EMA/772201/2021
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal Assessment report

Abylqis

International non-proprietary name: arachis hypogaea extract

Procedure No. EMEA/H/C/004810/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
AIT	Allergen immunotherapy
AR	Assessment report
Ara h	Arachis hypogaea (peanut)
BAL	Bronchoalveolar lavage
BAT	Basophil activation test
CF	correction factor
CFU	colony forming units
CoA	certificate of analysis
CPP	critical process parameters
CQA	critical quality attribute
CRD	Cumulative reactive dose
CSR	Clinical study report
DBPC	Double-blind placebo-controlled
DBPCFC	Double-blind placebo-controlled food challenge
DC	Dendritic cell
DP	Drug Product
DS	Drug Substance
DTR	Diphtheria toxin receptor
eCTD	Electronic common technical document
eCRF	Electronic case report form
ED	Eliciting dose
ELISA	enzyme-linked immunosorbent assay
EPIT	Epicutaneous immunotherapy
FDA	Food and Drug Administration
FWER	Family wise error rate
GC	gas chromatography
GCP	Good clinical practice
GLP	Good laboratory practice
HPLC	high-performance liquid chromatography
ICH	International Council for Harmonisation

IgE	Immunoglobulin-E
IgG4	Immunoglobulin-G4
IHRP	in-house reference preparation
IP	Investigational product
IPC	in-process control
IR	infrared
ISE	Integrated summary of efficacy
ISS	Integrated summary of safety
LC	Langerhans cell
ITT	Intent to treat
LC	liquid chromatography
LOD	limit of detection
LOQ	limit of quantification
LoQ	list of questions
MedDRA	Medical Dictionary for Regulatory Activities
NMT	not more than
NOAEL	No observed adverse effect level
OIT	Oral immunotherapy
OOS	out-of-specification
OVA	Ovalbumin
PD	Pharmacodynamic
PE	Polyethylene
PET	Polyethylene terephthalate
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic
PP	Peanut protein
PPE	Peanut protein extract
PPQ	process performance qualification
PT	Preferred term
QRA	Quantitative risk assessment
RP	reverse-phase
RSD	relative standard deviation
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous

SCE	Summary of Clinical Efficacy
SCIT	Subcutaneous allergen immunotherapy
SCS	Summary of Clinical Safety
SE	size exclusion
SM	source material
SMQ	Standardized MedDRA query
SOC	System organ class
SPT	Skin prick test
SY	Subject-year
TAMC	total aerobic microbial count
TEAE	Treatment-emergent adverse event
TYMC	total combined yeasts/ moulds count
US	United States

1. CHMP Recommendations

Based on the review of the data and the applicant's response to the CHMP LoQ on quality, safety, and efficacy, the application for Abylqis, for epicutaneous allergen immunotherapy (EPIT) of peanut allergy in children 4 to 11 years old with a diagnosed IgE-mediated peanut allergy, is not approvable since one major objection still remain, which preclude a recommendation for marketing authorisation at the present time.

The major objection precluding a recommendation of marketing authorisation, pertain to the following principal deficiencies:

Clinical:

- Considering the low desensitization rate (GM ED below study entry criterion, which was defined as ≤300 mg peanut protein) in combination with twice as much higher rates of anaphylactic reactions (due to the patch per se, as well as due to voluntary/accidental peanut consumption), respectively the increased need for epinephrine intake in the DBV712 treated group compared to Placebo, the B/R ratio is unfavourable.

Questions to be posed to additional experts

For the time being, there is no need for additional expert involvement.

Inspection issues

GMP inspection(s)

A GMP inspection is not deemed necessary.

GCP inspection(s)

All of the studies included in the submission were conducted in accordance with the principles of the Declaration of Helsinki and GCP. The appropriate ethics committees and institutional review boards reviewed and approved all studies. Of note, the pivotal study V712-301 was conducted by 31 Primary Investigators/ in 31 centers localized in 5 countries (Australia, Canada, Germany, Ireland and United States of America USA). GCP inspections had been carried out for V712-301 (PEPITES) in five centers/ 4 countries (Dublin, IE by the HPRA; Berlin, Germany; Aurora, USA; Boston, USA; Québec, Canada by the FDA) and for study V712-303 (PEPITES follow-up) in 1 center (Dublin, Ireland by the HPRA).

No GCP inspection is regarded necessary with regard to this procedure.

New active substance status

No claim for new active substance has been submitted for the peanut extract by the applicant. Therefore, Abylqis is considered a known active substance.

Additional data exclusivity / Marketing protection

N/A

Derogation(s) from market exclusivity

N/A

2. Executive summary

2.1. Problem statement

2.1.1. Disease or condition

IgE-mediated Peanut allergy affects approximately 1-2% of the paediatric population in Europe. It is generally a lifelong condition, with up to 80% of allergic children likely to remain allergic for their entire life. Peanut allergy is a common cause of food allergic reactions. Reactions are rarely fatal but contribute to a considerable burden to the affected patients and families. The most common current management of peanut allergy consists of strict allergen avoidance diet and administration of medication in the event of an allergic reaction.

2.1.2. Epidemiology and risk factors, screening tools/prevention

Peanut allergy is one of the most common cause of severe and fatal allergic reactions related to food. In the European Anaphylaxis Registry, collected from 10 European countries between July 2007 and March 2018, anaphylaxis due to peanut was recorded in 459 patients younger than 18 years (median age 5 years). Respiratory (92%, 423) and skin (91%, 418) symptoms were predominant, with the majority of cases (66%, 304) labelled as severe anaphylaxis (grade III-IV according to Ring-Messner classification). If 24% (110) of the cases were solely lay treated, professional treatment, mainly carried out by emergency physicians was necessary in 39% (119/306 cases) of the cases. Intramuscular adrenaline was administered as first line treatment in 39% of cases, 62% of 276 cases with known hospitalisation status required admission, including 6% to Intensive Care Unit. There were 3 cases of fatal anaphylaxis (Maris et al, 2019).

Since peanut is ubiquitous in many foods and meals, and undeclared contamination of foods with peanut is common, strict avoidance is difficult to achieve and accidental exposure to peanut remains a common issue.

Peanut allergy imposes an adverse psychosocial impact on patients and caregivers, leading to frustration, stress, and isolation. Most respondents in an online questionnaire survey conducted in 8 European countries (United Kingdom, France, Germany, Ireland, Spain, Italy, Denmark, and Netherlands, Allergy to Peanuts ImPacting Emotions And Life APPEAL-1) reported lifestyle restrictions regarding food (84-93%) and additional domains including parties and socializing, holiday activities and destinations, and taking public transport (53-89%).

Unlike some food allergies, peanut sensitivity commonly lasts throughout adult life and does not fade (Filder, 2019). It is generally a lifelong condition, with up to 80% of allergic children likely to remain allergic for their entire life (Ho et al, 2008).

2.1.3. Aetiology and pathogenesis

Genetic and environmental factors are involved within the pathogenesis of food allergies. An impaired barrier function of the skin is one area of focus.

IgE-mediated peanut sensitization often begins in infancy and progresses to a symptomatic allergy with increasing age. In most patients, peanut allergy is life-long.

Some studies have reported that approximately 20% of children diagnosed with peanut allergy outgrow their allergy (Ho, 2008; Fleischer, 2003; Skolnick, 2001). Natural tolerance development in peanut allergy is reported by Peters et al, where peanut allergy resolved in 22% (95% CI, 14% to 31%) of children by age 4 years (Peters et al, JACI 2015 May;135(5):1257). In patients who become

tolerant to peanut, resolution of peanut allergy is rather discussed to occur by age 6 years and at a much lower frequency after age 10 years (Bégin, 2013). A very recent work depicts that peanut allergy resolved in 15.8% of South African children with a median age of 9 years and 6 months (Gray CL, Levin ME, Du Toit G. S Afr Med J. 2019 Apr 29;109(5):323-327).

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Clinical features of food allergy may present with a heterogeneous pattern of clinical symptoms. The majority of food induced allergic reactions are IgE-mediated (immediate type, type I hypersensitivity). IgE-mediated allergic reactions may affect every organ system (e.g. skin: flares, urticarial, worsening of atopic dermatitis,; gastrointestinal: vomiting, diarrhoea, stomach pain; respiratory tract: dyspnoea, wheezing, stridor, cough or rhino conjunctivitis,; cardiovascular: system hypotension, tachycardia/arrhythmia or cardio-vascular arrest. In addition to objective symptoms, subjective symptoms may be heard to measure, such as dizziness, tingling/burning in mouth and throat, itchiness of skin, eyes or nose, a general discomfort, dysphagia, nausea and others.

Multiple factors can influence the severity of an allergic reaction, including a history of anaphylaxis to peanut, comorbid conditions (e.g. asthma, cardiovascular disease, mastocytosis), concurrent use of certain medications (e.g. nonselective beta blockers and nonsteroidal anti-inflammatory drugs [NSAIDs]), and exercise. In addition, the severity of an allergic reaction after food allergen exposure is not predictable based on any prior reactions or any specific diagnostic marker (Brough, 2015).

Peanut allergy is the leading cause of severe and life-threatening anaphylactic reactions and death from food allergic reactions (Sicherer SH et al., 2003).

Diagnosing food allergy (peanut allergy) is challenging. Although molecular diagnostics have shown to help, the gold standard remains the oral food challenge.

Unlike other childhood allergen reactivity (like milk or egg), peanut allergy does not resolve with increasing age.

2.1.5. Management

The most common current management of peanut allergy consists of strict allergen avoidance and administration of medication in the event of an allergic reaction. Prompt treatment with intramuscular epinephrine is the first-line treatment for severe systemic allergic reactions (Muraro, 2007). However, not all patients may have ready access to an epinephrine auto-injector. In addition, inadequate use may delay treatment and result in adverse outcomes including hospitalization and in rare cases, death (Grabenhenrich, 2018). Since peanut is ubiquitous in many foods, and undeclared contamination of foods with peanut is common, strict avoidance is difficult to achieve and accidental exposure to peanut remains a common issue (Hefle et al, 2007).

The current management of peanut allergy is unsatisfactory and highlights the need for safe and effective treatments that can induce clinical desensitisation (i.e. increased tolerance to peanut allergen), thus minimising the risk of reaction due to accidental ingestion (Greenhawt et al, 2018).

Allergen immunotherapy (AIT) is recognised as a biological response modifier in IgE-mediated allergic disease (Malling and Weeke, 1993), since it modulates the immune response to the offending allergen. In January 2020, the first AIT for peanut allergy was approved by the FDA via medicinal product *Palforzia*. On 17 December 2020, the EU commission issued a marketing authorisation in the European Union for the same product. The medicinal product *Palforzia* is intended for desensitising children and adolescents to peanut allergy by oral allergen administration, thus it is called oral immunotherapy (OIT).

2.2. About the product

General remark: The product was named “Viaskin® Peanut”, respectively “DBV712 250 µg or DBV712” during product development. At start of this MAA procedure the name “Abylqis” was introduced. Throughout the assessment reports “Viaskin® Peanut”, “DBV712 250 µg″ and “Abylqis” are used interchangeably.

Mode of action: Peanut allergy may be classified as an IgE-mediated type I hypersensitivity reaction upon allergen (peanut) contact. In such reactions, peanut-specific IgE antibodies are thought to bind to high-affinity receptors on mast cells and basophils. Allergen-specific immunotherapy (SIT) is a variously-studied approach, where increasing amounts of an allergen are administered to patients with IgE-mediated allergy to raise the threshold and decrease the severity of allergic responses to the allergenic agents. An oral route of administration of (especially food) allergens like peanut for allergen immunotherapy is called Oral specific ImmunoTherapy (OIT). The current product, Abylqis or DBV712, utilizes an epicutaneous administration route, and thus it is called: epicutaneous immunotherapy (EPIT). The application concerns the product DBV712, consistent of a cutaneous patch containing microgram quantities (250 µg) of a formulated peanut allergen extract. The patch is described as an epicutaneous delivery system (Viaskin), which is applied once per day on intact skin.

One central structure of this “epicutaneous delivery system” is a foam crown, which forms a seal and thus creates a kind of occlusive condensation chamber. Water by perspiration and generated by the natural transepidermal (skin) water loss are suggested to lead to solubilization of peanut proteins that are deposited on the backing of an occlusive film. A fraction of these are suggested in turn to penetrate the epidermis where they are taken up by target immune cells. These migrate to the draining lymph nodes where they can modulate immune response.

Claimed indication:

The indication sought for DBV712, Abylqis is: Abylqis is indicated as epicutaneous immunotherapy (EPIT) for the treatment of children aged 4 to 11 years at the time of treatment initiation diagnosed with peanut allergy that has been confirmed with a positive skin prick test or in vitro testing for peanut-specific IgE antibodies. Thus, the following wording of the therapeutic indication in section 4.1, SmPC is given at beginning of MAA:

“TRADENAME is indicated as immunotherapy for the treatment of children diagnosed with peanut allergy that has been confirmed with a positive skin prick test or in vitro testing for peanut-specific IgE antibodies.

TRADENAME is indicated in children aged 4 to 11 years at the time of treatment initiation.

TRADENAME is not indicated for the immediate relief of allergy symptoms.”

The wording of the indication is discussed at the LoQ120. In response to the applicants D120 answers, the CHMP proposed the following:

“TRADENAME is indicated for the treatment of children diagnosed with peanut allergy.

TRADENAME is indicated in children aged 4 to 11 years at the time of treatment initiation. Tradename should be used in conjunction with a peanut-avoidant diet.”

Noteworthy, the overall benefit:risk is still under consideration.

The precise mechanism of action underlying peanut immunotherapy induced by DBV712 is not fully understood. However, generally, allergen immunotherapy (AIT) lead changes in key immunologic markers, such as IgE, IgG4, and their ratio, which suggests immunomodulation of the underlying allergic condition.

2.3. The development programme/compliance with CHMP guidance/scientific advice

Nonclinical development

DBV Technologies has conducted an extensive non-clinical testing program in support of the clinical development of DBV712 as a combination product made of a device component, the patch delivery system, and the biological drug substance, the peanut allergen extract.

Several species were used for the non-clinical testing of DBV712 including rabbits, rats, minipigs, guinea pigs and mice. Animal models of peanut allergy were established in guinea pigs, mice and minipigs and used for various pharmacology assessments and pivotal repeated-dose toxicity evaluation. Local tolerance of DBV712 was extensively evaluated as part of repeated-dose toxicity study in peanut-sensitized guinea pigs and in separate local tolerance studies in naïve rabbits. *Ex vivo* studies were performed with human skin samples in order to investigate skin permeation of the PP. Mutagenicity was evaluated by in vitro genotoxicity standard test series. A pilot reproductive toxicity study was performed in non-pregnant female rats in order to evaluate the feasibility of this animal model for possible reproductive toxicity studies. Subsequent reproductive studies have not been performed after discussion with PEI and EMA (see below). Finally, phototoxicity studies in guinea pigs as well as ISO 10993-compliant biocompatibility studies in rabbits and guinea pigs with the different device systems manufactured during the development of DBV712 are part of the non-clinical development.

Several scientific advices have been received during the development of DBV712 from CHMP (23-04 2015), FDA (pre IND meeting 18-02-2010; EOP1 meeting 15-03-2012) and PEI (23-02-2012; 09-09-2014). Discussion of the adequacy of the non-clinical safety program for marketing authorization with EMA and PEI identified two core issues to be considered when filing the DBV712 approval dossier:

- convincing and reliable data for the comparability of the different backing device (see section 2 below)
- a thorough justification for a shorter duration than six months of the pivotal repeated-dose toxicity study
- Compliance with ICH guideline M3 (R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals" need to be confirmed from the applicant´s side

The CHMP concluded after review of the non-clinical data package that from a safety point of view, there is no other concern than a high incidence of local side effects associated with DBV712 treatment, thus special attention should be paid on skin reactions at the application side during Phase III clinical development.

Clinical development

The clinical development programme for Abylqis in support of the proposed indication comprises three Phase 1 studies (V712-101 (PEP01.09); V712-102 (SOLAR); V712-103 (BIOPOT)), four Phase 2 studies (V712-201-E (ARACHILD); V712-202 (VIPES); V712-203 (OLFUS-VIPES); V712-204-E (CoFAR6) and four Phase 3 studies, including the completed pivotal study V712-301 (PEPITES): Pivotal study to assess the safety and efficacy of DBV712 250 µg in peanut-allergic children (4-11 years); conducted in Europe (Germany and Ireland), Australia, the United States, and Canada); its ongoing Open-label extension study V712-303 (PEOPLE): to assess long-term efficacy and safety of DBV712 250 µg [study in progress]; conducted in Europe (Germany and Ireland) and V712-302 (REALISE):

Study to assess the safety and therapeutic benefit of DBV712 250 µg in peanut-allergic children (4-11 years); conducted in Canada, United States only.
Besides the proposed age group for the MA, the phase 3 studies EPITOE and EPOPEX are running in younger children: V712-304 (EPITOPE): Dose-finding (Part A) and pivotal study to assess the safety and efficacy of DBV712 in peanut-allergic toddlers (1-3 years) [study in progress]. V712-305 (EPOPEX): Follow-up study of the EPITOPE study - Open-label Extension Study to Evaluate the Long-term (up to 3 years) Clinical Benefit and Safety of DBV712

Scientific advice on the clinical development programme was given by the FDA and the PEI (February 2012). In addition, advice has been given by the PDCO within discussion on PIPs / paediatric development plans. The advice by PEI 2012 concentrated on the following topics: dose and dosing regimen selection (emphasising the importance of an efficacy plateau); critical discussion on primary and secondary endpoints as proposed for the planed Phase IIb/III study; including a clinically meaningful protection against adverse reactions in everyday life.

Two Pre-MAA-submission Meeting(s) took place in 2018 and 2020, among others, the following points were raised: The applicant was referred to the EMA points to consider on applications with one pivotal study and the requirement for compelling results. The applicant was asked to address the following points in the dossier:

- The clinical relevance of the relatively modest increase in peanut protein tolerated dose;
- Present Eliciting Dose data by showing the net increase by subject;
- Marker or baseline characteristics for responders or non-responders (e.g. age, ED, medical history, sensitization profile, epitope spreading, etc);
- Explain the magnitude of the placebo effect
- Justify that the dose selected is the optimal dose;
- Present any data related to long-term efficacy
- Quality of Life data.

Patients foreseen for a treatment with DBV712 should be clearly diagnosed as peanut allergic based on national respectively international guidelines.

In addition, several discussions had been held with the FDA, on 18 February 2010 (preIND meeting) and 15 March 2012 (EOP1 meeting). The initial US BLA was submitted in October 2018, but was withdrawn in December 2018, following discussions with FDA regarding the need for additional data on manufacturing procedures and quality controls. The US BLA was resubmitted in August 2019, and on 03 August 2020, the FDA issued a Complete Response Letter (CRL). The key issues cited in the CRL are that the clinical data submitted in the BLA do not support a definitive conclusion that efficacy is not adversely affected by adhesion failure and that the patch will need to be reformulated. The applicant does not agree with these positions nor with the view that DBV712 should be assessed as a transdermal (TD) patch, specifically as it relates to the intersection of detachment and efficacy.

Thus, the applicant stated that a post-submission meeting with the FDA is going to be requested to discuss the concerns raised in the CRL. This meeting is expected to take place within approximately 90-120 days from receipt of the CRL. The applicant stated to keep the CHMP apprised of any relevant updates regarding the FDA BLA.

Of the 9 clinical studies referred to in the agreed PIP, compliance with the Agency's Decision P/0342/2018 issued on 9 November 2018“ was confirmed on 5 PIP studies: V712-101 (PEP01.09 /

Study 1), V712-202 (VIPES / Study 2), V712-203 (OLFUS-VIPES / Study 3), V712-301 (PEPITES / Study 4) and V712-303 (PEOPLE / Study 6) (reference: C1-001481-PIP01-13-M03).

Timelines for the deferred studies in the adolescent population (V712-306) / Study 5 and V712-307 / Study 7) have been updated (Ref. EMEA-001481-PIP01-13-M04) as well as completion dates for the deferred studies ongoing in children from 1 to less than 4 years of age (V712-304 or EPITOPE / Study 8 and V712-305 or EPOPEX / Study 9) (Ref. EMEA-001481-PIP01-13-M04). EMA Decision number of Paediatric Investigation Plan: P/389/2020.

Generally, the applicant has complied with the given advice.

2.4. General comments on compliance with GMP, GLP, GCP

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

All relevant non-clinical safety studies were performed in compliance with GLP rules. GLP compliance is not confirmed for pharmacodynamic and pharmacokinetic investigations, which is acceptable as according studies are not explicitly requested for allergen immunotherapy products as laid down in CHMP/EWP/18504/2006.

2.5. Type of application and other comments on the submitted dossier

Legal basis

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

PRIME

N/A

Accelerated assessment

N/A

Conditional marketing authorisation

N/A

Marketing authorisation under exceptional circumstances

N/A

Biosimilarity

N/A

Additional data exclusivity/ marketing protection

N/A

New active substance status

N/A

Orphan designation

N/A

Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0389/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMEA-001481-PIP01-13-M04 was not yet completed as some measures were deferred.

Of the 9 clinical studies referred to in the agreed PIP, compliance with the Agency's Decision P/0342/2018 issued on 9 November 2018“ was confirmed on 5 PIP studies: V712-101 (PEP01.09 / Study 1), V712-202 (VIPES / Study 2), V712-203 (OLFUS-VIPES / Study 3), V712-301 (PEPITES / Study 4) and V712-303 (PEOPLE / Study 6) (Compliant document reference: C1-001481-PIP01-13-M03).

Timelines for the deferred studies in the adolescent population (V712-306) / Study 5 and V712-307 / Study 7) have been updated (Ref. EMEA-001481-PIP01-13-M04).

Completion dates for the deferred studies ongoing in children from 1 to less than 4 years of age have been updated (V712-304 or EPITOPE / Study 8 and V712-305 or EPOPEX / Study 9) (Ref. EMEA-001481-PIP01-13-M04).

3. Scientific overview and discussion

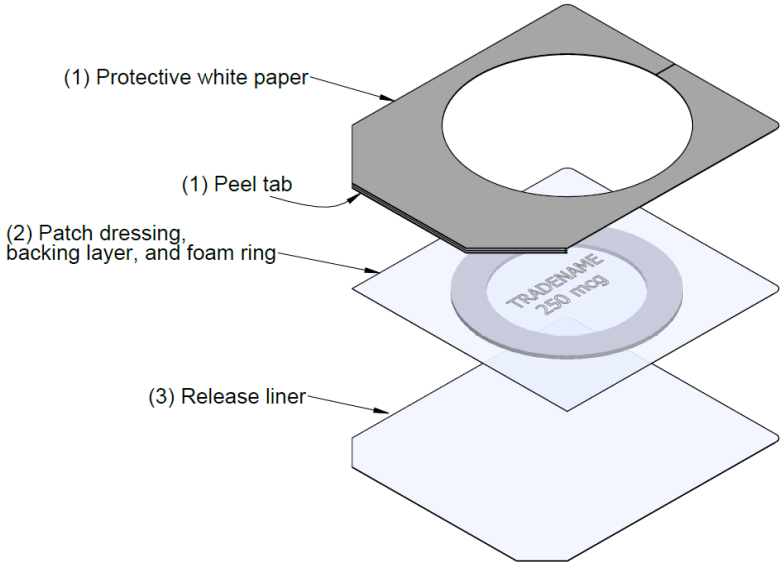
3.1. Quality aspects

3.1.1. Introduction

Abylqis is a cutaneous patch containing 250 µg of peanut protein. It is a rectangular patch consisting of a clear protective liner, a white paper applicator and functional layers (Figure 1). Proceeding from the outer surface towards the surface adhering to the skin, the layers are: (1) a peel-off protective white paper with a peel tab; a dressing; (2) a backing layer of polyester film containing the active substance; and an foam ring surrounding the active substance peanut allergen extract and (3) a removable liner. The patch is printed with ‘Abylqis 250 mcg’.

Before use, the release liner covering the adhesive dressing is removed and discarded. After application to the skin, the protective white paper and the peel tab are peeled-off and discarded.

Figure 1



3.1.2. Active Substance

General Information

The drug substance (DS) is a defatted lyophilized peanut extract of *Arachis hypogaea*, semen, i.e. a mixture of allergenic and non-allergenic proteins, carbohydrates, fats and minerals for which an INN does not exist. The most clinically relevant allergens were specified.

Manufacture, process controls and characterisation

Peanut seeds

The source material (SM) and subsequently the drug substance (DS) are prepared from raw peanut seeds. The seeds are harvested and shelled in the USA, before being transferred to the SM and DS manufacturer Sanofi Chimie (France).

Defatted peanut powder (SM)

The peanut seeds are processed to defatted peanut powder (SM). Validation of the manufacturing process was based on three consecutive SM batches of commercial scale.

Peanut allergen extract (DS)

The DS is an unmodified, lyophilized allergen extract produced via extraction and freeze-drying of defatted peanut powder (SM).

The manufacturing processes of DS has been successfully validated. The main process performance qualification included three consecutive DS batches, produced from three different SM and peanut seed batches. Additional validation studies focused on aspects like in-process material hold time, maximum processing time and shipping. Continued Process Verification is described.

The characterisation of the peanut protein extract that composes the Abylqis DS is performed with state of the art analytical methods for protein chemistry and immunochemistry. It is mainly characterized by its protein content, biological activity and physicochemical properties.

Specification, analytical procedures, reference standards, batch analysis, and container closure

Peanut seeds

Quality of peanut seeds is controlled by the SM and DS manufacturer Sanofi Chimie upon receipt of the material according to specifications.

Batch analysis data for peanut seed batches were submitted. Batch data support comparable quality of peanut seeds over several years of harvesting.

Source Material

Release specifications of the SM (defatted peanut powder) cover all major quality aspects.

The analytical methods are described or reference is made to the description of analytical procedures of the DS. The validation studies performed with these analytical procedures have been successfully concluded.

Apart from the reference standard described above, the quantification of major allergen content requires additional reference standards.

Batch data are presented for SM batches. Although tests and specifications have evolved, the dataset is suitable to confirm constant quality of the SM over six years of production.

Regarding the SM container closure system, information on the used PE bags is provided, including confirmation of compliance with Ph. Eur. 3.1.4.

Drug Substance

DS specifications include tests and assays as indicated in the monograph “Allergen Products” (01/2019:1063) of the Ph. Eur. including assays for total allergenic activity, relevant allergens, protein and allergen profile, protein content as well as water content are performed.

The description of analytical procedures encompasses DS release tests, the DS stability tests (if any), the in-process controls (if any), and the DS incoming tests. For each procedure, the general principle, sampling, equipment, reagents, preparation of standards and samples, procedure, system suitability testing, calculations and reporting of results are presented in sufficient detail. All analytical procedure have been successfully validated in accordance with ICH Q2 (R1) recommendations and the information demonstrates that the analytical procedures used are suitable for their intended purpose.

Batch data are presented in two separate sections, for those batches produced with development process (=Developmental Batches) and those batches produces with registration Process (=Registration batches). The number of batches tested is sufficient to allow an estimation of manufacturing process consistency. Based on the risk assessment and the toxicological evaluation, the residual risk of extractables and leachables for the glass vials and rubber stoppers is low and no study is required.

The container closure system of the DS are glass vials with a stopper and an aluminium crimp seal. Container closure integrity has been conducted documenting the appropriate sealing of the elastomeric closure of the packaging system on authentic samples (i.e. container closure system containing the

DS) from different DS lots as well as Moisture Vapor Transmission Rate assessment. In conclusion, the DS container closure system is described in sufficient detail.

Stability

Stability data support the proposed shelf-life of the shelled peanuts as well as the SM (defatted peanut powder). The studies are performed in line with ICH Q1A and ICH Q5C as well as EMA-guideline EMEA/CHMP/BWP/304831/2007.

This claim of DS shelf-life is supported by stability studies performed with DS batches produced in the current manufacturing process. Additional stability data are presented on DS batches produced in manufacturing process b. All results were within specifications and no trends were observed.

Stress studies, photo-stability studies and temperature excursion studies have been performed with the DS. The DS proved to be very stable. Only heat stress combined with high humidity resulted in some degradation of the lyophilized DS. The described studies support the claim that the selected analytical procedures are stability indicating.

The stability program for the post approval period consists of one batch per year.

3.1.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

The distinct layers of the DP (DBV712) are:

(1) a dressing;

(2) a backing layer upon which the formulated peanut allergen extract is deposited;

(3) a foam ring to constitute the occlusive chamber with the backing film;

(4) a film protecting the adhesive parts of the patch.

Each DBV712 unit is individually packaged in a small pouch.

The active substance concentration in the deposit on the patch is 250 µg peanut protein/patch.

As the DS is electrosprayed on the backing layer of DBV712, the DS was designed to generate a suitable liquid bulk DP formulation after reconstitution.

DBV712 is a patch for epicutaneous application developed to desensitize to peanut allergy. It contains a solid deposit of a peanut allergen extract electrosprayed on a backing film and forms an occlusive condensation chamber covered by a breathable dressing allowing the patch to remain on the skin during the targeted application period. The patch has undergone several versions in the course of its development (type I to type IV), but the dimensions of the occlusive chamber remained the same from the initial to the commercial patch design.

Manufacture of the product and process controls

The DP is manufactured by DBV Technologies (France). The main steps of the process are Formulation, Electrospray and “Web converting” (Cutting/Assembling/Primary Packaging) and Secondary Packaging.

Manufacturing process validation was successfully performed on three consecutively produced DP batches, demonstrating that the process (when executed within the defined operating range) performs consistently and meets pre-established acceptance criteria. A special focus of the validation exercise

was on homogeneity. Further validation studies evaluated intermediate holding times, extractables/leachables (which need to be described in more detail) and shipping. Continued process verification is described. The validation is considered successfully completed for all the steps of the process. The drug product process is considered validated.

Product specification, analytical procedures, batch analysis

DP bulk formulation

All analytical procedures used in DP bulk formulation control are listed and described. For each procedure, the topics principle, sampling, equipment, reagents, preparation of standards, preparation of samples, procedure, system suitability testing, calculations/interpretations and report of results are presented. The analytical procedures have been validated.

Regarding batch data, results for DP bulk formulation batches are presented, confirming comparable quality of the bulk over three years of production.

Drug Product

The DP specifications are described

Testing of uniformity of dosage units and Dissolution testing is in line with the requirements of the Ph. Eur. Monograph on transdermal patches.

All analytical procedures used in DP quality control are listed and sufficiently described. For each procedure, the topics principle, sampling, equipment, reagents, preparation of standards, preparation of samples, procedure, system suitability testing, calculations/interpretations and report of results are presented. All analytical procedures have been successfully validated.

Batch analysis at DP level included presentation of supportive batches produced in the previous DP development manufacturing processes, including also batches with different target strength. In addition, DP batches are presented that were produced with the current manufacturing process. The release of all DP batches was based on the specifications valid at the time and all results were within specifications. Batch analysis data have confirmed the ability of the process to produce the DP in reproducible quality.

Stability of the product

For the DP, a shelf-life with no specific storage conditions is claimed. The studies are performed in line with ICH Q1A and ICH Q5C as well as EMA-guideline EMEA/CHMP/BWP/304831/2007.

Post approval change management protocol(s)

N/A

Adventitious agents

No raw materials or excipients derived from animals with a transmissible spongiform encephalopathy (TSE)-risk have been identified. Adhesive foam, which is part of the crown around the condensation chamber of the device, contains one or more ingredients used that may have been synthesized from hydrolyzed animal fats (bovine tallow) into fatty acids. However, the processing of tallow at high temperatures, high pressures and long residence times is adequate to inactivate any TSE agents

present in the starting material. Ink is compliant with Regulation (EC) No. 1333/2008 on food additives.

DBV712 is in compliance with the Note for Guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev.3). In summary, virus and TSE safety has been sufficiently demonstrated.

GMO

N/A

3.1.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

The provided information on the quality of Abylqis was initially considered to be not sufficient to allow a final assessment. In several sections of the dossier, information has been added in accordance with the d120 list of questions. The most relevant points requiring clarification are described in this summary.

