs.
- Record all concomitant medications.
- DBPCFC to peanut or placebo (see Section 10.10).
- Record all AEs/allergic symptom(s) (subjective or objective) (volunteered or in response to an open question) and grade them following the OFC Symptom Score Sheet (Appendix 3).
- Record all concomitant medication(s) to treat allergic symptoms.
Check if there was any significant information reported by the subject in the diary card and discuss this with the subject: medical event(s), any peanut consumption.

Dispense diary cards (re-instruct subject on use if necessary).

Collect the previous treatment box dispensed to the subject, check used/unused medication and assess medication compliance.

Complete and record the questionnaire on the tolerability, adhesivity and comfort of the integrated patch for the last 2 weeks before Month 24 visit (Visit 7).

Check the expiry date of the epinephrine auto-injector. A new auto-injector should be provided to the subject prior to product expiry.

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

9.11 Visit 8: Month 24; within 7 days of Visit 7 (+ 7 days)

This visit corresponds to the second day of the DBPCFC after 24 months of treatment (i.e. second day of the second DBPCFC) in the OLFUS-VIPES study (see Section 10.10). This visit will be the end of study visit for subjects who react objectively to a cumulative dose of 1,440 mg of peanut protein or below. Subjects who are unresponsive (i.e. showing no objective symptoms) at a cumulative dose of 1,440 mg of peanut protein or above will attend Visit 9 and Visit 10.

The following assessments/procedures will be performed:

- Physical examination (including a complete skin examination).
- Vital signs will be measured in a sitting position.
- PEF
- Record all AEs.
- Record all concomitant medications.
- DBPCFC to peanut or placebo (see Section 10.10).
- Record all AEs/allergic symptom(s) (subjective or objective) (volunteered or in response to an open question) and grade them following the OFC Symptom Score Sheet (Appendix 3).
- Record all concomitant medication(s) given to treat the allergic symptom(s).
- Check if there was any significant information reported by the subject in the diary card and discuss this with the subject: medical event(s), any peanut consumption.
- Dispense diary cards (re-instruct subject on use if necessary) to subjects continuing to Visits 9 and 10.
- Check the expiry date of the epinephrine auto-injector. A new auto-injector should be provided to the subject prior to product expiry for subjects continuing to Visits 9 and 10.

The subject may be discharged after a minimum observation period of 3 hours after the last dose of the challenge formula administered. The observation period can be extended beyond 3 hours if deemed necessary by the Investigator.
9.12 Visit 9: Month 26 (± 14 days)

Visit 9 will be performed only for those subjects who were unresponsive (i.e. showing no objective symptoms) to the cumulative dose of 1,440 mg peanut protein or above at the Month 24 DBPCFC. This visit corresponds to the first day of the DBPCFC after 2 months without treatment (i.e. first day of the third DBPCFC) in the OLFUS-VIPES study (see Section 10.10).

The following assessments/procedures will be performed:

- Physical examination (including a complete skin examination).
- Vital signs will be measured in a sitting position.
- PEF.
- SPT to peanut.
- Blood collection for immunological markers, peanut components and laboratory tests.
- Record all AEs.
- Record all concomitant medications.
- DBPCFC to peanut or placebo (see Section 10.10).
- Record all AEs/allergic symptom(s) (subjective or objective) (volunteered or in response to an open question) and grade them following the OFC Symptom Score Sheet (Appendix 3).
- Record all concomitant medication(s) given to treat the allergic symptom(s).
- Check if there was any significant information reported by the subject in the diary card and discuss this with the subject: medical event(s), any peanut consumption.
- Dispense diary cards (re-instruct subject on use if necessary).
- Check the expiry date of the epinephrine auto-injector. A new auto-injector should be provided to the subject prior to product expiry.

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

9.13 Visit 10: Month 26; within 7 days of Visit 9 (+7 days)

Visit 10 is the end of study visit only for those subjects who were unresponsive (i.e. showing no objective symptoms) to a cumulative dose of 1,440 mg peanut protein or above at Month 24 DBPCFC. This visit corresponds to the second day of the DBPCFC after 2 months without treatment (i.e. second day of the third DBPCFC) in the OLFUS-VIPES study (see Section 10.10).

The following assessments/procedures will be performed:

- Physical examination (including a complete skin examination).
Vital signs will be measured in a sitting position.
Record all AEs.
Record all concomitant medications.
DBPCFC to peanut or placebo (see Section 10.10).
Record all AEs/allergic symptom(s) (subjective or objective) (volunteered or in response to an open question) and grade them following the OFC Symptom Score Sheet (Appendix 3).
Record all concomitant medication(s) given to treat the allergic symptom(s).
Check if there was any significant information reported by the subject in the diary card and discuss this with the subject: medical event(s), any peanut consumption.

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

9.14 Early Termination Visit

This visit corresponds to the last visit for subjects withdrawing prematurely from the study and willing to perform this last visit. The DBPCFC will not be conducted.

The following assessments/procedures will be performed:

- Physical examination (including a complete skin examination).
- Vital signs will be measured in a sitting position.
- FAQLQ/FAIM
- Spirometry (FEV$_1$), PEF.
- SPT to peanut.
- Blood collection for immunological markers, peanut components and laboratory tests.
- Record all AEs.
- Record all concomitant medications.
- Check if there was any significant information reported by the subject in the diary card and discuss this with the subject: medical event(s), any peanut consumption.
- Collect the previous treatment box dispensed to the subject, check used/unused medication dispensed to the subject and assess medication compliance.

Investigators or their staff members can contact the subjects at their discretion between the visits described above from section 9.1 to section 9.13.
10. METHODS OF ASSESSMENT

10.1 Food Allergy Quality of Life Questionnaire/Food Allergy Independent Measure

Subjects will complete the FAQLQ and the FAIM (Appendix 6) (25-28) where the age specific forms and translated versions are available and provided. Most of the FAQLQ forms have been validated in the different languages. Completing the FAIM, will help validate (re-validate) all FAQLQs at the end. The form corresponding to the subject’s age range (child, adolescent or adult) will be used. Parent(s)/guardian(s) of children and adolescents will also have to complete the Parent Forms specific to children or adolescents.

FAQLQ and FAIM will be completed in the countries where they are available in local languages. 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 or parent(s)/guardians(s) whilst they are completing the forms.

10.2 Pregnancy Test

Pregnancy will be determined by evaluation of urine pregnancy tests. Subjects who become pregnant during the OLFUS-VIPES study must be discontinued from the study.

The Investigator will inform the Sponsor immediately of any female subject who becomes pregnant while participating in this study and collect information on the case. The subject will also be followed to determine the outcome of the pregnancy. Procedures to be followed in case of pregnancy are described in Section 11.10.

10.3 Physical Examination

Physical examinations will be performed by a physician and master level clinicians (Nurse Practitioners and physician assistants) 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 and nervous system. For each body system, an assessment of normal or abnormal will be recorded in the eCRF at Visit 11 of the VIPES/Visit 1 of the OLFUS-VIPES study and the abnormality will be documented. During the study, any clinically relevant changes observed during physical examinations will be reported as AEs.

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.
10.4 Vital Signs, Weight and Height

Vital signs will include sitting systolic and diastolic blood pressure, heart rate, respiratory rate and temperature. Systolic blood pressure and diastolic blood pressure will be measured on the same arm after the subject has been in a sitting position for 5 minutes. Heart rate will be recorded simultaneously with blood pressure measurements, followed by respiratory rate and body temperature.

Body weight (kg) will be measured without shoes or jacket at Visit 1. During the study, the measurement of vital signs, weight and height may be repeated at the discretion of the Investigator for safety reasons. Clinically relevant abnormal findings will be reported as AEs.

Vital signs 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.

10.5 Spirometry Tests

FEV$_1$ will be measured on a standardized calibrated spirometer following the American Thoracic Society (ATS) guidelines. At least three acceptable maneuvers will be obtained and the highest values will be recorded in the eCRF. For subjects too young to perform the spirometry according to the ATS, the PEF values will be used. Again, at least three acceptable maneuvers will be obtained and the highest values will be recorded in the eCRF.

10.6 Skin Prick Tests

Peanut extract plus negative control and positive control will be used for skin prick testing. All materials will be provided centrally to all sites.

A detailed procedure manual will be provided for the SPT.

The subjects must be off antihistamines for 3 to 7 days prior to the test. Briefly, a skin lancet is pressed through a small drop of the commercial extract of peanut or positive (histamine) and negative controls and into the epidermis of the volar surface of the forearm or back of the forearm. The area is measured for the average wheal diameter after 15 minutes (in mm). The average wheal diameter corresponds to the average of the largest diameter and the corresponding orthogonal diameter. 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 transport tape should be used to lift the tracing; the tape tracing should be stuck in the subject’s dossier.
10.7 Immunological Markers

Venous blood samples will be taken and serum prepared for assessment of the following immunological markers: peanut-specific IgE and peanut-specific IgG4 at the visits specified in the study flow chart. Analysis of samples will be conducted centrally by Quintiles Laboratory. Further details of the procedures to be followed for sample collection, storage, and shipment will be documented in a Laboratory Manual.

10.8 Peanut Components

Venous blood samples will be taken and serum prepared for assessment of the following peanut components: Component-Resolved Diagnosis for specific IgE for Ara h 1, h 2, h 3, h 8 and h 9 at the visits specified in the study flow chart. Analysis of samples will be conducted centrally by Quintiles Laboratory. Further details of the procedures to be followed for sample collection, storage, and shipment will be documented in a Laboratory Manual.

10.9 Clinical Laboratory Testing

Venous blood samples will be taken for hematology and biochemistry testing. The following parameters will be determined:

- **Hematology:** hemoglobin, hematocrit, platelets, red blood cells, white blood cells.
- **Biochemistry:** aspartate aminotransferase, alanine aminotransferase, total bilirubin, total protein, blood urea nitrogen, creatinine.

Analysis of blood samples/sera will be conducted centrally by Quintiles Laboratory. Further details of the procedures to be followed for sample collection and shipment will be documented in a Laboratory Manual.

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

10.10 Double-Blind Placebo-Controlled Food Challenge (DBPCFC) to Peanut

The DBPCFC is the gold standard to diagnose and assess food allergy. The subject will be gradually fed increasing amounts of peanut under medical observation. The challenge occurs over two days and must take place under direct medical supervision in a hospital/clinic setting with resuscitation equipment and emergency medications and staff immediately available. An intravenous (i.v.) line should be established prior to the challenge for all subjects. A local anesthetic cream can be used for establishing this i.v. line, especially for children. If a site prefers to have the subjects come to the hospital the day before the conduct of the DBPCFC, to prepare them for the following day, this is allowed and will not be considered an SAE.
Subjects must be off antihistamines 3 to 7 days (depending on the half-life) prior to any DBPCFC. Subjects will not be allowed to use long-acting β2 agonists (e.g., formoterol) within 36 hours prior to any DBPCFC. Subjects who received more than a 3-day course of systemic corticosteroids within 4 weeks of a DBPCFC should have the DBPCFC delayed to allow for 4 weeks of corticosteroid wash-out. For subjects who require more than 1 day of systemic corticosteroids to treat a reaction that occurs during the first day of the DBPCFC, the second day of the DBPCFC can be conducted only from the fourth day onwards.

The subject should have a light breakfast and may drink water at home at least two hours before starting the DBPCFC at the hospital. However, during the conduct of the challenge, no other food should be consumed by the subject but the challenge food. Water should ideally not be drunk either. However, should a sip of water help swallow the formula, this is authorized.

