A double-blind, placebo-controlled, randomized phase III trial to assess the safety and efficacy of Viaskin Peanut in peanut-allergic young children 1-3 years of age (EPITOPE study)

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To assess the safety and efficacy of DBV712 in initiating desensitisation of peanut in children aged 1 to 3 years with peanut allergy, after 12 months of treatment with Epicutaneous Immunotherapy EPIT).

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Allergic conditions
Study type	Interventional

Summary

ID

NL-OMON49306

Source
ToetsingOnline

Brief title
EPITOPE

Condition

- Allergic conditions

Synonym
Peanut-allergy

Research involving
Human

Sponsors and support

Primary sponsor: DBV Technologies S.A.
Source(s) of monetary or material Support: DBV

Intervention

Keyword: peanut-allergic, Phase III, Viaskin Peanut

Outcome measures

Primary outcome

The primary efficacy endpoint in this study is the difference between the percentage of treatment responders in the selected active Viaskin Peanut group (250 µg) compared to the placebo group after 12 months of EPIT treatment.
The primary efficacy analysis will be performed on the mITT population using missing=failure imputation method (i.e. subjects with missing DBPCFC peanut eliciting dose value at Month 12 will be considered as non-responders).
The primary measure of treatment effect will be the difference in response rates between active and placebo treatment groups. The primary analysis will apply a Wald test at a 2-sided 5% significance level to evaluate a null hypothesis of no difference, and a 2-sided 95% Newcombe confidence interval (CI) for the difference in response rates will be calculated. The pre-specified thresold for the primary analysis will be defined by a >=15% lower confidence bound, and this condition will determine whether the primary objective has been successfully met.
A supportive analysis will be performed in subjects randomized in part B, using the same statistical method as for the primary analysis.

Secondary outcome

The peanut protein Cumulative Reactive Dose (CRD) at Month 12 and the peanut protein ED at Month 12 will be summarized descriptively by treatment group for the mITT population using Baseline- Observation-Carried-Forward (BOCF) imputation, as well as for the PP population. In addition, the peanut protein CRD and the peanut protein ED in each treatment group at Month 12 will be compared.

In order to handle multiple key efficacy secondary endpoints, the overall type-I error will be controlled by the use of a hierarchical inferential approach.

Study description

Background summary

See section: 1.1 "Background in the protocol"

Study objective

To assess the safety and efficacy of DBV712 in initiating desensitisation of peanut in children aged 1 to 3 years with peanut allergy, after 12 months of treatment with Epicutaneous Immunotherapy EPIT).

Study design

In previous clinical studies in peanut allergic children 4 to 11 years old, Viaskin Peanut 250 µg has been demonstrated as a safe and effective treatment for inducing desensitization to peanut.
However, Viaskin Peanut has never been assessed in younger children from 1 to 3 years old. The present study is designed to assess in this population the safety of 2 doses of Viaskin® Peanut in the first part of the study (Part A) and then to demonstrate the efficacy and safety of the selected dose in the second part (Part B).
Part A has already been completed abroad. Only Part B of the study will run in The Netherlands.

This is a 12-month, phase III, double-blind, placebo-controlled, randomized

trial to assess the safety and efficacy of Viaskin Peanut in peanut-allergic children 1 to 3 years of age.
The trial will be conducted in between 20-40 sites with Investigators and staffs trained and experienced in the diagnosis and the management of peanut allergy and anaphylaxis, and capable to perform Double-Blind Placebo-Controlled Food Challenge (DBPCFC) in toddlers and young children.
Peanut allergic children meeting the following key inclusion criteria will be selected: physician-diagnosed peanut allergy or high suspicion of peanut allergy as assessed by the physician (child presenting signs, symptoms and a medical and/or a family history putting him/her at high risk of having a peanut allergy and/or history of presence of peanut-specific immunoglobulin E [IgE] and/or positive Skin Prick Test [SPT]); subject currently following a strict peanut-free diet; presence of peanut-specific IgE > 0.7 KU/L; positive SPT to peanut extract with the largest wheal diameter >= 6 mm; positive DBPCFC to peanut with an Eliciting Dose (ED) <= 300 mg of peanut protein.