The DS is an unmodified, lyophilized allergen extract produced via extraction and freeze-drying of defatted peanut powder (SM) originating from raw peanut seeds. Release specifications of the SM cover all major quality aspects. Also testing for pesticides and elemental impurities is performed at this step. It was initially requested in the d120 LoQ to align the specifications for Cadmium, Lead and Mercury with the limits for herbal drugs as stated in Ph. Eur. monograph 1433 herbal drug. With the response to the d120 LoQ the issue has been solved by providing further justification for the selected specifications. Regarding microbial quality, significant heterogeneity in results is observed at the level of the peanut seeds but also the defatted peanut powder, which became even more definite when the tests were adapted to five independent samples instead of one. It had not regarded as evident that the current test procedure is suitable to give a representative estimate of the microbiological contamination, but the applicant has presented additional information demonstrating that further optimization of the sampling mode is not necessary. However, for final solution of the issue, information is requested regarding the number of observed out-of-specification results which were missing in the answer to the d120 LoQ (LoOI). As microbial quality is also controlled at all subsequent production levels and the DS manufacturing process is designed to reduce microbial contamination, the issue has not regarded as major.

The DS is designed to be easy to reconstitute and have low conductivity in order to enable electrospraying and is a lyophilized peanut allergen extract. DS specifications include assays for total allergenic activity, relevant allergens, protein and allergen profile, protein content as well as water or loss on drying are performed.

The DP (Abylqis or DBV712) is a cutaneous patch packed in a small pouch. The means by which each of the defined quality product elements were selected has been sufficiently described in the answer to the d120 LoQ in relation to the relevant characteristics of each layer like flexibility, tensile strength, occlusion and chemical inertness.

The DP manufacturing process consists of three major parts: Preparation of the DP bulk formulation, the electrospraying step and the so-called “web converting step” including cutting, assembly and packaging. The specifications controlling DP quality cover all aspects of the product, including a dissolution test.

For the DP, a shelf-life is claimed, without requiring special storage conditions. The stability of the patches at extreme temperatures has been demonstrated in temperature excursion stress studies.

As the MO raised on nitrosamine impurities has been solved, only few minor outstanding issues remain for clarification before a positive opinion can be given, with regard to quality aspects, on Abylqis.

3.2. Non clinical aspects

3.2.1. Pharmacology

The pharmacology program encompasses proof-of-concept studies investigating the role of Langerhans cells (LCs) in EPIT as well as the impact of the patch size and amount of loaded peanut protein extract (PPE) on CD11c positive dendritic cell (epidermal mouse LCs) activation employing ovalbumin- (OVA-) and peanut-sensitized mice models and an ex vivo human skin model.

Designated non-clinical efficacy and local tolerance studies have been conducted in peanut-sensitized mice and minipigs, the latter sharing striking similarities to the human skin, as postulated by the applicant. The role of LCs was studied in OVA-sensitized LC-depleted (Langerin-eGFP-DTR transgenic mice) and LC+ mice undergoing 8 weeks EPIT with 100 µg OVA. Upon oral challenge with 50 mg ovalbumin LC+ mice showed less severe signs of anaphylaxis (as measured by a significantly lower drop in body temperature compared to LC-depleted mice) and a significant increase of Tregs, respectively decrease of OVA-specific IgEs and cytokine production by in vitro reactivated splenocytes compared to non-treated mice, which was not observed in LC-depleted mice. Even though the distinct mechanism of action of EPIT remains to be elucidated these experiments indicate that presence/functionality of LCs is crucial to mediate effects of EPIT.

Peanut allergen uptake by murine epidermal LCs and migration to the draining lymph node (as measured by flow cytometry analysis of inguinal lymph nodes) in dependence of the patch size and amount of deposited PPE were studied in peanut-sensitized mice treated with FluoProbes®488 labelled PPE via EPIT. Larger patch size and increased quantity of PPE resulted in an increased PPE uptake by LCs with a saturation effect at 100 µg deposited PPE/cm2. It is concluded that due to anatomical and functional differences between human and murine skin (e.g. thicker epidermis/dermis in humans, substantially more hair-follicle in fur-covered mouse skin (Gudjonsson et al. 2007, Romani et al. 2007) and species-specific differences in LC-subtypes according study results can numerically not be transferred to humans. Study results, however, indicate that not only the PPE concentration but also the patch size is a critical variable impacting the treatment effect of peanut EPIT.

The penetration of PPE conjugated with a fluorescent dye and co-localization with Langerhans cells stained with anti-CD207 (langerin) and anti-CD1a antibodies was investigated in experiments with abdominal native ex vivo skin models from two female donors after patch application over 12 and 24 hours. Study results indicate that PPE from the DBV712 patch is capable to pass the human skin barrier in intact skin as it concentrates in the epidermis, it appears however that only a small proportion of PP crosses the basal membrane and reaches lower sections of the dermis. Overall only a small proportion of skin permeated peanut protein was found co-localized with CD1a and sporadically with CD207 positive cells in the epidermis, the latter only detectable in in situ skin preparations by 3D imaging. Viaskin patch with or without PPE was applied for 12 and 24 hours. Discrepancies in the study report regarding the presence of fluorescent dye in the wo test systems (active and placebo patches) were clarified with D120 responses, the study report, however, was not corrected. The applicant is asked to add an addendum to Report DE207 (LoOI).

Efficacy and immunological effects of EPIT (patch wearing time over 48 hours) and SCIT with peanut protein at a dose of 100 µg administered once weekly over 8 weeks in comparison to sensitized control animals treated with an empty patch were studied in peanut-sensitized mice. After treatment a significantly decreased sIgG1/sIgG2a ratio and significant lower Th2 cytokine and eotaxin levels in sera

and bronchoalveolar lavage (BAL) fluids in EPIT and SCIT treated animals in comparison to control group were reported. Further alleviation of IgE mediated immediate allergic reaction by means of a significantly reduced signal in the basal activation test (BAT) in plasma of EPIT-treated mice compared to sham controls after oral peanut challenge was observed. This data is considered supportive that peanut EPIT in mice might promote a more Th1-driven immune response with comparable effects as SCIT. Airway challenge and subsequent experimental read outs like BAL, measurement of allergen-induced bronchial hyper-responsiveness as performed in these studies are considered less relevant in a food allergy model as these are typical read outs for a model of allergic airway disease.

Finally efficacy and local tolerance of DBV712 were tested in peanut-sensitized Gottingen minipigs after treatment with one250 µg patch, two small 250 µg patches, one large 500 µg patch or two placebo patches. For efficacy evaluation, minipigs underwent intravenous PPE challenge before and after treatment. Clinical improvement was scored based on the change of the eliciting dose between the baseline challenge and post-treatment challenge.

During the intravenous peanut challenge, minipigs developed plenty of symptoms in an unpredictable manner including signs of severe discomfort and stress, which resulted in sudden death in 5 out 27 animals during the baseline challenge. The suitability of the minipig for anaphylaxis studies taking into consideration the species-specific susceptibility to stress, was questioned at D120. The applicant was further asked to comment on the rationale to use the intravenous challenge route for peanut exposure as the likelihood for anaphylactic reactions is increased compared to the oral route due to the immediate systemic antigen exposure. The applicant agrees that the intravenous peanut application does not resemble the real-life condition and that the associated stress by the required manipulation and the challenge itself may have worsen anaphylactic symptoms. He argues, however, that oral peanut exposure did not induce sufficient allergic symptoms in the minipigs in order to perform efficacy evaluation. He further justifies the selection of the minipig for these studies with its comparable epidermis to that in humans but commits that this is not a perfect model to study peanut-induced anaphylaxis (inability to induce anaphylaxis by oral challenge; species-specific susceptibility to stress). With respect to fatal events during the baseline challenge the applicant suggests (D120 responses) that these could have been also attributed to inadequate mixing of the PPE solution prior to iv injection resulting in an inhomogeneous suspension as well as insufficient medical care during these medical emergencies.

Efficacy results itself are not conclusive as e.g. one small patch with 250 µg PPE performed better than concomitant treatment with two of these patches, the latter yielding the same efficacy outcome as treatment with placebo. Local tolerance data, however, indicate that the patch was well tolerated on non-damaged porcine skin in most animals.

Overall, scientific value of this study is considered questionable and accordingly any conclusions should be drawn with caution, which is agreed by the applicant with the D120 response.

3.2.2. Pharmacokinetics

No formal pharmacokinetic studies have been performed, which is acceptable due to the nature of the product consisting of proteins, which are rapidly metabolised to peptides and amino acids not detectable in body fluids. Nevertheless, systemic absorption and local skin penetration of the PP, respectively major peanut allergens has been investigated *in vivo* in mice and *in vitro* Naïve mice were treated with a 500 µg peanut protein patch applied on either intact or tape-stripped skin up to 48 h in order to investigate whether major allergen reaches the bloodstream. At sacrifice, no major allergen could be detected in the blood of mice with patch application on intact skin in contrast to tape-stripped mice and the group, which received 500 µg PP by subcutaneous injection (positive control for systemic delivery of PP). Blood allergen levels in mice with patch application on stripped skin was 40 ± 21

ng/mL at 2 hours and 11 ± 5 ng/mL at 8 hours. In mice treated by SC injection a high quantity of allergen was detected at 2, 8, 24 and 48 hours, with a peak at 8 hours (148 ± 21 ng/mL). These results suggest that delivery of peanut protein systemically in infants with skin barrier impairment may be a risk for anaphylaxis, which is now taken into account by the instruction that the patch should be applied onto non-inflamed skin only (SmPC section 4.2) and an according warning in SmPC section 4.4, which however needs to be slightly adapted (see LoOI/Clinic).

To further investigate skin penetration of peanut protein and the ability to reach compartments of systemic absorption skin diffusion of 125I-labelled PPE and of the three major allergens of peanut was studied in several experiments with *ex vivo* human skin samples in Franz cells. The protein level in the receptor side was < 1 % of the deposited amount of peanut protein, respectively below or close to the limit of quantification for individual allergens. Overall, only a small proportion of deposited PP, of total measured allergen quantities), respectively, could be recovered from the stratum corneum and epidermis, with a high variability of values between donors and replicates. Allergen content in the dermis was close to the detection limit. No clear dose-relationship could be observed in neither of the studies.

3.2.3. Toxicology

Toxicity of DBV712 was studied *in vivo* in different test species including guinea pigs, mice, rats and rabbits with special emphasize on local tolerance of the combination product and patch device itself. One pivotal repeated-dose toxicity study was performed in a rodent model of peanut allergy. Toxicity studies further covered the standard genotoxicity test series as outlined in ICH Topic S2 (R1), phototoxicity studies in guinea pigs and *in vivo* and *in vitro* biocompatibility studies. All relevant toxicity studies were performed in compliance with GLP rules.

No signs of toxicity were observed up to 14 days after a single intravenous dose of peanut protein extract (PPE) in rats at the dose of 250 µg/kg.

Repeated-dose toxicity was studied in a previously established model of peanut sensitized guinea pigs during 2 or 13-weeks of treatment with DBV712 patches) l applied every 24 or 48 hours or once weekly over 48 hours in comparison to placebo (patches with excipients only) and control (empty patches). Patches were applied on clipped and moistened back skin at four rotating sites. 15 respectively 12 animals per sex were included in the treatment groups and placebo, respectively control group. The selection of the guinea pig as a test species for the pivotal repeated-dose toxicity evaluation was justified based on the suitability as sensitization model.

The selected dose of 500 µg PP provides a sufficient safety margin to the human dose (35- to 250-fold depending on age) and the administration via epicutaneous route resembles the application form of DBV712 in humans, as requested in ICH M3 (R2).

The applicant´s justification for a shorter duration than 6 months of the (only) pivotal repeated-dose toxicity study, as it is requested by ICH M3 (R2) if deviation from the recommended study length of in this case six months is present, is not fully agreed. The applicant argues that sensitization status in guinea pigs cannot be maintained over 6 months as seen by weaning IgG-levels in the course of the study in placebo animals. However, on completion of treatment IgG-levels in active groups were still increased compared to baseline, thus sensitization status can most likely be maintained by booster injections with PP. In addition, toxic effects without allergic aethiopathogenesis can also be studied in non-sensitized animals. Nevertheless, from the CHMP´s perspective, an additional long-term toxicity study does not necessarily add any value due to the following reasons/aspects:

- the absence of toxic effects other than local allergic reactions in the completed 3 months repeated-dose toxicity study (as also argued by the applicant)

- the availability of preclinical safety data in other species (e.g., local tolerance data in minipigs and rabbits, tolerability data in peanut-sensitized mice) and

- the extensive clinical experience with DBV712 in children not identifying any toxic signal, which cannot be attributed to the underlying peanut allergy

Finally, in the absence of additional value the CHMP refrains from demanding another long-term repeated-dose toxicity study in test animals for ethical reasons considering the 3 R´s principle.

Limitation of pivotal toxicity evaluation to only one rodent species is acceptable in view of the availability of additional safety data in the minipig, rabbit, rat and mouse. Also, the use of the former backing patch system does not diminish the relevance of the study, since it could be shown that no pharmaceutical differences are expected between the different patch devices manufactured during the development of DBV712 (please refer to the quality AR). In line biocompatibility studies did not identify any differences between the different backing film device (see below).

Regarding study results no signs of systemic toxicity including anaphylactic reactions in response to treatment were observed in any of the dose groups, neither on macroscopic nor microscopic level. No differences in blood laboratory parameters and urinalysis were reported between treated, placebo and control groups.

Slight to moderate erythema at the patch application site, corresponding to a negligible to slight maximum mean Weekly Irritation Index (WI) were observed in all animals in the surrounding and central patch area (corresponding to the occlusion chamber), with a slightly higher irritant effect in the central area in actively treated animals compared to control and placebo animals. Severe cutaneous reactions such as wound, liquid discharge, edema, scabs and/or desquamation were observed in about 15% of actively treated animals across both dose groups, which were judged as test-item related. In view of these severe application site reactions in some animals the proposed NOAEL of 500 µg PPE was not agreed for local toxicity (D120 LoQ) and this issue remains unsolved at D150 (LoOI). In accordance with ICH S2 (R1) the standard battery of GLP-compliant genotoxicity tests was performed. The PPE did not exhibit any mutagenic activity in the bacterial reverse mutation assay and on somatic mammalian cell lines (TK- Mouse Lymphoma assay) up to the recommended dose/concentrations of 5000 µg/plate, 5000 µg/mL, respectively.

The omission of *in vivo* genotoxicity studies is agreed in light of the absence of any genotoxic effect in the completed in vitro studies.

The omission of carcinogenicity studies is also agreed in the absence of any mutagenic activity of the PPE on salmonella strains and mammalian cell lines in GLP-compliant genotoxicity assays and the nature of the product originated from a common food protein.

Dedicated reproductive and developmental toxicity studies have not been performed. Female and male reproductive organs underwent macroscopic and microscopic evaluation in the repeated-dose toxicity study, however, no data is available on functional fertility due to the lack of mating studies. As long as the exposure of pregnant woman is not foreseen the omission of reproductive and developmental studies is acceptable. This also applies to juvenile toxicity studies in the presence of exhaustive clinical data in children not indicating any specific safety signal as outlined by ICH M3 (R2). The lack of reproductive and developmental toxicity studies is correctly displayed in section 5.3 SmPC.

Three additional local tolerance studies were conducted in naïve rabbits using the former and current patch system containing 500 µg PPE manufactured from bulk intermediates formulations FV5 or FV6, the latter intended for marketing. Local tolerance of the central patch area (corresponding to the condensation chamber) and surrounding patch area (corresponding to the adhesive foam ring) were evaluated in comparison to control (empty) and placebo patches after a single and repeated

applications over 4 weeks on intact and scarified skin. Cutaneous reactions (erythema and edema) were scored after each patch change according to the Draize dermal irritation scoring system as described in OECD Guideline 404.

Both patch systems turned out to have a slight to moderate irritation potential regardless whether it was loaded with PPE, excipients only or was empty. Also skin reactions did not differ between the central and surrounding treatment areas and between intact and scarified skin. It is concluded that the device system itself causes the skin irritation also taking into account that rabbits were not sensitized to peanut protein in this study. DBV patch manufactured with bulk intermediate formulation FV6 resulted in slightly more severe and a slightly higher incidence of skin reactions than patches with FV5 bulk. The applicant assumes that the combination of peanut protein and buffering agents in bulk formulation FV6 were slightly more irritant than the formulation FV5 not containing these agents. In contrast to the results of repeated-dose toxicity study in peanut-sensitized guinea pigs (see above) severe skin reactions were not observed in non-sensitized rabbits, which may be attributed to the sensitization status but also species differences.

No phototoxic effects could be detected in guinea pigs after 4 days treatment with the 250 µg DBV712 patch after exposure to the solar spectrum radiation. Biocompatibility of the different delivery systems manufactured during the development of DBV712 was evaluated in accordance with requirements of ISO 10993-1. This included *in vitro* cytotoxicity on MRC-5 cells (human lung fibroblast cell line), acute skin irritation in non-sensitized rabbits and skin sensitization studies in guinea pigs using the empty patch systems.

All three device systems were found to be non-cytotoxic on MRC-5 cells, negligible or slightly irritant when applied for 4 hours on intact rabbit skin and non-sensitizing in guinea pigs.

3.2.4. Ecotoxicity/environmental risk assessment

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, DBV712 is not expected to pose a risk to the environment. Dedicated ERA studies are not considered necessary and the expert statement provided in Module 1.6 justifying the omission of environmental risk assessment studies for DBV712 is acceptable.

3.2.5. Discussion on non-clinical aspects

All relevant non-clinical safety studies were performed in accordance with Good Laboratory Practice (GLP). GLP compliance is not confirmed for pharmacodynamic and pharmacokinetic investigations, which is acceptable as according studies are not explicitly requested for allergen immunotherapy products as laid down in CHMP/EWP/18504/2006. With exception of the shorter duration than six months of pivotal repeated-dose toxicity study in guinea pigs, which is for the aforementioned reasons acceptable from regulatory side, the preclinical development studies followed the principles of ICH M3 (R2).

As requested by the EMA sufficient quality data on pharmaceutical comparability of the different device systems, respectively bulk intermediates/drug substances, manufactured during the development of the DBV712 patch has been provided. As detailed in the quality part of this report relevant pharmaceutical differences are not expected, thus no concern arises from the fact that pivotal toxicity studies were performed with the former patch version, also considering results of above described biocompatibility studies.

Pharmacology studies encompassing in vivo (in mice) and ex vivo (with human skin samples) proof-of-concept studies as well as efficacy studies in peanut-sensitized animal models show that the PP is

released from the device system and is capable to permeate intact skin, where it concentrates in the epidermis. A small proportion of permeated PP could be found co-localized with human LCs, indicating that it was uptaken by resident LCs. Migrating LCs that captured the PP, were detected in the draining lymph node, as shown in peanut-sensitized mice. Experiments in LC-depleted mice also point to LCs as primary target cells of EPIT, however, no evidence based data is available on the subsequent pathway of tolerance induction. Accordingly the proposed mechanism of action of DBV712 as outlined in SmPC Section 5.1 'Pharmacodynamic properties' has been worded more carefully as requested at D120, however, this has not been done with sufficient consistency (LoOI).

Preliminary efficacy results in peanut sensitized mice confirm immunogenicity of the PP if applied via EPIT, while the immune response shows characteristics of a more Th1-driven reaction. Data on clinical efficacy of EPIT in minipigs is inconclusive and scientific value of the according study questionable. Thus, confirmatory data on clinical efficacy of the DBV712 patch in a relevant animal model in support of the clinical administration is not available.

In vivo study in mice investigating the systemic absorption of one major allergen following patch application on intact and stripped skin (a model for skin barrier impairment) underpin the rule, that the patch must not be applied on skin areas with any signs of chronic inflammation as this increases the risk for anaphylaxis, which is still insufficiently reflected in the SmPC (see LoOI/Clinic). Especially in young children the risk of anaphylaxis has to be taken very serious and careful skin examination before patch application in any patient is paramount to take account of this risk.

Diffusion studies in Franz cells employing ex vivo human skin samples indicate that neither the PP nor individual Ara h allergens reach the dermis, respectively compartments of systemic absorption to a relevant degree, apparently do hardly cross the basal membrane. However, overall only a small proportion of delivered PP, of total allergen amount, respectively, could be recovered from the epidermis, thus permeated into the skin. Further a high variability of values between donors and replicates was noted in these studies. Conclusion that the delivered PP does not reach compartments of systemic absorption in vivo should therefore be drawn with caution. Also in view of the fact that skin samples were obtained from healthy adult donors, thus do not reflect the target group of DBV712 (peanut allergic children). Transdermal diffusion of PP might be increased in skin samples with skin barrier impairment and might also be influenced by skin maturation. Regarding safety of the drug substance itself, no toxic potential is anticipated as it is extracted from a natural and common food, namely defatted peanut flour, and does not undergo chemical modification. Safety concerns are pertained to the drug substance as offending allergen potentially eliciting systemic allergic reactions in the target patient and the novel delivery form by EPIT. Thus, local tolerance of the patch device itself and drug product is of paramount importance in order to permit for administration in children and to ensure a good compliance. Toxicity studies focussed on the extensive evaluation of the irritation potential of the patch device itself and local tolerance of the drug product employing peanut-sensitized animal models and naïve animals of various rodent and non-rodent species. Local tolerance and sensitization potential of the different patch systems manufactured during the development of DBV712 was considered by biocompatibility studies.

Hardly all treated animals, respectively species, showed application site reactions of slight to moderate intensity, regardless whether they were sensitized to peanut or not. Thus, local adverse reactions are not only attributable to allergic reactions to the deposited PPE but also to the irritation potential of the patch device itself. In peanut-sensitized guinea pigs local skin reactions were found to be severe in about 15% of animals. As issued at D120 the high incidence of application site reactions in all test animals need to be reflected in SmPC section 5.3, which was added with D150 response. Severe skin reactions, however, observed in about 15% of test animals in repeated-dose toxicity study are described as 'rare' and 'sporadic' events, which is not agreed and need to be revised in SmPC section 5.3 (LoOI). Further clarification is required whether test animals suffering from severe cutaneous

reactions were included in the recovery group in this study (LoOI). The high incidence of local side effects associated with DBV712 treatment in test animals, arising from the slight to moderate irritation potential of the patch system itself and allergic reactions to the deposited PPE are consistent with clinical reports of DBV712 application in peanut-sensitized children.

No signs of systemic toxicity nor mutagenic or phototoxic potential of the DBV712 patch were detected. It is considered a drawback, however, that preclinical safety data on scarified skin is only available in non-sensitized animals. In the pivotal repeated-dose toxicity study in peanut-sensitized guinea pigs patches were applied on intact skin only. Hence, the risk for anaphylactic reactions due to systemic absorption of the PP was not studied. This again highlights the usage restriction that the DBV712 patch must only be applied on skin areas without any signs of skin barrier impairment and the importance of strict reporting and management of local side effects in daily clinical practice after MA, particularly in very young children. Conclusion on non-clinical aspects

Primary pharmacology studies provided evidence that the PP is released from the device system, concentrating in the epidermis and co-localising with migrating and resident epidermal LCs. The subsequent mechanism of tolerance induction is yet to be proven. Pre-clinical efficacy data in terms of immunological effects points to a more Th1 driven response. Data on a clinical improvement after DBV712 EPIT in peanut-sensitized minipigs are inconclusive.

Relevant non-clinical safety findings primarily refer to the slight to moderate irritation potential of the epicutaneous delivery system itself and local allergic reactions to the deposited PPE. The topical treatment with DBV712 induced in all test animals, respectively species (guinea pigs, mice, rabbits, rats, minipigs) mild to moderate local side effects (mainly erythema), while severe cutaneous reactions were reported in about 10-15% of peanut-sensitized guinea pigs. In view of these severe application site reactions in a considerable proportion of animals the NOAEL of 500 µg PPE cannot be agreed for local toxicity, which is again issued at D150 (LoOI).

If applied on skin areas with obvious skin barrier impairment systemic uptake of the PP may also occur, as shown in in vivo experiments with tape striped mouse skin, which in turn may elicit anaphylactic reactions. This diminishes safety of the epicutaneous delivery system particularly in very young patients suffering from concomitant chronic skin diseases (i.e. atopic dermatitis). Special emphasize need to be put on careful skin examination before patch application and during treatment and patches mustn´t be applied on skin areas with obvious skin barrier impairment.

No other toxicity-related findings have been identified during the non-clinical development.

3.3. Clinical aspects

Table 1 Tabular overview of clinical studies

Type of study	Study Identifier [eCTD section] Countries	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage, Regimen; Route of Administration	Number of Enrolled Subjects	Healthy Subjects or Diagnosis of Patients	Treatment Duration	Study Status; Type of report
Phase 1b Safety	V712-101 (PEP01.09) ClinicalTrials.gov identifier: NCT01170286 [Section 5.3.5.1] 5 active centers in the United States	Safety and tolerability of repeated-application of DBV712 in adult, adolescent, and child subjects with a known allergy to peanut	Randomized double-blind, placebo-controlled 20 Cohorts of 5 subjects. Randomization 4:1 (DBV712: placebo) in each cohort.	DBV712 patch, 4 different doses of peanut protein per patch (20 µg, 100 µg, 250 µg and 500 µg) or placebo patch 2 regimens /dose: 1 patch application per 24 hours, and 1 patch application per 48 hours Route of administration: Epicutaneous	100 subjects in 3 age groups (6 – 50 years, *i.e.* children, adolescent, adults)	Subjects with a history of peanut allergy confirmed by positive SPT and peanut- specific IgE levels Cohorts of non-severe and severe (adults only) subjects(a)	2 weeks	Complete Last Subject, Last Visit: 27 Feb 2012; Full

Phase 2 (pilot) Safety and efficacy	V712-201-E (ARACHILD) Sponsor: AP-HP ClinicalTrials.gov identifier: NCT01197053 [Section 5.3.5.1] 6 active centers in Europe (France)	Efficacy of DBV712 to significantly desensitize peanut-allergic subjects after up to 36 months of treatment; Safety assessment	Randomized (1:1) double-blind, placebo-controlled for the first 6 months, then open label single arm extension	DBV712 patch at the dose of 100 µg or placebo patch for the first 6 months. DBV712 patch at the dose of 100 µg for 12, 30 or 36 additional months Regimen: 1 patch application every day Route of administration: Epicutaneous	54 children aged 5-17 years	Subjects with a history of peanut allergy (severe anaphylaxis excluded), confirmed by positive SPT and peanut- specific IgE levels and reacting to a cumulated value < 300 mg of peanut proteins during the baseline DBPCFC	6-month randomized double-blind placebo-controlled period Open-label: up to 36 months of active treatment followed by 3 months without treatment after 36 months	Complete Last Subject, Last Visit: 10 Dec 2014; Full

Phase 2b (dose-finding, key supportive) Efficacy and safety	V712-202 (VIPES) EudraCT: 2011-002550-32 ClinicalTrials.gov identifier: NCT01675882 [Section 5.3.5.1] 22 active centers in Europe (3 countries), Canada, United States	Efficacy of several doses of DBV712 to significantly desensitize peanut-allergic subjects to peanut after 12 months of EPIT Long-term safety assessment in adults, adolescents and children	Randomized (1:1:1:1) double-blind, placebo-controlled	DBV712 patch, 3 different doses of peanut protein per patch (50 µg, 100 µg and 250 µg) or placebo patch Regimen: 1 patch application per 24 hours Route of administration: Epicutaneous	221 subjects aged 6-55 years in 2 age strata, i.e. children (6- 11 years), and adolescents through adults (≥12 years)	Subjects with a history of peanut allergy (severe anaphylaxis excluded) confirmed by positive SPT and peanut- specific levels. Positive DBPCFC at ≤300 mg of Peanut proteins.	12 months	Complete Last Subject, Last Visit: 31 Jul 2014; Full
Phase 2b Efficacy and safety	V712-204-E (CoFAR6) Sponsor: NIAID ClinicalTrials.gov identifier: NCT01904604 [Section 5.3.5.1] 5 investigational centers in the United States	Efficacy of DBV712 to significantly desensitize peanut-allergic subjects after up to 30 months of treatment Safety assessments	Randomized (1:1:1) double-blind, placebo-controlled	DBV712 patch, 2 different doses of peanut protein per patch (100 µg and 250 µg) or placebo patch Regimen: 1 patch application per 24 hours Route of administration: Epicutaneous	75 subjects aged 4-25 years	Physician diagnosed, or convincing history of peanut allergy (severe anaphylaxis excluded) confirmed by positive SPT and peanut- specific levels and a positive DBPCFC at cumulative reactive dose of ≤1044 mg peanut protein.	30 months followed by 8 to 20 weeks without treatment in subjects with CRD ≥ 5044 mg after 30 months	Complete Last Subject last Visit: 21 August 2018; Full

Phase 3 (pivotal) Efficacy and safety	V712-301 (PEPITES) EudraCT: 015-002461-37 ClinicalTrials.gov identifier: NCT02636699 [Section 5.3.5.1] 31 active centers in Australia, Canada, Europe (2 countries), Unites States	Efficacy and safety of DBV712 to induce desensitization to peanut in peanut-allergic subjects 4 through 11 years of age after a 12- month treatment period by EPIT	Randomized (2:1; DBV712: placebo) double-blind, placebo-controlled	DBV712 patch at the dose of 250 µg or placebo patch Regimen: 1 patch application per 24 hours Route of administration: Epicutaneous	356 subjects aged 4-11 years	Physician- diagnosed peanut allergy confirmed by positive SPT and peanut- specific levels. Positive DBPCFC with eliciting dose ≤300 mg of peanut proteins. History of severe anaphylaxis excluded.	12 months	Complete Last Subject Last Visit: 18 Aug 2017; Full

Phase 3 Safety	V712-302 (REALISE) ClinicalTrials.gov identifier: NCT02916446 [Section 5.3.5.1] 32 active centers in Canada, Unites States	To characterize the safety of DBV712 250 µg in peanut-allergic children over a 36- month treatment period To explore the therapeutic benefit of a long-term treatment (up to 36 months) with DBV712 250 µg in peanut-allergic children To gain experience about the use of DBV712 250ug the real-life conditions of medical practices	Randomized (3:1; DBV712: placebo) double-blind, placebo-controlled for the first 6 months, then open label	DBV712 patch at the dose of 250 µg or placebo patch for the first 6 months DBV712 patch at the dose of 250 µg for 30 to 36 additional months <u>Regimen</u>: 1 patch application per 24 hours <u>Route of administration:</u> Epicutaneous	393 subjects aged 4-11 years	Subjects with a history of peanut allergy (severe or non-severe) confirmed by positive SPT and peanut-specific IgE levels.	6-month randomized double-blind placebo-controlled period followed by open-label active treatment period up to 36 months	<u>Randomized period:</u> Complete Last Subject Last Visit: 22 Sept 2017; Interim <u>Open-label period:</u> Ongoing[b] Not reported yet

Phase 2b extension study	V712-203 (OLFUS-VIPES EudraCT: 2013-001754-10 ClinicalTrials.gov identifier: NCT01955109 [Section 5.3.5.2] 21 active centers in Canada, Europe (2 countries), United States	Efficacy of DBV712 to significantly desensitize peanut-allergic subjects after up to 36 months of treatment Safety of long- term treatment with DBV712 Evaluation of sustained unresponsiveness after 2 months without treatment	Open label	DBV712 patch at the dose of 250 µg (or DBV712 patch at the 50 µg or 100 µg dose then switched to 250 µg at Month 6) Regimen: 1 patch application per 24 hours Route of administration: Epicutaneous	171 subjects from the V712-202 study	Subjects who completed the V712- 202 study (i.e. subjects previously treated in the V712- 202 study for 1 year and with a documented DBPCFC at Month 12)	24-month treatment period followed by 2 months without treatment after 24 months	Complete Last Subject Last Visit: 29 Sep 2016; Full
Phase 3 Efficacy and safety	V712-303 (PEOPLE) EudraCT: 2016-002916-42 ClinicalTrials.gov identifier NCT03013517 : [Section 5.3.5.2] 31 active centers in Australia, Canada, Europe (2 countries), US	To assess the efficacy and safety of DBV712 250 µg after up to 36 months of EPIT to induce/maintain desensitization to peanut in peanut-allergic children	Open-label	DBV712 patch at the dose of 250 µg Regimen: 1 patch application per 24 hours Route of administration Epicutaneous	298 subjects from the V712-301 study	Subjects who completed the V712- 301 study and with a completed documented DBPCFC	36 months of active treatment (including the active treatment period received during the V712-301 study)	Ongoing[b] First Subject in: 23 Jan 2017; Interim (not fully reported)
Phase 1 Residual drug study	V712-102 (SOLAR)	To assess, at different time points upon removal, the amount of residual peanut proteins on the DBV712 patch after application in adult healthy	Open-label	8 patches of DBV712 at the dose of 250 µg and 2 control patches applied for up to 24 hours Route of administration : Epicutaneous	30 subjects aged 18-25 years	Healthy subjects	24 hours	Complete Last Subject Last Visit:1 Mar 2017; Full

	EudraCT: 2016-003348-35 [Section 5.3.5.4] 1 active center in Europe (France)	volunteers						
Phase 1 Biological potency of peanut allergens extract	V712-103 (BIOPOT) Clinicaltrials.gov: NCT03352726 [Section 5.3.5.4] 2 active centers in Unites States	To assess the biological potency of the In-House Reference preparation for peanut allergens extract by a quantitative skin prick test method in adolescent and adult peanut-allergic subjects.	Open-label	Sterile 50% glycerinated peanut allergen extract derived from the lyophilized extract produced from the extraction and freeze drying of defatted peanut powder of biological origin (10^{-1} to 10^{-5} dilutions with a 50% glycerol-saline solvent) Route of administration: Skin prick	27 subjects aged 12-50 years	Physician diagnosed peanut allergy or documented medical history of IgE-mediated symptoms after ingestion of peanut and currently following a strict peanut-free diet.	Single administration	Complete Last Subject Last Visit: 29 June 2018; Full

Abbreviations: CRD: Cumulative Reactive Dose; DBPCFC: Double-Blind Placebo-Controlled Food Challenge; IHRP: In-House Reference Preparation; IND: Investigational New Drug (Application); NIAID: National Institute of Allergy and Infectious Diseases; SPT: Skin Prick Test.