After the last dose of the food challenge, the medical staff should wait at least one hour before feeding the subject with any other food and/or water. This first feeding should be light.

A detailed Manual of Procedures for the conduct of the DBPCFC will be provided to the Investigators and site staffs/dieticians/pharmacists. An outline of the procedures is specified below.

**Preparation of Peanut Formulas**

Standardized dessert “mousse” formulas, centrally produced (22), will be distributed to all participating sites for the DBPCFC. One of the formulas will be peanut-free (placebo) and the other one will contain peanut.

The formulas must be prepared and stored in the refrigerator (at 2-8°C) at least 2 hours prior to being consumed during the challenge. An unblinded dietician or nurse or pharmacist not involved in the challenge itself will be responsible for the preparation and adequate labeling of the pots containing the rehydrated dessert, with protocol reference, subject number and pot sequence number. It is recommended to prepare the formula the day before the challenge and to store it in the refrigerator overnight.

**The DBPCFC: time interval, doses, stopping symptoms**

The order of the formulas to be consumed (peanut or placebo) during the first and the second day of the DBPCFC will be determined at random by the dietician or the nurse or the pharmacist preparing the formula using a specific table provided to her/him. Other members of the site staff (e.g., the Investigator, study coordinators, and study nurses), the subject, the subject’s family will remain blinded to the order of consumption. Up to seven days (one week) between the two days of the DBPCFC will be permitted. Some reactions during the first challenge may require that more than seven days have elapsed before the second day of the challenge. This is accepted. Also, if a subject’s schedule or the site’s logistics does not allow that the second day of the challenge is performed within seven days of the first day of challenge, the second day of the challenge can be rescheduled accordingly. Overall, it is recommended to remain within a duration of 14 days between the 2 days of the DBPCFC even in these exceptional cases.
The challenge will consist of giving doses of peanut protein or placebo in gradually increasing doses at 30-minute intervals. This standard interval has been used safely in the past, especially in the VIPES study, but the Investigator may use clinical judgment to increase the intervals between doses if there is a concern that an objective reaction may be developing.

The starting dose is 10 mg of peanut protein; overall the maximum cumulative dose given is capped to 5,040 mg of peanut protein.

**The conduct of the DBPCFCs**

All 3 DBPCFC in OLFUS-VIPES will be conducted similarly.

**The first DBPCFC** in the OLFUS-VIPES study will be conducted after 12 months (Visits 4 and 5) of treatment up to a cumulative dose of 5,040 mg peanut protein.

Subjects will receive one formula (placebo or peanut) on the first day and the other formula (peanut or placebo) on the second day. All subjects should undergo both days of the DBPCFC. The second day of a challenge might not be performed ONLY if the subject reacted severely or seriously during the first day of the challenge (see Appendix 2 for the definition of a severe anaphylactic reaction), leaving no doubt about the nature of the formula administered, i.e. peanut. In this rare case and in this case only, the formula will be unblinded to confirm that the subject effectively received the peanut formula.

At the end of the second day of challenge, the sequence of the two formulas given will be unblinded and revealed to the medical staff by the unblinded dietician or nurse or pharmacist and the results of the challenge will be established.

Only **clear-cut objective immediate-type symptoms** will be considered to stop the DBPCFC and determine the eliciting dose. Ideally, the symptoms should **require a treatment**. The main objective symptoms to expect are as follows (list not exhaustive; also see Appendix 3, the OFC Symptom Score Sheet):

Generalized pruritus, flushing, local or generalized urticaria, hives, swollen lips, swollen tongue, throat tightness, vomiting, diarrhea, dyspnea, rhinorrhea, sneezing, wheezing, conjunctivitis, asthma, drop of the PEF, hypoxia, hypotension, hypotonia, decreased level of consciousness associated with collapse and/or incontinence or other life threatening symptoms.

More specifically, the challenge should be stopped if:

- there is a >1 point rise in any objective symptom from any category in the OFC symptom Score Sheet;
- 2 or more categories in the OFC symptom Score Sheet show at least 1 point rise in an objective symptom;
- there is 1 point rise in an objective symptom from any category in the OFC symptom Score Sheet with the following exceptions
  - I.B. Pruritus (0 to 1)
  - I.C. Urticaria (0 to 1)
  - I.D. Rash (0 to 1)
II. Sneeze (0 to 1)
   - II.A. Sneeze (0 to 1)
   - II.B. Nasal congestion (0 to 1)
   - II.C. Rhinorrhea (0 to 1)
   - II.D. Laryngeal (0 to 1 if explainable and not persistent)

Further details are provided in the Manual of Procedures for the DBPCFC.

In case of subjective symptoms, e.g. mouth pruritus, throat pruritus, nausea, abdominal pains or any other subjective symptoms at a specific dose, deemed significant enough to question whether an objective symptom could occur, the Investigator can extend the time between the last dose and the next dose to see how the subject’s symptom(s) evolve(s). The same dose can be repeated one more time to check whether the subjective symptom(s) reappear(s) or not and with what intensity, or whether (an) objective symptom(s) now clearly appear(s). If (an) objective symptom appear(s), that would be the end of the food challenge. If only (a) subjective symptom(s) still persist(s) with no appearance of an objective symptom, the next higher dose is then given to the subject, and the challenge should continue until the appearance of a clear objective symptom, at which time the challenge will be stopped.
As a safety precaution, the objective symptom(s) signaling the end of the DBPCFC will be treated by administration of the best medications to the subject as per the Investigator’s judgment.

The Investigator and medical staff will use their own clinical judgment for the most effective treatment to give to the subject considering its age, the type of the allergic reactions and their severity. Also refer to recommendations made by Sampson et al (23) for treating anaphylaxis.

Suggested treatments for the different objective symptoms are detailed in the Manual of Procedures for the DBPCFC provided to the sites.

Should epinephrine be required to be administered, it should be injected intramuscularly in the anterolateral thigh.

Unless a subject is admitted into an Intensive Care Unit in hospital settings to treat the severity of the reactions, **intravenous epinephrine should NOT be considered at the investigative sites** to treat the 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 3 hours to ensure that all symptoms have subsided before the subject is discharged. For instance, overnight stay may be considered necessary by the Investigator if the symptom(s) has (have) not completely resolved within the 3 hours or if the symptoms have been severe or serious and require longer observation periods.

Complete information of all reactions will be reported in the eCRF, along with doses given, symptoms observed and their highest grades, first time of appearance of the symptoms and an Investigator’s assessment of the eliciting dose.

**The second DBPCFC** after 24 months is conducted at Visits 7 and 8 following exactly the same procedures described above for the first DBPCFC. The second DBPCFC will be conducted for all subjects up to a cumulative dose of 5,040 mg peanut protein.

**The third DBPCFC** in the study at Month 26 (Visit 9 and Visit 10) will be conducted following exactly the same procedures described above. The third DBPCFC will be conducted for all subjects being assessed for sustained unresponsiveness to a cumulative dose of 1,440 mg peanut protein or above.

Throughout the OLFUS-VIPES study period, subjects will be instructed to remain on a peanut-free diet. The re-introduction or not of peanut into the subject’s diet at the end of their participation in the OLFUS-VIPES study will be left to the Investigator’s decision.

During the duration of the study, DBPCFCs to other food cannot be conducted for any treated subject as long as the subject has not completed the study. Subjects who withdraw prematurely from the study at any time are free to continue with other DBPCFCs to any food as long as they have also conducted their End of Study visit.
10.11 Subject Diary

Diary cards will be provided to each subject. Subjects (or their parent/guardian) will be asked to record in the diary cards any medical event which occurred between the visits. This will be used for the Investigators to further interview the subject and establish the AEs which took place. Subjects will also be instructed to record any concomitant medication or treatment taken for any type of AEs.

The diary cards will also be used for the subjects to report any consumption of peanut that occurred. At site, upon review of the diary cards, the investigative staff will interview the subject to know whether the peanut consumption was either accidental or voluntary. This will be useful for the Investigators to assess whether there has been any risk taking behavior and as much information as possible around those cases.

Subjects must bring their diary back to the Investigator at each visit, and the Investigator must check the diary for conducting his interview. All diary cards must be returned at completion of the study, or if the subject discontinues.

10.12 Questionnaires on Patch’s Tolerability, Adhesivity and Comfort

The subjects (or their parents/guardians) who switched to the integrated Viaskin® Peanut patch at the Month 18 visit (Visit 6) will be asked to answer three questionnaires, evaluating the tolerability, the adhesivity and the comfort of each type of patch over a 2-week period.

The first questionnaire will assess the tolerability, the adhesivity and the comfort of the patch with the added Tegaderm™ during the 2 weeks preceding the Month 18 visit (Visit 6).

The second questionnaire will assess the tolerability, the adhesivity and the comfort of the integrated patch during the first 2 weeks after applying the integrated patch.

The third questionnaire will again assess the tolerability, the adhesivity and the comfort of the integrated patch during the last 2 weeks of application prior to Month 24 visit (visit 7).

11. SAFETY MEASUREMENTS AND VARIABLES

11.1 Adverse Events

An AE is any untoward medical occurrence that does not necessarily have a causal relationship with the investigational medicinal product. An AE can therefore be any unfavorable or unintended sign, including an abnormal laboratory finding, symptom or disease temporally associated with the use of an investigational medicinal product whether or not considered related to the investigational medicinal product.

AEs will be monitored throughout the entire study. Investigators will ask the subject at each visit if they have experienced any untoward effects since the last study visit. All AEs will be recorded on the eCRFs provided. A description of the event, severity, time of occurrence, duration, any action (e.g. treatment and follow-up tests) and the outcome should be provided along with the Investigator’s assessment of the relationship to the study treatment.
AEs will be recorded in the OLFUS-VIPES study only from Visit 1 onwards. AEs/SAEs occurring after the time the written informed consent of OLFUS-VIPES study is signed until the time of Visit 1 will be recorded in the VIPES study only.

Also, knowing that Visit 11 of VIPES study and Visit 1 of the OLFUS-VIPES study can be conducted concomitantly, any AEs/SAEs occurring during the Visit 11 DBPCFC of the VIPES study should be recorded in the VIPES study only, and not in the OLFUS-VIPES study.

AEs 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.

If known, the name or diagnosis of the illness should be recorded, rather than a listing of individual signs or symptoms. AEs must be graded as being mild, moderate or severe and their start and end dates given. Definitions of severity are as follows:

- **Mild**: an AE usually transient in nature and generally not interfering with normal activities
- **Moderate**: an AE that is sufficiently discomforting to interfere with normal activities;
- **Severe**: an AE that is incapacitating and prevents normal activities.

Even if the Investigator feels there is no relationship to the study drug, all adverse experiences MUST be recorded in the eCRF. The Investigator is requested to assess the relationship of any clinical adverse experience to treatment using the following definitions:

- **Unrelated**: those AEs which are clearly and incontrovertibly due to extraneous causes (concurrent drugs, environment etc.) and do not meet the criteria for drug relationship listed under Unlikely, Possible, Probable or Related.

- **Unlikely**: an adverse experience may be considered unlikely if it includes at least the first two features:
  - It does not follow a reasonable temporal sequence from administration of the drug.
  - It could readily have been produced by the subject’s clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.
  - It does not follow a known pattern to the suspected drug.
  - It does not reappear or worsen when the drug is re-administered.