Study part B:
The second part of the study will aim at assessing the safety and efficacy of the selected dose after a 12-month treatment versus placebo. This part will be initiated after the choice of the highest safe dose upon the DSMB meeting. As from protocol v6.0, the selected highest safe dose for part B upon DSMB recommendation is 250 µg. Additional subjects will be recruited in the active selected dose arm and in the placebo arm to reach the targeted total number of subjects.
In accordance with the calculated sample size for this study, a total of 350 additional subjects will be randomized in the second part or Part B of the study. These subjects will be randomized with a 2:1 ratio in favor of the active arm, i.e. 233 subjects in the active arm and 117 subjects in the placebo arm.
An interim analysis to evidence the treatment activity on the immune system of children 1 to 3 years old is planned when the first 50 subjects have reached 6 months of active treatment with Viaskin Peanut 250 µg. This analysis will be specifically conducted on the peanut- specific IgG4 measurements. The relative change from baseline of the peanut-specific IgG4

levels in the Viaskin Peanut 250 µg treatment group at Month 6 will be numerically compared to the relative change from baseline of the peanut-specific IgG4 levels in the placebo group at Month 6. The median relative change in IgG4 of the selected active Viaskin Peanut treatment group is expected to be greater than the median relative change in IgG4 of the placebo treatment group.
In the situation where the median relative change from baseline of the peanut-specific IgG4 in the Viaskin Peanut 250 µg group is equal to or lower than the median relative change from baseline of the peanut-specific IgG4 in the placebo group, the premature stop of the study will be considered for lack of evidence of therapeutic benefit. This unblinded data review will be

conducted by the DSMB who will be responsible of issuing the recommendation to the Sponsor.
The overall maximum study duration for each subject is approximately 60 weeks (6-week screening period, 12-month (or 52 weeks) treatment period and a 2-week follow-up period). During the screening period, subjects will perform a first screening visit and an entry DBPCFC to peanut to confirm their allergy and their entry peanut ED. The starting dose of the challenge will be set to 1 mg peanut protein up to the highest dose of 300 mg peanut protein. Subjects who react at or below the dose of 300 mg peanut protein will be eligible and will be randomized in the study.
A post-treatment DBPCFC will be performed at Month 12, starting at the dose of 1 mg peanut protein and proceeding up to the highest dose of 2,000 mg peanut protein. The primary efficacy endpoint of this phase III study is the difference between the percentage of treatment responders in the selected DBV712 group (250 µg) compared to the placebo group at Month 12, determined on the peanut protein ED during the food challenge.
Other efficacy assessments at months 3, 6 and 12, include immunological changes in peanut- specific IgE and IgG4 and SPTs.
Key assessments of global safety will be performed at each study visit including skin observation of the patch areas of application, vital signs, physical examinations, clinical laboratory assessments. Atopic dermatitis will also be assessed at baseline and at months 3, 6 and 12 using the SCORing Atopic Dermatitis (SCORAD).
Between the visits, the severity of 3 pre-specified local skin reactions will be assessed on a daily basis by the parents/guardians in a diary, for the first 6 months of treatment for part A subjects, and during the whole treatment duration for part B subjects. Any other Adverse Events (AEs) (including any local skin reactions other than the 3 pre-specified ones at any time of the study, and any pre-specified local skin reactions occurring after the first 6 months of treatment for part A subjects), and any concomitant medications will be also reported in the diary by the parents/guardians and this will be reviewed by the site medical staff at each subject visit.
At screening and at Month 12, the subjects* parents/guardians will complete quality of life questionnaires (FAQLQ/FAIM Food Allergy Quality of Life Questionnaire / Food Allergy Independent Measure-parent form / EQ-5D-5L [part B only]) to assess the impact of 12-month treatment with Viaskin Peanut on their quality of life.
In addition, the adhesion of the Viaskin patch to the skin and the occlusion of the condensation chamber will be assessed daily by the subjects* parents/guardians in a diary during the whole duration of treatment. This assessment will be conducted in part B only. The trained site staff will also assess the patch adhesion of all subjects at each subject visit.
After completion of this 12-month blinded study, eligible subjects, including the subjects in the placebo group and in the non-selected active treatment group (100 µg), will be offered the opportunity to participate in an extension study to receive 24 additional months of treatment with Viaskin Peanut 250 µg. Subjects satisfying the inclusion and exclusion criteria of the extension study

will be invited to participate in the extension study

Intervention

Viaskin Peanut 250 µg for 12 months. This is done by comparing it with a placebo for the entire 12 months to demonstrate that the effect is really due to the medication and is independent of interpretation from participants or study doctors. To make this comparison between Viaskin Peanut 250 µg and Viaskin placebo.

There is no approved treatment other than strict avoidance for peanut food allergy. If the subject is not enrolled, there is no treatment proposed. Therefore, he/she will receive the standard-of-care treatment, that is to say, *strict avoidance*.

Study burden and risks

Possible risks and discomfort
As with all research studies, the study patches and study procedures may involve unknown risks. Any medication can have temporary and permanent side effects and can cause unforeseen adverse reactions. The study patches may fail to control/reduce your child*s peanut allergy. The procedures for peanut allergy in this study - either routine in medical practice or experimental for study purposes - do not have special risks. In some cases, examinations, Skin Prick Tests, blood samples or the Viaskin patches administration, especially at the start, may cause some discomfort.