(a) Severe = Subject with history of severe anaphylactic reactions (such as dyspnea and/or wheezing and/or cyanosis and/or hypotension and/or neurological compromise); Non- severe = Subjects without history of severe anaphylactic reactions

(b) Ongoing: Last Subject Last Visit not performed at time of eCTD cut-off date

3.3.1. Pharmacokinetics

The DBV712 development program focused on AIT (EPIT) in the treatment of peanut allergy. Microgram quantities of peanut allergen extract are to be administered via the skin using a daily application of an epicutaneous system (i.e. a skin patch, Viaskin). One central structure of this "epicutaneous delivery system" is a foam crown, which forms a seal and thus creates a kind of occlusive condensation chamber. Water by perspiration and generated by the natural transepidermal (skin) water loss are suggested to lead to solubilisation of peanut proteins that are deposited on the backing of an occlusive film. A fraction of these solubilised proteins are suggested in turn to penetrate the epidermis where they are taken up by target immune cells. These migrate to the draining lymph nodes where they can modulate immune response.

Based on the structure of the skin patch, the applicant declares that no direct connection to the systemic circulation exists and thereby limiting the systemic passage of allergen.

No formal clinical pharmacology studies were conducted in humans with DBV712. In view of the mode of administration and mechanism of action, human pharmacology studies were not conducted.

As in opposite to transdermal product guidelines, guidelines for defining adequate adhesion for epicutaneous allergenic products currently do not exist (FDA: Transdermal and Topical Delivery Systems - Product Development and Quality Considerations November 2019; EMA Guideline on quality of transdermal patches EMA/CHMP/QWP/608924/2014). The following study was performed, not least based on discussion with the FDA:

V712-102 - A Phase I Study with an Open-Label design to assess the Amount of Residual peanut proteins on Viaskin Peanut 250 µg patch in adult healthy volunteers (SOLAR study)

The objective of the V712-102 study was to assess the amount of residual peanut proteins (total peanut proteins and peanut-specific allergen Ara h 6) on the Viaskin patch, at different time points (ranging from 2-24 hours), after application.

The SOLAR study was performed in healthy, adult, non-peanut sensitized, nor peanut–allergic subjects who regularly consume peanuts. Based on the exclusion criteria, all participants were non atopics (exclusion criterion: no peanut allergy or any other documented allergy history (either physician-diagnosed or a well-documented medical history of IgE-mediated reactions after ingestion of peanut or any other food, or allergy to any aeroallergen such as pollen or house dust mite) and did not suffer from dermatologic disease (including atopic dermatitis). The study depicted that the mean total peanut protein and Ara h 6 contents remaining in the chamber of the patch numerically decreased over time, and the largest part of this phenomenon seemed to occur within 12 hours of application on the back. Consequently, this study is not a direct pharmacokinetic study, as the drug product is not analysed "in human/in vivo". Residual peanut protein was analysed on the patch.

The applicant concluded, "this shows that most of the theoretical 250 µg of proteins initially present were transferred from the film of the patch chamber to the subjects' skin after 24 hours of application, making peanut allergen available for uptake by immunological cells". However, this assumption was not further pursued in the SOLAR study, although the gained data already indicated different effects for instance based on the anatomic patch localization. Factors, which may interact with the "solubilisation rate" like activity, sport, localization/anatomic region of the patch, body temperature, and others are not further addressed.

The SOLAR study presents data on the release of the active substance from the patch on healthy, non-atopic adults (mean (±SD) age 21.2±2 years). Factors dealing with the patch on its own (like patch size, chamber width or height), or of the patch carrier per se (like skin thickness, amount of sweat

glands or density of immune cells, (immunological) susceptibility for sensitization etc.) are not addressed. Within the day 120 responses, the applicant did not precise corresponding data. Therefore, especially with regard to aimed treatment of atopic children, this needs to be reflected accordingly in the SmPC (LoOI).

3.3.2. Pharmacodynamics

In general changes of immunoglobulins and in wheal-size following SPT should be placed in section "Clinical pharmacology" - and not in the efficacy part of the dossier. Of note, in the SmPC, the applicant included correctly the data on peanut specific IgE and IgG4 in section 5.1 Pharmacodynamic properties. Actually, localisation of presented data should be harmonised. However, as all data are included in the dossier the issue is not further pursued for now.

The applicant should specify on genetic differences in PD responses. As "skin barrier" and "immune cells" in the epidermis are of major importance, the applicant should address issues regarding primary (genetic differences in PD) and secondary skin barrier defects. Within the D120 response, the applicant specified that e.g. children with Netherton's syndrome "would not be suitable candidates for EPIT". In this line, the SmPC still needs to be updated, and children with severe genodermatosis like the Netherton's syndrome (severe skin barrier impairments) need to be listed as contraindicated (LoOI).

3.3.3. Discussion on clinical pharmacology

The applicant declares that clinical pharmacology studies were not "required" and not conducted. This approach is in accordance with the CHMP guideline CHMP/EWP/18504/2006 stating that pharmacokinetic and pharmacodynamics studies are not possible for allergen products.

It is stated that "the epicutaneous delivery system … was engineered to not have the active allergenic component (peanut protein) applied directly to the skin, in direct contrast to a true transdermal (TD) patch…. Thus, unlike a TD patch where application time on the skin correlates directly with the pharmacokinetic/pharmacodynamic (PK/PD) properties of the patch, DBV712 does not follow this paradigm" (cited from the DBV712 Briefing Document_19_Aug 2020). The applicant declares "Allergen exposure to only the non-vascularised epidermis is expected to limit systemic absorption, thus minimizing systemic adverse reactions".

Nevertheless, systemic effects are a relevant topic to be addressed in the PK section. There are cases described in the literature that EPIT induces systemic side effects (Senti G et al. JACI 2012 Jan;129(1):128-35). Systemic reactions also occurred within the presented clinical studies with Abylqis. Thus, the statement regarding "limited systemic absorption" based on the patch design needs critical reflection. The applicant is asked to comment on further analysis with regard to general factors influencing the function of the patch like:

Absorption and Distribution:

-permeability issues of the skin barrier per se (especially barrier dysfunctions in patients with atopic dermatitis compared to non-atopic individuals). Please correlate with findings from the non-clinic report No 54., where it is stated that "major allergen was not detected in blood of animals treated by patch application on intact skin, in contrast to treatment on stripped skin or by SC injection." Correspondingly, this statement explains that major allergen was detected in blood of animals treated by patch application on stripped skin, suggesting the delivery of peanut proteins systemically in infants with atopic dermatitis.

-influence of body temperature (sport, infection, anatomic patch localization) and blood circulation/perfusion on solubilisation of the peanut protein as well as on the degree of hydration of the epidermis

Method:

- the applicant pronounces that EPIT is “superior” to TD patches, however underlying data is missing

-as the applicant made clear that the distance between skin and the protein film are the key element in the function of the EPIT (in contrast to TD patches), the applicant is asked to present data on the evaluation of “best” distance /, what is the “best” distance?) for a therapeutically utilized patch

-adhesion effects and “stability” of the patch – focusing on the persistence of the distance between the skin and peanut protein built up by the foam crown (e.g. does diminishing of the distance leads to a transdermal application?)*Dose proportionality and time dependency*:

-association of above factors within the duration of patch adhesion and the amount of different peanut doses/concentrations applied on the backing of the film

-association of the number/density of immune cells (Langerhans cells) based on individual factors (e.g. history of severity of atopic dermatitis) and local site of application on efficacy and safety of the patch

Finally, the applicant is asked to comment on “residual peanut protein” which is not absorbed but remains on the skin with cross-reference to non-clinic data, where considerable amounts of peanut allergens had been detected in the washing-fraction. However within the D120 responses, the applicant declared that these general/basic factors suggested by the CHMP as potentially influencing the function of DBV712, or the rate of peanut allergen uptake into the skin have not been assessed in human Phase 1 clinical studies. Correspondingly, this needs to be implemented in the SmPC (LoOI).

Efficacy and safety issues are discussed further in the following on comments on dose finding.

3.3.4. Conclusions on clinical pharmacology

In accordance with the CHMP guideline CHMP/EWP/18504/2006, it is acknowledged that no formal PK-studies are necessary. PD-parameters are evaluated within the efficacy section. However, as EPIT induced systemic effects are described in the literature, and also occurred within the presented non-clinical as well as clinical studies with Abylqis, the applicant is asked to present further analysis with regard to general factors influencing the function of the patch for safety reason. However, the applicant declared in the D120 response, that no additional analysis has been performed. Correspondingly, the clinical development is limited to the presented data. This should be implemented in the SmPC (LoOI).

3.3.5. Clinical efficacy

The indication sought for DBV712, Abylqis is: Abylqis is indicated as epicutaneous immunotherapy (EPIT) for the treatment of children aged 4 to 11 years at the time of treatment initiation diagnosed with peanut allergy that has been confirmed with a positive skin prick test or in vitro testing for peanut-specific IgE antibodies.

Thus, the following wording of the therapeutic indication in section 4.1, SmPC is given:

TRADENAME is indicated for the treatment of children diagnosed with peanut allergy.

TRADENAME is indicated in children aged 4 to 11 years at the time of treatment initiation. Tradename should be used in conjunction with a peanut-avoidant diet.

The efficacy of Abylqis is evaluated in

- One completed pivotal Phase 3 study: V712-301 (PEPITES, conducted in Europe (Germany and Ireland), Australia, the United States, and Canada) with its ongoing extension study: V712-303 (PEOPLE, conducted in Europe (Germany and Ireland), Australia, the US, and Canada); (Study V712-302 (REALISE, conducted in Canada, United States only) focusses on safety) and
- Four Phase 2 studies:
    - a completed phase 2 studies: V712-201-E (ARACHILD, conducted in France)
    - a completed key supportive Phase 2b study V712-202 (VIPES, conducted in the US, Canada, and Europe: France, Netherlands, Poland) with its single-arm extension study with DBV 250 ug (OLFUS-VIPES, V712-203, conducted in the US, Canada, and Europe: France, Netherlands)
    - V712-204-E (Phase IIb, CoFAR6 study, conducted in the US only). Please see section 3.7, “Supportive studies”

Studies were conducted in accordance with GCP.

Efficacy data is based on n = 284 subjects, aged 4-11 years exposed to DBV712 250 µg with double blind efficacy outcomes.

Within the MAA the efficacy results of the pivotal Phase 3 study V712-301 and the key supportive Phase 2b study V712-202 are of special interest.

An overview of the studies evaluating the clinical efficacy of DBV712 based on d120 responses is given below.

Table 2 Number of treated subjects aged 4-11 years exposed to DBV712 250 µg and Placebo

Study Number	DBV712 250 µg (n)	Placebo (n)	Total Subjects (n)
V712-301	238	118	356
V712-302	294	99	393
V712-202	28	31	113
V712-204-E	18	18	53
V712-101	8	2	10
V712-203	75	0	75
V712-204-E Open Label extension	33	0	33

Dose-response studies and main clinical studies

The clinical programme aimed at the assessment of the efficacy and the safety of DBV712 in peanut-allergic subjects compared with placebo.

Based on early examples of epicutaneous/transcutaneous allergen-specific immunotherapy existing in the literature, the applicant performed first human pilot studies with the Viaskin patch system using cow’s milk powder. Focusing on peanut allergy, the

- Phase Ib study V712-101 (PEP01.09 study) investigating the safety and tolerability of 2-week repeated administrations of DBV712 in adult and paediatric cohorts of peanut allergic subjects (n = 100 total, DBV712 patch, 4 different doses of peanut protein per patch (20µg, 100µg, 250µg and 500µg) or placebo patch, 2 regimens: 1 patch application per 24 hours and 1 patch application per 48 hours). Selected Results: Pooled Treatments versus Pooled Placebo (overall): There did not seem to be any difference in duration of Local cutaneous-TEAEs between the different dosage groups of DBV712, or between the 2 regimens of application. Pooled Treatments versus Pooled Placebo (overall): Adverse events of special interest were reported with DBV712 in the 100-µg, 250-µg, and 500-µg dose groups only without clear evidence of any dose effect. Overall Conclusion: The peanut-allergic non-severe and severe adults, non-severe adolescents, and non-severe children randomized in this study presented high peanut-specific IgE levels (mean value of 25.47 kU/L and median value of 11.20 kU/L). In (polyallergic) subjects, DBV712 was safe and well tolerated. Both regimens of application, 1 Viaskin patch/24 hours and 1 Viaskin patch/48 hours were safe. There was no statistically significant difference in the overall TEAEs among the non-severe and the severe DBV712-treated subjects versus placebo-treated subjects. However, DBV712 triggered more local reactions than placebo in peanut-allergic subjects.
- Pilot Phase II Study Arachild, (randomized, double-blind, placebo-controlled), performed in France (n= 54 total, DBV712 patch, one dose of 100 **µg** peanut protein per patch or placebo patch, regimen: 1 patch application per 24 hours, treatment duration 6 month), analysed safety and also efficacy by assessing the proportion of subjects who reached a cumulative reactive dose (CRD) of peanut protein >1,000 mg, or a greater than 10-fold increase in CRD from baseline as determined during the DBPCFC at month 6. The applicant concluded: DBV712 at the dose of 100 µg did not show any efficacy for desensitizing peanut allergic subjects after 6 months of treatment. However, exploratory analyses suggest that a longer treatment of at least 18 months with DBV712 100 µg could be beneficial in children aged 5 to 11 years. (Please see at section *supportive studies* for more details).

Phase 2b V712-202 (VIPES) Dose-selection study

In this Phase 2b, dose-ranging trial in children and adults, conducted in USA, Canada and Europe (France, the Netherlands and Poland) Viaskin Peanut was administered at 3 dose-levels (50 µg, 100 µg, 250 µg peanut protein/patch) to study its efficacy and safety *versus* placebo for 12 months in 221 subjects aged 6-55 years (113 children aged 6-11 years, 108 adolescents and adults (12 and above). Of note: DBV712 250 µg included: 56 subjects (28 children and 28 adolescents/adults).

Primary Efficacy Endpoint:

The primary efficacy endpoint was the percentage of treatment responders for each active treatment compared to placebo. A treatment responder was defined as a subject with a peanut protein ED ≥ 1000 mg peanut proteins based on the results of the DBPC peanut challenge after 12 months of treatment or a subject with a ≥ 10-fold increase of the ED at 12 months, compared to the initial ED.

Key Efficacy (for All Subjects and by Stratum):

For most efficacy endpoints analysed there tended to be a better response with the highest dose of Viaskin Peanut (250 µg) than with the lowest two doses (50 µg and 100 µg) compared with placebo. There were statistically significant differences between the active treatment groups and the placebo treatment group (p-value < 0.05) for some of the efficacy parameters. The results of the child stratum were very favourable in most of the analyses, meaning that they were generally even more pronounced with better statistical significances than the results seen in the whole population, in spite of a halved sample size in the child stratum.

Treatment Responders by Age Stratum:

In the 250 µg Viaskin Peanut treatment group 15 (53.6%) children responded,
in the 100 µg Viaskin Peanut treatment group 12 (46.2%) children responded, and
in the 50 µg Viaskin Peanut treatment group 16 (57.1%) children responded.
In the placebo treatment group 6 (19.4%) children were responders; this was slightly lower than in the overall study population (Table 3).
Among children, response rates for the three active peanut treatment doses were estimated to be 2.4 to nearly 3 fold higher than in the placebo treatment group (Table 4).

Table 3: Analysis of Treatment Responders at Month 12 by Treatment Group in Children 6-11 Years Old – V712-202 Study (FAS)

Treatment Response at 12 months	DBV712 50 µg (N=28)	DBV712 100 µg (N=26)	DBV712 250 µg (N=28)	Placebo (N=31)
Responder, n (%)	16 (57.1%)	12 (46.2%)	15 (53.6%)	6 (19.4%)
95% CI	(37.18, 75.54)	(26.59, 66.63)	(33.87, 72.49)	(7.45, 37.47)
ED ≥1000 mg[a], n (%)	8 (28.6%)	8 (30.8%)	9 (32.1%)	2 (6.5%)
≥10-fold increase of ED[a], n (%)	13 (46.4%)	11 (42.3%)	15 (53.6%)	4 (12.9%)
P-Value DBV712 vs Placebo (1)	0.0035	0.0453	0.0076	
Relative risk	2.95	2.38	2.77	
95% CI for relative risk	(1.34, 6.49)	(1.04, 5.47)	(1.25, 6.14)	
90% CI for relative risk (2)	(1.53, 5.71)	(1.19, 4.79)	(1.42, 5.40)	

Table 14.2.2.1; CSR V712-202
Abbreviations: CI= Confidence Interval; ED= Eliciting Dose; FAS= Full Analysis Set. Percentages were based on the number of subjects in the FAS for each treatment group.
A treatment responder was defined as a subject with an ED of peanut protein ≥1000 mg peanut proteins after 12 months of treatment or a subject with a ≥10-fold increase of the ED at 12 months compared to the initial ED, based on the results of the two double-blind placebo-controlled peanut challenges. For subjects with missing treatment response at Month 12, LOCF imputation was used (i.e. subjects were considered as Non-responders).
[a] A subject could meet both sets of criteria and would therefore be categorised in both criteria category counts.
(1) P-value was based on Fisher's Exact test.(2) Within age strata, the treatment group comparisons were conducted at a two-sided 10% significance level; 90% CIs were therefore provided (in addition to 95% CIs).

Table 4 Actual Values and Change from Baseline in Peanut Protein Eliciting Dose at Month 12 using LOCF imputation by Treatment Group and Age Group: Children (6-11 years of age) (Full Analysis Set)

Actual Values and Change from Baseline in Peanut Protein Eliciting Dose at Month 12 using LOCF imputation by Treatment Group and Age Group: Children (6-11 years of age) (Full Analysis Set)

Peanut Protein Eliciting Dose (mg)	Statistic	50 µg Peanut Protein (N=28)	100 µg Peanut Protein (N=26)	250 µg Peanut Protein (N=28)	Placebo (N=31)	Total (N=113)
Baseline	n	28	26	28	31	113
	Mean (SD)	87.9 (107.23)	88.9 (88.12)	58.9 (63.54)	121.2 (122.27)	89.4 (100.00)
	Median	30.0	100.0	30.0	100.0	30.0
	Min, Max	1, 300	3, 300	1, 300	1, 300	1, 300
Month 12 - Actual Value	n	28	26	28	31	113
	Mean (SD)	397.1 (510.13)	441.2 (511.26)	652.5 (766.93)	160.5 (244.00)	405.6 (557.68)
	Median	100.0	300.0	300.0	100.0	100.0
	Min, Max	10, 2000	10, 2000	10, 2000	1, 1000	1, 2000
	n(%) >2000*	0	1 (3.85)	4 (14.29)	0	5 (4.42)
Month 12 - Change from Baseline	n	28	26	28	31	113
	Mean (SD)	309.3 (472.02)	355.3 (495.15)	593.6 (772.78)	39.3 (214.86)	316.2 (552.82)
	Median	90.0	80.0	235.0	0.0	70.0
	Min, Max	-290, 1900	-70, 1900	-200, 1999	-270, 700	-290, 1999

Note: Patients in this table will be analysed from Baseline through to Month 12. LOCF will be used for premature withdrawals
*If a subject consumed a 2000mg dose of peanut protein without any objective symptoms then the peanut protein eliciting dose is >2000 mg. Values of 2000 are used for maximums and to calculate means in this table. However, in the ANCOVA modeling values of 3000 are imputed prior to log-transformation.

Cross-reference: Listing 16.2.6.1
Program: t_mppsum.sas, Output: T_14_02_09_02_mppsum.rtf, Generated on: 26NOV2014 20:31, Page 1 of 1

In the adolescent/adult stratum, there was no statistically significant response rate at any dose: in the 250 µg Viaskin Peanut treatment group who showed the highest response rate of all three active doses, 13 (46.4%) adolescents/adults were responders compared with 8 (32.0%) adolescent/adults in the placebo treatment group (p-value = 0.3998).

The dose of 250 µg was thus chosen for DBV712 Phase 3 programme in subjects aged 4 through 11 years.

Phase 2 V712-203 (OLFUS-VIPES) - Open-Label Extension of the VIPES Study

In addition, the tolerability and clinical benefit of long(er)-term treatment up to 36 months with DBV712 has been investigated in an open-label extension study (V712-203, OLFUS-VIPES). 171 subjects who completed the V712- 202 study were included and treated with DBV712 patch at the dose of 250 µg (or DBV712 patch at the 50 µg or 100 µg dose then switched to 250 µg at Month 6). Thus, of the 171 (82.6% of the 207 subjects completing the V712-202) subjects, 168 received DBV712 at the 250 µg dose during V712-203 study (either from study start, or after 6 months of treatment at 50 µg or 100 µg). Of the 171 enrolled subjects, 117 (68.4%) completed the study (main reason for withdrawal was unwillingness to continue).

The applicant concluded: Long-term therapy with Viaskin Peanut 250 µg was effective and well tolerated in subjects with peanut allergy particularly in children. The vast majority of children continued to respond to Viaskin Peanut 250 µg for up to 36 months. Moreover, the beneficial effects of Viaskin Peanut 250 µg seen in the previous VIPES study persisted and improved with the increased study treatment duration (from 55.3% to 76.0%). Overall, at Month 12 and at Month 24 in study V712-203, the highest response rate was observed in children who were already on Viaskin Peanut 250 µg in the VIPES study, to achieve up to 15/18 responders (83.3%) at Month 24.

Table 5 Summary and Analysis of Treatment Response at Month 12 and Month 24 by VIPES Initial Treatment Group and Age Group: Children (6-11 years of age) (Full Analysis Set)

	50 µg Peanut Protein (N=25)	100 µg Peanut Protein (N=22)	250 µg Peanut Protein (N=21)	All doses Peanut Protein (N=68)	Placebo (N=29)	Total (N=97)
Responder at OLFUS Baseline [a]	15/25 (60.0)	11/22 (50.0)	12/21 (57.1)	38/68 (55.9)	5/29 (17.2)	43/97 (44.3)
Responder at Month 12 [a]	15/22 (68.2)	11/20 (55.0)	16/20 (80.0)	42/62 (67.7)	15/28 (53.6)[c]	57/90 (63.3)
95% CI for Response[b]	(45.1, 86.1)	(31.5, 76.9)	(56.3, 94.3)	(54.7, 79.1)	(33.9, 72.5)	(52.5, 73.2)
Eliciting dose ≥ 1,000 mg	8/22 (36.4)	9/20 (45.0)	12/20 (60.0)	29/62 (46.8)	8/28 (28.6)	37/90 (41.1)
≥ 10-fold increase of the eliciting dose	14/22 (63.6)	10/20 (50.0)	16/20 (80.0)	40/62 (64.5)	13/28 (46.4)	53/90 (58.9)
Responder at both Month 12 and OLFUS Baseline	11/22 (50.0)	7/20 (35.0)	11/20 (55.0)	29/62 (46.8)	4/28 (14.3)	33/90 (36.7)
Non-Responder at Month 12	7/22 (31.8)	9/20 (45.0)	4/20 (20.0)	20/62 (32.3)	13/28 (46.4)	33/90 (36.7)
Non-Responder at both Month 12 and OLFUS Baseline	6/22 (27.3)	5/20 (25.0)	3/20 (15.0)	14/62 (22.6)	12/28 (42.9)	26/90 (28.9)
Responder at Month 24 [a]	11/17 (64.7)	13/19 (68.4)	15/18 (83.3)	39/54 (72.2)	15/25 (60.0[2])	54/79 (68.4)
95% CI for Response[b]	(38.3, 85.8)	(43.4, 87.4)	(58.6, 96.4)	(58.4, 83.5)	(38.7, 78.9)	(56.9, 78.4)
Eliciting dose ≥ 1,000 mg	6/17 (35.3)	8/19 (42.1)	11/18 (61.1)	25/54 (46.3)	6/25 (24.0)	31/79 (39.2)
≥ 10-fold increase of the eliciting dose	10/17 (58.8)	12/19 (63.2)	15/18 (83.3)	37/54 (68.5)	12/25 (48.0)	49/79 (62.0)
Responder at Month 24, Month 12 and OLFUS Baseline	8/17 (47.1)	6/19 (31.6)	10/18 (55.6)	24/54 (44.4)	3/25 (12.0)	27/79 (34.2)
Responder at Month 24 and Non-Responder at both Month 12 and OLFUS Baseline	0	1/19 (5.3)	2/18 (11.1)	3/54 (5.6)	3/25 (12.0)	6/79 (7.6)
Non-Responder at Month 24	6/17 (35.3)	6/19 (31.6)	3/18 (16.7)	15/54 (27.8)	10/25 (40.0)	25/79 (31.6)
Non-Responder at Month 24, Month 12 and OLFUS Baseline	5/17 (29.4)	3/19 (15.8)	0	8/54 (14.8)	7/25 (28.0)	15/79 (19.0)
Non-Responder at Month 24 and Responder at either Month 12 and OLFUS Baseline	1/17 (5.9)	3/19 (15.8)	3/18 (16.7)	7/54 (13.0)	3/25 (12.0)	10/79 (12.7)

Source: Summary Table 14.2.2.1 and Listing 16.2.6.1.
CI = confidence interval. Percentages were based on the number of subjects in the FAS for each treatment group.
[a] Treatment responder was defined as an eliciting dose ≥ 1,000 mg or a ≥ 10-fold increase of the eliciting dose based on VIPES Baseline value
[b] Using Clopper-Pearson method
[c]Among the 28 placebo patients who performed the FC: 6 were 50 µg Peanut Protein at OLFUS baseline then 250 µg Peanut Protein at Month 6: 2/6 (33%) were responder at Month 12, 6 were 100 µg Peanut Protein at OLFUS baseline then 250 µg Peanut Protein at Month 6: 1/6 (17%) were responder at Month 12, 16 were 250 µg Peanut Protein at OLFUS baseline: 12/16 (75%) were responder at Month 12.
Among the 25 placebo patients who performed FC at Month 24: 5 were 50 µg Peanut Protein at OLFUS baseline then 250 µg Peanut Protein at Month 6: 1/5 (20%) were responder at Month 24, 5 were 100 µg Peanut Protein at OLFUS baseline then 250 µg Peanut Protein at Month 6: 2/5 (40%) were responder at Month 24, 15 were 250 µg Peanut Protein at

At D150, the applicant added data on the GM:

Table 6 Geometric mean eliciting dose (ED) of peanut protein in children 6-11 years old – DBV712 250 µg group – V712-203 Study

Peanut Protein Eliciting Dose (mg)	Initial DBV712 250 µg group* (N=21)
V712-202 Baseline	
N	21
Geometric Mean (SE)	**24.4** (1.34)
Two-sided 95% CI	(13.6, 43.9)
Month 12	
N	21
Geometric Mean (SE)	**311.1** (1.34)
Two-sided 95% CI	(173.3, 558.7)
Ratio (Month 12/Baseline) (SE)	12.7 (1.44)
Two-sided 95% CI	(6.2, 26.3)
Month 24	
N	20
Geometric Mean (SE)	**488.2** (1.35)
Two-sided 95% CI	(268.3, 888.5)
Ratio (Month 24/Baseline) (SE)	20.0 (1.44)
Two-sided 95% CI	(9.6, 41.7)
Month 36	
N	18
Geometric Mean (SE)	**556.6** (1.37)
Two-sided 95% CI	(297.0, 1043.1)
Ratio (Month 36/Baseline) (SE)	22.8 (1.46)
Two-sided 95% CI	(10.7, 48.7)

SE: Standard Error; CI: Confidence Interval.
Values from MMRM model with log-transformed Eliciting Dose (ED) of Peanut Protein as response variable, timepoint as factor and log-transformed baseline ED value as covariate. Back-transformed results are presented.
* Subject randomized in the DBV712 250 µg group in the V712-202 study

Main study(ies)

The application includes one pivotal phase 3 study, V712-301(PEPITES, 238 subjects aged 4-11 years were treated with DBV712 250 µg), with data partially available from study V712-303 (PEOPLE) the open-label extension study of V712-301.

Data is supplemented by supportive data from a (dose-finding) phase 2 study, V712-202 (VIPES), and its extension V712-203 (OLFUS-VIPES, 96 subjects aged 6-11 treated with DBV712 250 µg) as well as from the phase 2b study V712-204-E (CoFAR6; 18 subjects 4-11 yrs treated with DBV712 250 µg)). The studies have been conducted in the US, Canada, Australia and across Europe.

V712-301 (PEPITES)

Methods

Study Participants

Main Inclusion criteria in the pivotal study V712-301

- Male or female children aged 4 through 11 years at Visit 1
- Physician diagnosis of peanut allergy or children with a well-documented medical history of IgE-mediated symptoms after ingestion of peanut and currently following a strict peanut-free diet, but without a physician diagnosis
- Peanut-sIgE level (ImmunoCAP system) >0.7 kU/L

- Positive peanut SPT with a largest wheal diameter:

  ≥6 mm for children 4 through 5 years of age at Visit 1

  ≥8 mm for children 6 years and above at Visit 1

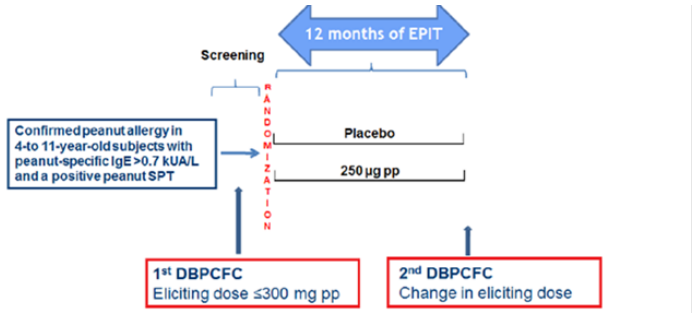
- Positive DBPCFC at ≤300 mg peanut protein: the ED of peanut protein during the entry/screening DBPCFC was capped to 300 mg, that is, subjects had to have objective IgE-mediated symptoms to peanut leading to stopping the challenge at ≤300 mg peanut protein

Main exclusion criteria in the pivotal study V712-301

- History of severe anaphylaxis to peanut
- Generalized dermatologic disease (for example active atopic dermatitis, uncontrolled generalized active eczema, ichthyosis vulgaris)
- Known hypersensitivity to any of the DBV712 or placebo patch components (except peanut), including the adhesive film
- Diagnosis of severe or uncontrolled asthma
- Receiving β-blocking agents, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, calcium channel blockers or tricyclic antidepressant therapy
- Received anti-tumor necrosis factor (TNF) drugs or anti-IgE drugs (such as omalizumab) or any biologic immunomodulatory therapy; receiving cyclosporine or other immunosuppressive agents; Use of systemic long-acting corticosteroids within 12 weeks prior to Visit 1
- Past or currently active disease(s), including but not limited to eosinophilic gastrointestinal disorders, autoimmune disorders, immunodeficiency, malignancy, uncontrolled diseases (for example hypertension, psychiatric illness, cardiac disease), or other disorders (for example liver, gastrointestinal, kidney, cardiovascular, pulmonary disease, or blood disorders)
- Any disorder in which epinephrine is contraindicated such as coronary artery disease, uncontrolled hypertension, or serious ventricular arrhythmias
- Diagnosis of mast cell disorders including mastocytosis or urticaria pigmentosa as well as hereditary or idiopathic angioedema

Treatments

The design of the pivotal study DBV712-301 is a double-blind, Placebo-controlled, Randomized Phase III Trial conducted in in 5 countries (Australia, Canada, Germany, Ireland and USA) is depicted below. Subjects who successfully completed study V712-301, including the mandatory DBPCFC at the end of the study were eligible for enrolment in the extension study (not depicted).