- **Possible**: an adverse experience may be considered possible if it includes at least the first two features:
  - It follows a reasonable temporal sequence from administration of the drug.
  - It could readily have been produced by the subject’s clinical state, environment or toxic factors, or other modes of therapy administered to the subject.
  - It follows a known response pattern to the suspected drug.
Probable: an adverse experience may be considered probable if it includes at least the first three features:

- It follows a reasonable temporal sequence from administration of the drug.
- It could not be reasonably explained by the known characteristics of the subject’s clinical state, environmental or toxic factors or other modes of therapy administered to the subject.
- It disappears or decreased on cessation or reduction in dose. There are exceptions when an AE does not disappear upon discontinuation of the drug (e.g. bone marrow depression, fixed drug eruptions, tardive dyskinesia, etc).
- It follows a known pattern of response to the suspected drug.

Related: an adverse experience may be considered related if it includes all of the following features:

- It follows a reasonable temporal sequence from administration of the drug.
- It could not be reasonably explained by the known characteristics of the subject’s clinical state, environmental or toxic factors or other modes of therapy administered to the subject.
- It disappears or decreased on cessation or reduction in dose. There are exceptions when an AE does not disappear upon discontinuation of the drug. For example: bone marrow depression, fixed drug eruptions, tardive dyskinesia, etc.
- It follows a known pattern of response to the suspected drug.
- It reappears or worsens if the drug is re-administered.

11.2 Serious Adverse Events

An SAE is any untoward medical occurrence or effect that fulfills any of the following criteria:

- results in death;
- is life-threatening;
- requires hospitalization or prolongation of existing in-subject hospitalization;
- results in persistent or significant disability or incapacity;
- is a congenital abnormality/birth defect;
- important medical events not captured by the above but which may, for example, require medical intervention to prevent one of the outcomes above.

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

a) Evaluation or treatment of a pre-existing condition and non-exacerbating condition as long as the condition(s) associated with the hospitalization:

  - existed prior to the subject’s entry into the study and has been recorded in the subject’s medical history as documented in the eCRF (e.g. degenerative disease)
  - has not worsened in severity or frequency during the subject’s exposure to study medication
has not required a change in treatment management during the subject’s exposure to the study medication.

b) Treatment which is elective or pre-planned of a pre-existing condition and nonexacerbating condition.

c) Early hospitalization of subjects the day prior to the day of DBPCFCs in order to have them prepared in advance.

11.3 Reporting of Serious Adverse Events

Reporting requirements for SAEs will be managed on behalf of DBV Technologies by the CRO PRA International. Full details of the procedures to be adopted will be documented in a safety management plan approved by responsible parties, in brief:

Any AE which occurs in any subject after entering into treatment in this study through the last visit must be reported. All SAEs that occur within 30 days following cessation of the last dose of treatment with the study drug, whether or not considered related to the investigational product, must also be reported. All subjects with SAEs must be followed up for outcome.

All SAEs must be reported within 24 hours of learning about the event. This can be done by faxing a completed SAE Fax Cover Sheet and SAE report.

Fax information to the Drug Safety Unit of the CRO PRA International. For the attention of:

For sites located in North America (USA and Canada):

PRA Drug Safety Associate
Phone: 1 800 772 2215 or 1 434 951 3489
Fax: 1 888 772 6919 or 1 434 951 3482
E-mail: CHOSafety@PRAIntl.com

For sites located in Europe:

PRA Drug Safety Associate
Phone: +49 621 878 2154
Fax: +44 1792 525 720
E-mail: MHGSafety@praintl.com

The initial report should be promptly followed by detailed, written reports, which will include copies of hospital case reports, autopsy reports and other documents when requested and applicable. This additional information will be requested, if necessary, by the Drug Safety Associate within 5 days of receipt of the alert report. This is to ensure that the initial reporting of SAEs is made to regulatory authorities within the required time period.

For a follow-up report to the authorities, the monitor may be required to collect further information for a final evaluation of the case. Reporting to the Health Authorities will be the responsibility of PRA International and of Sponsor.
PRA International will also be responsible for informing the Independent Review Board (IRB(s))/Independent Ethics Committee (IEC(s)) of SAEs as required. Correspondence with the IRB(s)/IEC(s) relating to the reporting of SAEs will be retained in the study file. In addition to informing the IRB(s)/IEC(s) of SAEs (as required), PRA International will inform the Investigators of SAEs (as required) omitting unblinded treatment information.

11.4 Monitoring of Subjects with Adverse Events

Each subject must be carefully monitored for AEs. This includes clinical laboratory variables. Assessments must be made of the seriousness, intensity and relationship to the administration of the study treatment. After the initial AE/SAE report, the Investigator is required to follow-up each subject proactively and provide further information to PRA International on the subject’s condition. During the study, all AE/SAEs should be followed to resolution unless the event is considered by the Investigator to be unlikely to resolve due to the subject’s underlying disease, or the subject is lost to follow-up.

11.5 Procedures to be Followed in the Event of Abnormal Laboratory Test Values

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

11.6 Clinical Laboratory Parameters and Abnormal Laboratory Test Results

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

11.7 Abnormal Physical Examination Findings

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

11.8 Additional Safety Assessments

Safety will be assessed using AEs, observed local and systemic allergic symptoms, physical examinations, hematology, biochemistry, vital signs and PEF and spirometry results.

11.9 Treatment of Overdose of Study Medication

There is no experience with overdosing of Viaskin®. No specific treatment for overdosing is known. Treatment given to a subject in case of overdosing should be symptomatic and supportive.

Any overdose, with or without associated AEs, in a clinical study must be reported to PRA International. Overdose will be reported in the eCRF. All reports of overdoses must be filed in the
Study Center File. Any AEs associated with the overdose should be reported on relevant AE/SAE sections in the eCRF.

11.10 Procedures in Case of Pregnancy

Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. All pregnancies and outcomes of pregnancy must be reported to PRA International using the specific reports.

11.11 Adverse Events of Special Interest to the Sponsor

AEs of special interest to Sponsor in this study include Grade 4 local skin reactions seen under the patch while the patch is still applied on the skin or upon removal of the patches from the skin. Specifically, the appearance of any vesicle(s) or ulcerative skin lesion(s) or any other significant skin lesion(s) which could potentially lead to skin barrier disruption at sites of Viaskin® patch applications will be considered AEs of special interest.

In these rare specific cases, subjects should transiently discontinue patch application and go back to the site 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 site for 1 hour before being discharged, and a call to the subject be made the next day by the site staff after removal of the previous patch to ensure that there were no further local blisters or vehicles anymore and the treatment could continue normally.

The zone with vesicles or lesions should not be used for patch application until complete healing.

Any occurrence of systemic (or distant) allergic reaction related to Viaskin® Peanut application will be considered an AE of special interest to the Sponsor and will be analyzed as such at the end of the study.

Reactions triggered by accidental consumption of peanut during the follow-up study and reactions triggered by deliberate consumption of peanut will be analyzed as part of the exploratory analyses (See Section 12.6.7 for full details).
12. DATA MANAGEMENT AND STATISTICAL ANALYSIS

The data management and statistical analysis of this study will be performed by an external CRO, PRA International.

12.1 Data Management

An eCRF will be used for the current study, and a data management plan will be prepared by the CRO, PRA International.

Previous and concomitant medications will be coded using the latest available World Health Organization Drug Reference Dictionary (WhoDRUG). Coexistent diseases and AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA).

When the database has been declared to be complete and accurate, the database will be locked. Any changes to the database after that time can only be made by written agreement between DBV Technologies and the PRA International project team.

12.2 Sample Size Estimation

All subjects who have completed the VIPES study will be offered enrollment in this follow-up/extension OLFUS-VIPES study. It is estimated that approximately 220 subjects could be enrolled in the OLFUS-VIPES study.

12.3 Statistical Analysis Plan

A Statistical Analysis Plan (SAP) will be written and finalized shortly after the final protocol, well ahead of the database lock. The SAP will provide a fully detailed description of the statistical methods and analyses performed on all efficacy and safety parameters and will expand on the details provided here in the protocol. Additional analyses may be added. Tables, listing and figures shells will also be provided at a later stage prior to database lock.
12.4 Randomization

This is an open-label follow-up study or extension study for subjects who previously were randomized and have completed the VIPES study. Subjects will be offered enrollment in this follow-up study to receive 24 months of Viaskin® Peanut treatment followed by a period of 2 months without treatment and a peanut-free diet.

After Protocol Amendment 1 is approved, there will be only one open-label dose group and there will be no randomization in the study.

12.5 Analysis Populations

12.5.1 Safety Population

The safety population will be comprised of all subjects who received at least one dose of study drug. This population will be used to assess comparative safety information.

12.5.2 Intent-to-treat Population

The intent-to-treat (ITT) population (full analysis set) will be comprised of all subjects.

12.5.3 Per Protocol Population

The per protocol (PP) population will include all subjects in the ITT population who do not have pre-defined major deviations from the protocol that may affect the endpoints. The deviations to consider will be listed more exhaustively in the SAP.

12.6 Statistical Methods

The statistical analyses for the entire study as further outlined in the SAP will be included in the Clinical Study Report for this protocol. 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 finalized shortly after the final protocol and well 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 released for unblinding. Statistical analyses using SAS® Version 9.1 or higher (SAS Institute, Cary, NC 27513).

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, median, and maximum).

The OLFUS-VIPES study will have two treatment groups: Treatment Group 1 will consist of subjects who had received placebo in the VIPES study; Treatment Group 2 will consist of subjects who had received Viaskin® Peanut in the VIPES study.
Depending on the variable to analyze, baseline values will be taken from either data collected at Visit 11 in the VIPES study/Visit 1 in OLFUS-VIPES study or from the baseline screening data values from Visit 1 up to Visit 3 in the VIPES study.

12.6.1 Missing Data

Every attempt must be made by the Investigator to provide complete data. The analysis of treatment responders will be performed on data without imputation. However, exploratory analyses using the multiple imputation method and last observation carried forward should be utilized to assess the robustness of the data.

Analyses of efficacy measures will be based on the ITT population, with missing values imputed using the last value (value of threshold sensitivity at Month 12 (Visit 4) DBPCFC) carried forward analysis. Subjects who discontinue from the study prior to Month 12 and Month 24 of the DBPCFCs will be counted as non-responders in the efficacy analyses. The robustness of the efficacy analyses conclusions will be explored via sensitivity analyses that will exclude subjects who discontinue from the study prior to Month 12 and Month 24 of the DBPCFCs.

12.6.2 Demographic and Baseline Data

Descriptive statistics will be produced for continuous demographic and baseline characteristics (including age, height, weight, FEV₁, 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, ethnicity, SPT) will be tabulated by treatment group and overall. Log transformation of some of these variables will be performed wherever deemed more appropriate in the analysis.

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

12.6.3 Subject Disposition

Subject disposition will be summarized for the ITT population. The number and percentage of subjects randomized, subjects in each study population (Safety, ITT, PP), and subjects who received study medication, who completed the 12 and 24 months of treatment, who discontinued after 12 and 24 months of the treatment period, and the primary reason for discontinuation up to 12 months and after the 24 months of treatment will be tabulated by treatment group and overall.