Known Side effects of Viaskin Peanut
The study medication may cause some side effects. These could include:
• Skin reactions (for example application site pruritus (itching), erythema (redness), macule (small circumscribed changes in the color of skin that are neither raised (elevated) nor depressed), papule (small solid rounded bumps rising from the skin), irritation and application site eczema (redness,swelling, crusting, and thickening of the skin) are the most frequently reported adverse reactions, occurring in more than 10% of patients; other skin reaction at application site: swelling, urticaria and darkened coloring of the skin are commonly reported adverse reaction, occurring in less than 10% of patients (>=1% and <10%). The less frequently reported skin application site adverse reaction (Uncommon: >=0.1% and <1%) are application site excoriation, application site bleeding, application site infection and application site pain. Most of local adverse reactions associated with patch application were mild to moderate in severity.
• Severe skin reactions (pruritus, erythema, swelling) at the patch application site or possibly extending beyond the patch application area may also occur.
• Reactions distant from the site of patch application such as symptoms that may suggest a local transitory allergic reaction due to presence of peanut

allergen trace amount on fingers following contact with the patch and further touching of the eyes have been reported. These reactions include conjunctivitis allergic, eye swelling and redness of eyes . These distant symptoms occur in less than 10% ofpatients (>=1% and <10%);
• Anaphylaxis, which can potentially be life-threatening, include distant symptoms, as well such as hives, itchy throat, lip swelling, rash,difficult breathing, coughing, sneezing, vomiting, abdominal pain and, in the most severe cases, may lead to a general feeling of uneasiness. Anaphylaxis has been reported in less than 10% of patients (>=1% and <10%) during testing of study treatment in children with more than one allergy. In completed studies, systemic allergic reactions reported as anaphylacitic reactions were reported in slightly numerically more patients treated with Viaskin® Peanut than with placebo (5.1% vs 2.8%). All anaphylactic reaction reported as related to Viaskin® Peanut were mild to moderate, characterized mainly by skin reactions as well as subjective respiratory symptoms with no cardiovascular nor respiratory compromise. In Viaskin Peanut treated patients, these anaphylactic reactions tended to occur early during the treatment (within 2 months from treatment initiation), led to brief treatment interruption and did not recur while continuing treatment. The majority resolved either without epinephrine or following one injectable epinephrine administered at home.
If your child experienced any other symptoms you can talk with your study doctor. Please ask the study doctor if you have any questions about the known and possible side effects of Viaskin Peanut. See Appendix D on the ICF for more information

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

• Male or female from 1-3 years of age at Visit 1;
• Physician-diagnosed peanut allergy or high suspicion of peanut allergy as assessed by the physician: child presenting signs, symptoms and a medical and/or a family history putting him/her at high risk of having a peanut allergy and/or history of presence of peanut-specific IgE and/or positive SPT;
• Subject currently following a strict peanut-free diet;
• Peanut-specific IgE level (ImmunoCAP system) > 0.7 kU/L;
• Positive peanut SPT with a largest wheal diameter >= 6 mm;
• Positive DBPCFC to peanut, with symptoms meeting the challenge stopping criteria at an ED <= 300 mg peanut protein.

Exclusion criteria

• Diagnosed asthma not controlled or requiring Step 3 controller treatment or higher (as per Global Initiative for Asthma [GINA] latest guidelines);
• Presence of more than 3 episodes of wheezing in the past year (each lasting more than 10 consecutive days, apart from colds) or presence of respiratory symptoms between these episodes, and/or other respiratory symptoms suggesting either undiagnosed asthma or asthma not controlled by asthma treatment (as per GINA latest guidelines).
• Prior intubation/mechanical ventilation for asthma within one year prior to Visit 1.
• Peanut allergic subjects presenting a medical history of severe anaphylaxis to peanut will be excluded from this study. Severe anaphylaxis is defined by the Grade 3 of the Anaphylaxis Staging System (see Appendix 4), including either:
- Severe hypoxia, persistent hypotension or more than 20% drop in systolic or diastolic blood pressure, or neurological compromise, or
- Cyanosis or SpO2 <= 92% at any stage, confusion, cardiovascular collapse, loss of consciousness, bradychardia, cardiac arrest.
- Prior immunotherapy to any food (e.g. oral immunotherapy [except for prior oral immunotherapy of less than 1-month duration which ended at least 3 months

before Visit 1], sublingual immunotherapy, specific oral tolerance induction) or other immunotherapy (aeroallergens, venom*);
- Generalized severe dermatologic disease (e.g. severe atopic dermatitis, uncontrolled generalized eczema, ichthyosis vulgaris) extending widely on the skin and especially on the back with no intact zones available to apply the Viaskin patches

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	05-11-2019
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Viaskin Peanut (DBV712)
Generic name:	na

Ethics review

Approved WMO

Date:	09-04-2019

Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-10-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-11-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-01-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-02-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-06-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-07-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-09-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	17-01-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2016-003679-23-NL
CCMO	NL68481.078.19