Abbreviations: DBPCFC = Double-blind, placebo-controlled food challenge; EPIT = Epicutaneous immunotherapy; IgE = Immunoglobulin E; pp = peanut protein; SPT = Skin prick test.

Figure 1: Study Design

Subjects were randomized (2:1 ratio) to receive either active DBV712 250 µg or placebo. During a 12-month blinded treatment period, except for the first 2 weeks (see below), the "epicutaneous delivery system" DBV712 250 µg or placebo patch was applied on the skin for 24 hours (±4 hours of allowance) every day and renewed on a daily basis, 1 new patch per day. To better ensure the safety of the DBV712 250 µg or placebo patch at the initiation of treatment, the duration of patch application was progressively increased as follows:

1. During the first week (from Day 1 through Day 7) application for 6 hours every day;
2. During the second week (from Day 8 through Day 14) application for 12 hours every day;
3. From the third week onwards (Day 15) application for the entire 24 hours.

After the first application of the patch at the study site, all subjects were observed for 3 hours before being discharged to check and grade any reactions under or around the patch.

Application of the DBV712 250 µg or placebo patch at a similar time for each daily application (morning or evening) was recommended, if possible at the daily shower/bath time. The previous DBV712 250 µg or placebo patch was removed, and the new patch was applied a few minutes after the shower/bath and after drying the skin. If the subject did not bathe or shower daily or at the same time daily, it was recommended that the zone to which the patch was applied be cleaned with a moist disposable napkin or tissue and dried prior to application.

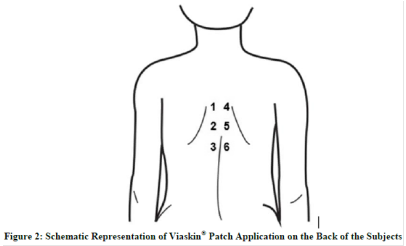


Figure 2: Schematic Representation of Viaskin® Patch Application on the Back of the Subjects

The location of patch application was the inter-scapular area of the back of the subjects. There were 6 zones for applying the patch, 3 on each side of the spine (see Figure above). The first DBV712 250 µg or placebo patch was applied on zone 1, the second on zone 2 (after removal of the first patch), and so forth, until all 6 zones were used. Finally, dosing restarted with zone 1 and continued sequentially.

Patch Adhesion or Patch Adjustment

In case a patch came off, it was to be immediately discarded. A new patch could be applied the same day to replace the previous patch that came off only if that patch came off within 2 hours after being applied. However, no new patch was to be applied the same day if the previous patch came off more than 2 hours after being applied. In that case, a new patch was applied once 24 hours had passed since the previous patch (the one that came off) was applied.

If subjects were unable to apply the DBV712 250 µg or placebo patch for the recommended durations due to local intense or severe reactions under or adjacent to the patch site, the following safety precautions were to be followed: the patch was to be removed immediately, the site of application was to be wiped with a moist disposable tissue, and a topical corticosteroid medication could be applied to treat the reaction. The parents/guardians were to take a photo of the back of the subject to document how intense and extensive the local reactions were. In the case of local intense or severe reactions, it was mandatory that the next patch was applied only the next day on the next zone; no other patch could be applied on the same day. In case of re-appearance of the local intense or severe reactions after application of the next patch the following day, the patch had to be removed. The next patch was to be applied only the next day on the next zone. The same process was repeated on each day that local intense or severe reactions occurred after patch application.

In case of any suspected systemic reactions related to patch application (including cutaneous reactions distant from the sites of patch application), the same safety precautions were to be followed as above. Treatment for the reaction could include antihistamines or topical corticosteroids with additional oral corticosteroids or similar anti-allergic drugs, as deemed necessary by the Investigator. The next patch was applied the next day on the next zone.

As a consequence, the daily duration of DBV712 patch application was to be adjusted/reduced as necessary, and subjects may have needed more than the 14 days before they could apply and tolerate the patch for the full 24 hours daily.

The subject's parents were instructed to contact the Investigator in case of intense or severe local reactions lasting for more than 1 day or any unexpected reactions during the treatment period, in particular in case of appearance of vesicles under the patch or close to the patch site application.

Objectives

The objective of the pivotal study was to investigate the efficacy and safety of DBV712 to induce desensitization to peanut in peanut-allergic subjects 4 through 11 years of age after a 12-month treatment period by epicutaneous immunotherapy (EPIT) compared to placebo. The study *was* designed as prospective, randomised, double-blind, placebo-controlled trial, evaluating DBV712 250 µg included 12 months of randomised, double-blind controlled duration.

Outcomes/endpoints

ENDPOINTS:
Efficacy:

Primary efficacy endpoint:
The primary efficacy endpoint was the difference in the percentage of treatment responders at Month 12 between the active DBV712 250 µg group and the placebo group in the overall population. A subject was defined as treatment responder if: the initial ED was ≤10 mg peanut protein (Screening ED subgroup 1) and the ED was ≥300 mg peanut protein at the Month 12 DBPCFC; or the initial ED was >10 mg peanut protein (Screening ED subgroup 2) and the ED was ≥1000 mg peanut protein at the Month 12 DBPCFC.

Secondary efficacy endpoints:

- Percentage of treatment responders at Month 12 in the active DBV712 250 µg group compared to the placebo group in each Screening ED subgroup;
- Percentage of treatment responders at Month 12 in the active DBV712 250 µg group compared to the placebo group in each age subgroup (4- to 5-year-old subjects and 6- to 11-year-old subjects);
- Mean and median cumulative reactive dose (CRD) of peanut protein and change from baseline at Month 12 in the active DBV712 250 µg group versus the placebo group, in the overall population and for each Screening ED subgroup;
- Mean and median ED of peanut protein and change from baseline at Month 12 in the active DBV712 250 µg group versus the placebo group, in the overall population and for each Screening ED subgroup;
- Percentage of subjects responsive (those showing objective symptoms leading to DBPCFC stop) to a cumulative dose ≥1444 mg peanut protein at the Month 12 DBPCFC in the active DBV712 250 µg group versus the placebo group, in the overall population and for each Screening ED subgroup;
- Percentage of subjects unresponsive (those showing no objective symptoms leading to DBPCFC stop) to a cumulative dose ≥1444 mg peanut protein at the Month 12 DBPCFC in the active DBV712 250 µg group versus the placebo group, in the overall population and for each Screening ED subgroup;
- Percentage of subjects unresponsive (those showing no objective symptoms leading to DBPCFC stop) to the highest dose of peanut protein, which is the percentage of subjects who passed the Month 12 DBPCFC in the active DBV712 250 µg group versus the placebo group, in the overall population and for each Screening ED subgroup.

Other efficacy endpoints:

- Change from baseline in peanut-specific IgE and IgG4 at Month 3, Month 6, and Month 12 in the active DBV712 250 µg group versus the placebo group, in the overall population and for each Screening ED subgroup;
- Change from baseline in peanut SPT mean wheal diameters at Month 3, Month 6, and Month 12 in the active DBV712 250 µg group versus the placebo group, in the overall population and for each Screening ED subgroup;
- Quality of life questionnaires scores (Food Allergy Quality of Life Questionnaire [FAQLQ]/Food Allergy Independent Measure [FAIM]) at baseline and at Month 12 and change from baseline in FAQLQ and FAIM scores at Month 12 in the overall population.

Peanut protein starting doses, maximum doses and dose increments for the entry/screening DBPCFC and Month 12 DBPCFC are shown in Table 7.

Table 7 Peanut Protein Starting Doses, Maximum Doses and Dose Increments in Double Blind Food Challenge

	Entry/screening DBPCFC	Post-treatment DBPCFC at Month 12
Peanut Protein Starting Dose	1 mg	1 mg
Maximum Peanut Protein Dose	300 mg*	2,000 mg
Peanut Protein Dose Increments	1 mg, 3 mg, 10 mg, 30 mg, 100 mg, and 300 mg	1 mg, 3 mg, 10 mg, 30 mg, 100 mg, 300 mg, 1,000 mg and 2,000 mg

Abbreviations: DBPCFC=Double-blind, placebo-controlled food challenge.
**The entry/screening DBPCFC challenge was stopped at the 300 mg dose as a maximum, regardless of whether a reaction occurred before or not.*

Randomisation and blinding (masking)

Randomization Scheme

An Interactive Web Response System, IWRS randomized subjects and assigned the appropriate treatment number or kit number. Randomization: 2:1 to Viaskin Peanut 250 µg or placebo.

Randomization was planned to be stratified by center and by screening ED and managed centrally. The randomization scheme ensured that the ratio treatment / placebo is maintained in Stratum 1 and 2.

Allocation/Randomization of Patients to Treatment

Randomization of subjects to treatment occurred at Visit 4 after all screening procedures had been performed and eligibility for the study confirmed. Each randomized subject was assigned by the IWRS a kit number based on a pre-defined algorithm/pre-defined randomization list.

Blinding (masking)

It was a double-blind study. All peanut and placebo challenges were double blinded, such that neither the subject nor the study personnel were aware of whether peanut or placebo was being administered on a given day. This required the use of food challenge matrices where peanut and placebo matrices were identical in appearance and taste.

The order of the matrices to be consumed (peanut or placebo) during the first and the second day of the DBPCFC was blinded and determined using a randomisation list.

Statistical methods

Continuous data were planned to be summarized in terms of number of subjects or observations with non-missing data, mean, standard deviation, first quartile, median, third quartile, minimum and maximum.

Categorical data were planned to be summarized in terms of the number of subjects or observations providing non-missing data at the relevant time point (n), frequency counts and percentages.

Analysis Populations:

- Screened Population: Subjects whose parents/guardians had signed informed consent.
- Intent-to-treat (ITT) Population: All subjects who were randomized. This population was planned to be used to assess comparative efficacy information. Subjects were planned to be analyzed according to the treatment they had been randomized to.
- Full Analysis Set (FAS): All ITT subjects who were randomized and performed at least the peanut challenge of the second DBPCFC at Month 12. Subjects were planned to be analyzed according to the treatment they had been randomized to.
- Per Protocol (PP) Population: All subjects from the ITT Population who did not have major deviations from the protocol that may have affected the primary (and secondary) efficacy endpoints and who performed at least the peanut challenge of the second DBPCFC at Month 12. The PP Population was planned to be used to perform sensitivity analyses of the primary and secondary efficacy evaluations. Subjects were planned to be analyzed according to the treatment they had actually received.
- Safety Population: All subjects who were randomized and received at least 1 dose of IP. This population was planned to be used to assess comparative safety information. In case the wrong IP was dispensed, the subject was planned to be analyzed according to the IP received for the longest

period of time.

Efficacy Analyses:

Population

The ITT population was planned to be comprised of all subjects who are randomized. This population was planned to be used to assess comparative efficacy information.

Outcome variable

The primary efficacy endpoint was planned to be the percentage of treatment responders at Month 12 in the active Viaskin Peanut 250 µg group compared to the placebo group in the overall population. A subject is defined as a treatment responder if:

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

Significance level and confidence level

A 2-sided, 1% significance level was planned to be used to test the null hypothesis. 95% confidence intervals were planned to be used for estimation.

Analysis and success criterion

According to the study protocol, an exact logistic regression was planned to be used to compare the percentage of treatment responders at Month 12 in the active group versus the placebo group, adjusting for screening ED stratum and including the treatment group as fixed effect.

The study was planned to be considered positive, if the p-value from the exact logistic regression is significant ($p<0.01$) and the lower bound of the 95% CI of the difference between active treatment and placebo response rates is higher or equal to 15%.

According to the SAP, the primary analysis was planned to apply a Wald test at a 2-sided 5% significance level on the difference in response rates between active and placebo treatment groups to evaluate the null hypothesis of no difference. The clinical relevance criterion for the primary analysis was defined as the lower limit of the 2-sided 95% Newcombe confidence interval for the difference in response rates being ≥15%, and it was planned that this condition will determine whether the primary objective has been successfully met.

Missing values

Analyses of primary and secondary efficacy endpoints were planned to be based on the ITT population, with missing values imputed using last observation carried forward (LOCF) imputation (whereby the last value was planned to be considered as the value of threshold sensitivity at entry/screening DBPCFC). Because threshold sensitivity to peanut protein for all randomized subjects was planned to be ≤300 mg (based on the exclusion criteria), subjects who discontinued prior to the post-treatment DBPCFC were planned to be counted as non-responders in the efficacy analyses.

Sensitivity Analyses of Primary Efficacy Endpoint:

The primary efficacy endpoint analysis was planned to be repeated on the FAS and PP Population with no imputation for missing data and on the ITT Population using the multiple imputation method, worst-case imputation for missing data, and missing=failure imputation for missing data (with screening ED stratum, region, and age group as stratification variable).

Examination of subgroups for the Primary Efficacy Endpoint

The treatment effect for the primary efficacy variable was planned to be examined as secondary efficacy analyses in each of the subgroups defined according to the screening ED, using the actual screening ED value, and not the ED stratum used for randomization.

The treatment effect for the primary efficacy variable was also examined as secondary efficacy analyses for the age groups 4 to 5 years and 6 to 11 years.

In addition, a sensitivity analysis with the region (Australia/Europe/North America) and the interaction between region and treatment group as covariate was planned to be performed.

Multiplicity

In order to handle the multiple comparisons versus placebo, the overall type-I error was planned to be controlled by the use of a hierarchical inferential approach. Statistical significance of the primary efficacy criterion in the overall population at the 1% alpha level is required before drawing inferential conclusion about the first secondary efficacy criterion (percentage of treatment responders in Stratum 1). Statistical significance of the first secondary efficacy endpoint at the 5% alpha level is required before drawing inferential conclusion about the next endpoint (percentage of treatment responders in Stratum 2). Inferential conclusion about successive secondary efficacy endpoints require statistical significance at the 5% alpha level of the previous one. Specifically, the pre-defined hierarchical order is as summarized in the following table.

Table 8 Pre-defined Hierarchical Order for Analysis of Efficacy Endpoints

Order	Efficacy endpoints (at Month 12)	Population	Missing data imputation method	Alpha	Method
1	Percentage of treatment responders	ITT Overall	LOCF imputation	0.01	Exact logistic regression
2	Percentage of treatment responders	ITT Screening ED Stratum 1	LOCF imputation	0.05	Exact logistic regression
3	Percentage of treatment responders	ITT Screening ED Stratum 2	LOCF imputation	0.05	Exact logistic regression
4	Cumulative reactive dose	ITT Overall	LOCF imputation	0.05	ANCOVA
5	Peanut protein ED	ITT Overall	LOCF imputation	0.05	ANCOVA
6	Percentage of treatment responders	ITT Age subgroup 6 to 11 years-old	LOCF imputation	0.10	Exact logistic regression
7	Percentage of treatment responders	ITT Age subgroup 4 to 5 years-old	LOCF imputation	0.10	Exact logistic regression
8	Percentage of subjects responsive to a cumulative dose ≥1,444 mg peanut protein	ITT Overall	LOCF imputation	0.05	Exact logistic regression
9	Percentage of subjects unresponsive to a cumulative dose ≥1,444 mg peanut protein	ITT Overall	LOCF imputation	0.05	Exact logistic regression
10	Cumulative reactive dose	ITT Screening ED Stratum 1	LOCF imputation	0.05	ANCOVA
11	Peanut protein ED	ITT Screening ED Stratum 1	LOCF imputation	0.05	ANCOVA
12	Cumulative reactive dose	ITT Screening ED Stratum 2	LOCF imputation	0.05	ANCOVA
13	Peanut protein ED	ITT Screening ED Stratum 2	LOCF imputation	0.05	ANCOVA
14	Percentage of subjects passing the challenge	ITT Overall	LOCF imputation	0.05	Exact logistic regression

Abbreviations: ANCOVA = Analysis of covariance; ED = Eliciting dose; ITT = Intent-to-treat; LOCF = Last observation carried forward.

This table was specified in the study protocol, but was amended in the SAP. The hierarchy of hypotheses was not changed, but in line with the changes on the primary analysis, logistic regression models were replaced by the lower bound of the Newcombe 95% confidence intervals for the risk difference to be >0% for secondary and ≥15% for the primary analysis.

Changes from the Protocol to the Statistical Analysis Plan

The original SAP Version 1.0, dated 22 Jul 2016, was amended 3 times as SAP version 2.0, dated 04 May 2017; SAP version 3.0, dated 25 Sep 2017; and SAP version 4.0, dated 04 Oct 2017. Updates to the SAP were made prior to database lock and study unblinding, and were mainly subsequent to meetings and discussions with the FDA.

Table 9 (see below) provides key details for major changes to the statistical analysis, from the protocol to the final SAP Version 4.0, dated 04 Oct 2017.

Table 9 Statistical Analysis Plan Changes

Description of Statistical Changes
• To handle cases of randomization stratum error (i.e., if the stratum recorded in IWRS differed from the actual one documented in the e-CRF), Screening ED subgroups were to be considered for secondary analyses using actual screening ED value (i.e., subjects were considered in the Screening ED subgroup corresponding to their actual screening ED value).
• The primary measure of treatment effect was to be the difference in response rates between active and placebo treatment groups (instead of comparison in percentage of treatment responders by exact logistic regression as previously planned in the protocol). The primary analysis was to apply a Wald test at a 2-sided 5% significance level to evaluate a null hypothesis of no difference and a 2-sided Newcombe 95% CI for the calculation of the difference in response rates. The clinical relevance criterion for the primary analysis was to be defined by a ≥15% lower confidence bound of the Newcombe CI to determine whether the primary objective has been successfully met, as recommended by the FDA. The 2-sided Wilson 95% CIs of individual treatment response rate were to be presented by treatment group.
• Descriptions by age group (4 to 5 years, 6 to 11 years) for treatment response rates were to be provided for CRD, percentage of subjects responsive/unresponsive to a cumulative dose of ≥1,444 mg peanut protein, and percentage of subjects unresponsive to the highest cumulative dose of peanut protein.
• As per protocol, peanut-sIgE and -sIgG4 values at Month 12 were to be analyzed using an ANCOVA model. As per SAP, this was changed as follows: peanut-sIgE and -sIgG4 results were to be analyzed using a repeated-measures ANCOVA model taking into account all time points up to Month 12 to compare the mean absolute change from baseline in the DBV712 250 µg group versus placebo.
• SPT description was to be performed in the overall population, as well as for each Screening ED subgroup (instead of overall population only).
• FAQLQ questionnaires (Child form and Parent form) were to be analyzed using a global score (as described in the protocol) and, additionally, by domain and by item.
• The region effect was to be explored for the primary efficacy endpoint only; exploration of region effect for secondary analyses was removed. A sensitivity analysis of the primary analysis was to be done on the ITT Population using missing=failure imputation for missing data, CMH method with region as stratification variable to compute a Newcombe 95% CI for the region-adjusted difference in response rates. Response rates by treatment groups and treatment effect were also to be provided descriptively, as exploratory analysis, for each region.
• The proportion of days with mild, moderate, or severe TEAE occurring during the exposure period was to be studied. This additional safety description was to be performed on the Safety Population.
• Description of risk-taking behavior was to be performed on the Safety Population (instead of the ITT Population).
• Randomization was not stratified by site, which was a protocol deviation. Simulations designed to compare randomization stratified by center or not were performed, and showed that the impact was much more pronounced on the intra-center randomization ratios than on the number of centers (and of patients in these centers) where the two treatment arms (or one single arm) were represented, which were similar for the two methods of randomization. The primary endpoint of the study was unlikely to be influenced by the center or the investigator. The statistical analysis planned in the protocol did not take into account any center effect or center-by-treatment interaction. The statistical analysis presented in the protocol thus remained applicable and not stratifying by center did not

make necessary to amend either the primary analysis or the sensitivity analyses. This issue was addressed in the SAP at the region level (Australia/Europe/North America) via a sensitivity analysis of the primary endpoint, stratified by region; response rates by treatment groups and treatment effect were to be provided descriptively, as exploratory analysis, for each region. (Results of the impact analysis are available in Appendix 16.1.9).

- Methodologies to impute missing data at Month 12 for primary and secondary analyses were revised to address the cases where:
  - The DBPCFC was stopped without the objective symptoms leading to ending the DBPCFC (stopping rules) OR
  - The subject took the 2,000 mg dose without any objective symptom leading to ending the DBPCFC.

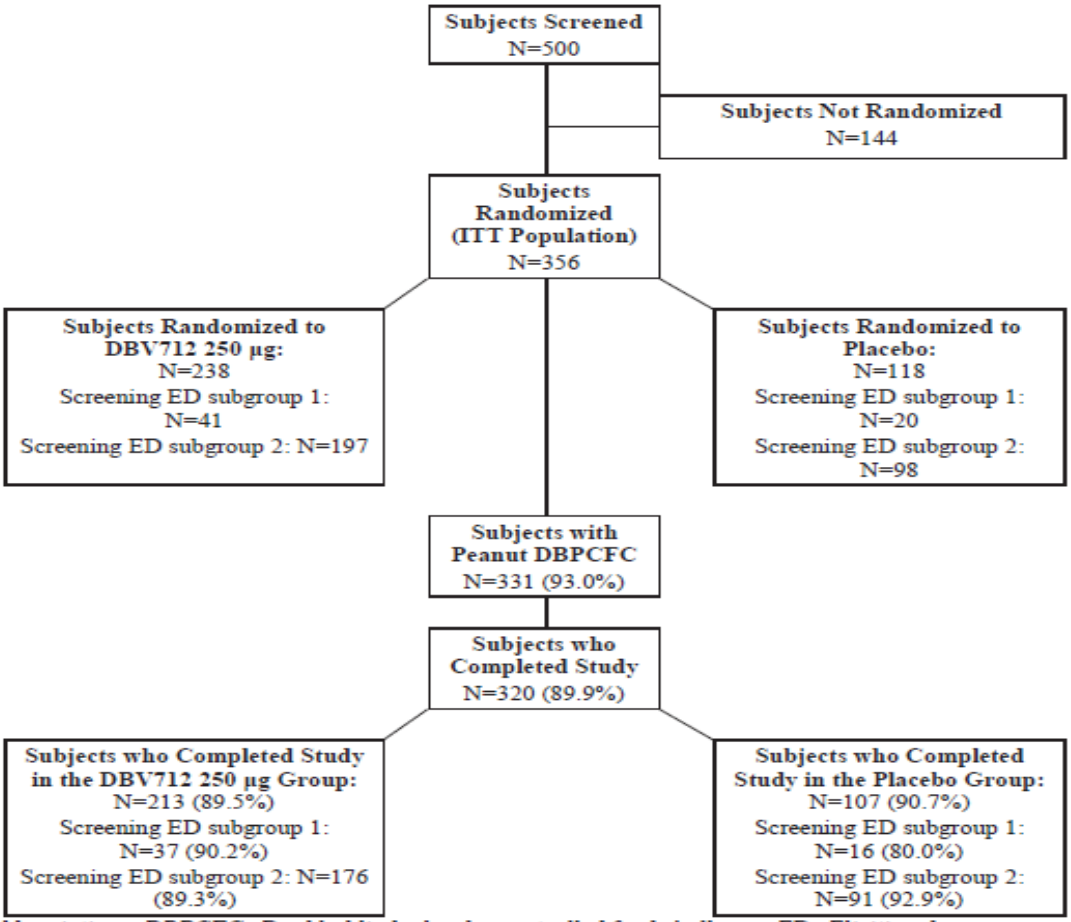
Results

Participant flow

The participant flow in the pivotal phase 3 study V712-301 (PEPITES) is shown below.

Figure 2 Subject Disposition Flowchart

Figure 2: Subject Disposition Flowchart



Abbreviations: DBPCFC=Double-blind, placebo-controlled food challenge; ED=Eliciting dose; ITT=Intent-to-treat.
Source: Section 14, Table 14.1.1.1 and Table 14.1.1.2.

Overall, 36 (10.1%) subjects discontinued the study; the discontinuation rates were similar between the DBV712 250 µg group and the placebo group: 25 (10.5%) subjects in the DBV712 250 µg group and 11 (9.3%) subjects in the placebo group discontinued from the study.

Conduct of the study

The study was conducted between December 2015 and August 2017.

A protocol deviation, in the study conduct, was detected as follows: the IWRS randomization scheme did not include a stratification by site, as originally planned in the protocol. The impact analysis of this deviation did not demonstrate any consequence for the primary endpoint evaluation.

In addition, from 15 to 19 January 2018, i.e. post-database lock, the Irish Agency (The Health Products Regulatory Authority) conducted an inspection at an investigational site. A deviation from protocol, which was related to deficiencies in the management of trial participant diaries, was identified: diary entries that appeared to be possible AEs and/or concomitant medications were indeed not reported in the eCRF for 4 subjects.

Protocol amendments

A total of 500 subjects were screened, 356 subjects were randomized (ITT Population), 331 had an evaluable DBPCFC at Month 12 (FAS population), 320 subjects completed the study, and 36 subjects (10.1%) subjects discontinued the study; the discontinuation rates were similar between the DBV712 250 µg group and the placebo group: 25 (10.5%) subjects in the DBV712 250 µg group and 11 (9.3%) subjects in the placebo group discontinued from the study.

Versions and Dates of Protocol

Protocol Version 1.0, 20 Jul 2015

Protocol Version 2.0, 09 Dec 2015 (including Protocol Amendment 1)

The original protocol, dated 20 Jul 2015, was amended once in order to address queries from the FDA and the Paul-Ehrlich-Institut.

Changes in the Planned Analyses/Changes from the Protocol to the Statistical Analysis Plan

Please see above, section “Statistical methods”.

Findings GCP inspections

Please see section above: From 15 to 19 January 2018, i.e. post-database lock, the Irish Agency (The Health Products Regulatory Authority) conducted an inspection at an investigational site. A deviation from protocol, which was related to deficiencies in the management of trial participant diaries, was identified (see above, “protocol deviation”).

Breaking of the Blind

A single report containing unblinded information for study V712-301/PEPITES treatment group was inadvertently made accessible on the V712-303/PEOPLE study IWRS to one individual from the DBV Technologies blinded team.

At the start of the V712-303 (which is the follow-up study for subjects completing the V712-301 study), when the first 5 subjects had been included, one DBV technologies clinical team member accessed this report which contained the schedule of visits for these 5 subjects, while, after the first 12 months in the V712-303 study, the schedule of visits was different for subjects who were in the active (A) or placebo (P) arm in V712-301; the visits, from Visit 5 until the end of the study, were labelled with a ‘P’ or with an ‘A’ which indicated the initial treatment group in V712-301. The 5 subjects had completed the V712-301 study when the unblinding occurred through the IWRS of the V712-303 study.

Study compliance

The overall treatment compliance was high (compliance rate of 98.45% (4.293): 98.65% (3.886) in the DBV712 250 µg group and 98.05% (5.008) in the placebo group).

Baseline data

- The demographics of patients included in the pivotal phase 3 study are displayed below. Overall, 218 (61.2%) subjects were male and the median age at enrolment was 7.0 years (range: 4-11 years), with 87 (24.4%) subjects aged 4-5 years and 269 (75.6%) aged 6-11 years. The majority of subjects were of Caucasian race/ethnic origin (290 [81.5%] subjects), followed by "Other" designation (34 [9.6%] subjects) and Asian race/ethnic origin (27 [7.6%] subjects).
- The distribution of demographic characteristics (sex, age, proportion of subjects in age category, ethnicity and race) was balanced between the DBV712 250 µg group and the placebo group.

Sensitization parameters

- The median baseline of the mean SPT wheal size diameter was 11.0 mm, the median peanut-specific IgE titer was 84.90 kU/L and the median peanut-specific IgG4 titer was 0.700 mg/L. Overall, these subjects had a confirmed sensitization to peanut. In the Safety/ITT population, the median peanut-sIgE levels were 77.95 kU/L and 101.00 kU/L in DBV712 250 µg group and placebo group, respectively (84.90 kU/L in the overall population); the median peanutsIgG4 levels were 0.690 mg/L and 0.740 mg/L in DV712 250 µg group and placebo group, respectively (0.700 mg/L in the overall population); the median of the mean wheal diameters (SPT) was 11.00 mm for both the DBV712 250 µg group and placebo group.

Medical History

- At baseline, in the overall Safety/ITT Population, the distribution of subjects with atopic condition(s) was balanced between groups, including for "asthma" (169 [47.5%] subjects overall), "allergic rhinitis" (199 [55.9%] subjects overall), any "other allergy than peanut" (305 [85.7%] subjects overall), or filaggrin gene mutations (48 [19.1%] subjects overall; 47 [18.7%] subjects with heterozygous and 1 [0.4%] subject with homozygous mutation). However, a medical history of eczema/atopic dermatitis was reported in 139 (58.4%) subjects in DBV712 250 µg group, and 79 (66.9%) subjects in the placebo group for the ITT overall population Similar results were observed across analysis populations and across the Screening ED subgroups. Of note, eczema/atopic dermatitis was reported in 23 (56.1%) subjects in DBV712 250 µg group, and 15 (75.0%) subjects in the placebo group, in the Screening ED subgroup 1.

Table 10 Demography by Treatment Group and Screening Elicting Dose Subgroup (Safety Population)

	DBV712 250 µg	Placebo	Total
Screening ED Subgroup 1: Subjects with a Screening ED of 1 mg, 3 mg or 10 mg			
	(N=41)	(N=20)	(N=61)
Age (Years) (1)			
n	41	20	61
Mean (SD)	7.2 (2.00)	7.6 (2.37)	7.4 (2.11)
Median	7.0	7.5	7.0
Q1, Q3	6.0, 9.0	6.0, 9.5	6.0, 9.0
Min, Max	4, 11	4, 11	4, 11
Age Group (Years) (2)			
4 to 5	9 (22.0%)	4 (20.0%)	13 (21.3%)
6 to 11	32 (78.0%)	16 (80.0%)	48 (78.7%)
6 to 8	20 (48.8%)	8 (40.0%)	28 (45.9%)
9 to 11	12 (29.3%)	8 (40.0%)	20 (32.8%)
Sex			
n	41	20	61
Male	27 (65.9%)	16 (80.0%)	43 (70.5%)
Female	14 (34.1%)	4 (20.0%)	18 (29.5%)
Race/Ethnic Origin as per e-CRF			
n	41	20	61
Caucasian	34 (82.9%)	15 (75.0%)	49 (80.3%)
Black	0	1 (5.0%)	1 (1.6%)
Hispanic	1 (2.4%)	0	1 (1.6%)
Asian	3 (7.3%)	2 (10.0%)	5 (8.2%)
Other	3 (7.3%)	2 (10.0%)	5 (8.2%)
Race (3)			
n	41	20	61
White	34 (82.9%)	15 (75.0%)	49 (80.3%)
Black or African American	0	1 (5.0%)	1 (1.6%)
Asian	3 (7.3%)	2 (10.0%)	5 (8.2%)
Other	4 (9.8%)	2 (10.0%)	6 (9.8%)
Screening ED subgroup 2: Children with a screening ED of 30 mg, 100 mg or 300 mg			
	(N=197)	(N=98)	(N=295)
Age (Years) (1)			
n	197	98	295
Mean (SD)	7.4 (2.13)	7.2 (2.30)	7.3 (2.19)
Median	7.0	7.0	7.0
Q1, Q3	6.0, 9.0	5.0, 9.0	5.0, 9.0
Min, Max	4, 11	4, 11	4, 11
Age Group (Years) (2)			
4 to 5	46 (23.4%)	28 (28.6%)	74 (25.1%)
6 to 11	151 (76.6%)	70 (71.4%)	221 (74.9%)
6 to 8	81 (41.1%)	40 (40.8%)	121 (41.0%)
9 to 11	70 (35.5%)	30 (30.6%)	100 (33.9%)
Sex			
n	197	98	295
Male	122 (61.9%)	53 (54.1%)	175 (59.3%)
Female	75 (38.1%)	45 (45.9%)	120 (40.7%)
Race/Ethnic Origin as per e-CRF			
n	197	98	295
Caucasian	160 (81.2%)	81 (82.7%)	241 (81.7%)
Black	1 (0.5%)	1 (1.0%)	2 (0.7%)
Hispanic	1 (0.5%)	0	1 (0.3%)
Asian	16 (8.1%)	6 (6.1%)	22 (7.5%)
Other	19 (9.6%)	10 (10.2%)	29 (9.8%)

Race (3)			
n	197	98	295
White	160 (81.2%)	81 (82.7%)	241 (81.7%)
Black or African American	1 (0.5%)	1 (1.0%)	2 (0.7)
Asian	16 (8.1%)	6 (6.1%)	22 (7.5%)
Other	20 (10.2%)	10 (10.2%)	30 (10.2%)

Abbreviations: e-CRF=Electronic case report form; ED=Eliciting dose; IWRS=Interactive Web Response System; Min, max=Minimum, maximum; N=Number of subjects in treatment group/overall; n=Number of subjects with evaluable data; SD=Standard deviation; Q1, Q3=First quartile, third quartile.
Note: Percentages are based on the number of subjects with non-missing data in the Safety Population for each treatment group.
(1) As populated by the IWRS system.
(2) 4 to 5 is defined as subjects 4 to less than 6-years old. The same rule applies for other age groups.
(3) White corresponds to Caucasian, African American corresponds to Black, Other includes Other and Hispanic.
Source: Section 14, Table 14.1.4.2.2.