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 end date – start date +1 by site, 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.
12.6.4 Efficacy
12.6.4.1 Efficacy Variables

The following efficacy endpoints will be assessed:

**Eliciting Doses**
The proportion of subjects with a peanut protein eliciting dose equal to or greater than 1,000 mg peanut or with a $\geq 10$-fold increase of the eliciting dose compared to their baseline eliciting dose observed in the VIPES study will be presented.

The number and proportion of these subjects observed at Month 12 and Month 24 in the OLFUS-VIPES study will be presented by treatment group.

The proportion of these subjects at Month 12 and Month 24 will also be assessed for those subjects in Treatment Group 2 of the OLFUS-VIPES study, split by those who received 50, 100 and 250 μg during the VIPES study.

**Median and Mean Cumulative Reactive Doses**
The number and proportion of subjects unresponsive to a cumulative dose of 1,440 mg peanut protein or above at Month 12 and Month 24 will also be presented, as well as the number and percentage of subjects showing a sustained unresponsiveness at Month 26 (defined as the proportion of subjects unresponsive to a cumulative dose of 1,440 mg peanut protein or above during DBPCFC after 2 months without treatment).

The median and mean cumulative reactive dose of peanut protein at Month 12 and Month 24 in the OLFUS-VIPES study will be summarized descriptively by treatment group. Changes from baseline will also be presented.

**Immunological Markers**
Peanut-specific IgE and peanut-specific IgG4 results will be summarized descriptively at Month 6, Month 12, Month 18 and Month 24 compared to baseline and at additional time points. Changes from baseline for each subject will also be presented. In addition, the geometric mean and 95% confidence intervals will be calculated using log-transformation change from baseline value at each time point.

The null hypothesis that the peanut-specific IgE and peanut-specific IgG4 results are the same in each treatment group will be tested using the two-sided Wilcoxon Rank-Sum test, which can be obtained from the NPAR1WAY procedure in SAS®. A two-sided, 5% significance level will be used to test the null hypothesis. If rejected at the 5% level (p < 0.05), it will be concluded that there is a statistically significant difference in the peanut-specific IgE and peanut-specific IgG4 results between the two treatment groups.

In addition, the log-transformed results for peanut-specific IgE and peanut-specific IgG4 at each time point will be analyzed using an ANCOVA model. The ANCOVA model will include treatment group, age-group and site as covariates. The null hypothesis that the mean peanut-specific IgE and peanut-specific IgG4 results are the same for active treatment groups will be tested against the two-sided alternative hypothesis that the results are different in each treatment group at the 0.05
significance level.

The back-transformed least square means for the treatment groups, difference in least square means between the treatment groups, effect size calculated as the absolute difference in least square means between active group divided by the root mean square, and p-value for difference between treatment groups will be presented.

**Skin Prick Test**
The change in the average wheal diameter of undiluted skin prick testing after 6, 12, 18 and 24 months of treatment and at the Early Termination Visit will be assessed at each time point versus baseline. The number and percentage of subjects per treatment group with an average wheal diameter of SPT divided by 2 as compared to baseline and also equal to 0 mm at Month 6, Month 12, Month 18, Month 24 and Early Termination Visit will be presented.

In addition, summary statistics will be presented for the mean value of SPT average wheal diameter in each treatment group after 6, 12, 18 and 24 months of treatment and at the Early Termination Visit.

**Change in the Quality of Life at Month 12 and Month 24 compared to Day 1**
The summary statistics for the data from the FAQLQ will be summarized for each treatment group at Day 1, 12 months and 24 months of treatment. Changes from Day 1 will also be presented at 12 months and 24 months of treatment, globally and by treatment group.

Data collected from the FAIM questionnaires will help test the validation of the different forms of FAQLQs.

12.6.5 **Pharmacokinetics**

Not applicable, no pharmacokinetic assessments will be performed during this study

12.6.6 **Safety**

No formal statistical analysis of safety endpoints will be carried out.

12.6.6.1 **Adverse Events**

All AEs will be coded by system organ class and preferred term using MedDRA. TEAEs will be defined as any AEs, regardless of relationship to study drug, which occur during or after the initial Viaskin® application of study drug or any event already present that worsens in either intensity or relationship to study drug following exposure to the Viaskin® since the beginning of the OLFUS-VIPES study (distinguished from symptoms/reactions elicited during the DBPCFs). If relationship information is missing, the AE will be considered drug-related. Any skin reactions, local or distant, including allergic reactions will be considered TEAEs.

An overall summary of TEAEs will be provided showing the number and percentage of subjects in each initial treatment group with any TEAE, any potentially drug-related TEAE, any severe TEAE, any serious TEAE, any TEAE leading to discontinuation, and any TEAE 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 one AE will be summarized by system organ class, preferred term and treatment group. The incidence of the following events will be summarized:

- TEAEs since the beginning of the OLFUS-VIPES study (distinguished from symptoms/reactions elicited during the DBCFCs): incidence, severity and duration.
- Potentially drug-related TEAEs.
- Discontinuations due to TEAEs.
- Systemic allergic symptoms (see Appendix 2).
- Potentially drug-related systemic allergic symptoms.
- SAEs.
- Potentially drug-related SAEs.

In addition, TEAEs will be summarized by relationship to study drug and by severity. If a subject has more than one occurrence of the same TEAE with different severities or relationship to study drug, then the TEAE will be assigned to the highest severity category and/or most related relationship category. If the intensity or relationship is missing, then the ‘worst case’ will be assumed (i.e., severe for intensity and drug-related for relationship). The proportion of subjects who experience systemic allergic symptoms will be summarized by treatment. All TEAEs will be listed.

Besides, TEAEs between 18 and 24 months will be described for the subset of subjects who switched to the integrated patch at the Month 18 visit versus the rest of the population.

AEs/SAEs unresolved at time of the End of study visit will be followed until resolution or for a maximum of 30 days.

Specific reactions triggered by an accidental consumption of peanut and the conditions around that accidental consumption will be collected. These AEs will be classified and analyzed separately.

12.6.6.2 DBPCFC to Peanut: Symptoms/Reactions

The AEs appearing during a DBPCFC (as they are expressly provoked) will be differentiated from those AEs occurring outside of the DBPCFC. Objective and subjective symptoms/reactions elicited during the DBPCFCs in the different treatment groups (see Section 10.10 for full details) will be summarized separately. Any objective or subjective symptoms/reactions not mentioned specifically in the e-CRF but experienced during the DBPCFCs and reported as such by the Investigators must be coded and summarized.
12.6.6.3 Laboratory Assessments

Descriptive statistics will be calculated for clinical laboratory tests (hematology and biochemistry) performed at baseline, Visit 3 (Month 6), Visit 4 (Month 12), Visit 6 (Month 18), Visit 7 (Month 24), Visit 9 (Month 26) and Early Termination Visit. Categorical variables will be summarized by frequency and percentages of subjects in corresponding categories. Changes from baseline will also be presented.

In addition, summaries of laboratory values categorized based on Common Toxicity Criteria grade will also be presented.

All laboratory data will be listed. Listing of values that are out of normal ranges will be flagged in the data listings.

12.6.6.4 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 the incidence of clinically relevant abnormalities. The number of subjects evaluated and the number and percentage of subjects with clinically relevant post-baseline abnormalities at each visit will be presented.

12.6.6.5 Spirometry and Peak Expiratory Flow Results

Percent predicted values for FEV₁ and PEF and changes from baseline will be descriptively summarized separately by visit and treatment group and age stratum. All FEV₁ and PEF data will be listed.

12.6.6.6 Concomitant Medications

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

12.6.7 Exploratory Analyses

Exploratory criteria include:

- Enumeration and characterization of reactions triggered by accidental consumption of peanut during the follow-up study.
- Analysis of “Risk-taking behavior” of subjects (or voluntary peanut consumption as assessed by the investigators) during the follow-up study.
Both information will be collected from patient Diary Cards and voluntary or accidental consumption will be assessed by the investigative staffs while interviewing the subjects. Frequency of accidental consumption, conditions around the accidental consumption, estimated quantity consumed at each occurrence, and associated reactions and severity of reactions will be analyzed specifically and separately. These AEs will be classified and analyzed separately and specifically.

Risk-taking behaviors: frequency of deliberate consumption of peanut, conditions around the consumption, estimated quantity consumed at each occurrence and associated reactions with these consumptions. These AEs will be classified and analyzed separately and specifically. Relatedness to the subject’s age category will also be analyzed.

Additional exploratory criteria:
- Tolerability, adhesivity and comfort of the integrated patch versus the patch with the added Tegaderm™ for the subset of subjects who switched to the integrated patch at the Month 18 visit (Visit 6).

This information will be collected from specific questionnaires recorded at Month 18 visit for the current patch with the added Tegaderm™ and at the time of the PC2 and at Month 24 visit for the integrated patch. Questionnaires will be described by type of patch and time point (patch with the added Tegaderm™ at Month 18, integrated Viaskin® patch at time of PC2, integrated Viaskin® patch at Month 24). The number and percentage of subjects for each modality of tolerability, adhesivity and comfort will be summarized. Besides, the number and percentage of subjects who reported:
  - none or mild skin reactions,
  - none or 1 patch fallen off,
  - very comfortable or comfortable use using the integrated Viaskin® patch versus the patch with the added Tegaderm™ will be presented.

12.6.8 Additional Data

Physical examination data will be summarized where appropriate and listed. Study drug compliance and accountability will be listed.

12.6.9 Data and Safety Monitoring Board

A DSMB composed of experts in food allergy and in the methodology of clinical trials 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 or when conveyed by Sponsor. The DSMB will review blinded data, but may have access to unblinded data as deemed necessary by the DSMB members. 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 of the DSMB.
13. MONITORING PROCEDURES (QUALITY ASSURANCE)

The Sponsor has ethical, legal, and scientific obligations to conduct this study in accordance with established research principles and ICH GCP guidelines. As such, in order to fulfill these obligations and to maintain current of study progress, the Sponsor's monitors or representatives will visit the investigative sites during study conduct, in addition to maintaining telephone and written communication. On-site visits, telephone calls, and regular inspection of the eCRFs will be conducted in order to assess subject enrollment, compliance with protocol procedures, completeness and accuracy of data entered on the eCRFs, verification of eCRF data against original source documents, and occurrence of AEs. The Investigator must provide the monitor with full access to all source and study documents.

13.1 Routine Monitoring

Sponsor assigned monitors will conduct regular site visits to the investigational facilities for the purpose of monitoring various aspects of the study. The Investigator must agree to Sponsor-authorized personnel having direct access to the clinical (or associated) files and clinical study supplies (dispensing and storage areas) for all study subjects considered for study entry for the purpose of verifying entries made in the eCRF, and assist with their activities, if requested. Adequate time and space for monitoring visits should be made available by the Investigator.

The site must complete the eCRFs in a timely manner and on an ongoing basis to allow regular review by the study monitor.

Whenever a subject name is revealed on a document that is to be collected for the Sponsor, the name must be blacked out permanently by the site personnel, leaving the initials visible, and annotated with the subject number as identification.

13.2 Inspections and Auditing Procedures

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

Government regulatory authorities may also inspect the Investigator during or after the study. The Investigator or designee should contact the Sponsor/CRO immediately if this occurs. He/she must cooperate fully with regulatory authorities or other audits conducted at a convenient time in a reasonable manner.

The purpose of an audit is to assess whether ethics, regulatory and quality requirements are fulfilled.
14. STUDY MANAGEMENT AND MATERIALS

14.1 Electronic Case Report Forms

An eCRF will be used to store and transmit subject information. The eCRF must be reviewed and electronically signed and dated by the Investigator.