The screening ED values as reported for randomization in IWRS (screening ED strata) were very close to the actual screening ED values reported in the e-CRF (Screening ED subgroups), Table 11.

Table 11 Screening Elicting Dose by Treatment Group (Intent-to-treat Population)

Screening ED	DBV712 250 µg (N=238)	Placebo (N=118)	Total (N=356)
Screening ED Reported for Randomization			
Stratum 1	36 (15.1%)	18 (15.3%)	54 (15.2%)
1 mg	3 (1.3%)	1 (0.8%)	4 (1.1%)
3 mg	8 (3.4%)	6 (5.1%)	14 (3.9%)
10 mg	25 (10.5%)	11 (9.3%)	36 (10.1%)
Stratum 2	202 (84.9%)	100 (84.7%)	302 (84.8%)
30 mg	32 (13.4%)	20 (16.9%)	52 (14.6%)
100 mg	94 (39.5%)	38 (32.2%)	132 (37.1%)
300 mg	76 (31.9%)	42 (35.6%)	118 (33.1%)
Actual Screening ED			
Subgroup 1	41 (17.2%)	20 (16.9%)	61 (17.1%)
1 mg	3 (1.3%)	3 (2.5%)	6 (1.7%)
3 mg	10 (4.2%)	7 (5.9%)	17 (4.8%)
10 mg	28 (11.8%)	10 (8.5%)	38 (10.7%)
Subgroup 2	197 (82.8%)	98 (83.1%)	295 (82.9%)
30 mg	24 (10.1%)	19 (16.1%)	43 (12.1%)
100 mg	97 (40.8%)	40 (33.9%)	137 (38.5%)
300 mg	76 (31.9%)	39 (33.1%)	115 (32.3%)

Abbreviations: ED=Eliciting dose.
Note: Percentages are based on the number of subjects in the ITT population.
Source: Section 14, Table 14.1.4.1.

Numbers analysed

Intent-to-treat Population = all randomized subjects; used to assess comparative efficacy information.

Full Analysis Set = all ITT subjects who performed at least the peanut challenge of the second DBPCFC at Month 12.

Per Protocol Population = all subjects from the ITT Population who did not have major deviations from the protocol that may have affected the primary (and secondary) efficacy endpoints and who performed at least the peanut challenge of the second DBPCFC at Month 12. The PP Population was used to perform sensitivity analyses of the primary and secondary efficacy evaluations. In case the wrong IP was taken, the subjects were analysed according to the IP received for the longest period of time. In the event that a subject was stratified incorrectly (i.e., the screening ED recorded in the IWRS differed from the actual one), the actual screening ED value was used rather than the stratum to which the subject was randomized.

Safety Population = included all subjects who were randomized and received at least 1 dose of IP. This population was used to assess comparative safety information. In case the wrong IP was dispensed,

the subject was analysed according to the IP received for the longest period of time. In the event that a subject was stratified incorrectly, the actual screening ED value was used rather than the stratum to which the subject was randomized. A subject was assumed to have received at least 1 dose of IP if the date/time of first dose was completed in the e-CRF, or if at least 1 patch adhesion scoring was completed (in case the date of the first dose was missing).

The Safety Population was identical with the ITT Population and, therefore, had efficacy and safety results that are identical to those of the ITT Population.

Table 12 Analysis Populations

Analysis Sets	DBV712 250 µg n (%)	Placebo n (%)	Total n (%)
Overall			
ITT Population	238 (100%)	118 (100%)	356 (100%)
Safety Population	238 (100%)	118 (100%)	356 (100%)
FAS	222 (93.3%)	109 (92.4%)	331 (93.0%)
PP Population	201 (84.5%)	100 (84.7%)	301 (84.6%)
Screening ED Subgroup 1: Subjects with a Screening ED of 1 mg, 3 mg or 10 mg			
ITT Population	41 (100%)	20 (100%)	61 (100%)
Safety Population	41 (100%)	20 (100%)	61 (100%)
FAS	38 (92.7%)	17 (85.0%)	55 (90.2%)
PP Population	33 (80.5%)	15 (75.0%)	48 (78.7%)
Screening ED Subgroup 2: Subjects with a Screening ED of 30 mg, 100 mg or 300 mg			
ITT Population	197 (100%)	98 (100%)	295 (100%)
Safety Population	197 (100%)	98 (100%)	295 (100%)
FAS	184 (93.4%)	92 (93.9%)	276 (93.6%)
PP Population	168 (85.3%)	85 (86.7%)	253 (85.8%)

Abbreviations: ED=Eliciting dose; FAS=Full Analysis Set; ITT=Intent-to-treat; PP=Per Protocol.
Note: Percentages are based on the number of subjects in the ITT Population.
Source: Section 14, Table 14.1.1.1 and Table 14.1.1.2.

Outcomes and estimation

The primary efficacy endpoint was the difference in response rates (%) between the active treatment group and the placebo group at Month 12.

A treatment responder was defined as follows:

- If the baseline ED was ≤10 mg peanut protein the ED was required to reach ≥300 mg peanut protein at the Month 12 DBPCFC; or
- If the baseline ED was >10 mg peanut protein the ED was required to reach ≥1000 mg peanut protein at the Month 12 DBPCFC.

Table 13 Analysis of Treatment Responders at Month 12 by Treatment Group ("Missing-Failure" Imputation) – V712-301 Study (ITT Population)

Treatment Response at Month 12	DBV712 250 µg (N=238)	Placebo (N=118)	p-value
Responders [1]			
n (%)	84 (35.3%)	16 (13.6%)	
Two-sided Wilson 95% CI	(29.5, 41.6)	(8.5, 20.9)	
Difference in Response Rates [2]			
DBV712 250 µg – Placebo	21.7		<0.001
Two-sided Newcombe 95% CI	(12.4, 29.8)		

Source: Table 14.2.1.1; CSR V712-301
Abbreviations: CI = Confidence interval; DBPCFC = Double-blind placebo-controlled food challenge; ED = Eliciting Dose; ITT = Intent-to-treat.
Note: Percentages were based on the number of subjects in the ITT population for each treatment group.
If the last dose given during a DBPCFC was only partially ingested by the subject prior to the DBPCFC stop, then the ED reported by the Investigator was:

- The previous dose given, if the actual ingested quantity of the last dose was the same as or smaller than the previous dose ingested;
- The last dose given, if the actual ingested quantity of the last dose was larger than the previous dose ingested.

A subject was defined as a treatment responder if the initial ED was ≤10 mg peanut protein and the ED at Month 12 was ≥300 mg peanut protein, or if the initial ED was >10 mg peanut protein and the ED at Month 12 was ≥1000 mg peanut protein.
Subjects with missing treatment response at Month 12 were imputed as failure (i.e. non-responders).
[1] Number and percentage of responders and 2-sided 95% Wilson CI of the response rate.
[2] Difference in response rates between DBV712 250 µg and placebo groups and 2-sided 95% Newcombe CI. P-value was obtained from a 2-sided 5% test to evaluate the null hypothesis of no difference in response rates between treatment groups using the Wald method. The lower bound of the Newcombe CI of the difference in response rates was to be ≥0.15.

After 12 months, a larger proportion of subjects in the DBV712 250 µg group (84/238 (35.3%) subjects) were defined as treatment responders (based on above) compared to the placebo group (16/118 [13.6%] subjects). There was a statistically significant difference in the response rates of 21.7% (in favour of DBV712 250 µg: p-value<0.001). The 95% CI of this difference was (12.4, 29.8), thus the pre-specified criterion of the lower bound of the 95% CI **≥15%** for the risk difference was not achieved.

As the pre-specified clinical success criterion was not met (12.4% <15%), the hierarchical testing procedure should stop, and all subsequent analyses are considered descriptive.

Some of the initially planned Secondary efficacy endpoints are presented in a descriptive manner below – in reflection of the fact that these are not confirmatory anymore:

Treatment Responders by Screening ED Subgroup

A summary of treatment responders at Month 12 by treatment group and by screening ED subgroup is provided in Table 14, using the same statistical methods as those for the primary efficacy analysis.

Table 14 Analysis of Treatment Responders at Month 12 by Treatment Group and Screening ED Subgroup ("Missing=Failure" Imputation) – V712-301 Study (ITT Population)

Treatment Response at Month 12	DBV712 250 µg	Placebo	p-value
Screening ED subgroup 1: Children with a screening ED of 1 mg, 3 mg or 10 mg	**(N=41)**	**(N=20)**	
Responders [1]			
n (%)	16 (39.0%)	4 (20.0%)	
Two-sided Wilson 95% CI	(25.7, 54.3)	(8.1, 41.6)	
Difference in Response Rates [2]			
DBV712 250 µg – Placebo	19.0		0.105
Two-sided Newcombe 95% CI	(-6.4, 38.4)		
Screening ED subgroup 2: Children with a screening ED of 30 mg, 100 mg or 300 mg	**(N=197)**	**(N=98)**	
Responders [1]			
n (%)	68 (34.5%)	12 (12.2%)	
Two-sided Wilson 95% CI	(28.2, 41.4)	(7.1, 20.2)	
Difference in Response Rates [2]			
DBV712 250 µg – Placebo	22.3		<0.001
Treatment Response at Month 12	**DBV712 250 µg**	**Placebo**	**p-value**
Two-sided Newcombe 95% CI	(12.1, 30.8)		

Source: Table 14.2.2.1.1.1; CSR V712-301
Abbreviations: CI = Confidence Interval; ED = Eliciting Dose.
Percentages were based on the number of subjects in the ITT population for each treatment group.
A subject was defined as a treatment responder if:
- The screening ED was ≤10 mg peanut protein and the ED was ≥300 mg peanut protein at Month 12; or
- The screening ED was >10 mg peanut protein and the ED was ≥1000 mg peanut protein at Month 12.
Subjects with missing treatment response at Month 12 are imputed as failure (i.e. non-responders).
[1] Numbers and percentages of responders and two-sided Wilson 95% CI of the response rate.
[2] Difference in response rates between DBV712 and Placebo groups and two-sided Newcombe 95% CI. P-value was obtained from a two-sided 5% test to evaluate the null hypothesis of no difference in response rates between treatment groups using Wald Method.

Changes in Geometric Mean ED (additional analysis D120 response)

Clinical relevance between active treatment and placebo is reflected in the increase in mg peanut protein of the ED assessed during a double-blind, placebo-controlled, food challenge (DBPCFC) compared to baseline. As the data are not normally distributed, the GM of mg peanut protein was assessed. In the Study V712-301, the GM ED at Month 12 was 277.62 mg in the active group and 81.80 mg in the Placebo group, corresponding to a 3.39 active/placebo ratio, with a p-value <0.001 (Table 15). The GM ratio (Month 12 / Baseline) of ED demonstrates a treatment effect (Table 16) with a ratio (95% CI) of 3.61 (2.98, 4.37) for DBV712 250 µg, whereas the placebo arm does not show an improvement with a ratio (95% CI) of 1.13 (0.86, 1.47), with a p-value of <0.001 and a CI bound for DBV712 250 µg which does not cross 1.

Table 15 Geometric Mean of ED at Month 12 – V712-301 Study (ITT Population)

Log-Transformed Peanut Protein Eliciting Dose Statistics	DBV712 250 µg (N=238)	Placebo (N=118)	p-value
Month 12 (log10-transformed data)			
Geometric LS Mean			
Estimate (SE)	277.62 (1.09)	81.80 (1.12)	
Two-sided 95% CI	(236.19, 326.32)	(65.02, 102.92)	
Geometric LS mean ratio			
DBV712 250 µg / Placebo	3.39		<0.001
Two-sided 95% CI	(2.56, 4.49)		

Source: Table 14.2.2.3.1.2B, CSR V712-301

Geometric Least square Means, Geometric LS Mean ratio and corresponding Confidence intervals (CI) and P-Value are based on type III sum of squares from an ANCOVA model of the log10-transformed Peanut Protein Eliciting Dose at Month 12 (using mBOCF imputation), including treatment group, adjusted on log10-Baseline value. Back transformed results are presented. The back-transformed least squares mean is a geometric least squares mean.

Table 16 GM ED Ratio by ED Subgroup V712-301 Study (ITT population)

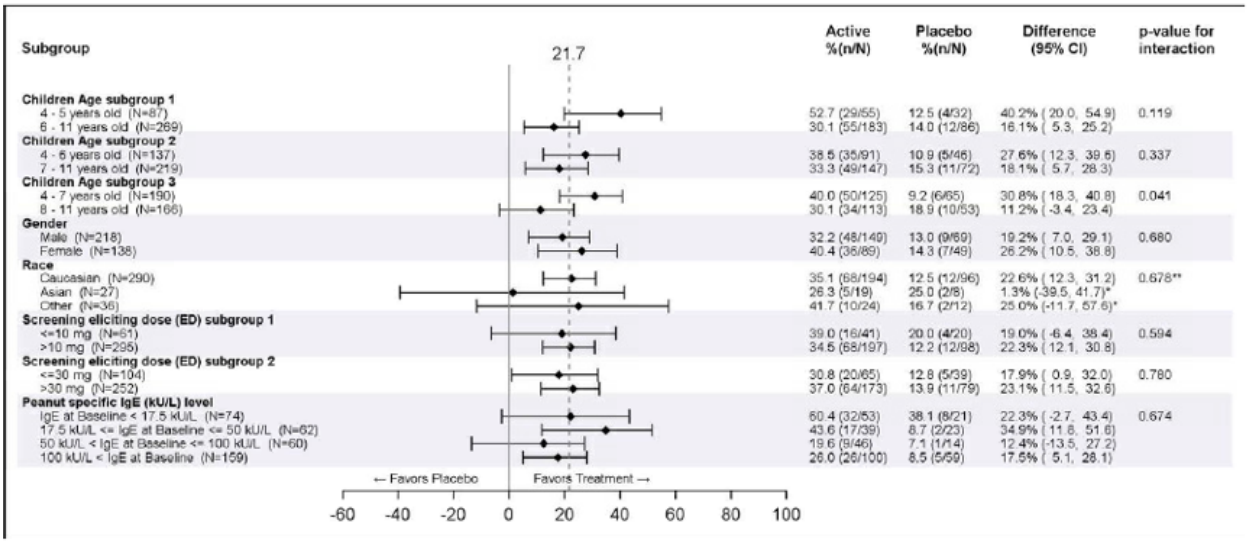
Peanut Protein Eliciting Dose (mg)	DBV712 250 µg	Placebo
ED Subgroup 1	**N=41**	**N=20**
Month 0 (log10-transformed data)		
Geometric Mean (SE)	6.3 (1.20)	4.6 (1.32)
Two-sided 95% CI	(4.4, 9.0)	(2.6, 8.2)
Month 12 (log10-transformed data)		
Geometric Mean (SE)	117.1 (1.20)	22.0 (1.32)
Two-sided 95% CI	(81.6, 168.0)	(12.5, 38.9)
Geometric ratio Month 12 / Month 0	18.58	4.74
Two-sided 95% CI	(11.15, 30.97)	(2.12, 10.60)
ED Subgroup 2	**N=197**	**N=98**
Month 0 (log10-transformed data)		
Geometric Mean (SE)	**131.9 (1.06)**	**122.6 (1.09)**
Two-sided 95% CI	(117.4, 148.2)	(103.5, 145.3)
Month 12 (log10-transformed data)		
Geometric Mean (SE)	338.6 (1.06)	103.0 (1.09)
Two-sided 95% CI	(301.3, 380.4)	(86.9, 122.0)
Geometric ratio Month 12 / Month 0	2.57	0.84
Two-sided 95% CI	(2.18, 3.03)	(0.66, 1.07)

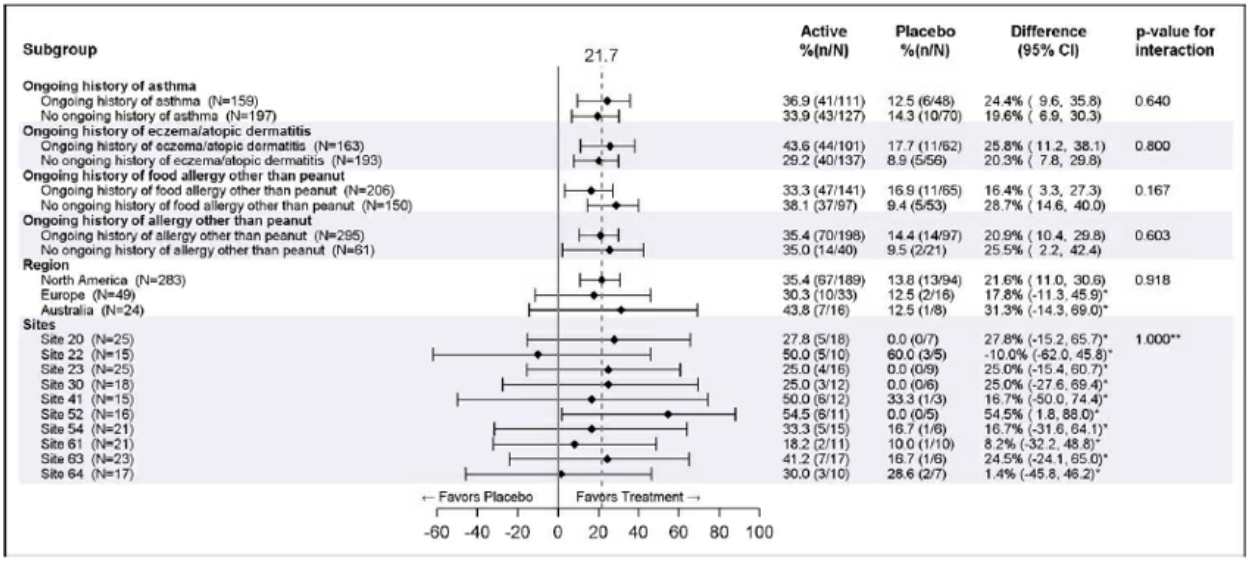
Source: Post-hoc Analysis, V712-301

Footnote Values from MMRM model with log-transformed Eliciting Dose (ED) of Peanut Protein as response variable, timepoint as factor and log-transformed baseline ED value as covariate. Back-transformed results are presented.

Supportive analyses regarding efficacy by age groups and regions are provided below:

Figure 3 Difference in Response Rates at Month 12 between DBV712 250 µg and Placebo by Subgroups ("Missing=Failure" Imputation) – V712-301 Study (ITT Population)





Source: Post-hoc Analysis Figure 10; 2.7.3
Sites with ≥15 subjects only are presented.
Difference in response rate (DBV712 250 µg - Placebo) and two-sided 95% Newcombe CI.
Vertical dotted line represents the difference in response rate (DBV712 250 µg – Placebo) for the overall population.
*Exact 2-sided 95% CIs were provided for any N<50.
**Convergence criterion not met, but quasi-complete separation of data points detected.

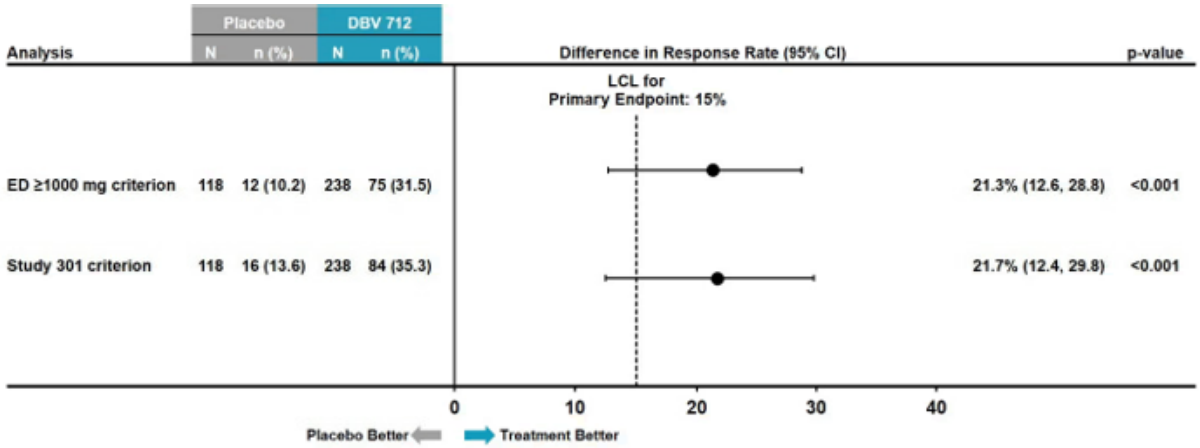
Response Rates by ED ≥1000 mg Criteria (additional analysis D120 response)

The ≥1000 mg endpoint represents a more stringent responder criterion and also provides a single criterion (equivalent to approximately 3-4 peanuts) that needs to be obtained regardless of entry ED. In a post-hoc analysis of V712-301, using a single criterion of subjects reaching an ED of ≥1000 mg, irrespective of baseline ED, a clear statistically significant difference in response rate was observed.

The placebo group had 10.2% (12/118) of subjects meeting this criterion while the DBV712 250 µg group achieved 31.5% (75/235) of subjects. The absolute difference in response rate was 21.3% (95% CI 12.6-28.8; p<0.001), which was almost identical to the primary endpoint treatment effect of 21.7%

(12.4, 29.8; p<0.001), as shown in Figure 4. This analysis further demonstrates both the consistency and the clinical relevance of the treatment effect.

Figure 4 Treatment Responders at Month 12, Sensitivity Analyses on Responder Criterion V712-301 Study (ITT Population, Post-hoc)



Source: Post-hoc Analysis, Study V712-301
LCL: lower confidence limit

Post-hoc analyses on Peanut Protein Eliciting Dose

More subjects treated with DBV712 250 µg reached the highest ED levels of 300, 1000 and 2000 mg compared with subjects who received placebo Table 17).

Table 17 Summary of Month 12 Eliciting Dose by Treatment Group (mBOCF Imputation) – V712-301 Study (ITT Population)

ED at Month 12	DBV712 250 µg (N=238)	Placebo (N=118)
1 mg	1 (0.4%)	1 (0.8%)
3 mg	0	3 (2.5%)
10 mg	6 (2.5%)	19 (16.1%)
30 mg	11 (4.6%)	21 (17.8%)
100 mg	69 (29.0%)	38 (32.2%)
300 mg	**76 (31.9%)**	**24 (20.3%)**
1000 mg	**43 (18.1%)**	**8 (6.8%)**
2000 mg	**32 (13.4%)**	**4 (3.4%)**

Source: Post-hoc Analysis Table 13; 2.7.3
Modified baseline observation carried forward (mBOCF) method for imputation of missing data.

Because any increase in ED is associated with some reduction in risk of accidental ingestion reaction, and therefore potentially is clinically meaningful to a patient and their caregivers regardless of whether the predefined "responder" definition is achieved, it is worth examining results in terms of those whose ED increased by any amount compared with those who did not. As seen in Figure 3.

Response Rates by Tolerated Dose (additional analysis D120 response)

Another way of assessing clinical relevance is the tolerated dose. Table 18 presents the percentage of responders based on a 300 mg tolerated dose and on a 1000 mg tolerated dose by post-hoc analysis of V712-301. As shown, both differences in response rates are statistically significant. The DBPCFC outcomes in studies of DBV712 were assessed using a scoring system and a dosage regimen designed to identify an ED, not a tolerated dose or tolerated dose without doselimiting symptoms. Therefore, the actual tolerated dose in V712-301 may have been higher than estimated in this analysis. However, even with that limitation, it is clear that there is a meaningful difference in the proportion of subjects

who were able to tolerate 300 mg (a single peanut) and 1000 mg (approximately 3 peanuts) between subjects receiving DBV712 250 µg and placebo at Month 12.

Table 18 Response Rates Based on Tolerated Dose – V712-301 Study (ITT Population, Post-hoc)

Treatment response at Month 12 Category Statistics	DBV712 250 µg (N=238)	Placebo (N=118)	Total (N=356)	p-value
Tolerated dose ≥300 mg				
Responders (1)				
n (%)	88 (37)	12 (10.2)	100 (28.1)	
Two-sided Wilson 95% CI	(31.1, 43.3)	(5.9, 16.9)	(23.7, 33)	
Difference in response rates (2)				
DBV712 250 µg - Placebo	26.8			<0.001
Two-sided Newcombe 95% CI	(17.8, 34.4)			
Tolerated dose ≥1000 mg				
Responders (1)				
n (%)	40 (16.8)	4 (3.4)	44 (12.4)	
Two-sided Wilson 95% CI	(12.6, 22.1)	(1.3, 8.4)	(9.3, 16.2)	
Difference in response rates (2)				
DBV712 250 µg - Placebo	13.4			<0.001
Two-sided Newcombe 95% CI	(6.9, 19.1)			

Source: Post-hoc Analysis, Study V712-301
Tolerated dose ≥1000 mg: the subject has started the 2000 mg dose. Tolerated dose ≥300 mg: the subject has started the 1000 mg dose.
(1) Number and percentage of responders and two-sided Wilson 95% CI of the response rate.
(2) Difference in response rates between DBV712 250 µg and Placebo groups and two-sided Newcombe 95% CI.

Treatment Responders by Age Group

Treatment responders at Month 12 by treatment group and by age group are provided in Figure 5.

The response rates were higher in the DBV712 250 µg group compared to placebo both in the 4-5 years age group (difference in response rate: 40.2%; 95% CI: 20.0, 54.9) and in the 6-11 years age group (difference in response rate: 16.1%; 95% CI: 5.3, 22.5). The treatment by age group interaction p-value was 0.119 (Figure 5).

In a post-hoc analysis of age groups, the effect was smaller and not statistically significant for the age-group of 8-11 years with a p-value for interaction of 0.041 (Figure 5). As such, the estimates were 30.8% (18.3;40.8) for 4-6 years old and 11.2% (-3.4;23.4) for 8-11 years old.

Table 19 Analysis of Treatment Responders at Month 12 by Treatment Group and Age Group ("Missing=Failure") Imputation) – V712-301 Study (ITT Population)

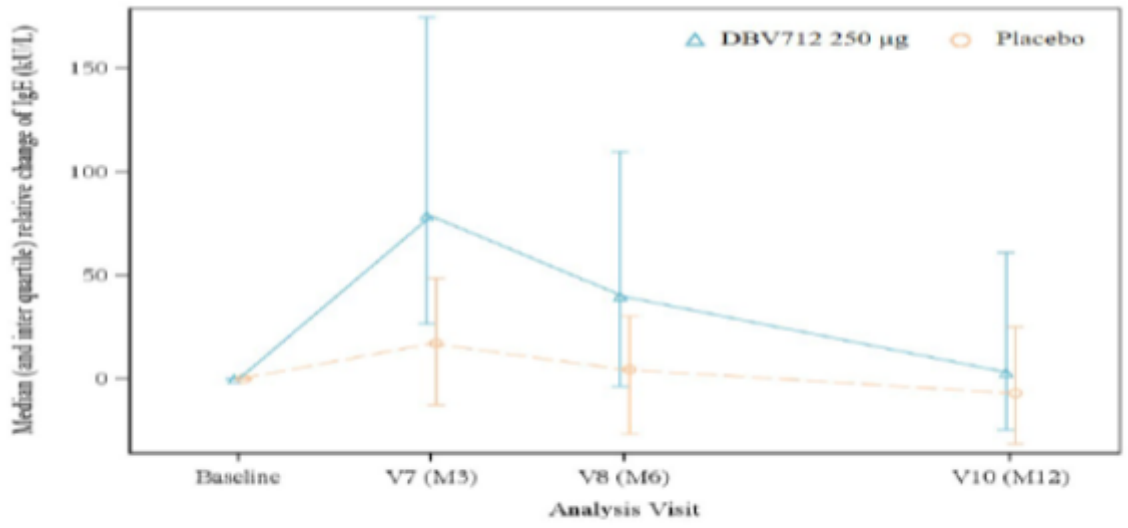
Treatment response at Month 12	DBV712 250 µg	Placebo	p-value
Age group: 4-5 years	**(N=55)**	**(N=32)**	
Responders [1]			
n (%)	29 (52.7%)	4 (12.5%)	
Two-sided Wilson 95% CI	(39.8, 65.3)	(5.0, 28.1)	
Difference in Response Rates [2]			
DBV712 250 µg – Placebo	40.2		<0.001
Two-sided Newcombe 95% CI	(20.0, 54.9)		
Age group: 6-11 years	**(N=183)**	**(N=86)**	
Responders [1]			
n (%)	55 (30.1%)	12 (14.0%)	
2-sided Wilson 95% CI	(23.9, 37.1)	(8.2, 22.8)	
Difference in Response Rates [2]			
DBV712 250 µg – Placebo	16.1	0.001	
Two-sided Newcombe 95% CI	(5.3, 25.2)		

Source: Table 14.2.2.1.2.1; CSR V712-301
Abbreviations: CI = Confidence Interval; ED = Eliciting Dose
Percentages are based on the number of subjects in the ITT population for each treatment group.
A subject is defined as a treatment responder if:
- The screening ED was ≤10 mg peanut protein and the ED is ≥300 mg peanut protein at Month 12; or
- The screening ED was >10 mg peanut protein and the ED is ≥1000 mg peanut protein at Month 12.
Subjects with missing treatment response at Month 12 are imputed as failure (i.e. non-responders).
[1] Numbers and percentages of responders and two-sided Wilson 95% CI of the response rates.
[2] Difference in response rates between DBV712 and Placebo groups and two-sided Newcombe 95% CI. P-value is obtained from a two-sided 5% test to evaluate the null hypothesis of no difference in response rates between treatment groups using Wald Method.

Immunological Markers

In general changes in immunoglobulin levels reflect the characteristic for allergen immunotherapy: increasing of IgE over time bevor it normalises again, increasing of IgG4. However, a pronounced scattering range is noted, especially after DBV712 treatment. The IgE/IgG4 ratio is not shown.

Figure 5 Peanut-Specific IgE 712Over Time by Treatment Group – V712-301 Study (ITT Population)



Source: Figure 6, CSR V712-301 (Fleischer et al, 2019)
Abbreviations: IgE=Peanut-specific immunoglobulin E; M=Month; V=Visit.
Relative change from baseline (expressed as %)=100×(value at the visit–value at baseline)/value at baseline.

The observations are additionally supported by changes in SPT-wheal size, which on average decreased in the DBV712 250 µg group, as compared to placebo. Here again, a pronounced scattering range is observed.

Ancillary analyses

Additional Patch Adhesion Analysis

Guidelines for defining adequate adhesion for epicutaneous allergenic products do not exist. The applicant refers to the FDA and the corresponding Guideline on Transdermal and Topical Delivery Systems - Product Development and Quality Considerations November 2019. In EU, the EMA Guideline on quality of transdermal patches EMA/CHMP/QWP/608924/2014 focuses mainly on transdermal devices, and Cutaneous patches (where the active substance is not intended to be systemically absorbed) are out of the scope of this guideline. However, it pronounces also that some aspects may be relevant and applicable based on the close interphase between transdermal, cutaneous respectively epicutaneous delivery systems. Thus, overlapping quality, non-clinical and clinical issues need consideration also within the development program of the EPIT patch.