Access to the eCRF will be strictly password protected and limited to personnel directly participating in the study. Data should be entered into the eCRF completely by examining personnel or the study coordinator. The eCRF must be completed as soon as possible after any subject evaluation or communication. If data is to be changed due to erroneous input or other reason, an electronic audit trail will track these changes. The eCRFs and computers that store them must be accessible to study monitors and other regulatory auditors.

14.2 Data Collection

During each study visit, a physician participating in the study will maintain progress notes, in ink, in the subject’s medical records to document all significant observations. At a minimum, these notes will contain:

- The date of the visit and the corresponding day or visit in the study schedule (e.g., Day 1, Month 1, etc.).
- General condition and status remarks by the subject, including any significant medical findings. The severity, frequency, duration, and resolution of any reported AE, and the Investigator's assessment as to whether or not the reported AE is study drug-related should be recorded.
- Changes in concomitant medications or dosages.
- A general reference to the procedures completed.
- The signature or initials of all physicians making an entry in the medical record (progress notes).

In addition, any contact with the subject via telephone or other means that provides significant clinical information will also be documented in the medical record (progress notes), as described above.

Information from the medical records (progress notes) and other source documents will be promptly transcribed to the appropriate section of the eCRF. Changes to information in the medical record (progress notes), eCRF, and other source documents will be initialed and dated on the day the change is made by the Investigator or designee. If the reason for the change is not apparent, a brief explanation for the change will be written adjacent to the change.
14.3 Source Documents Maintenance

Source documents contain the results of original observations and activities of a clinical investigation. Source documents include, but are not limited to, medical records (progress notes), computer printouts, screening logs and recorded data from automated instruments.

All source documents from this study will be maintained by the Investigator and made available for inspection by authorized persons. The original signed informed consent for each subject shall be filed with records kept by the Investigator, and a copy shall be given to the subject.

14.4 Record Maintenance

All data derived from the study will remain the property of DBV Technologies. Records must be retained in accordance with the current ICH Guidelines on GCP. All essential study documents including records of subjects, source documents, eCRFs and study drug inventory must be kept on file.

US Food and Drug Administration (FDA) regulations (21 Code of Federal Regulations [CFR] 312.62[c]) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including eCRFs, consent forms, laboratory test results, and medical inventory records, must be retained by the Principal Investigator for two years after marketing application approval. If no application is filed, these records must be kept two years after the investigation is discontinued and the US FDA and the applicable national and local health authorities are notified. The Sponsor or their representative will notify the Principal Investigator of these events.

The Investigator will not dispose of any records relevant to this study without written permission from the Sponsor, and will provide the Sponsor the opportunity to collect such records. 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.

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 an investigation 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.

14.5 Confidentiality

All information 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 eCRFs and other documents submitted to the Sponsor or the CRO, subjects must not be identified by name. Instead, subjects will only be known by the unique subject screening 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.

In order to comply with government regulatory guidelines and to ensure subject safety, it may be necessary for the Sponsor and its representative, the CRO personnel, the local research review board, or the US FDA to review subjects’ medical records as they relate to this study. Only the subject’s unique number on the eCRFs will identify him/her, but their full names may be made known to a drug 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 or the CRO (e.g., consent forms) will be maintained by the Investigator in strict confidence, except to the extent necessary to allow monitoring by the Sponsor and the CRO, and auditing 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.

15. ETHICS

15.1 Ethics Committee

This study will be conducted in compliance with IEC/IRB and ICH GCP Guidelines including Title 21 Part 56 of the USA CFR relating to IRBs and GCP as described in the US FDA CFR (21 CFR § 50, 56, 312) - in accordance with applicable regulations regarding clinical safety data management (E2A, E2B(R3)), European Community directives 2001/20, 2001/83, 2003/94 and 2005/28 as enacted into local law, and with ICH guidelines regarding scientific integrity (E4, E8, E9 and E10). In addition, this study will adhere to all local regulatory requirements, and requirements for data protection.

Before initiating a trial/study, the Investigator/institution must have written and dated approval/favorable opinion from the IEC/IRB for the study protocol/amendment(s), written informed consent form (ICF), any consent form updates, subject recruitment procedures (e.g. advertisements), and any written information to be provided to subjects and a statement from the IEC/IRB that they comply with GCP requirements. The IEC/IRB approval must identify the protocol version as well as the documents reviewed.

15.2 Ethical Conduct of the Study

This study will be conducted in accordance with the Note for Guidance on GCP (ICH Harmonized Tripartite Guideline E6 (R1); FDA CFR (21 CFR § 50, 56, 312)), Declaration of Helsinki (Seoul 2008) (Appendix 1) and all applicable regulatory requirements.
15.3 Subject Information and Consent

The Investigator is responsible for and will obtain informed consent from each subject in the study, in accordance with the ICH-GCP Guidelines, the Declaration of Helsinki, and applicable regulatory requirements.

Subjects 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 must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time. The subject should read the ICF before signing and dating it and a copy of the signed document should be given to the subject. No subject can enter the study before his/her informed consent has been obtained. Children 7-11 years of age and adolescents 12 to 17 years of age will sign an assent form specific to their ages, wherever that is required by local country laws. The parents or legal representative(s) of all children and adolescents regardless of age must sign the ICF. Subjects aged 18 years or older are considered adults and will sign the standard ICF by themselves.

The consent form may need to be revised during the study should important new information become available that may be relevant to the safety of the subject. In this instance, approval should always be given by the IRB/IEC and existing subjects informed of the changes and re-consented. This is documented in the same way as previously described.

The Investigator should keep a copy of the consent of the subject, inform the subject’s primary physician about participation in the clinical study wherever required.

16. ADMINISTRATION PROCEDURES

16.1 Regulatory Approval

DBV Technologies or their appointed agents will be responsible for ensuring that appropriate regulatory authority approvals are obtained, according to local country requirements.

No subject may enter the study until this approval has been obtained. A copy of the approval (where one is provided, according to local country requirements) will be provided to the Investigator and to the IRB(s)/IEC(s).

16.2 Protocol Amendments

In accordance with ICH Topic E6 (R1) Guideline for GCP, the Investigator should not implement any deviation from, or changes of, the protocol without agreement by the Sponsor and documented approval from the IRB/IECs of a protocol amendment, except where necessary to eliminate an immediate hazard(s) to study subjects, or when the change(s) involve(s) only logistical or administrative aspect(s) of the study (e.g., change in monitor(s), change of telephone number(s)).

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. In these cases, the IRB/IEC must be notified within 5 days of the change.

All 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 modification. 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 subjects enrolled in the study before participation continues.

16.3 Protocol Adherence and Deviations

The protocol must be read thoroughly and the instructions must be followed. However, exceptions will be made in emergency situations when the protection, safety, and well-being of the subject requires immediate intervention based on the judgment of the Investigator or a responsible, appropriately trained, and credentialed professional(s) designated by the Investigator as a sub-Investigator.

In the event of a significant protocol deviation due to an emergency, accident, or error, the Investigator or designee must contact the Medical Monitor at the earliest possible time by telephone. This allows for an early joint decision to be made as to whether or not the subject should continue in the study. The Investigator, the Sponsor, and the Medical Monitor will document this decision.

16.4 Publication Policy

After completion of the study, the Investigator(s) may prepare a joint publication with the Sponsor. The Investigator(s) must undertake not to submit any part of the data from this protocol for publication without the prior written approval of DBV Technologies.

16.5 Clinical Study Report

Two clinical study reports will be prepared for the OLFUS-VIPES study: an interim clinical study report will be prepared after 12 months of treatment and conduct of Month 12 DBPCFC, i.e. when all subjects have completed Visit 5; and a full clinical study report at the end of the study. The clinical study reports 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 for retention.
16.6 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.

16.7 Insurance, Indemnity and Compensation

DBV Technologies undertakes to maintain an appropriate clinical study insurance policy. 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.

16.8 Discontinuation of the Study

This study may be terminated by the Sponsor. The study may also be terminated prematurely at any time when agreed to by both the Investigators and the Sponsor as being in the best interests of subjects, and justified on either medical or ethical grounds. In terminating the study, DBV Technologies, the CRO (PRA International) and the Investigator will ensure that adequate consideration is given to the protection of the subjects’ interests.

16.9 Study Center File Management

The Investigator is responsible for assuring that the Study Center File is maintained. The Study Center File will contain, but will not be limited to, the information listed below:

1. Investigator’s Brochure;
2. Current, signed version of the protocol and any previous versions of the protocol;
3. Protocol amendments (if applicable);
4. Operations Manual (if applicable);
5. Current ICF (blank) and any previous versions of the ICF;
6. Curricula Vitae of Investigator(s) and Sub-Investigator(s) and photocopy of their respective license(s) where required by law; Original US FDA Form 1572 (for all studies conducted under US Investigational New Drug [IND] regulations), signed by all Principal Investigators. The names of any Sub-Investigators must appear on this form. Investigators must also complete all regulatory documentation as required the ICH GCP and by local or national regulations;
7. Documentation of IRB/IEC approval of the protocol, the ICF, any protocol amendments, and any ICF revisions;
8. All correspondence between the Investigator, IRB/IEC, and the Sponsor/CRO relating to study conduct;
9. Laboratory certification(s);
10. Monitoring log;
(11) Study drug invoices;
(12) Signature list of all staff completing eCRFs; and
(13) Signature list of all staff completing drug accountability summaries.
17. **REFERENCE LIST**


27. Flokstra de Blok BMJ, Van der Meulen BN, DunnGalvin A, Vlieg-Boerstra B et al. Development and validation of the Food Allergy Quality of Life Questionnaire – Adult Form. *Allergy* 2009; 64; 1209-1217.

18. APPENDICES

18.1 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
  53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
  55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
  59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

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 not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of subjects, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

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

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. 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 current interventions must be
evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

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

9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should 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.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

12. 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.

13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.

14. The design and performance of each research study involving human subjects must be clearly described 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, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. 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 change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on subjects or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

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

19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

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

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

23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

24. In medical research involving competent human subjects, 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, 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.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized 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 population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

28. When a potential research subject who is deemed incompetent 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 authorized representative. The potential subject’s dissent should be respected.

29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious subjects, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized 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 should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors 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. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.
C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research 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 subjects who serve as research subjects.

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

- The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or

- Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the subjects who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, subjects entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the subject which aspects of the care are related to the research. The refusal of a subject to participate in a study or the subject’s decision to withdraw from the study must never interfere with the subject-physician relationship.

35. In the treatment of a subject, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the subject or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.
18.2 Appendix 2: Anaphylaxis Staging System

Anaphylaxis is a generalized allergic reaction that is rapid in onset and may progress to death (23).