Given the lack of precedent for EPIT, and following the Clinical End of Phase 2 meeting with the FDA in May 2015, it was agreed that in vivo adhesion studies would provide the greatest predictor of adequate adhesion of the proposed commercial drug product during use. As such, an adhesion analysis was performed as part of Study V712-301, including among others:

- Collection of Adhesion Data from Subject Diaries

Analysis of Patch Adhesion Based on Grade of Detachment (Adhesion Diary)A patch adhesion assessment was performed in detail over a 28-day period and by daily diary over the whole 12-month study. The main results on the assessment of patch adhesion were as follows:

- The rates of patch detachment (i.e., proportion of patches graded 2 or 3 at the time of patch removal) were higher than the pre-specified maximum rate of 10%, and higher in the DBV712 treatment group compared to the placebo group: 38.7% versus 18.7%, respectively. The mean (SD) duration of application for patches graded 2 or 3 at removal was similar in the DBV712 250 µg treatment group and the placebo group (20.4 [5.43] hours versus 21.2 [5.72] hours, respectively), and close to the recommended 24±4 hours of application.
- Scratching was more frequently reported as a suspected reason leading to patch detachment for DBV712 250 µg patches, than for placebo patches (34.3% versus 11.1%, respectively). This conclusion could also be drawn from the analysis of suspected reasons for patch detachment in subjects with more than 10% of patches scored as 2 or 3: 34.1% versus 10.8%.
- The mean itching scores tended to be higher in the highest detachment deciles, which along with higher baseline peanut-sIgE and lower baseline ED, could indicate a greater overall sensitivity and local reactivity to peanut protein in those subjects experiencing highest patch detachment.
- The rate of responders among subjects with more than 10% of active patches graded 2 or 3, was similar to the rate of responders in the overall active group (33.0% versus 35.3%, respectively).

Summary of main efficacy results

Table 20 Summary of efficacy for V712-301 / PEPITES

Title: A Double-blind, Placebo-controlled, Randomized Phase III Pivotal Trial to Assess the Efficacy and Safety of Peanut Epicutaneous Immunotherapy with Viaskin Peanut in Peanut-allergic Children			
Study identifier	V712-301 / PEPITES EudraCT number: 2015-002461-37 NCT: NCT02636699		
Design	Double-blind, placebo-controlled, randomised study Randomisation of eligible peanut-allergic subjects 4-11 years old occurred in a 2:1 ratio to DBV712 250 µg (active treatment) or placebo. This study was conducted by 31 Primary Investigators in 5 countries (Australia, Canada, Germany, Ireland and United States of America [USA]).		
	Duration of main phase:		12 months
Hypothesis	Superiority		
Treatments groups	DBV712 250 µg		238 subjects received DBV712 250 µg
	Placebo		118 subjects received the placebo
Endpoints and definitions	Primary endpoint	Treatment responders at Month 12	Percentage of treatment responders at month 12 in the DBV712 250 µg group compared to the placebo group using missing=failure imputation. A subject was defined as a treatment responder if: - Baseline ED >10 mg peanut protein and ≥1000 mg peanut protein at M12 DBPCFC; or - Baseline ED ≤10 mg peanut protein and ≥300 mg peanut protein at M12 DBPCFC.
	Secondary	Treatment responders at Month 12 by screening ED group	Percentage of treatment responders at month 12 in the DBV712 250 µg group compared to the placebo group by screening ED group using missing=failure imputation. Screening ED subgroup 1: Children with a screening ED of 1 mg, 3 mg or 10 mg Screening ED subgroup 2: Children with a screening ED of 30 mg, 100 mg or 300 mg
	Secondary	Peanut protein ED	Median ED of peanut protein and change from baseline at month 12 in the DBV712 250 µg group versus the placebo group, in the overall population.
	Secondary	Peanut protein CRD	Median cumulative reactive dose of peanut protein and change from baseline at month 12 in the DBV712 250 µg group versus the placebo group, in the overall population.
	Other prespecified efficacy endpoint	Peanut-specific IgG4 and IgE	Relative change from baseline in peanut-specific IgG4 and IgE at months 3, 6 and 12 in the DBV712 250 µg group versus the placebo group, in the overall population.

	Post Hoc Analysis	Peanut protein ED	Change in ED from baseline to month 12 by treatment group.
	Post Hoc Analysis	Peanut protein ED	Geometric mean ED at baseline and month 12 by treatment group.
	Post Hoc Analysis	Peanut protein ED	Geometric mean ED at month 12 according to baseline sensitivity by treatment group.
	Post Hoc Analysis	Peanut protein ED	Subjects achieving ED of ≥1000 mg at month 12 across baseline sensitivity by treatment group.
	Post Hoc Analysis	Changes in Reaction Severity Assessed by DBPCFC at baseline and Month 12	Maximum severity of objective signs/symptoms to peanut by treatment group during month 0 and month 12 DBPCFC.
	Post Hoc Analysis	Changes in Reaction Severity Assessed by DBPCFC at baseline and Month 12	Maximum severity of 5 key objective signs/symptoms (wheezing, cardiovascular, laryngeal, vomiting, diarrhoea) to peanut by treatment group during month 0 and month 12 DBPCFC.

Database lock	13 October 2017		
Results and Analysis			
Analysis description	Primary Analysis: Treatment responders at month 12 in the overall population (4-11 years old)		
Analysis population and timepoint description	ITT Results at Month 12		
Descriptive statistics and estimate variability	Treatment group	DBV712 250 µg	Placebo
	Number of subjects	N=238	N=118
	Responders n (%) Two-sided Wilson 95% CI	 84 (35.3%) 29.5, 41.6	 16 (13.6%) 8.5, 20.9

	Difference in Response Rate DBV712 250 µg – Placebo Two-sided Newcombe 95% CI p-value DBV712 250 µg vs Placebo (based on two-sided Wald test)	 21.7 12.4, 29.8 <0.001	
Notes	For subjects with missing treatment response at Month 12, missing=failure imputation was used (i.e. subjects are considered as non-responders). After 12 months, a larger proportion of subjects in the DBV712 250 µg group (84/238 (35.3%) subjects) were defined as treatment responders (based on above, note different responder definition in subgroups) compared to the placebo group (16/118 [13.6%] subjects). There was a statistically significant difference in the response rates of 21.7% (in favour of DBV712 250 µg: p-value <0.001). The 95% CI of this difference was (12.4, 29.8), thus the pre-specified criterion of a lower bound of the CI (≥15%) of the difference was not achieved. Overall, 10.1% of subjects discontinued the study; the discontinuation rates were similar between treatment groups: 10.5% vs 9.3% of subjects in the DBV712 250 µg group and the placebo group, respectively. The most frequent reason for study discontinuation was withdrawal of consent, 5.5% vs 5.1% of subjects in the DBV712 250 µg and placebo groups, respectively. The proportion of subjects who withdrew due to adverse events was 1.7% in the DBV712 250 µg group and no subjects in the placebo group.		
Analysis description	Secondary Analysis (pre-specified): Treatment responders at month 12 by screening ED subgroup		
Analysis population and timepoint description	ITT Results at Month 12		
Descriptive statistics and estimate variability	Treatment group	DBV712 250 µg	Placebo
	Screening ED subgroup 1: Children with a screening ED of 1 mg, 3 mg or 10 mg		
	Number of subjects	N=41	N=20
	Responders n (%) Two-sided Wilson 95% CI	 16 (39.0%) 25.7, 54.3	 4 (20.0%) 8.1, 41.6

	Difference in Response Rate DBV712 250 µg – Placebo	19.0	
	Two-sided Newcombe 95% CI	-6.4, 38.4	
	p-value (based on two-sided Wald test)	0.105	
	Screening ED subgroup 2: Children with a screening ED of 30 mg, 100 mg or 300 mg		
	Number of subjects	N=197	N=98
	Responders n (%) Two-sided Wilson 95% CI	68 (34.5%) 28.2, 41.4	12 (12.2%) 7.1, 20.2
	Difference in Response Rate DBV712 250 µg – Placebo	22.3	
	Two-sided Newcombe 95% CI	12.1, 30.8	
	p-value (based on two-sided Wald test)	<0.001	
Notes	Note that due to different response definition in the above subgroups results may not be fully comparable. Subjects with missing treatment response at Month 12 were imputed as failure (i.e. non-responders). Responder rates were similar in the two pre-defined subgroups of subjects treated with DBV712 250 µg: 39.0% in those more sensitive subjects who entered with an ED of ≤10 mg, and 34.5% in those who began the study with an ED >10 mg and ≤300 mg.		
Analysis description	Secondary Endpoint (pre-specified): ED (mg) of peanut protein and change from baseline at month 12 in the overall population (4-11 years old)		
Analysis population and timepoint description	ITT Results at Baseline, Month 12, and change from baseline		
Descriptive statistics and estimate variability	Treatment group	DBV712 250 µg	Placebo
	Number of subjects	N=238	N=118

	Baseline Median Q1, Q3	 100.0 30.0, 300.0	 100.0 30.0, 300.0
	Month 12 Median Q1, Q3	 300.0 100.0, 1000.0	 100.0 30.0, 300.0
	Change from baseline Median Q1, Q3	 200.0 0.0, 700.0	 0.0 -70.0, 7.0
Notes	Modified Baseline Observation Carried Forward (mBOCF) method for imputation of missing data. Following 12 months of treatment, the group treated with DBV712 250 µg experienced a median ED increase of 200 mg, while that of the placebo group was unchanged.		
Analysis description	Secondary Endpoint (pre-specified): CRD (mg) of peanut protein and change from baseline at month 12 in the overall population (4-11 years old)		
Analysis population and timepoint description	ITT Results at Baseline, Month 12, and change from baseline		
Descriptive statistics and estimate variability	Treatment group	DBV712 250 µg	Placebo
	Number of subjects	N=238	N=118
	Baseline Median Q1, Q3	 144.0 44.0, 444.0	 144.0 44.0, 444.0
	Month 12 Median Q1, Q3	 444.0 144.0, 1444.0	 144.0 44.0, 444.0
	Change from baseline Median Q1, Q3	 280.0 0.0, 1000.0	 0.0 -100.0, 100.0
Notes	Modified Baseline Observation Carried Forward (mBOCF) method for imputation of missing data. Following 12 months of treatment, the group treated with DBV712 250 µg experienced a median CRD increase of 280 mg, while that of the placebo group was unchanged.		
Analysis description	Other efficacy endpoint (pre-specified): Peanut-specific IgG4 (mg/L) over time in the overall population (4-11 years old)		
Analysis population and timepoint description	ITT Relative change from Baseline to Month 3, Month 6, Month 12		
Descriptive statistics and estimate variability	Treatment group	DBV712 250 µg	Placebo
	Number of subjects	N=238	N=118

	Relative change from Baseline to Month 3 N Median Q1, Q3	 231 127.778 55.660, 259.615	 115 14.286 0.000, 45.833
	Relative change from Baseline to Month 6 N Median Q1, Q3	 229 258.491 107.843, 549.351	 110 11.492 -9.677, 42.105
	Relative change from Baseline to Month 12 N Median Q1, Q3	 224 513.487 196.458, 1105.235	 109 10.496 -10.108, 33.333
Notes	Following initiation of treatment with DBV712 250 µg, increases in peanut-specific IgG4 levels consistent with immunomodulation were apparent at Month 3, when first assessed, and continued to increase until Month 12, with no change seen in the placebo group.		
Analysis description	Other efficacy endpoint (pre-specified): Peanut-specific IgE (kU_A/L) over time in the overall population (4-11 years old)		
Analysis population and timepoint description	ITT Relative change from Baseline to Month 3, Month 6, Month 12		
Descriptive statistics and estimate variability	Treatment group	DBV712 250 µg	Placebo
	Number of subjects	N=238	N=118
	Relative change from Baseline to Month 3 N Median Q1, Q3	 232 78.716 26.557, 174.588	 115 16.964 -12.591, 48.802
	Relative change from Baseline to Month 6 N Median Q1, Q3	 229 39.716 -3.676, 109.690	 111 4.605 -26.380, 30.352
	Relative change from Baseline to Month 12 N Median Q1, Q3	 224 2.858 -24.739, 61.058	 108 -6.919 -31.468, 25.291
Notes	Also consistent with immunomodulation related to immunotherapy, and with what was observed in Phase 2, peanut-specific IgE levels increased initially following start of DBV712 250 µg treatment, before declining back towards baseline by Month 12. This pattern is well-described in injection forms of immunotherapy for inhalant and venom allergens.		

Analysis performed across trials (pooled analyses and meta-analysis)

Results from the population of children under the age of 12 in the Phase 2 study (V712-202; 6-11 years) and the pivotal Phase 3 study (V712-301; 4-11 years) have been presented. Analysing V712-202 data by applying the definition of treatment response used in study V712-301 also provides a comparison across the two studies.

In principle, studies support each other, although relevant efficacy data are only derived from the V712-301 study as single pivotal study. However, it remains to discuss, if the gained effect is clinically relevant. The mean dose leading to symptoms was 576.0 mg peanut protein (SD 648.19) in the active group vs 235.8 mg (SD 413.42) in the placebo group in V712-301 and 625.5 mg (SD 766.93; active) vs 160.5 mg (SD 244.0; placebo) in V712-202.

Of note, analysis was performed post-hoc. As such, the value of the “adoption” of criteria according to a “more or less stringent” primary endpoint from study V712-301 to V712-202 is to consider with reservations. The same is true for “selected” age distributions within the post-hoc analysis. In the PEPITES trial a higher response rate was analysed in the 4-5 years age group, 40.2% (95% CI: 20.0, 54.9) compared to 6-11years old children (response rate 16.1%; 95% CI: 5.3, 22.5). In the VIPES trial, only 6-11 year old children had been included. Thus, a post-hoc analysis across studies including age-matched data sets is considered as more consequent.

As already pointed out within the analysis of the VIPES study V712-202, the Mean (SD) peanut protein eliciting dose in the placebo group of the VIPES study was 121.2 (122.27), Median 100.0. In DBV712 250 ug treated children the mean was 58.9 (63.54), Median 30 mg. In V712-301, for DBV712 and placebo, the Mean (SD) peanut protein eliciting dose was around 140mg, median 100mg. Thus, children in the placebo group of the VIPES study V712-202 reacted already at baseline at lower EDs (being more sensitive). This observed heterogeneity and its consequence for gained efficacy results between EDs according to treatment groups in studies V712-301 to V712-202 has not been addressed.

Clinical studies in special populations

Data is provided for children (the pivotal study V712-301 (PEPITES) included children aged 4-11 years; study V712-202 was conducted on subjects 6-55 years). For this population (children aged 4-11 years) the indication is sought. There were no studies in patients with renal or hepatic impairment. Generally, allergen immunotherapy is not dependent on renal or hepatic impairment.

Supportive study(ies)

The supportive (efficacy) studies include

- V712-201-E (ARACHILD),
- V712-204-E (CoFAR) and the
- V712-303 (PEOPLE), ongoing extension study to V712-301 (PEPITES)

Phase 2a V712-201-E (ARACHILD) Pilot Study

Study Design and Methodology

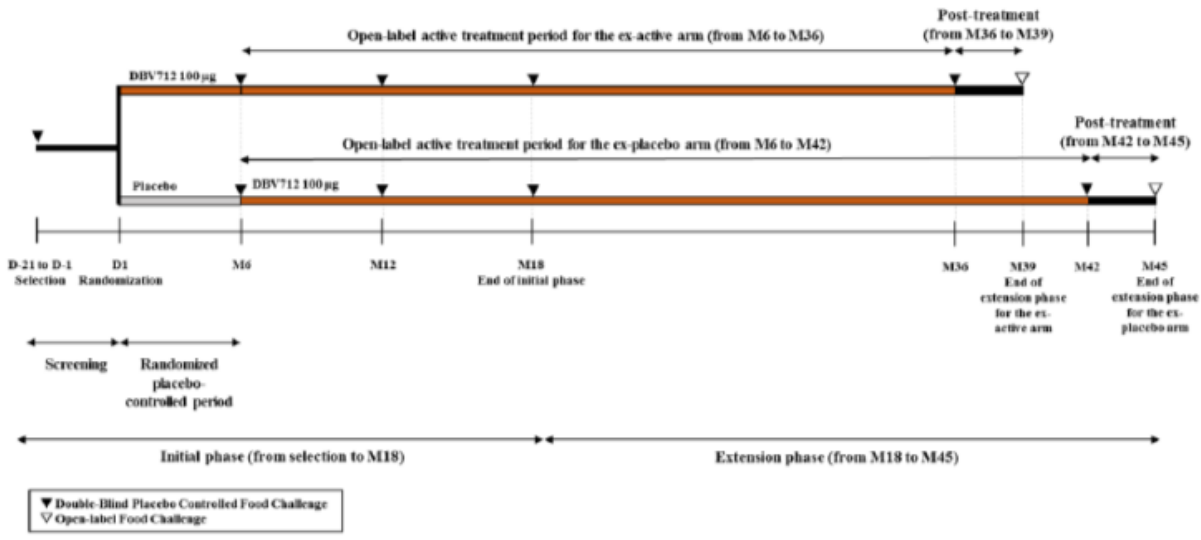
A national (France) multicenter, prospective, double-blind, randomized (1:1 ratio), placebo-controlled pilot Phase 2a study, followed by an open-label active treatment period in peanut-allergic subjects aged 5 to 17 years; conducted from 28 September 2010 to 10 December 2014

Diagnosis and main inclusion/exclusion criteria

- Male or female between 5 and 17 years, with documented peanut allergy (i.e., peanut-specific immunoglobulin (Ig) E [IgE] >5 kU/L and/or positive skin prick test [SPT] to peanut [wheal diameter ≥8 mm]), who provided their informed consent (including informed consent from their parents/legal guardians), and who met the following criteria:
    - Subject reacting to a cumulative dose of peanut protein <300 mg during the baseline DBPCFC, with no reaction to placebo (randomization criterion);
    - No history of anaphylactic shock to peanut; No breathing difficulty or uncontrolled asthma; No diabetes or immune deficiency; No generalized non-controlled eczema or extensive skin lesions precluding the application of the patches.

Study Design

Figure 6 Schematic of Study Design



Ex-active arm corresponds to subjects initially randomized in the active arm. Ex-placebo arm corresponds to subjects initially randomized in the placebo arm.
The participation in the extension phase was optional. Open-label Food Challenge was to be performed only in eligible subjects, depending on the results of their last Double-Blind Placebo-Controlled Food Challenge (DBPCFC).
D: Day; M: Month.

Duration of treatment

DBV712 (overall active treatment duration, including both double-blind and open-label periods, hereafter “active treatment period”): subjects were treated with DBV712 from 1 to 3 years, depending on their initial treatment arm and whether they participated or not in the extension phase:

-12 months (M6 to M18) for subjects of the ex-placebo arm who participated only in the initial phase;

-18 months (D1 to M18) for subjects of the ex-active arm who participated only in the initial phase;

-36 months for subjects who participated in the extension phase (from M6 to M42 for the ex-placebo arm; and from D1 to M36 for the ex-active arm). Viaskin Placebo: 6 months (from D1 to M6) for subjects randomized in the placebo arm.

SUMMARY OF RESULTS AND CONCLUSIONS

Subject disposition

A total of 60 subjects were screened. Of them, 54 were included and randomized to DBV712 100 µg (28 subjects) or Placebo (26 subjects) for 6 months. Of the 47 subjects who completed the initial phase, 30 agreed to participate in the extension phase and 24 completed the full study.

Demography and baseline characteristics

54 randomized subjects, 61.1% were male, mean age (± standard deviation [S.D.]) was 10.9 ± 3.1 years. 35 subjects (64.8%) were children aged 5 to 11 years. 81.5% had a family history of atopy and personal history of eczema (79.6%). 63.0% reported other food allergies in addition to peanuts. At baseline, median peanut wheal size (SPT) was 10.0 mm, and median CRD was 16.3 mg. Overall, demographic and baseline characteristics were comparable between treatment arms.

EFFICACY RESULTS:

Primary Efficacy Analysis:

Proportion of subjects who reached a CRD of peanut protein >1,000 mg, or a greater than 10-fold increase in CRD from baseline as determined during the DBPCFC at M6.

In the FAS, the responder rate after 6 months of treatment was comparable between treatment arms: there were 2/27 (7.4%) responders in the active arm *versus* 2/26 (7.7%) in the placebo arm. All 4 responders were children aged 5 to 11 years at screening.

Primary efficacy endpoint — All subjects and by age subgroup (FAS)

	DBV712 100 µg (N=27)	**Placebo (N=26)**
Responders at M6 — All subjects		
N_{All}	27	26
n (%)	2 (7.4%)	2 (7.7%)
95% CI	[0.9%, 24.3%]	[0.9%, 25.1%]
Responders at M6 — Children aged [5;11] years		
$N_{Subgroup}$	16	19
n (%)	2 (12.5%)	2 (10.5%)
95% CI	[1.6%, 38.3%]	[1.3%, 33.1%]
Responders at M6 — Adolescents aged [12;17] years		
$N_{Subgroup}$	11	7
n (%)	0 (0.0%)	0 (0.0%)
95% CI	[0.0%, 28.5%]	[0.0%, 41.0%]

N_{All}/$N_{Subgroup}$: Number of subjects with data in all subjects/in each considered age subgroup.
CI: confidence interval; FAS: full analysis efficacy set; M: Month.

Main Conclusions on Efficacy Results in Study V712-201-E

In this pilot Phase 2a study, DBV712 at the suboptimal dose of 100 µg did not show any efficacy after 6 months of treatment for desensitising peanut allergic patients. However, exploratory analyses suggest that a longer treatment of at least 12 months could be beneficial to subjects aged 5-11 years. These long-term data up to 36 months should be considered with caution in view of the methodological bias and the absence of a placebo control group, precluding any firm conclusion.

Phase 2b V712-204-E (CoFAR)

Study Design and Methodology

A randomized, double-blind, placebo-controlled, Phase II Study in peanut-allergic subjects aged 4 to 25 years; aiming at efficacy and safety of DBV712 at 2 different doses (100 µg and 250 µg); conducted from 21 October 2013 to 21 August 2018 consisted of

- A randomised, double-blind, placebo-controlled period for 52 weeks (12 months) and
- An open-label active treatment part with DBV712 250 µg for up to 130 weeks (30 months).

Primary Objective

The primary objective was to identify an effective Viaskin® Peanut patch treatment dose to induce a desensitized state that would protect participants from allergic reactions following accidental peanut ingestions. An increase in the cumulative tolerated dose following 5044 mg of peanut protein oral food challenge (OFC) after 52 weeks of therapy was analysed.

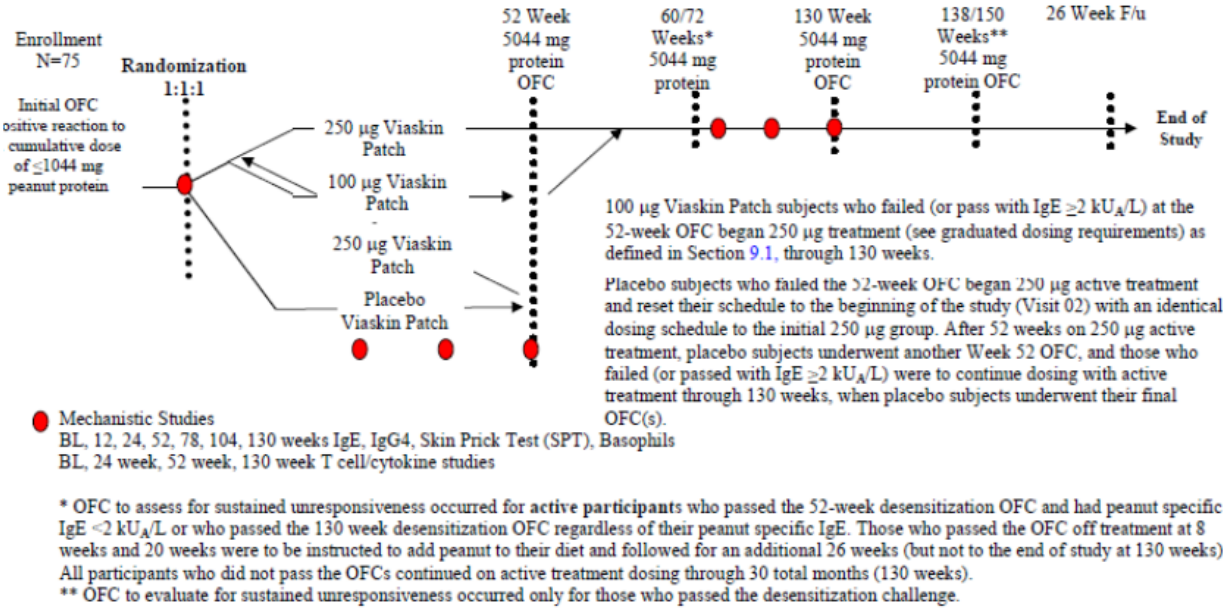
Diagnosis and main inclusion/exclusion criteria

Main Inclusion Criteria: Peanut sensitized children and adults with peanut allergy, Ages 4 to 25 years; and a positive reaction to cumulative dose of <1044 mg peanut protein in the initial qualifying OFC.

Main Exclusion Criteria: History of severe anaphylaxis to peanut; Severe or poorly controlled atopic dermatitis; Use of systemic steroid medications, Use of omalizumab or other non-traditional forms of allergen immunotherapy or immunomodulatory or biologic therapy in the past year, Use of beta-adrenergic blockers, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, or calcium channel blockers in the past 30 days; History of cardiovascular disease, uncontrolled hypertension, arrhythmias, chronic lung disease, active eosinophilic gastrointestinal disease, or other medical conditions including immunologic disorders or HIV infection.

Study Design

Figure 7 CoFAR6 Peanut EPIT Study: Overall Schematic (Ages 4-25)



EFFICACY RESULTS

Primary Efficacy Analysis

Treatment Responders at 52 Weeks

A treatment responder was defined as a subject who could consume a cumulative dose ≥5044 mg of peanut protein or with a ≥10-fold increase in cumulative dose of peanut protein at the 52-week DBPCFC, when compared to the baseline DBPCFC.

Table 21 Oral Food Challenge Results at Week 52 by Treatment Group (All Participants)-Analysis Population[1]

Week 52 OFC Results	Placebo (N=25)	VP100 (N=24)	VP250 (N=25)	Total (N=74)
Success[2] – n (%)	3 (12.0)	11 (45.8)	12 (48.0)	26 (35.1)
Passed OFC[3]	1 (4.0)	0	0	1 (1.4)
Met Tenfold Increase	2 (8.0)	11 (45.8)	12 (48.0)	25 (33.8)
Failure – n (%)	22 (88.0)	13 (54.2)	13 (52.0)	48 (64.9)
Failed OFC, not Tenfold Increase	19 (76.0)	10 (41.7)	13 (52.0)	42 (56.8)
Withdrew/ Discontinued Dosing	3 (12.0)	3 (12.5)	0	6 (8.1)
Pairwise Comparison to Placebo[4]		0.005	0.003	

Data source Table 14.2.1.1.1
Note: [1]The analysis population includes all treated participants and excludes one untreated participant.
[2]Logistic regression results showed a significant interaction between treatment and age for this outcome (p=0.006).
[3]Exact 95% confidence intervals were: Placebo (0.1%, 20.4%), VP100 (0%, 14.3%) and VP250 (0%, 13.7%).
[4]Barnard's one-sided exact pairwise test was used to make comparison between treatment groups and placebo. Note that similar comparison between VP250 and VP100 resulted in p-value=0.480.

Secondary Efficacy Analyses

Secondary and tertiary objectives included assessment of desensitisation, as defined below, at Week 130, as well as other endpoints at Weeks 52 and 130 presented below.

Table 22 Oral Food Challenge Desensitisation[1] Results by Treatment Group (Ages 4 to 11) Analysis Population Subset[2] – V712-204-E Study

	Placebo/Placebo Crossover[3] (N=18/N=16)		DBV712 100 µg (N=17)		DBV712 250 µg (N=18)		Total (N=53/N=51)	
	n (%)	95% Exact CI	n (%)	95% Exact CI	n (%)	95% Exact CI	n (%)	95% Exact CI
Week 52 Desensitization Success[4]	0	(0.0, 18.5)	2 (11.8)	(1.5, 36.4)	5 (27.8)	(9.7, 53.5)	7 (13.2)	(74.7, 94.5)
SCD>=444 mg, Baseline SCD=0 to 44 mg	0		1 (5.9)		5 (27.8)		6 (11.3)	
SCD>=10 times Baseline SCD of >44 to <444 mg	0		1 (5.9)		0		1 (1.9)	
Crossover Week 52 Desensitization Success[5]	3 (18.8)		na		na			
SCD>=444 mg, Baseline SCD=0 to 44 mg	2 (12.5)	(4.0, 45.6)	na	na	na	na		na
SCD>=10 times Baseline SCD of >44 to <444 mg	1 (6.3)		na		na			
Week 130 Desensitization Success[6]	1 (6.3)	(0.2, 30.2)	4 (23.5)	(6.8, 49.9)	9 (50.0)	(26.0, 74.0)	14 (27.5)	(15.9, 41.7)
SCD>=444 mg, Baseline SCD=0 to 44 mg	1 (6.3)		4 (23.5)		9 (50.0)		14 (27.5)	

Source: Table 14.2.1.3.2; CSR V712-204-E

[1]Desensitization was based on the successfully consumed dose (SCD) at baseline (BL) (in mg protein): SCD>=444 mg if BL SCD=0 to 44 mg, SCD>=10 times BL SCD if BL SCD>44 to <444 mg,
SCD=5044 mg if BL SCD>=444 to <1044 mg.

[2]The analysis population subset includes only treated participants who were 4 to 11 years of age at enrolment.

[3]Only Placebo participants who were 4 to 11 years of age at time of crossover were used in the calculations for Crossover Week 52 and Week 130.

[4]Barnard's two-sided exact test p-values are: Placebo vs. DBV712 100 µg p-value=0.18, Placebo vs. DBV712 250 µg p-value=0.017, DBV712 100 µg vs. DBV712 250 µg p value=0.27.

[5]None of the Placebo Crossover participants passed the Crossover Week 52 oral food challenge.

[6]The initial Week 52 OFC SCD used as baseline for Placebo Crossover participants; 1 had a Week 52 OFC SCD >1044 mg but a Week 130 OFC SCD < 5044 mg and was considered a failure.

Main Conclusions on Efficacy Results in Study V712-204-E

Study V712-204-E was a 52-week randomised, double-blind, placebo-controlled study to evaluate the efficacy of DBV712 at 2 doses (100 µg and 250 µg) with an open-label extension out to a total study duration of 130 weeks.

After 52 weeks of treatment, the response rate was higher in both active treatment groups compared with the placebo group, but no statistically significant difference was observed between the 2 doses. The treatment effect was more robust in subjects aged 4-11 years.

Following the open label extension, with treatment at 250 µg up until week 130 for all subjects, more subjects randomised to the DBV712 250 µg group from baseline reached some level of desensitisation success when compared with those who began the study on placebo or DBV712 100µg. Notably, successes were reached in subjects who were more sensitive to peanut and predominantly among 4-11-year-old subjects. While the study was not powered to look for differences in desensitisation between Week 130 and Week 52, the observation that 50% of 4-11-year-old children treated with DBV712 250 µg achieved desensitisation success at week 130 compared with only 27.8% at week 52 is consistent with the continued treatment response seen beyond 12 months in Study V712-303.

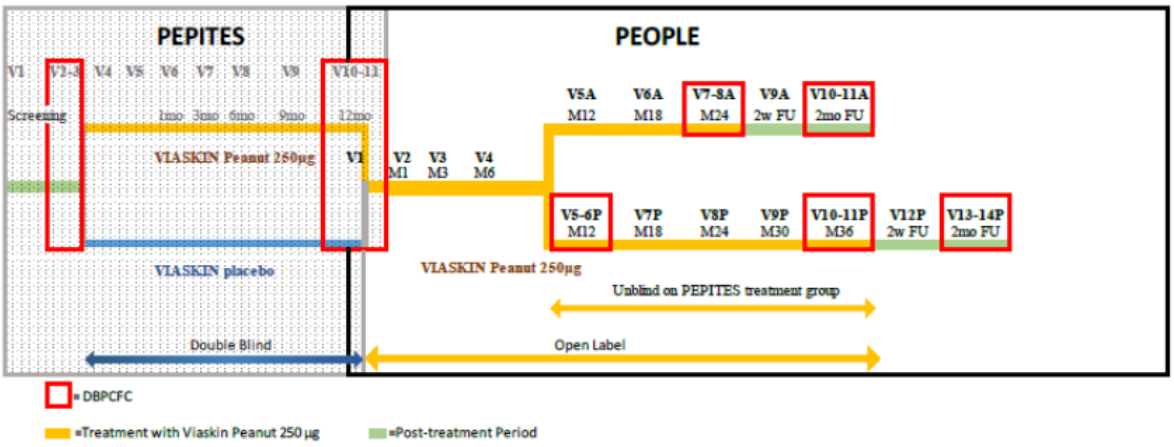
Phase 3 V712-303 (PEOPLE) - Ongoing extension study to V712-301 (PEPITES)

Study Design and Methodology

Study V712-303 is an ongoing open-label, multicentre, follow-up study to assess the long-term efficacy and safety of DBV712 250 µg after up to 5 years of EPIT in children who have completed V712-301.