<table>
<thead>
<tr>
<th>Stage</th>
<th>Defined By</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Mild</strong> <em>(skin &amp; subcutaneous tissues, GI, &amp;/or mild respiratory)</em></td>
<td>Flushing, urticaria, periorbital or facial angioedema; mild dyspnea, wheeze or upper respiratory symptoms; mild abdominal pain and/or emesis</td>
</tr>
<tr>
<td><strong>2. Moderate</strong> <em>(mild symptoms + features suggesting moderate respiratory, cardiovascular or GI symptoms)</em></td>
<td>Marked dysphagia, hoarseness, and/or stridor; shortness of breath, wheezing &amp; retractions; crampy abdominal pain, recurrent vomiting and/or diarrhea; and/or mild dizziness</td>
</tr>
<tr>
<td><strong>3. Severe</strong> <em>(hypoxia, hypotension, or neurological compromise)</em></td>
<td>Cyanosis or SpO₂ ≤ 92% at any stage, hypotension, confusion, collapse, loss of consciousness; or incontinence</td>
</tr>
</tbody>
</table>
18.3 Appendix 3: Oral Food Challenge Symptom Score Sheet (24)

Oral food challenge symptom score sheet

Possible reactions

I. Skin
   A. Erythematous rash: % area involved (see body surface area diagram)
   B. Pruritus
      0 = Absent
      1 = Mild, occasional scratching
      2 = Moderate: scratching continuously for > 2 minutes at a time
      3 = Severe: hard continuous scratching
   C. Urticaria / angioedema
      0 = Absent
      1 = Mild: less than 3 hives
      2 = Moderate: more than 3 and less than 10 hives
      3 = Severe: generalized involvement
   D. Rash
      0 = Absent
      1 = Mild: few areas of faint erythema
      2 = Moderate: areas of erythema, macular and raised rash
      3 = Severe: generalized marked erythema (>50%), extensive raised lesion (>25%), vesiculation and / or pilarerection

II. Upper respiratory
   A. Sneezing / itching
      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
      0 = Absent
      1 = Mild: some hindrance to breathing
      2 = Moderate: nostrils feel blocked, breathing through mouth most of the time
      3 = Severe: nostrils occluded
   C. Rhinorrhea
      0 = Absent
      1 = Mild: occasional sniffing
      2 = Moderate: frequent sniffing, requires tissues
      3 = Severe: nose runs freely despite sniffing and tissues
   D. Laryngitis
      0 = Absent
      1 = Mild: throat clearing, occasional cough
      2 = Moderate: hoarseness, frequent dry cough
      3 = Severe: inspiratory stridor

III. Lower respiratory
   A. Wheezing
      0 = Absent
      1 = Mild: expiratory wheezing to auscultation
      2 = Moderate: dyspnea, inspiratory and expiratory wheezing
      3 = Severe: dyspnea, use of accessory muscles, audible wheezing

IV. Gastrointestinal
   A. Subjective Complaints
      0 = Absent
      1 = Mild: itchy mouth, nausea, abdominal pain, no change in activity
      2 = Moderate: frequent complaints of nausea or pain, decreased activity
      3 = Severe: patient in bed, crying, notably distressed
   B. Objective Complaints
      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

V. Cardiovascular
   0 = Absent: normal heart rate and / or blood pressure for age or patient's baseline
   1 = Mild: color change, subjective response (weak, dizzy), mental status change, tachycardia
   2 = Moderate: drop in blood pressure >20% from baseline
   3 = Severe: cardiovascular collapse, signs of impaired circulation, unconsciousness, bradycardia
18.4 Appendix 4: Subject Card and Anaphylaxis Emergency Action Plan

The Subject Card and Anaphylaxis Emergency Action Plan are on the next page.
My appointments

Please use DD/MMM/YYYY and 24-hr clock entries

Visit 1 (Day 1/corresponds to Visit 11 in the VIPES study): ___/___/____@ ___:___
Visit 2 (M1 ± 7 days): ___/___/____@ ___:___
Visit 3 (M6 ± 14 days): ___/___/____@ ___:___
Visit 4 (M12 ± 14 days /DBPCFC Day 1): ___/___/____@ ___:___
Visit 5 (M12 + 7 days + 7 days max/DBPCFC Day 2): ___/___/____@ ___:___
Visit 6 (M18 ± 14 days): ___/___/____@ ___:___
Visit 7 (M24 ± 14 days /DBPCFC Day 1): ___/___/____@ ___:___
Visit 8 (M24 + 7 days + 7 days max /DBPCFC Day 2/Last Visit for Subjects Reacting Objectively at a Cumulative Dose of 1,440 mg Peanut Protein or Below at M24): ___/___/____@ ___:___
Visit 9 (M26 ± 14 days /DBPCFC Day 1/for Subjects Unresponsive to a Cumulative Dose of 1,440 mg Peanut Protein or Above at M24): ___/___/____@ ___:___
Visit 10 (M26 + 7 days + 7 days max/DBPCFC Day 2/Last Visit for Subjects Unresponsive to a Cumulative Dose of 1,440 mg Peanut Protein or Above at M24): ___/___/____@ ___:___
Early Termination Visit: ___/___/____@ ___:___

Instructions for this card

- Please present your “Subject’s card” to all other doctors in order to inform them that you are participating in a clinical trial.
- If you are hospitalized for any reason, you must notify your research doctor immediately.
- Do not forget to complete your patient diary card on a daily basis and note any adverse events.
- Please keep the Anaphylaxis Emergency Action Plan with you at all time.
- Please carry your epinephrine Autoinjector with you at all time.
- Please continue to avoid peanut-containing foods while on the research study.
- If the Viaskin® patch comes off during the day, subject/parent should wipe off the zone with a disposable napkin or tissue and wash their hands to prevent accidental transmission of allergic proteins.
- Please store patches in the refrigerator at 2°C-8°C and protect from moisture.

Study Protocol: OLFUS-VIPES

“An Open-Label Follow-Up Study of the VIPES Study to Evaluate Long-Term Efficacy and Safety of the Viaskin® Peanut (OLFUS-VIPES Study)"
Subject participation is approximately 27 months (including a 24-month treatment period followed by a period of 2 months without treatment)

Important Contacts

In case of an emergency or if you have any questions, please contact your research doctor:

PI Name: _______________________________
PI Phone #: _____________________________
Other Emergency contact #2:
Home: __________________________________
Work: __________________________________
Mobile: _________________________________
Other Emergency contact #3:
Home: __________________________________
Work: __________________________________
Mobile: _________________________________

If this card is found or misplaced, please return to: ________________________________
ANAPHYLAXIS Emergency Action Plan

Age: __________

Allergy to: ____________________

Asthma  □ Yes (high risk for severe reaction)  □ No

Other Health Problems besides anaphylaxis:
________________________________________________
________________________________________________

Concurrent medications, if any:
____________________________________________________
____________________________________________________

Symptoms of Anaphylaxis include:

MOUTH: itching, swelling of lips, and/or tongue
THROAT*: itching, tightness/closure, hoarseness
SKIN: itching, hives, redness, swelling
GUT: vomiting, diarrhea, cramps
LUNG: shortness of breath, cough, wheeze
HEART: weak pulse, dizziness, passing out

* Only a few symptoms may be present. Severity of symptoms can change quickly. Some symptoms can be life-threatening! ACT FAST!

What to do:
1. Inject epinephrine in thigh using:
   □ EpiPenJr 0.15mg  □ Twinject 0.15 mg
   □ EpiPen 0.3mg  □ Twinject 0.3 mg
   Other medication/dose/route: ____________________________

IMPORTANT: ASTHMA PUFFERS AND/OR ANTIHISTAMINES CAN’T BE DEPENDED ON IN ANAPHYLAXIS

2. CALL 911 OR RESCUE SQUAD (BEFORE CALLING CONTACTS)!
   DO NOT HESITATE TO GIVE EPINEPHRINE!

Comments:
____________________________________________________
____________________________________________________
____________________________________________________
____________________________________________________
____________________________________________________

Visit Reminders

- Please remember to bring your patient diary card at every visit during the Treatment period.
- Please remember to bring back your treatment boxes with the unused patches at each visit during the treatment period.
- Please remember to apply one patch at about the same time every day.
- Please take a light breakfast at home on each day of your food challenges.

Other medications:

- Refrain from short acting antihistamines for 3-5 days prior to V3, V4, V5, V6, V7, V8, V9, V10 and Early Termination Visit as a Skin prick test (SPT) and/or food challenge will occur at these visits.
- Refrain from long acting antihistamines for at least 5-7 days prior to skin prick tests or food challenges (V3, V4, V5, V6, V7, V8, V9, V10).
- You will be given a topical corticosteroid ointment for your use during the study for any local skin reactions to the investigational medication.
- Oral antihistamines or oral corticosteroids are ONLY allowed to treat adverse reactions or allergic reactions. Otherwise they should not be used while the subject is on the study. Please contact the Investigator site prior to use, if possible.
18.5 Appendix 5: Dosages of Inhaled Corticosteroids (from NAEPP 2007)

FOR YOUTHS ≥12 YEARS OF AGE AND ADULTS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Low Daily Dose</th>
<th>Medium Daily Dose</th>
<th>High Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone HFA</td>
<td>40 or 80 mcg/puff</td>
<td>80–240 mcg</td>
<td>&gt;240–480 mcg</td>
</tr>
<tr>
<td>Budesonide DPI</td>
<td>90, 180, or 200 mcg/inhalation</td>
<td>180–600 mcg</td>
<td>&gt;600–1,200 mcg</td>
</tr>
<tr>
<td>Flunisolide</td>
<td>250 mcg/puff</td>
<td>500–1,000 mcg</td>
<td>&gt;1,000–2,000 mcg</td>
</tr>
<tr>
<td>Flunisolide HFA</td>
<td>80 mcg/puff</td>
<td>320 mcg</td>
<td>&gt;320–640 mcg</td>
</tr>
<tr>
<td>Fluticasone HFA/MDI</td>
<td>44, 110, or 220 mcg/puff</td>
<td>88–264 mcg</td>
<td>&gt;264–440 mcg</td>
</tr>
<tr>
<td>DPI</td>
<td>50, 100, or 250 mcg/inhalation</td>
<td>100–300 mcg</td>
<td>&gt;300–500 mcg</td>
</tr>
<tr>
<td>Mometasone DPI</td>
<td>200 mcg/inhalation</td>
<td>200 mcg</td>
<td>400 mcg</td>
</tr>
<tr>
<td>Triamcinolone acetonide</td>
<td>75 mcg/puff</td>
<td>300–750 mcg</td>
<td>&gt;750–1,500 mcg</td>
</tr>
</tbody>
</table>

Key: DPI, dry powder inhaler; HFA, hydrofluoroalkane; MDI, metered-dose inhaler

FOR CHILDREN 5-11 YEARS OF AGE

<table>
<thead>
<tr>
<th>Drug</th>
<th>Low Daily Dose</th>
<th>Medium Daily Dose</th>
<th>High Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone HFA</td>
<td>40 or 80 mcg/puff</td>
<td>80–160 mcg</td>
<td>&gt;160–320 mcg</td>
</tr>
<tr>
<td>Budesonide DPI</td>
<td>90, 180, or 200 mcg/inhalation</td>
<td>180–400 mcg</td>
<td>&gt;400–800 mcg</td>
</tr>
<tr>
<td>Budesonide inhaled</td>
<td>Inhalation suspension for nebulization</td>
<td>0.5 mg</td>
<td>1.0 mg</td>
</tr>
<tr>
<td>Flunisolide</td>
<td>250 mcg/puff</td>
<td>500–750 mcg</td>
<td>1,000–1,250 mcg</td>
</tr>
<tr>
<td>Flunisolide HFA</td>
<td>80 mcg/puff</td>
<td>160 mcg</td>
<td>320 mcg</td>
</tr>
<tr>
<td>Fluticasone HFA/MDI</td>
<td>44, 110, or 220 mcg/puff</td>
<td>88–176 mcg</td>
<td>&gt;176–352 mcg</td>
</tr>
<tr>
<td>DPI</td>
<td>50, 100, or 250 mcg/inhalation</td>
<td>100–200 mcg</td>
<td>&gt;200–400 mcg</td>
</tr>
<tr>
<td>Mometasone DPI</td>
<td>200 mcg/inhalation</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Triamcinolone acetonide</td>
<td>75 mcg/puff</td>
<td>300–600 mcg</td>
<td>&gt;600–900 mcg</td>
</tr>
</tbody>
</table>

Key: HFA, hydrofluoroalkane; NA, not approved and no data available for this age category.
18.6 Appendix 6: Food Allergy Quality of Life Questionnaire (FAQLQ), Food Allergy Independent Measure (FAIM) and the Corresponding Parent Forms (25-28)
Food Allergy Quality of Life Questionnaire - Child Form (8-12 years)

The questions are about the influence of your food allergy on your quality of life. It is important that you fill in the answers yourself. You may ask your parents for help, but they are not allowed to tell you which answer to give. Answer every question by putting an ‘x’ in the proper box. You may choose from the following answers.