Date first subject enrolled on 23th of January 2017. The study is ongoing. Data cut-off date for the 3-year analysis of the VP250+VP250 group (last subject last visit of the 3-year treatment period including the two-months off-treatment period for the group of subjects who previously received DBV712 250 µg in the V712-301 study): 28 November 2019.

Figure 8 Study Design for the 3-year treatment period of the V712-303 study



DBPCFC = Double-blind placebo-controlled food challenge; FU = follow-up; mo = month; w = week.
The DBPCFC at 2 months follow-up will only be performed for subjects reaching an ED ≥1,000 mg at the 3-year DBPCFC (subject to signature of a specific informed consent).

OBJECTIVES:

- To assess the clinical benefit of DBV712 250 µg after up to 36 months of Epicutaneous Immunotherapy (EPIT) to induce/maintain desensitization to peanut in peanut-allergic children.
- To explore the clinical benefit of DBV712 250 µg after up to 5 years of EPIT to induce/maintain desensitization to peanut in peanut-allergic children.
- To assess the sustained unresponsiveness to peanut (Eliciting Dose [ED] ≥1000 mg) after two months of treatment discontinuation.
- To evaluate the safety of long-term treatment with DBV712 250 µg in peanut-allergic children.
- To explore novel biomarkers that may be predictive of the clinical response.

The study is an extension to the PEPITES trial, please refer to PEPITES for description of the study and its participants.

In total, 300 subjects consented to participate in the V712-303 study and 198 subjects were screened and enrolled in the DBV712+DBV712 group. All these subjects were treated and 151 (76.3%) completed the 3-year treatment period until Month 36 (i.e. second day of the Month 36 DBPCFC and end of treatment form completed). Forty-seven (23.7%) subjects discontinued the treatment before Month 36 due to withdrawal of consent (19.2%), lost to follow-up (2.5%) or adverse event (2.0%).

Efficacy Results

Main Peanut Desensitisation Endpoint

The main endpoint for assessing peanut desensitisation was the percentage of subjects reaching an ED ≥1000 mg after 3 years of active treatment overall in the DBV712+DBV712 group compared to the percentage after 1 year of active treatment (end of the V712-301 study).

The difference between Month 12 and Month 36 in the percentage of subjects reaching an ED ≥1000 mg (95% CI) was 8.1% (-0.5; 16.5) for the Completer Population (Table 23). At Month 36, 49.3% of subjects reached an ED ≥1000 mg vs 41.2% at Month 12.

Table 23 Percentage of Subjects Reaching an Eliciting Dose ≥1000 mg – Primary Analysis – DBV712+DBV712 Group – V712-303 Study (Completer Population)

	DBV712+DBV712 (N=148)
Month 12	
n / N	61 / 148
% and 95% CI (a)	41.2 [33.6 ; 49.3]
Month 36	
n / N	73 / 148
% and 95% CI (a)	49.3 [41.4 ; 57.3]
Difference between Month 12 and Month 36	
n / N	12 / 148
Difference in % and 95% CI (b)	8.1 [-0.5 ; 16.5]

Source: Table 14.2.1.1; CSR V712-303 (Fleischer and Shreffler et al, 2020)
CI: Confidence Interval.
(a) Wilson score method.
(b) Newcombe method based on Wilson score intervals with continuity correction for the difference between paired binomial proportion.

Data within D120 responses:

A total of 148 subjects completed the extension period having evaluable DBPCFC data, with 141 subjects who did not have major deviations (per protocol [PP] analysis).

22% of subjects decreased their ED

78% (110/141) of subjects in the PP analysis of this open-label extension either maintained or increased their ED from Month 12 to Month 36.

67.4% (62/92) of subjects that had a baseline ED of <100 mg at the start of Study V712-301 were able to achieve a Month 36 ED of ≥300 mg.

51.8% (73/141), reached an ED of ≥1000 mg at Month 36, which was an improvement relative to Month 12 (40.4%; 57/141).

35 of 141 (24.8%) of subjects (PP analysis) reached an ED of ≥2000 mg.

18.4% (26/141) were able to consume a 3444 mg cumulative dose (the total amount of peanut protein consumed during the DBPCFC) at exit challenge,

13.5% (19/141) of subjects able to consume the entire food challenge of 5444 mg of peanut protein, which is equivalent to approximately 18 peanut kernels.

78% (110/141) of subjects in the PP analysis of this open-label extension either maintained or increased their ED from Month 12 to Month 36.

Peanut protein eliciting dose, n (%)

	Month 12		Month 36	
Category	Responder (N = 61)	Non Responder (N = 87)	Responder (N = 73)	Non Responder (N = 75)
n	61	87	73	75
1 mg	0	1 (1.1)	0	1 (1.3)
3 mg	1 (1.6)	4 (4.6)	1 (1.4)	4 (5.3)
10 mg	4 (6.6)	12 (13.8)	3 (4.1)	13 (17.3)
30 mg	4 (6.6)	14 (16.1)	8 (11.0)	10 (13.3)
100 mg	23 (37.7)	35 (40.2)	24 (32.9)	34 (45.3)
300 mg	29 (47.5)	21 (24.1)	37 (50.7)	13 (17.3)

N is the number of subjects in each subgroup of responder status
Responder is defined as Eliciting Dose ≥1000 mg at the Month 12 and the Month 36 DBPCFC
SD: Standard deviation; Q1: first quartile; Q3: third quartile
Percentages are based on the number of subjects with non missing values for each group

Category	Responder M12 & Responder M36 (N = 46)	Responder M12 & Non Responder M36 (N = 15)	Non Responder M12 & Responder M36 (N = 27)	Non Responder M12 & Non Responder M36 (N = 60)
n	46	15	27	60
1 mg	0	0	0	1 (1.7)
3 mg	0	1 (6.7)	1 (3.7)	3 (5.0)
10 mg	2 (4.3)	2 (13.3)	1 (3.7)	11 (18.3)
30 mg	3 (6.5)	1 (6.7)	5 (18.5)	9 (15.0)
100 mg	17 (37.0)	6 (40.0)	7 (25.9)	28 (46.7)
300 mg	24 (52.2)	5 (33.3)	13 (48.1)	8 (13.3)

N is the number of subjects in each subgroup of responder status
Responder is defined as Eliciting Dose ≥1000 mg at the corresponding DBPCFC
SD: Standard deviation; Q1: first quartile; Q3: third quartile
Percentages are based on the number of subjects with non missing values for each group

Other Peanut Desensitisation Endpoints

Geometric Mean Eliciting Dose (GMED) (additional analysis D120 response)

Table 24 GM ED at Month 0, 12 and 36 of Treatment – V712-303 Study (Completer Set)

	DBV712 250 µg (N=148)
Baseline (log-transformed data)	
n	148
Adjusted Geometric Means (SE)	84.0 (1.09)
Adjusted 95% CI	(70.48; 100.23)
Month 12 (log-transformed data)	
n	148
Adjusted Geometric Means (SE)	386.7 (1.09)
Adjusted 95% CI	(324.31; 461.19)
Month 36 (log-transformed data)	
n	148
Adjusted Geometric Means (SE)	425.0 (1.09)
Adjusted 95% CI	(356.42; 506.86)

Source: Table 14.2.2.2.2.1; CSR V712-303
SE = standard error; CI = confidence interval; ED = eliciting dose; MMRM = mixed model repeated measures.
Values from MMRM model with log-transformed ED of peanut protein as response variable, timepoint as factor and log-transformed baseline ED value as covariate. Back-transformed results are presented.

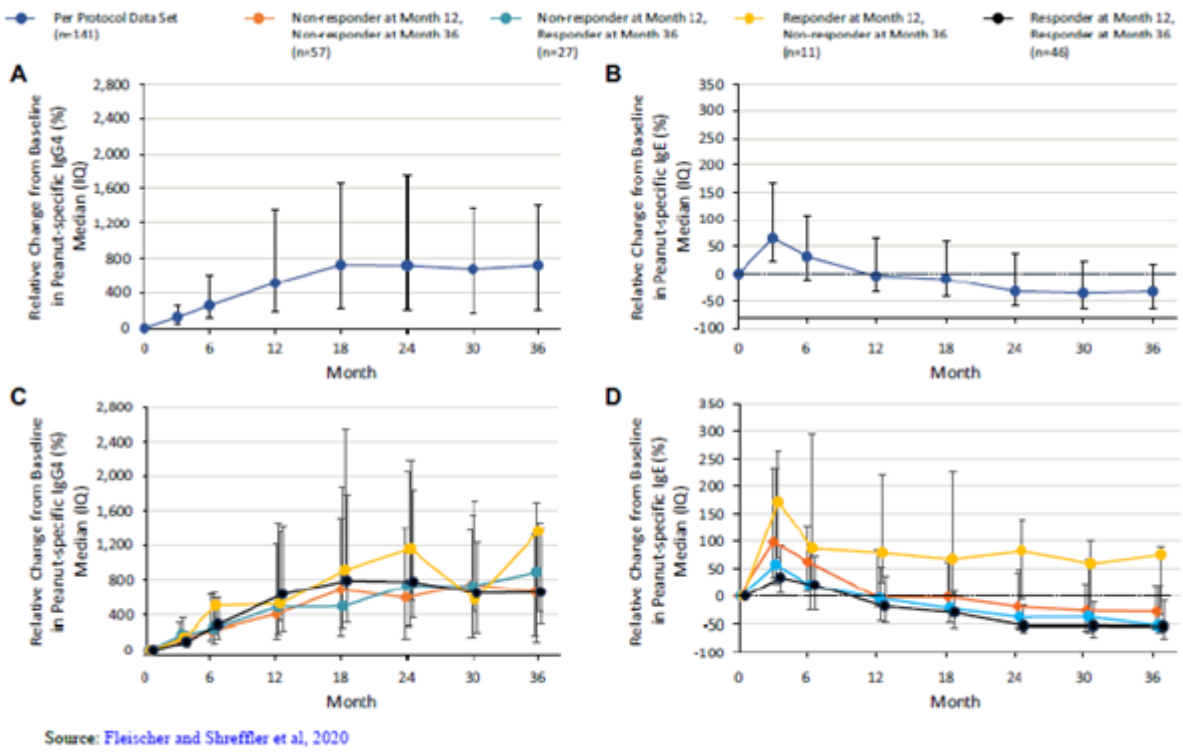
	DBV712+DBV712 (N=148)
Min ; Max	-1990 ; 1900

Source: Table 14.2.2.2.1.1; CSR V712-303 (Fleischer and Shreffler et al, 2020)
SD: Standard Deviation; Q1: first quartile; Q3: third quartile.

Immunological Markers

Figure 9 shows the median relative changes from baseline in peanut sIgG4 and sIgE, respectively, plotted by timepoint from V712-301. These serologic results demonstrate ongoing immunomodulation consistent with what is seen in other forms of allergen immunotherapy. DBV712 treatment has been associated with a marked increase from baseline in peanut-specific IgG4 levels, beginning as early as 3 months following treatment initiation. The effect persists through the first 18 months and then remains elevated over baseline up to Month 36 of treatment. Peanut-specific IgE levels also have been observed to increase at Month 3, before declining back towards baseline by Month 12 and then declining below baseline by 24-36 months of treatment. These changes are illustrated in the figures below from the pivotal Phase 3 study (placebo controlled for first 12 months, followed by open label). Similar trajectories are noted with component testing to major allergens (data not shown). Peanut-specific and component IgE/IgG4 ratios have been investigated as well, and corresponding trends are observed.

Figure 9 Relative change from baseline in peanut-sIgG4 and -sIgE over the 3-year treatment period in the per protocol data set (n=141) and by responder group – V712-301 Study



Source: Fleischer and Shreffler et al, 2020

Sustained Unresponsiveness

Table 25 Percentage of Subjects Reaching an ED≥1000 mg at Month 36 and Month 38 – Sustained – DBV712+DBV712 – V712-303 Study (Completer Population)

	DBV712+DBV712 (N=18)
Month 36	
n / N	18 / 18
% and 95% CI (a)	100.0 [82.4 ; 100.0]
Month 38	
n / N	14 / 18
% and 95% CI (a)	77.8 [54.8 ; 91.0]

Source: Table 14.2.3.1.1; CSR V712-303
ED: Eliciting Dose; CI: Confidence Interval.
(a) Wilson score method.

Among the 18 subjects who performed the DBPCFC after a 2-month off-treatment period, 14 (77.8%) maintained an ED ≥1000 mg (Table 25). Among the 4 subjects who did not continue to achieve an ED ≥1000 mg, three maintained a higher ED at Month 38 compared with their baseline.

Main Conclusions on Efficacy Results in Study V712-303

Approximately half of subjects in the Completer Population (49.3%), all of whom started in study V712-301 with a baseline ED of ≤300 mg, achieved an ED of ≥1000 mg at Month 36, which is equivalent to approximately 3-4 peanut kernels, vs 41.2% at Month 12 (Table 25). Within the Per-protocol Safety Population, just over half (51.8%) reached this reactivity threshold at Month 36 compared to 40.4% at Month 12.

3.3.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical documentation comprises 6 clinical studies which include data supporting the clinical efficacy: 4 Phase 2 studies, and 2 Phase 3 studies. One phase 3 study is ongoing, with efficacy data up to 36 months of treatment so far (V712-303). All studies were designed as double-blind, placebo-controlled; 3 extension/follow-up studies were performed in an open-label manner. The studies were conducted in the US, Canada, Australia and Europe and included different age groups. Within the D120 responses the applicant declared that efficacy data is based on 284 subjects, aged 4 - 11 years (the age group of interest within this application) exposed to DBV712 250 µg with double blind efficacy outcomes.

The submitted one pivotal study V712-301 (PEPITES) and the key supportive study V712-202 (VIPES), include rather small numbers of treated children with the dose of interest: n = 28 subjects (VIPES) and n = 238 subjects (PEPITES) aged 4-11 years. An application with one pivotal study only is associated with higher regulatory demands in terms of efficacy results and data robustness as laid down in the "Points to consider on application with 1. Meta-Analysis; 2. One Pivotal study (CPMP/EWP/2330/99)": Efficacy results have to be particularly compelling with respect to statistical significance (meaning a p-value more extreme than the conventional significance level of 0.05) and clinical relevance. In addition, narrow confidence intervals for the treatment effects would be expected.

The objective of the studies was to assess the efficacy of DBV712 in peanut-allergic children compared with placebo.

The inclusion and exclusion criteria selected a population that overall is considered representative of the general peanut allergic population. The study population in performed phase 2 studies included adults, adolescents, and children (6 - 55 years) whereas the phase 3 study V712-301 included only children aged 4-11 years. Particularly, inclusion criteria related to eliciting dose (ED) at baseline DBPCFC (300 mg or less), peanut-specific IgE (-sIgE) level and skin prick test (SPT) wheal sizes were consistent.

The DBPCFC is the current diagnostic gold standard and its utilization in food immunotherapy studies is in line with the CHMP guideline on AIT (CHMP/EWP/18504/2006). However, the sensitivity thresholds to peanut allergen vary, based on numerous intrinsic and extrinsic co-factors. Therefore, an extrapolation of a single DBPCFC result (especially at lower threshold levels) to *daily life* is questioned. Thus, with regard to the achieved levels in the presented clinical trials, the individuals' future risk of serious allergic reactions after the unmeant ingestion of peanut remains despite treatment (LoOI).

All efficacy studies excluded among others peanut-allergic subjects with history of severe anaphylaxis to peanut, severe uncontrolled asthma, and generalised dermatologic diseases. The contraindications mentioned in the SmPC should be reworked according to the applied exclusion criteria (LoOI).

All studies were conducted in accordance with the ICH GCP Guidelines and the ethical principles outlined in the declaration of Helsinki and in general, the applicant has complied with the scientific advice received.

The sought indication is reworded at D150 to "TRADENAME is indicated for the treatment of children diagnosed with peanut allergy. TRADENAME is indicated in children aged 4 to 11 years at the time of treatment initiation. Tradename should be used in conjunction with a peanut-avoidant diet."

This wording is agreed. However, remaining MOs preclude approval at the present time.
(see below).

<u>Development program</u>

The chosen dose of 250 µg was questioned, however additional data was not presented. In the dose-finding study V712-202 (VIPES), children and adults were randomised to DBV712 50 µg, 100 µg, 250 µg or placebo and received the study treatment for 12 months. The applicant concluded that the highest dose of 250 µg demonstrated efficacy, with a *larger* effect in children under the age of 12 (n=113 in total). However, even if focusing on the paediatric (sub-)population, questions remain as among the 3 tested doses no dose-dependent efficacy plateau was shown. In addition, the results of the PEP01.09 (safety) study, showed among others that e.g. adverse events of special interest were reported with DBV712 in the 100 µg, 250 µg, and 500 µg dose groups *without clear evidence* of any dose effect In the supportive CoFAR6 study no statistically significant difference was shown between with 100 µg or 250 µg treated subjects in the response rate after a treatment period of 52 weeks (12 month) likewise. Unfortunately, higher doses, e.g. 500 ug (2 x 250 ug) had not been tested. The submitted pivotal study has been performed with 250 ug.

Next to the dose, a prolonged treatment duration was regarded as beneficial by the applicant. This assumption was based on data gained in the ARACHILD phase I pilot study, where a longer treatment of at least 18 months with DBV712 100 µg *suggested* additional effects compared to no desensitization effects after 12 month treatment with 100 µg. Subsequently, treatment duration of 12 month (V712-202 VIPES study) with the "chosen" dose of 250 µg was prolonged in the extension study OLFUS-VIPES for up to 36 month. The analyses of the treatment response in the OLFUS-VIPES study *suggested* that the responder rates increased with the exposure. Again, younger subjects (children 6-11 years of age) had a higher response to treatment compared to adolescents/adults (12-55 years of age). In the subgroup of children 6-11 years old treated with DBV712 250 µg, n = 20 subjects participated in the open-follow-up up to Month 24, and n = 18 subjects participated up to Month 36. Although an increase of the geometric mean eliciting dose (GM ED) in this subgroup is noticed (after Month 24 GM ED 488 mg (268, 888), after Month 36 GM ED 556 mg (297, 1043), the broad distribution of EDs in combination with the open follow-up design, without placebo control, and the small number of participants, require an interpretation of gained results with caution.

The critical discussion of the appropriateness of the choice of the primary endpoint goes back to a scientific advice in 2012. For the proposed Phase IIb/III study it was accepted that a responder is defined as a subject with a peanut protein eliciting dose equal to or greater than 1,000 mg peanut proteins based on the results of the DBPCFC after 12 months of treatment or a subject with a ≥10-fold increase of the eliciting (ED) dose at 12 months, compared to the initial eliciting dose. Nevertheless for a confirmatory Phase III study, it was questioned whether a ≥ 10-fold increase of the ED would really be of sufficient clinical relevance in patients reacting initially to very low amounts of peanut proteins. Finally, in the pivotal Phase 3 study V712-301, the 10-fold increase criterion was replaced by a "more stringent criterion requiring an absolute reactivity threshold of at least 300 mg peanut protein to be reached by all subjects with low baseline ED (1 to 10 mg) after 12 months of treatment and a higher threshold of ED ≥1000 mg for subjects with baseline ED between 10 mg and ≤300 mg".

The different definition of endpoints in strata of ED in light of an expected heterogeneity due to screening ED within both strata raised concerns, as such heterogeneity cannot be robustly assessed in light of differing response criteria. The applicant confirmed that the expectations of a stronger treatment effect in stratum 1 were overly optimistic and could not be confirmed by the study. Thus, it is evident that the basis for planning of a pivotal study was not optimal. Further post-hoc analyses on the potential heterogeneity of the treatment effect due to baseline eliciting dose are discussed later. At this place, it should be noted that in other trials on peanut immunotherapy, not the eliciting dose is addressed, but mainly the single (or cumulative) tolerated dose, meaning a primary endpoint of tolerating 1.000 mg peanut protein single dose in a DBPCFC.

Particularities of the EPIT PATCH

Guidelines for defining adequate adhesion for cutaneous patches especially for allergenic products do not exist, in opposite to transdermal product guidelines (Guideline on quality of transdermal patches EMA/CHMP/QWP/608924/2014). Nevertheless, aspects dealing with “adhesion” are of major interest. It is noted that neither clinical data has been presented documenting the development of the patch per se, nor its superiority versus a transdermal application. Thus, general/basic factors influencing the function of the patch should be discussed in more detail. However, at D150, the applicant declares that available data on the analysis of factors influencing the patch function (safety or efficacy) is limited. Moreover, the handling of the patch in daily routine as well as in “special” conditions, which may require treatment adoptions including safety recommendations need further explanations in the SmPC (LoOI).

To sum up, in the phase I and phase II data of clinical development the applicant documented that in principle an immunomodulatory effect is gained by utilizing DBV712. Although, uncertainties remain regarding the “best” dose, regarding treatment duration as well as the choice/characteristics of the target population. In addition, questions remain on the functionality, respectively limitations (confounding factors and factors influencing efficacy or safety) of the presented patch system via EPIT (Proof of concept). It remains speculative, how and if the presented patch system via EPIT is beneficial compared to allergen delivery “systems” with e.g. direct skin contact (like transdermal application, intradermal applications or others). Thus, the claimed superiority of EPIT versus other deliverer routes via skin remains hypothetical (Proof of concept).

Subsequently, the phase III data needs to provide that the benefit–risk is compelling positive for the selected regimen (new B/R MO).

Efficacy data and additional analyses

The (statistical) analysis of the pivotal study V712-301 (PEPITES) raises questions. A total of 356 children were randomized (ITT Population) at 31 centres in five countries. Several questions were raised on the design and results of the study, and the assessment of responses confirmed some of the uncertainties pertaining the limitations of the data to currently conclude a substantial effect.

The study is highly overpowered to reject the null hypothesis of no effect, it seems that the power to demonstrate a clinically relevant difference based on the 15% threshold for the two-sided 95% confidence interval was not considered at the planning stage, and is at least not appropriately described in the protocol. No rationale was provided in the protocol for the choice of threshold of 15%, the threshold was changed in protocol version 2 from initially 10% to 15%. Thus, the planning assumptions regarding clinical relevance are uncertain and a clear rationale is lacking. Lack of a rationale for the 15% threshold was confirmed by the applicant, however no justification was provided to support a lower threshold. The 15% threshold was based on a request from the FDA. The threshold is considered arbitrary and is built upon on 2 other arbitrary thresholds (ED of 300 mg and ED of 1000 mg). Additional analyses of the outcome variable on a continuous scale (geometric mean of eliciting dose) are discussed below.

Recruitment was planned to be stratified in order to sufficiently represent age subgroups, but this was not reflected in the study design, e.g. by using age as a stratification factor. Further, it was planned to stratify randomization for centre but this stratum was ignored in the primary analysis. This is not in line with current regulatory requirements (study site heterogeneity is discussed below). Upon request, the applicant clarified that omission of study site as a stratification variable for randomization was not planned but happened erroneously and was only noted after recruitment was completed. While this does not necessarily affect the interpretation of results, it indicates uncertainty around compliance to GCP standards that might have prevented such an error.The applicant clarified upon request that permuted block randomization with fixed block length of 6 was used, which is acceptable.

The study protocol and SAP are inconsistent with regard to the analyses and success criterion. While the study protocol states that the primary analysis was planned to be conducted at the two-sided significance level of 1%, the SAP defines a two-sided significance level of 5%. This is not optimal, but is not considered relevant in light of the study results. The definition of an additional success criterion that the 95% confidence interval for the risk difference should be ≥ 15% is supported (despite uncertainties on the threshold and suitability of the study for this criterion), especially since this is a single pivotal study. Formally, the criterion should be strictly greater than 15%, in order to allow the conclusion that the effect exceeds a minimally relevant risk difference.

However, it is noted that this success criterion, as part of the primary endpoint is not met and the 95% confidence interval for the risk difference does not exclude 15%. After 12 months, there was a statistically significant difference in the response rates of 21.7% (in favour of DBV712 250 µg: p-value<0.001) and a larger proportion of subjects in the DBV712 250 µg group (84/238 (35.3%) subjects) were defined as treatment responders compared to the placebo group (16/118 [13.6%] subjects). However the 95% CI of this difference was 12.4, 29.8. Thus, the pre-specified clinical success criterion was not achieved (12.4% <15%), and furthermore, the clinical relevance of the effect size is questionable. As this condition was included to determine whether the primary objective was successfully met, it questions the appropriateness of the current data with one pivotal study for MA. As the lower limit of the 95% confidence interval for the risk difference was not greater than 15%, and this was planned as a gatekeeper for further hierarchical testing, further hypothesis tests in the hierarchical procedure cannot be considered confirmatory, as specified per SAP. Nominally significant results in subsequent analyses should be considered descriptive as there is no longer control of the type 1 error.

Responses rates were generally numerically higher in treated patients than in controls, overall and in the presented subgroups defined by screening ED > vs. ≤ 30 mg. However, as stated above none of these findings can be considered statistically significant, in a confirmatory sense. Although substantial heterogeneity was expected with regard to screening ED, results seem to be consistent, by means of similar point estimates for the risk difference in stratum 1 and stratum 2. However, it needs to be taken into account that the definition of response was different in the two strata, and heterogeneity may just not be observable due to the different definition of response. Additional post-hoc analyses of the geometric mean of eliciting dose were requested, and these analyses revealed a statistically significant interaction between treatment and eliciting dose, however the extent of it does not seem meaningful. Thus, some residual uncertainty remains. The fact that a substantially greater treatment effect was expected in subjects with low eliciting dose, which was not confirmed by the study results, makes it evident that the basis for planning of a pivotal study was not optimal. The primary analysis was finally conducted by means of a Wald test, ignoring randomization strata, although it was initially planned as a logistic regression adjusted for screening ED strata. In light of the expected heterogeneity due to screening ED, this is not understood. Upon request, the applicant provided results from the initially planned logistic regression, and these results do not alter any of the conclusions.

In addressing concerns around subgroup heterogeneity, no factors besides of age were identified by the applicant that may negatively affect the size of the treatment effect. While differences due to study site or Asian race are considered not plausible, some uncertainty remains whether these factors could indicate differences in other variables relevant to the treatment effect such as patient characteristics or co-medication. However, random heterogeneity is considered the most plausible explanation, but this rather supports the conclusion that the overall treatment effect may not be substantial. It seems rather unlikely to randomly observe effect estimates around or below zero in such subgroups if the effect was well away from zero.

Subgroup analyses by age indicate a larger effect in the youngest children. When the age groups are redefined as 4-7 years and 8-11 years, the effect estimate with 95% CI for the youngest group are

30.8% (18.3;40.8) and for the oldest group 11.2% (-3.4;23.4) with a statistically nominally significant p-value for the interaction (p=0.041). As such, the difference in estimated treatment effect between the youngest and oldest age group is around 20% and the efficacy in children of 8 years and above is questionable. This finding is apparently supported by subgroup analyses of age using other thresholds (6 years, 7 years), but it is not clear which threshold is most discriminating. "Additional" analysis of efficacy data at D150: Data addressing the geometric mean of the ED following 12 months of treatment reflect the treatment benefit on behalf of a given amount of peanut protein, which leads to symptoms. This means: the ED is the dose, where subjects react. As such, they do not tolerate the given dose. At D150, the applicant presents that the GM ED at Month 12 was 277.62 mg in the active group and 81.80 mg in the Placebo group. Thus, the reached amount in the active group is still "below" the study entry criterion, which was defined as ≤300 mg peanut protein. In opposite, 88/238 (37%) subjects are reported of tolerating a dose ≥300 mg (defined that the subjects have started the 1000 mg dose). This shows that the individual benefit was varying: 37.0% (n = 88) tolerated 300 mg; of which 16.8% (n = 40) tolerated even 1000 mg but the majority of DBV712 treated patients (63%) did not tolerate 300 mg peanut protein after 12 month of treatment (ITT population, see follow-up question, LoOI). Moreover, around 6.7% of patients, respectively 7.8% showed a worsening relative to baseline ED after 12, respectively 36 month of treatment. (The applicant is asked to precise these data, follow-up question, LoOI). Still, it is acknowledged that GM ED after treatment were higher compared to placebo (Placebo Month 12 81.80 mg (65.02; 102.92), n=118), supporting a treatment induced effect.

"Clinical relevance" with respect to the two ED subgroups: In higher sensitive patients (subgroup 1, baseline ED of 1, 3 and 10 mg of peanut protein; n = 41) the GM ED was 117.1 mg. Patel et al 2021 remarks on controlled OFC results in a systematic review within individual participant data meta-analysis: "In participants who react to low-level peanut exposures (e.g., <50 mg of peanut protein), there can be up to a 10-fold increase in threshold of because of this intrinsic variability rather than because of a specific treatment effect". This needs consideration and supports the CHMP concern of ED being not "cut in stone" especially with regards to lower provocation levels within the OFC. The applicant himself discusses the "desensitization effect" critically, by presenting the hypothesis that "DBV712 could be used in the highly sensitive patient population (…), to increase the ED to a level that significantly reduces the risks associated with initiation of OIT." However, correspondent data is not submitted and such an approach is not covered with the current MAA. This idea however suggest that the applicant himself is of the opinion that the patch application alone might not suffice to protect these highly sensitive patients.

Patients in subgroup 2 (baseline ED of 30 mg, 100 mg or 300 mg; n = 197) had a GM ED of 338.6 mg. As the ED = eliciting dose is depicted, it means that 1 peanut kernel (300 mg roughly 1 kernel) is not tolerated, again questioning the gained "desensitization" effect as preventive in real life. Considering both subgroups, 4.6 patients must be treated in order to have one patient who meet a responder criterion. Thus, this data describe that only 20% of treated patients are responders, which is not assessed as a convincing rate. As stated above, the majority of children did not tolerate 300 mg peanut protein after 12 month of treatment. In opposite, patients and families seem to feel "more safe" due to treatment, as being indicated by improvement of QoL. This may lead to severe allergic reactions in real world – as being indicated already: allergic reactions subsequent to accidental or voluntary peanut consumption were reported in 33 DBV712 subjects (6.2%) and led to epinephrine use in 11 (2.1%) of subjects. Thus, the "important" signal to be cautious might be disguised, as patients may have the false sense of security. Moreover, in real world treatment normally no OFC may be performed to "adjust" this mismatch (new B/R MO).

Please note, additionally, there are new questions regarding the QoL assessments LoOI).

The impact of cofactors in the clinical setting versus "real world": The response data, respectively the GM ED, was analysed within the trials (exit) DBPCFC under controlled, clinical conditions. However, cofactors like exercise, sleep deprivation and others play a role in influencing the reactions threshold to a relevant degree. Thus, taking this GM ED at Month 12 of 277.62 mg gained in the pivotal study (data from the open-label follow-up study where "selected participants continued" are inappropriate), it is not agreed with the applicant that due to cofactors a reduction in ED up to 45%, subjects treated with DBV712 would on average still have a sufficient "buffer" to cover an accidental peanut exposure in real life. The direct applicability of an amount of 125 (34-177) mg as "threshold margin" is questioned and lack any clinical verification. This amount of peanut protein was analysed within the MIRABEL study, a study in the context of PAL (precautionary allergen labelling) / pre-packed foods – thus, focused on a different issue. Accidental reactions on open, (non-prepacked) products are excluded. Variations between responses are not reflected.

The applicant declares in the response to D120 that to this point no clear association between responders/non-responders is possible. The applicant continuous to explain that this is also, because "neither of these parameters were sufficiently powered, statistically, to provide definitive guidance on predicting response". In this context, it is to remember that only limited patient's numbers had been treated, and only one pivotal study has been submitted (See points to consider with one pivotal study). Data on major allergens respectively IgE/IgG4 are regarded as important information supporting the analysed efficacy and safety parameters and are requested (LoOI).

The applicant discussed the possible mechanisms behind the large placebo response (13.6%) in the main study. It is agreed, that natural fluctuations in the biologic reaction to allergens are to be universally present in the target population

Going along with lower baseline ED and higher baseline peanut-sIgE, it is noticed that the mean itching scores tended to be higher in the highest detachment deciles. Thus, this should be discussed further respectively may be included as a warning for high allergic individuals in the SmPC, section 4.4 (LoOI).