Not  barely  a little bit  fairly  quite  very  extremely

<table>
<thead>
<tr>
<th>How troublesome do you find it, because of your food allergy, that you …</th>
<th>⚫</th>
<th>⚫</th>
<th>⚫</th>
<th>⚫</th>
<th>⚫</th>
<th>⚫</th>
<th>⚫</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>must always watch what you eat?</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
</tr>
<tr>
<td>2</td>
<td>can eat fewer things?</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
</tr>
<tr>
<td>3</td>
<td>are limited in buying things you like?</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
</tr>
<tr>
<td>4</td>
<td>have to read labels?</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
</tr>
<tr>
<td>5</td>
<td>have to refuse food when you do things with others?</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
</tr>
<tr>
<td>6</td>
<td>can less easily stay for a meal with someone?</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
</tr>
<tr>
<td>7</td>
<td>can taste or try fewer things when eating out?</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
</tr>
<tr>
<td>8</td>
<td>have to tell beforehand about what you are not allowed to eat when eating out?</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
</tr>
<tr>
<td>9</td>
<td>have to check yourself whether you can eat something when eating out?</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
</tr>
<tr>
<td>10</td>
<td>hesitate eating certain foods when you don’t know if it is safe?</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
</tr>
<tr>
<td>11</td>
<td>must watch out when touching certain foods?</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
</tr>
<tr>
<td>12</td>
<td>don’t get anything when someone is giving treats at school?</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>How troublesome is it, because of your food allergy, …</th>
<th>⚫</th>
<th>⚫</th>
<th>⚫</th>
<th>⚫</th>
<th>⚫</th>
<th>⚫</th>
<th>⚫</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>that the ingredients of a food change?</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
</tr>
<tr>
<td>14</td>
<td>that the label states: “May contain (traces of)…”?</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
</tr>
<tr>
<td>15</td>
<td>that you have to explain to people around you that you have a food allergy?</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
</tr>
<tr>
<td>16</td>
<td>that people around you forget that you have a food allergy?</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
</tr>
<tr>
<td>17</td>
<td>that others can eat the food you are allergic to when you do things with other people?</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
</tr>
<tr>
<td>18</td>
<td>that you don’t know how things taste which you can’t eat?</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>How frightened are you because of your food allergy …</th>
<th>⚫</th>
<th>⚫</th>
<th>⚫</th>
<th>⚫</th>
<th>⚫</th>
<th>⚫</th>
<th>⚫</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>of an allergic reaction?</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
</tr>
<tr>
<td>20</td>
<td>of eating the wrong food by accident?</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
</tr>
<tr>
<td>21</td>
<td>to eat something you have never eaten before?</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Answer the following questions:</th>
<th>⚫</th>
<th>⚫</th>
<th>⚫</th>
<th>⚫</th>
<th>⚫</th>
<th>⚫</th>
<th>⚫</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td>How concerned are you that you will never get rid of your food allergy?</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
</tr>
<tr>
<td>23</td>
<td>How disappointed are you when people don’t take your food allergy into account?</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
</tr>
<tr>
<td>24</td>
<td>How disappointed do you feel because you have a food allergy?</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
<td>⚫</td>
</tr>
</tbody>
</table>
Food Allergy Independent Measure – Child Form (8-12 years)

The following four questions are about the chance that you think you have of something happening to you because of your food allergy. Choose one of the answers. This is followed by two more questions about your food allergy. Answer every question by putting an ‘x’ in the box next to the proper answer.

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>never</td>
<td>very small chance</td>
<td>small chance</td>
<td>fair chance</td>
<td>big chance</td>
<td>very big chance</td>
<td>always (100% chance)</td>
</tr>
</tbody>
</table>

How big do you think the chance is that you …

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>will accidentally eat something to which you are allergic?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>2</td>
<td>will have a severe reaction if you accidentally eat something to which you are allergic?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>3</td>
<td>will die if you accidentally eat something to which you are allergic?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>4</td>
<td>can <strong>not</strong> do the right things for your allergic reaction should you accidentally eat something to which you are allergic?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

5. How many foods are you unable to eat because of your food allergy?

6. Everyone does things with other people, such as:
   - playing with friends,
   - going to a birthday party,
   - visiting,
   - staying over with someone for a meal or eating out.

How much does your food allergy affect things you do with others?

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐</td>
<td>so little I don’t actually notice it</td>
<td>☐</td>
<td>very little</td>
<td>☐</td>
<td>little</td>
<td>☐</td>
<td>moderately</td>
</tr>
<tr>
<td>☐</td>
<td>a good deal</td>
<td>☐</td>
<td>a great deal</td>
<td>☐</td>
<td>a very great deal</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Food Allergy Quality of Life Questionnaire - Adolescent Form (13-17 years)

The following questions concern the influence your food allergy has on your quality of life. Answer every question by marking the appropriate box with an ‘x’. You may choose from one of the following answers.

<table>
<thead>
<tr>
<th>How troublesome do you find it, because of your food allergy, that you …</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>must always be alert as to what you are eating?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>are able to eat fewer products?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>are limited as to the products you can buy?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>must read labels?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>have the feeling that you have less control of what you eat when eating out?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>are less able to spontaneously accept an invitation to stay for a meal?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>are less able to taste or try various products when eating out?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>must check yourself whether you can eat something when eating out?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>hesitate eating a product when you have doubts about it?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>must refuse treats at school or work?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>must be careful about touching certain foods?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>must carry an epinephrine auto-injector (e.g. EpiPen, Twinject, Anapen)? (If you don’t have an epinephrine auto-injector mark an ‘x’ here)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>How troublesome is it, because of your food allergy, …</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>that the ingredients of a food change?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>that the label states: “May contain (traces of)…”?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>that the labeling of the bulk packaging (for example box or bag) is different than the individual packages?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>that you have to explain to people around you that you have a food allergy?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>that during social activities others can eat the food to which you are allergic?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>that during social activities your food allergy is not taken into account enough?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>How frightened are you because of your food allergy …</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>of an allergic reaction?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>of accidentally eating the wrong food?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>to eat something you have never eaten before?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Answer the following questions:

| 22 | How discouraged do you feel during an allergic reaction? | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| 23 | How disappointed are you when people don’t take your food allergy into account? | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
Food Allergy Independent Measure – Adolescent Form (13-17 years)

The following four questions are about the chance that you think you have of something happening to you because of your food allergy. Choose one of the answers. This is followed by two more questions about your food allergy. Answer every question by putting an ‘x’ in the box next to the proper answer.

<table>
<thead>
<tr>
<th>How great do you think the chance is that you …</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>will accidentally eat something to which you are allergic?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>will have a severe reaction if you accidentally eat something to which you are allergic?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>will die if you accidentally eat something to which you are allergic?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>can not effectively deal with an allergic reaction should you accidentally eat something to which you are allergic?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5. How many products must you avoid because of your food allergy?

- almost none
- very few
- a few
- some
- many
- very many
- almost all

6. How great is the impact of your food allergy on your social life?

- negligibly small
- very small
- small
- moderate
- great
- very great
- extremely great
### Food Allergy Quality of Life Questionnaire – Adult Form

The following questions concern the influence your food allergy has on your quality of life. Answer every question by marking the appropriate box with an ‘x’. You may choose from one of the following answers.

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not</td>
<td>barely</td>
<td>slightly</td>
<td>moderately</td>
<td>quite</td>
<td>very</td>
<td>extremely</td>
</tr>
</tbody>
</table>

**How troublesome do you find it, because of your food allergy, that you …**

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>must always be alert as to what you are eating?</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>2</td>
<td>are able to eat fewer products?</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>3</td>
<td>are limited as to the products you can buy?</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>4</td>
<td>must read labels?</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>5</td>
<td>have the feeling that you have less control of what you eat when eating out?</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>6</td>
<td>must refuse many things during social activities?</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>7</td>
<td>sometimes frustrate people when they are making an effort to accommodate your food allergy?</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>8</td>
<td>are less able to taste or try various products when eating out?</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>9</td>
<td>must read labels?</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>10</td>
<td>can eat out less?</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>11</td>
<td>must personally check whether you can eat something when eating out?</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>12</td>
<td>hesitate eating a product when you have doubts about it?</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
</tbody>
</table>

**How troublesome is it, because of your food allergy, …**

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>that the ingredients of a product change?</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>14</td>
<td>that labels are incomplete?</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>15</td>
<td>that the lettering on labels is too small?</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>16</td>
<td>that the label states: “May contain (traces of)….”?</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>17</td>
<td>that ingredients are different in other countries (for example during vacation)?</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>18</td>
<td>that people underestimate your problems caused by food allergy?</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>19</td>
<td>that it is unclear to which foods you are allergic?</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>20</td>
<td>that you must explain to those around you that you have a food allergy?</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>21</td>
<td>for your host or hostess should you have an allergic reaction?</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
</tbody>
</table>

**How worried are you because of your food allergy …**

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td>about your health?</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>23</td>
<td>that the allergic reactions to foods will become increasingly severe?</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
</tbody>
</table>

**How frightened are you because of your food allergy …**

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>of an allergic reaction?</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>25</td>
<td>of accidentally eating the wrong food?</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>26</td>
<td>of an allergic reaction when eating out despite the fact that your dietary restrictions have been discussed beforehand?</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
</tbody>
</table>

**Answer the following questions:**

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>27</td>
<td>To what degree do you feel you are being a nuisance because you have a food allergy when eating out?</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>28</td>
<td>How discouraged do you feel during an allergic reaction?</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>29</td>
<td>How apprehensive are you about eating something you have never eaten before?</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
</tbody>
</table>
**Food Allergy Independent Measure – Adult Form**

The following four questions concern the chance that you think you have of an event related to your food allergy. You may choose from the following answers. This is followed by two further questions about your food allergy. Answer every question by marking an ‘x’ in the appropriate box.

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>never (0% chance)</td>
<td>very small chance</td>
<td>small chance</td>
<td>fair chance</td>
<td>great chance</td>
<td>very great chance</td>
<td>always (100% chance)</td>
</tr>
</tbody>
</table>

How great do you think the chance is that you …

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>will accidentally eat something to which you are allergic?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>2</td>
<td>will have a severe reaction if you accidentally eat something to which you are allergic?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>3</td>
<td>will die if you accidentally eat something to which you are allergic?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>4</td>
<td>can not effectively deal with an allergic reaction should you accidentally eat something to which you are allergic?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

5. How many products must you avoid because of your food allergy?

- ☐ almost none
- ☐ very few
- ☐ a few
- ☐ some
- ☐ many
- ☐ very many
- ☐ almost all

6. How great is the impact of your food allergy on your social life?

- ☐ negligibly small
- ☐ very small
- ☐ small
- ☐ moderate
- ☐ great
- ☐ very great
- ☐ extremely great
Instructions to Parents

- The following are scenarios that parents have told us affect children’s quality of life because of food allergy.

- Please indicate how much of an impact each scenario has on your child’s quality of life by placing a tick or an x in one of the boxes numbered 0-6.

Response Options

0 = not at all
1 = a little bit
2 = slightly
3 = moderately
4 = quite a bit
5 = very much
6 = extremely

All information given is completely confidential.

This questionnaire will only be identified by a code number.

There are 3 sections to this questionnaire: A, B, and C.

- If your child is aged 0 to 3 years, please answer Section A
- If your child is aged 4 to 6 years, please answer Section A and Section B
- If your child is aged 7 years and over, please answer Section A, Section B, and Section C.
### Section A: for all age groups

<table>
<thead>
<tr>
<th>Because of food allergy, my child feels……………</th>
<th>Not at all</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Worried about food</td>
<td>□ □ □ □ □</td>
<td>□ □ □ □ □</td>
</tr>
<tr>
<td>2 Different from other children</td>
<td>□ □ □ □ □</td>
<td>□ □ □ □ □</td>
</tr>
<tr>
<td>3 Frustrated by dietary restrictions</td>
<td>□ □ □ □ □</td>
<td>□ □ □ □ □</td>
</tr>
<tr>
<td>4 Afraid to try unfamiliar foods</td>
<td>□ □ □ □ □</td>
<td>□ □ □ □ □</td>
</tr>
<tr>
<td>5 Concerned that I am worried that he/she will have a reaction to food</td>
<td>□ □ □ □ □</td>
<td>□ □ □ □ □</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Because of food allergy, my child………………</th>
<th>Not at all</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 Experiences physical distress</td>
<td>□ □ □ □ □</td>
<td>□ □ □ □ □</td>
</tr>
<tr>
<td>7 Experiences emotional distress</td>
<td>□ □ □ □ □</td>
<td>□ □ □ □ □</td>
</tr>
<tr>
<td>8 Has a lack of variety in his/her diet</td>
<td>□ □ □ □ □</td>
<td>□ □ □ □ □</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Because of food allergy, my child has been negatively affected by……………</th>
<th>Not at all</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 Receiving more attention more attention than other children of his/her age</td>
<td>□ □ □ □ □</td>
<td>□ □ □ □ □</td>
</tr>
<tr>
<td>10 Having to grow up more quickly than other children of his/her age</td>
<td>□ □ □ □ □</td>
<td>□ □ □ □ □</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Because of food allergy, my child’s social environment is restricted because of limitations on………</th>
<th>Not at all</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 Restaurants we can safely go to as a family</td>
<td>□ □ □ □ □</td>
<td>□ □ □ □ □</td>
</tr>
<tr>
<td>13 Holiday destinations we can safely go to as a family</td>
<td>□ □ □ □ □</td>
<td>□ □ □ □ □</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Because of food allergy, my child’s ability to take part has been limited………</th>
<th>Not at all</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 In social activities in other people’s houses (sleepovers, parties, playtime)</td>
<td>□ □ □ □ □</td>
<td>□ □ □ □ □</td>
</tr>
</tbody>
</table>

### Section B: for children aged 4 to 12 years

<table>
<thead>
<tr>
<th>Because of food allergy, my child’s ability to take part has been limited………</th>
<th>Not at all</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 In preschool/school events involving food (class parties/treats/lunchtime)</td>
<td>□ □ □ □ □</td>
<td>□ □ □ □ □</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Because of food allergy, my child feels……………</th>
<th>Not at all</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td>16 Concerned when going to unfamiliar places</td>
<td>□ □ □ □ □</td>
<td>□ □ □ □ □</td>
</tr>
<tr>
<td>17 Concerned that he/she must always be cautious about food</td>
<td>□ □ □ □ □</td>
<td>□ □ □ □ □</td>
</tr>
<tr>
<td>18 ‘Left out’ in activities involving food</td>
<td>□ □ □ □ □</td>
<td>□ □ □ □ □</td>
</tr>
<tr>
<td>19 Upset that family social outings have been restricted by the need to plan ahead.</td>
<td>□ □ □ □ □</td>
<td>□ □ □ □ □</td>
</tr>
<tr>
<td>20 Concerned about accidentally eating an ingredient to which he/she is allergic</td>
<td>□ □ □ □ □</td>
<td>□ □ □ □ □</td>
</tr>
<tr>
<td>21 Concerned when eating with unfamiliar adults/children</td>
<td>□ □ □ □ □</td>
<td>□ □ □ □ □</td>
</tr>
<tr>
<td>22 Frustrated by social restrictions</td>
<td>□ □ □ □ □</td>
<td>□ □ □ □ □</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Because of food allergy, my child………………</th>
<th>Not at all</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td>23 Is more worried in general than other children of his/her age</td>
<td>□ □ □ □ □</td>
<td>□ □ □ □ □</td>
</tr>
<tr>
<td>24 Is more cautious in general than other children of his/her age</td>
<td>□ □ □ □ □</td>
<td>□ □ □ □ □</td>
</tr>
<tr>
<td>25 Is not as confident as other children of his/her age in social situations</td>
<td>□ □ □ □ □</td>
<td>□ □ □ □ □</td>
</tr>
<tr>
<td>26 Wishes his/her food allergy would go away</td>
<td>□ □ □ □ □</td>
<td>□ □ □ □ □</td>
</tr>
</tbody>
</table>

### Section C: for children aged 7 to 12 years

<table>
<thead>
<tr>
<th>Because of food allergy, my child feels……………</th>
<th>Not at all</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td>27 Concerned about his/her future(opportunities, relationships)</td>
<td>□ □ □ □ □</td>
<td>□ □ □ □ □</td>
</tr>
<tr>
<td>28 Many people do not understand the serious nature of food allergy</td>
<td>□ □ □ □ □</td>
<td>□ □ □ □ □</td>
</tr>
<tr>
<td>29 Concerned by poor labelling on food products</td>
<td>□ □ □ □ □</td>
<td>□ □ □ □ □</td>
</tr>
<tr>
<td>30 Food allergy limits his/her life in general</td>
<td>□ □ □ □ □</td>
<td>□ □ □ □ □</td>
</tr>
</tbody>
</table>
Food Allergy Independent Measure — Parent Form for Children aged 0-12 years

You and your child’s worries about food safety

Please answer the following questions with reference to the 6-point scale on the right

<table>
<thead>
<tr>
<th>Question</th>
<th>6-point Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 = extremely unlikely</td>
<td>1 = very unlikely</td>
</tr>
<tr>
<td>2 = somewhat unlikely</td>
<td>3 = likely</td>
</tr>
<tr>
<td>4 = quite likely</td>
<td>5 = very likely</td>
</tr>
<tr>
<td>6 = extremely likely</td>
<td></td>
</tr>
</tbody>
</table>

**Question 1.** What chance do you think your child has of ….? 

<table>
<thead>
<tr>
<th>Question</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>accidentally ingesting the food to which they are allergic?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>having a severe reaction if food is accidentally ingested?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dying from his/her food allergy following ingestion in the future?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>effectively treating him/herself, or receiving effective treatment from others (including Epipen administration), if he/she accidentally ingests a food to which he/she is allergic?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Question 2.** What chance does your child think he/she has of ….?  

<table>
<thead>
<tr>
<th>Question</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>accidentally ingesting the food to which they are allergic?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>having a severe reaction if food is accidentally ingested?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dying from his/her food allergy following ingestion in the future?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>effectively treating him/herself, or receiving effective treatment from others (including Epipen administration), if he/she accidentally ingests a food to which he/she is allergic?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
Food Allergy Quality of Life Questionnaire - Parent Form for Adolescents Aged 13-17 years

Please answer these questions with reference to the scale below:

0 = not at all  
1 = barely  
2 = slightly  
3 = moderately  
4 = quite a bit  
5 = very much  
6 = extremely

<table>
<thead>
<tr>
<th>Question</th>
<th>response choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. My teenager always eats the same foods because of food allergy</td>
<td></td>
</tr>
<tr>
<td>2. My teenager has a restricted diet because of food allergy</td>
<td></td>
</tr>
<tr>
<td>3. My teenager cannot experiment with different foods on holiday because of food allergy</td>
<td></td>
</tr>
<tr>
<td>4. My teenager misses out because of food allergy</td>
<td></td>
</tr>
<tr>
<td>5. My teenager is more cautious generally because of food allergy</td>
<td></td>
</tr>
<tr>
<td>6. My teenager sticks to foods he/she knows</td>
<td></td>
</tr>
<tr>
<td>7. My teenager has to be more sensitive than his/her peers because of food allergy</td>
<td></td>
</tr>
<tr>
<td>8. My teenager takes more of an interest in food because of food allergy</td>
<td></td>
</tr>
<tr>
<td>9. My teenager reads the label on everything he/she eats</td>
<td></td>
</tr>
<tr>
<td>10. My teenager is frustrated about food labelling</td>
<td></td>
</tr>
<tr>
<td>11. My teenager is more wary of situations because of food allergy</td>
<td></td>
</tr>
<tr>
<td>12. My teenager feels different because he/she cannot eat what his/her friends can eat</td>
<td></td>
</tr>
<tr>
<td>13. My teenager feels anxious in restaurants</td>
<td></td>
</tr>
<tr>
<td>14. My teenager finds it difficult to ask about food ingredients in restaurants</td>
<td></td>
</tr>
<tr>
<td>15. My teenager avoids telling people about his/her food allergy until he/she knows them well</td>
<td></td>
</tr>
<tr>
<td>16. My teenager gets irritated by his/her food allergy</td>
<td></td>
</tr>
<tr>
<td>17. My teenager worries that he/she always has to carry a bag because of his/her medication</td>
<td></td>
</tr>
</tbody>
</table>
Food Allergy Independent Measure - Parent Form for Adolescents Aged 13-17 years

Please answer these questions with reference to the 7-point scale below.

0 = extremely unlikely
1 = very unlikely
2 = somewhat unlikely
3 = likely
4 = quite likely
5 = very likely
6 = extremely likely

<table>
<thead>
<tr>
<th>Question</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>18. School trips away are not easy for my teenager</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>19. My teenager worries that he/she can only eat in a limited range of</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>20. My teenager has been really scared by having a reaction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21. My teenager feels nervous around the food they are allergic to</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22. My teenager gets frightened about food allergy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23. I feel my teenager has had to grow up more quickly because of food</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24. My teenager has to be more responsible than other teenagers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25. My teenager has been teased because of food allergy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26. My teenager gets frustrated because of food allergy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>27. My teenager feels different to other teenagers because of food</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. What chance do you think your teenager has of accidentally ingesting the food to which they are allergic?

2. What chance do you think your teenager has of having a severe reaction if food is accidentally ingested?

3. What chance do you think your teenager has of dying from his/her food allergy following ingestion in the future?

4. What chance do you think your teenager has of effectively treating him/herself or receiving effective treatment from others (including Epipen administration) if he/she accidentally ingests a food to which he/she is allergic?