Supportive studies/ Longer-term treatment

For study V712-201-E (ARACHILD) the applicant claimed, that, despite the use of a "suboptimal dose of 100 µg" which showed no efficacy after 6 months treatment, "exploratory analyses suggest that a longer treatment of at least 12 months could be beneficial to subjects aged 5-11 years". The CoFAR6 V712-204-E study showed no statistically significant difference between 100 µg or 250 µg treatment response rate after 52 weeks (12 month) but both showed efficacy above placebo. After a prolonged treatment (up to 130 weeks, nearly 2.5 years), the applicant describes "more subjects receiving DBV712 250 µg reached some level of desensitisation" when compared with those who began the study on placebo or DBV712 100 µg. A longer treatment duration was also the focus of presented data gained by the open follow-up study V712-303 (PEOPLE). The main endpoint for assessing peanut desensitisation was the percentage of subjects reaching an ED ≥1000 mg after 3 years of active treatment overall in the DBV712+DBV712 group compared to the percentage after 1 year of active treatment (end of the V712-301 study). The difference between Month 12 and Month 36 in the percentage of subjects reaching an ED ≥1000 mg (95% CI) was only 8.1% (-0.5; 16.5) for the Completer Population: At Month 12, 41.2% of subjects reached an ED ≥1000 mg and at Month 36, 49.3% of subjects reached an ED ≥1000 mg. In this context, the applicant clarified the definition of the completer population as compared to study treatment completers, which was addressed during D120.

In the completer population, the mean ED of peanut protein at month 12 was depicted with 710.9 (SD 697.98, median 300 mg) versus values at month 36 depicted with 824.6 (SD 742.16, median 300 mg). The mean CRD at month 12 was depicted with 1119.4 (SD 1166.21, median 444 mg) versus

doses reached at month 36 with 1698.4 (SD 1922.08, median 694 mg). This data suggests also no or only moderate improvements. In the Completer set following results (GM ED) had been obtained at D150: Baseline adjusted GM of 84.0 mg increased to 386.7 mg at Month 12 and to 425.0 mg at Month 36. In view of the CHMP, the reached “increase” in GM ED between Month 12 and Month 36 is questioned. The applicant should document, that this “gain” isn`t merely triggered by those n= 35 patients who reached an ED ≥ 2000 mg, respectively 13.5% (19/141) of subjects who were able to consume the entire food challenge of 5444 mg of peanut protein (longitudinal course) (LoOI).
The applicant should also comment on these subjects and on the likelihood that these individuals developed natural tolerance (see Peters et al., Health Nut study suggests around 20% natural tolerance development; see also Patel et al. “In children, a 1000-fold increase may imply natural resolution”). Of note, no placebo group was existent anymore as it was an open-follow-up (LoOI). Unfortunately, no association with predictors for response is possible, according to the applicant due to limited power.

In sum, focusing on a “shorter term” treatment (6 to 12 month) with DBV712 250 µg, data of supportive studies support the data gained in the pivotal study V712-301: a moderate increased eliciting dose for DBV712 treated subjects going in line with changes of immunological markers like sIgG, IgG4 or SPT is documented. The additional benefit of a prolonged treatment detected in open-follow-up, not placebo-controlled trials (130 weeks, CoFAR6 study; 36 month, PEOPLE study) seems weak, respectively is assumed to merely be driven by subjects who developed natural tolerance (Follow-up question, LoOI). Presently the optimal duration of treatment is unknown. It remains not convincing, if the gained (moderate) effect is clinically relevant, and what justifies treatment including treatment duration. Characteristics and possible predictors of responders, respectively non-responders after 12 month and after 36 month, and on subjects whose response decreased within the observed time period(s) could not have been identified – among others due to limited power. In addition, the applicant is further asked to precise statements on long-term treatment and treatment interruption in the SmPC (Follow-up question, LoOI).
First data on sustained unresponsiveness (2-month off-treatment period in n = 18 subjects with 14 subjects with remaining efficacy) seems promising but are very limited.

3.3.7. Conclusions on clinical efficacy

Questions remain regarding the product development, regarding the chosen primary endpoint as well as on the appropriateness of the EPIT device per se. The dose-finding study (VIPES) is less convincing, as no efficacy plateau has been observed, nor did other supportive studies (ARACHILD; CoFAR6) conclusively support the choice of the chosen dose of 250µg.

It is to conclude that the one pivotal study V712-301, PEPITES did not meet the pre-specified criterion for clinical relevance. However, the trial showed a statistically significant difference between DBV712 250 µg and placebo. The predefined threshold for clinical relevance (15%) is considered arbitrary and no clinical justification was presented for this or even a lower threshold. The applicant has provided data on continuous scales as requested at D120. The assessment of responses confirmed some of the uncertainties pertaining the limitations of the data to currently conclude a substantial effect: Uncertainties remain whether the primary response criterion is sufficiently meaningful. Subgroup analyses indicate heterogeneity associated with age, indicating that older children may not have a meaningful benefit, but replication with independent data is currently missing. Further subgroup findings (Asian race, study site) are most likely due to chance, but do not provide reassurance of a substantial effect. Of note, the clinical relevance criterion pre-specified by the applicant to be a CI lower bound ≥15%, included “to determine, whether the primary objective was successfully met”, was not reached. Consequently, no formal claims can be based on the hierarchical analysis of secondary

endpoints. However, these analyses could be considered supportive, and additional analyses were requested to address clinical relevance of the effect on a continuous scale of eliciting dose.

Based on these “additional” analyses of efficacy data, still, a true reduction of allergic reactions associated with accidental peanut exposure in the real world could not be argued convincingly. First, because the “medium change in increase” is low; second, most subjects did not respond (by means of tolerating 300 mg) and third, even some of them loosed their “ desensitization effect ” over time. Thus, the “ clinical relevance of the observed differences ” is not convincing.

Especially, as “the impact of cofactors has not been precisely defined in the context of accidental peanut exposure”, the combination of

1. uncertainties with regard to the nature of “accidental intake” per se,

2. the amount of ingested protein (MIRABEL data are not regarded as presenting the correct “threshold margin”),

3. the situation (cofactors) attending individual accidental exposure

4. Very limited data on factors influencing the patch and

5. Sparse efficacy data (stratum 1 n = 41; stratum 2 n = 197; only one pivotal study which failed is predefined success criterion)

recommends a careful evaluation.

A new B/R MO has been raised.

3.3.8. Clinical safety

The applicant performed an integrated safety analysis on data from peanut-allergic subjects who received at least one patch application (DBV712 or placebo) during any of 8 studies (Table 26).

Table 26 Studies Evaluation the Safety of DBV712

Phase	Study ID	Sponsor	Age range (years)	No. of randomised subjects	Status	Trial registration no.
3	V712-301/PEPITES	DBV	4-11	356	Completed	NCT02636699
	V712-302/REALISE	DBV	4-11	393	DB completed; OL ongoing[c]	NCT02916446
	V712-303/PEOPLE	DBV	5-12[a]	298	OL ongoing[d]	NCT03013517
2	V712-201-E/ARACHILD	AP-HP	5-17	54	Completed	NCT01197053
	V712-202/VIPES	DBV	6-55	221	Completed	NCT01675882
	V712-203/OLFUS VIPES	DBV	7-56[b]	171	Completed	NCT01955109
	V712-204-E/CoFAR6	NIAID-NIH	4-25	75	Completed	NCT01904604
1	V712-101/PEP01.09	DBV	6-50	100	Completed	NCT01170286

a: Subjects initially included in **V712-301** with an age at entry of 4-11 years.
b: Subjects initially included in **V712-202** with an age at entry of 6-55 years.
c: Only data from completed 6-month DB period of **V712-302** are included in this SCS.
d: **V712-303** is ongoing at the time of the cut-off data; only data from the first 24 months for those subjects receiving active treatment in **V712-301** are presented in this SCS.
For detailed information on design features and safety assessments of individual studies, please refer to Section 1.1.3 (Table 2, Table 3, and Table 4).

V712-302/REALISE study

This study has not been described in the AR before. Thus, please see details in Table 1 and below.

Study title: Long-term assessment of safety and therapeutic benefit of Viaskin Peanut epicutaneous treatment in peanut-allergic children: A 6-month randomised, double-blind, placebo-controlled, Phase III study followed by an open label active treatment.

The study consists of a completed 6-month double-blind, placebo-controlled period, in which 393 subjects were randomised (3:1) to receive either DBV712 250 µg (N=294) or placebo (N=99). This period was followed by an ongoing open-label single arm active treatment period with DBV712 250 µg. No DBPCFC was performed at screening for this study. Consequently, subjects with a clinical history of severe anaphylactic reactions to peanut were treated with DBV712 250 µg.

Key safety assessments included evaluation of AEs, local skin reactions (subject diaries and grading of patch application areas by the investigator), clinical laboratory tests (haematology, biochemistry), vital signs, spirometry FEV1, PEF, physical examination, and assessment of atopic dermatitis (SCORAD).

Pooled Safety Datasets

694 peanut-allergic subjects aged 4-11 years received DBV712 250 µg (total exposure of 1039.4 SY).

Three pooled datasets were defined for purposes of the analysis:

- Phase 3 placebo-controlled pool (P3PC Pool),
- Double-blind placebo-controlled pool (DBPC Pool) and the
- Global Pool.

5 DBV712 dose levels have been studied during clinical development: 20 µg, 50 µg, 100 µg, 250 µg, and 500 µg. To simplify analyses of safety data in the DBPC and Global Pools, the three lowest doses are grouped together, resulting in the DBV712 Low Dose (20 µg, 50 µg, 100 µg). The DBV712 All Doses consist of all 5 dose levels.

Table 27 Summary of Data Pools and Populations Used in the Integrated Safety Analysis

Data pool	Studies	Population	Pooled treatment groups
P3PC Pool (Phase 3 placebo-controlled)	• **V712-301/PEPITES** • **V712-302/REALISE** (6-month DB period)	Subjects (4-11 years) from two Phase 3 DBPC studies	DBV712 250 µg Placebo
DBPC Pool (Double-blind placebo-controlled)	**Studies in P3PC plus:** • **V712-202/VIPES** • **V712-201-E/ARACHILD** (6-month DB period) • **V712-204-E/CoFAR6** • **V712-101/PEP01.09**	Subjects (4-55 years) from all six DBPC studies	DBV712 Low Dose DBV712 250 µg DBV712 500 µg DBV712 All Doses Placebo
Global Pool	**Studies in DBPC plus:** • **V712-203/OLFUS VIPES** extension study • **V712-201-E/ARACHILD** (beyond 6-month DB period) • **V712-204-E/CoFAR6** (beyond 12-month DB period) • **V712-303 PEOPLE**[a]	All treated peanut-allergic subjects (including adolescents and adults) from any of the eight studies, regardless of study period	DBV712 Low Dose DBV712 250 µg[a] DBV712 500 µg DBV712 All Doses Placebo
a: 36 months of treatment for those subjects who received DBV712 in **V712-301**. See Section 1.1.4.1 for details of DBV712 doses used in individual studies.			

Phase 3 placebo-controlled pool (P3PC Pool) = Main safety data

The key safety population for evaluation of the DBV712 target dose (250 **µg)** and target population (subjects aged 4-11 years) is presented in the P3PC Pool: V712-301, PEPITES (12-months) and V712-302, REALISE (data from the 6-month double-blind period; no entry DBPCFC). This pool constitutes the key safety dataset for general safety assessments of DBV712 250 µg vs placebo and is the basis for identification of adverse drug reactions (ADRs) for labelling purposes.

Table 28 Design Features and Safety Assessments of Phase 3 Clinical Studies (P3PC pool)

	V712-301 (PEPITES)	V712-302 (REALISE)
Study objective(s)	Efficacy and safety of DBV712 to induce desensitisation to peanut in peanut-allergic subjects 4-11 years of age after a 12-month treatment period	Assess safety of DBV712 over a 36-month treatment period; Explore the therapeutic benefit of a long-term treatment; Gain experience on use of DBV712 in routine medical practice
Subject age	4-11 years	4-11 years
Diagnosis inclusion criteria	Peanut allergy: SPT ≥6 mm (age 4-5 years) or ≥8 mm (age ≥6 years); sIgE >0.7 kU/L Positive DBPCFC (ED ≤300 mg peanut protein)	Peanut allergy: SPT ≥8 mm; sIgE >14 kU/L No DBPCFC
Design	Randomised, DB, PC	Randomised, DB, PC (6 months), followed by OL active treatment
Treatment duration	12 months	6-month DB period followed by OL active treatment period up to 36 months
Study treatment	DBV712 patch 250 µg Placebo patch Regimen: 1 patch application/24h	DBV712 patch 250 µg Placebo patch Regimen: 1 patch application/24h
DBPCFC	Screening, M12	None
No. of study centres; location	31; Australia, Canada, Europe & US	32; Canada & US
Study start; Status, date	December 2015; Complete, August 2017	October 2016; DB period complete, September 2017; OL period ongoing
No. of randomised subjects	356	393
Abbreviations: D = Day; DB = double-blind; DBPCFC = double-blind placebo-controlled food challenge; ED = eliciting dose; FC = food challenge; M = Month; OL = open-label; PC = placebo-controlled; sIgE = specific immunoglobulin E; SPT = skin prick test; US = United States.		

Demographic and Baseline Characteristics - P3PC Pool

The treatment groups in the P3PC Pool were balanced with respect to demographic and baseline characteristics as outlined by the applicant. In both groups were more males (58.8% and 61.8%). Median (range) age at enrolment was 7.0 (4, 11) years in both groups, with balanced proportions in the DBV712 250 µg and Placebo groups aged 4-5 years (27.6% and 29.5%, respectively) and 6-11 years (72.4% and 70.5%, respectively). Body mass index (BMI) was very similar in both treatment groups. Most subjects were located in North America (90.8% and 88.9%) and of Caucasian race (78.9% and 77.0%). The non-Caucasian population mostly comprised of Asian (9.2% and 12.4%) or Other (8.1% and 7.8%) subjects.

Patient exposure

Treatment Time-Period: With regard to the different study durations of the two Phase 3 studies included the P3PC Pool (12 months for V712-301 and 6 months for V712-302), the safety analyses were performed for the overall treatment time-period (i.e. 0-12 months) and repeated by treatment time-period (0-6 and 6-12 months) for the P3PC and DBPC Pools. The Global Pool reflects the long-term safety profile of DBV712. Cut-off Dates: for eCTD and for study V712-303 (36-month data).

Table 29 Number of Peanut-Allergic Subjects Exposed to DBV712 in the P3PC, DBPC, and Global Pools, by Individual Study

	Number of treated subjects by DBV712 dose						Subject-years of exposure
	20 µg	50 µg	100 µg	250 µg	500 µg	All DBV712 doses	All DBV712 doses
P3PC pool	-	-	-	532	-	532	378.1
V712-301	-	-	-	238 (44.7%)	-	238 (44.7%)	235.8 (62.4%)
V712-302	-	-	-	294 (55.3%)	-	294 (55.3%)	142.3 (37.6%)
DBPC pool	8	53	124	645	24	854	604.5
P3PC pool	-	-	-	532 (82.5%)	-	532 (62.3%)	378.1 (62.5%)
V712-101[a]	8 (100%)	-	16 (12.9%)	32 (5.0%)	24 (100%)	80 (9.4%)	3.2 (0.5%)
V712-201-E[b]	-	-	28 (22.6%)	-	-	28 (3.3%)	14.2 (2.3%)
V712-202	-	53 (100%)	56 (45.2%)	56 (8.7%)	-	165 (19.3%)	161.6 (26.7%)
V712-204-E	-	-	24 (19.4%)	25 (3.9%)	-	49 (5.7%)	47.5 (7.9%)
Global pool[c]	8	60	159	816	24	948[d]	1477.0
DBPC pool	8	53	124	645	24	854	604.5 (40.9%)
V712-201-E OL[e]	-	-	26	-	-	26	98.0 (6.6%)
V712-203[f]	-	7	9	130	-	48	288.8 (19.6%)
V712-204-E[g]	-	-	-	41	-	20	113.6 (7.7%)
V712-303[h]	-	-	-	-	-	-	372.0 (25.2%)

Source: Table 8, SCS

DBPC = Double-Blind Placebo-Controlled; OL = Open-Label; P3PC = Phase 3 Placebo-Controlled.

a: For DBV712 20 µg, 100 µg, 250 µg, and 500 µg doses: includes subjects who received one patch per 24 hours and one patch per 48 hours.

b: Only the first 6 months of **V712-201-E**.

c: The Global pool includes the same subjects as in the DBPC pool with the addition of **V712-201-E OL** extension (where subjects transitioned from placebo to DBV712 100 µg), **V712-203** (where subjects transitioned from placebo to active treatment, as well as from DBV712 50 µg or 100 µg to DBV712 250 µg) and **V712-204-E OL** extension (where subjects transitioned from placebo to DBV712 250 µg). **For the OL extension studies, only subjects newly treated in the Global pool are shown.**

d: The All Doses group in the Global pool (948 subjects) includes 854 subjects treated with DBV712 in the DBPC pool, plus 94 subjects who received active treatment for the first time in the OL extension studies (26 subjects in **V712-201-E OL**, 48 subjects in **V712-203** and 20 subjects in **V712-204-E OL**).

e: A total of 26 subjects transitioned from placebo in **V712-201-E** to active treatment with DBV712 100 µg in **V712-201-E OL**.

f: A total of 48 subjects transitioned from placebo in **V712-202** to active treatment at **V712-203** entry (7 received DBV712 50 µg, 9 received DBV712 100 µg, and 32 received DBV712 250 µg). A total of 130 subjects not treated with DBV712 250 µg in **V712-202** received DBV712 250 µg in **V712-203** (either directly at **V712-203** entry or after 6 months of treatment with DBV712 50 µg or 100 µg).

g: A total of 41 subjects transitioned from placebo or DBV712 100 µg in **V712-204-E** to DBV712 250 µg in **V712-204-E OL**.

h: Available data are from subjects treated with active treatment in **V712-301**, thus no newly treated subjects are counted for **V712-303**.

Values are numbers (and percent, where indicated). Percentages are based on the number of treated subjects by pool or the number of subject-years of exposure (all DBV712 doses) by pool. No percentages are presented for the Global pool as subjects could be counted multiple times between DBPC and OL periods.

Treatment Exposure and Compliance - P3PC Pool

The number of subjects aged 4-11 years old receiving the target dose of 250 µg/24 h (±4) and corresponding subject years by duration of exposure are presented by study in Table 30.

In Study V712-101 (Phase 1 study), the 8 subjects receiving the 250 µg dose were treated for less than one month.

Exposure duration was missing (missing date of end of treatment) for 6 subjects from the V712-202/203 and 1 subject from the V712-302 study.

In total, 562 children were treated for at least 6 months, 365 for at least 12 months and 187 for 36 months.

Table 30 Number of subjects aged 4-11 years old receiving the target dose of 250 µg/24h and subject-years by duration of exposure by study

Number of subjects and subject-years by duration of exposure Category / Statistics	V712-101 (N=8)	V712-202/203 (N=103)	V712-204-E [1] (N=51)	V712-301/303 (N=238)	V712-302 (N=294)
Number of subjects					
>0 month	8 (100)	97 (94.2)	51 (100)	238 (100)	293 (99.7)
≥1 month	0	97 (94.2)	51 (100)	236 (99.2)	290 (98.6)
≥3 months	0	97 (94.2)	51 (100)	235 (98.7)	287 (97.6)
≥6 months	0	97 (94.2)	51 (100)	234 (98.3)	180 (61.2)
≥12 months	0	93 (90.3)	49 (96.1)	223 (93.7)	0
≥24 months	0	44 (42.7)	34 (66.7)	185 (77.7)	0
≥36 months	0	17 (16.5)	0	170 (71.4)	0
Number of subjects-years					
>0 month	0.3	180.4	108.5	607.8	142.3
≥1 month	0	180.4	108.5	607.8	142.1
≥3 months	0	180.4	108.5	607.6	141.8
≥6 months	0	180.4	108.5	607.3	91.0
≥12 months	0	177.6	107.0	598.7	0
≥24 months	0	107.3	84.7	554.9	0
≥36 months	0	51.2	0	517.6	0

[1] Including open-label period.
No subject aged 4-11 years old received the target dose of 250 µg in study V712-201-E
Percentages are based on the number of subjects in each study.
Overall treatment exposure = Date of last patch application - Date of first patch application + 1, irrespective of treatment interruption. If the date of last patch application is incomplete, then the last day of the month of the last patch application date will be considered.

Of the 749 subjects included in the P3PC Pool, 532 subjects were exposed to DBV712 250 µg for 378 SY and 217 received placebo for 164 SY Mean (SD) treatment exposure was similar at 260 (99) days for DBV712 250 µg and 276 (100) days for placebo. Mean (SD) exposure was similar for the two age groups, 4-5 and 6-11 years.

Table 31 Treatment Exposure Duration and Product Compliance (P3PC Pool)

		DBV712 250 µg (N=532[a])	Placebo (N=217)
Treatment exposure duration (days)	n	531	217
	Mean (SD)	260.1 (98.98)	275.9 (100.03)
	Median (min, max)	188.0 (4, 412)	355.0 (9, 398)
	Q1, Q3	181.0, 369.0	183.0, 371.0
	Subject-Year of Exposure	378.1	163.9
Exposure duration category (n, %)	≤1 month	5 (0.9)	2 (0.9)
	≤2 months	9 (1.7)	3 (1.4)
	≤3 months	9 (1.7)	4 (1.8)
	≤6 months	129 (24.2)	41 (18.9)
	≤12 months	313 (58.8)	110 (50.7)
	>12 months[b]	218 (41.0)	107 (49.3)
Total peanut protein dose (mg/year)	n	531	Not applicable
	Mean (SD)	84.9 (8.41)	
	Median (min, max)	88.0 (17, 91)	
	Q1, Q3	83.6, 89.8	
Overall product compliance (%)	n	531	217
	Mean (SD)	98.5 (4.48)	98.0 (5.09)
	Median (min, max)	100.0 (55, 100)	100.0 (66, 100)
	Q1, Q3	100.0, 100.0	98.7, 100.0
Overall product compliance category	<80%	7 (1.3)	5 (2.3)
	≥80%	524 (98.5)	212 (97.7)

Source: Table 4.1-A and Table 4.2-A

a: Exposure (and compliance) data were missing for 1 subject in the DBV712 250 µg group from **V712-302**, hence n=531.

b: In **V712-301**, subjects could be treated for a maximum duration of 365 (+7) days.

Percentages are based on the number of subjects in each treatment group.

Overall treatment exposure = Date of last patch application - Date of first patch application + 1, irrespective of treatment interruption. If the date of last patch application is incomplete, then the last day of the month of the last patch application date will be considered.

Total dose of protein (mg/year) = 365.25 x Sum of [Exposure duration (in days) under dosage i x Actual treatment dosage i] / (Total exposure duration).

Overall compliance: 100*(Number of patches dispensed - Number of patches returned) / (exposure duration [in days]).

Adverse events

Adverse Events in the P3PC Pool

Key safety assessments included evaluation of AEs, local skin reactions, clinical laboratory tests, vital signs, spirometry rs peak expiratory flow, physical examination, and assessment of atopic dermatitis using Scoring Atopic Dermatitis (SCORAD). A safety sub-analysis of local and systemic AEs, and spirometry results was performed in subjects with mutations in the filaggrin gene vs wild type subjects. TEAEs related to accidental peanut consumption were analysed separately.

Table 32 Overall Summary of TEAEs (P3PC Pool)

	DBV712 250 µg (N=532)	Placebo (N=217)
	n (%)	n (%)
TEAEs	489 (91.9)	188 (86.6)
Mild TEAEs	463 (87.0)	174 (80.2)
Moderate TEAEs	239 (44.9)	78 (35.9)
Severe TEAEs	18 (3.4)	3 (1.4)
Serious TEAEs	9 (1.7)	7 (3.2)
TEAEs considered related to IP[a]	230 (43.2)	53 (24.4)
Serious TEAEs considered related to IP[a]	4 (0.8)	0
TEAEs leading to permanent IP discontinuation	8 (1.5)	0
TEAEs leading to temporary IP discontinuation	74 (13.9)	18 (8.3)
TEAEs leading to death	0	0
DBV712-induced local TEAEs[b]	191 (35.9)	41 (18.9)

Source: ISS Table 5.1-A
TEAE = Treatment-emergent adverse event; IP = investigational product.
a: Considered related to study treatment when reported as possibly related, probably related or related. Considered unrelated to IP when reported as unlikely related or unrelated.
b: DBV712-induced local TEAEs are defined as TEAE considered related to IP with a MedDRA HLT equal to "Application and instillation site reactions".
AEs/SAEs related to food challenges and peanut consumptions are excluded.

Table 33 Rate and incidence of TEAEs by treatment group (P3PC Pool)

Category	DBV712 250 µg (FSY=383.1)		Placebo (FSY=166.3)	
	Rate	Incidence	Rate	Incidence
Any:				
TEAEs	883.3	669.2	680.6	391.8
Mild TEAEs	702.4	490.6	577.8	306.6
Moderate TEAEs	170.2	92.0	101.0	60.7
Severe TEAEs	10.7	4.8	1.8	1.8
Serious TEAEs	2.6	2.4	4.2	4.3
TEAEs considered related to IP [1]	189.0	89.1	104.6	38.3
Serious TEAEs considered related to IP [1]	1.3	1.0	0	0
TEAEs leading to permanent IP discontinuation	2.9	2.1	0	0
TEAEs leading to temporary IP discontinuation	30.3	21.2	15.0	11.4
TEAEs leading to death	0	0	0	0

Category	DBV712 250 µg (FSY=383.1)		Placebo (FSY=166.3)	
	Rate	Incidence	Rate	Incidence
DBV712-induced local TEAEs [2]	151.4	68.3	89.6	28.1
Systemic AESI [3]	9.4	9.3	4.2	4.3

Source: Table 5.2-A
AE/SAE related to food challenges and peanut consumptions are excluded.
SY = subject-years. FSY = Follow-up duration in SY. Rate = 100 x Events count / FSY.
Incidence = 100 x Count of subjects with event / sum of times to first event in SY.
Any TEAE with missing relationship will be considered as "related". Any TEAE with missing severity will be considered as "severe".
Adverse Events were classified into System Organ Class and Preferred Term using Version 20.1 of MedDRA.
[1] Considered related to Study treatment when reported as possibly related, probably related or related. Considered unrelated to Investigational product when reported as unlikely related or unrelated.
[2] DBV712-induced local TEAE are defined as TEAE considered related to investigational product with a MedDRA High Level Term equal to "Application and instillation site reactions".
[3] through the algorithm of the Anaphylactic Reaction Standardized MedDRA queries (SMQ). Rate is based on number of cases.

Adverse Events and Symptoms due to Peanut Consumption - P3PC Pool

In the DBV712 250 µg group, peanut consumption during the treatment period was reported for 36 subjects (6.8%) and this was confirmed as accidental in all but 1 subject. Allergic reactions subsequent to accidental/voluntary peanut consumption were reported in 33 (6.2%) subjects and led to epinephrine use in 11 (2.1%) subjects.

In the Placebo group, peanut consumption during the treatment period was reported for 11 (5.1%) subjects; all consumptions were confirmed as accidental. Allergic reactions were reported in 10 (4.6%) subjects and led to epinephrine use in 4 (1.8%) subjects.

The most frequently reported TEAEs and allergic reactions due to peanut consumption (PT ≥2% subjects in either treatment group) were hypersensitivity (15 [2.8%] and 6 [2.8%] in the DBV712 250 µg and Placebo groups, respectively) and anaphylactic reactions (13 [2.4%] and 4 [1.8%]).

Serious TEAEs due to Peanut Consumption

In the DBV712 250 µg group, 5 (0.9%) subjects experienced serious TEAEs due to peanut consumption (anaphylactic reaction in 4 subjects and hypersensitivity in 1 subject). In the Placebo group, 1 (0.5%) subject experienced a serious anaphylactic reaction due to peanut consumption.

Adverse Events and Symptoms due to Peanut Consumption in the follow- up / PEOPLE Study

Table 34 shows the TEAEs due to APC by SOC and PT. Treatment-emergent AEs due to APC were reported in 28 (14.1%) subjects, mainly anaphylactic reaction (14 subjects, 7.1%) and hypersensitivity reactions (10 subjects, 5.1%). Other allergic reactions induced by APC were throat irritation (1.5%), vomiting (0.5%), sensation of foreign body (0.5%), rash (0.5%) and food allergy (0.5%). Among the 15 anaphylactic reactions reported in the context of APC, two serious events occurred during the additional two years of treatment.

Table 34 Treatment-Emergent Adverse Events Due to APC by System Organ Class and Preferred Term – Safety Population

SOC PT	VP250+VP250 (N=198)	
	n (%)	m
At least one TEAE due to APC	28 (14.1%)	39
Immune system disorders	24 (12.1%)	32
Anaphylactic reaction	14 (7.1%)	15
Hypersensitivity	10 (5.1%)	16
Food allergy	1 (0.5%)	1
Respiratory, thoracic and mediastinal disorders	3 (1.5%)	3
Throat irritation	3 (1.5%)	3
Gastrointestinal disorders	1 (0.5%)	2
Vomiting	1 (0.5%)	2
General disorders and administration site conditions	1 (0.5%)	1
General disorders	1 (0.5%)	1
Sensation of foreign body	1 (0.5%)	1
Skin and subcutaneous tissue disorders	1 (0.5%)	1
Rash	1 (0.5%)	1

APC: Accidental Peanut Consumption; TEAE: Treatment-Emergent Adverse Event; SOC: System Organ Class; PT: Preferred Term.
n: number of subjects with at least one adverse event; m: number of adverse events.
Percentages were based on the number of subjects in the safety population.
Subjects were counted once per System Organ Class and once per Preferred Term.
All AEs related to Double-blind placebo-controlled food challenges were excluded.
MedDRA dictionary version 20.0.
Data Source: Table 14.3.2.2.16

Most Frequent Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

Table 35 TEAEs by SOC (P3PC Pool)

System Organ Class	DBV712 250 µg (N=532) n (%)	Placebo (N=217) n (%)
Any TEAE	489 (91.9)	188 (86.6)
Infections and infestations	360 (67.7)	134 (61.8)
General disorders and administration site conditions	265 (49.8)	66 (30.4)
General disorders[a]	119 (22.4)	42 (19.4)
Administration site conditions[a]	192 (36.1)	41 (18.9)
Respiratory, thoracic and mediastinal disorders	227 (42.7)	77 (35.5)
Skin and subcutaneous tissue disorders	145 (27.3)	59 (27.2)
Gastrointestinal disorders	131 (24.6)	44 (20.3)
Immune system disorders	108 (20.3)	32 (14.7)
Nervous system disorders	94 (17.7)	26 (12.0)
Injury, poisoning and procedural complications	86 (16.2)	34 (15.7)
Eye disorders	51 (9.6)	18 (8.3)
Musculoskeletal and connective tissue disorders	33 (6.2)	9 (4.1)
Ear and labyrinth disorders	28 (5.3)	4 (1.8)
Psychiatric disorders	11 (2.1)	4 (1.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	10 (1.9)	1 (0.5)
Blood and lymphatic system disorders	4 (0.8)	2 (0.9)
Metabolism and nutrition disorders	4 (0.8)	1 (0.5)
Vascular disorders	3 (0.6)	1 (0.5)
Investigations	2 (0.4)	2 (0.9)
Renal and urinary disorders	2 (0.4)	0
Reproductive system and breast disorders	2 (0.4)	0
Surgical and medical procedures	1 (0.2)	1 (0.5)
Cardiac disorders	1 (0.2)	0
Congenital, familial and genetic disorders	1 (0.2)	0
Hepatobiliary disorders	1 (0.2)	0
Social circumstances	0	2 (0.9)

Source: Table 6.1.1-A
a: General disorder/Administration site conditions = HLT not equal / equal to "Application and instillation site reactions".
n (%) = Number (%) of subjects experiencing at least one event, with percentages based on the number of subjects in each treatment group.
AEs/SAEs related to food challenges and peanut consumptions are excluded.
AEs were classified into System Organ Class using Version 20.1 of MedDRA.

Overall, the most frequently reported TEAE by individual PT was upper respiratory tract infection, reported in a similar proportion of subjects in both treatment groups (23.5% of subjects in the DBV712 250 µg group and 24.4% in the placebo group) (Table 36, SCS).

Table 36 Most Frequent TEAEs Reported in ≥1% of Subjects Overall by PT (P3PC Pool)

	DBV712 250 µg (N=532)	Placebo (N=217)
Preferred Term	n (%)	n (%)
Upper respiratory tract infection	125 (23.5)	53 (24.4)
Pyrexia	98 (18.4)	36 (16.6)
Application site pruritus	85 (16.0)	15 (6.9)
Nasopharyngitis	81 (15.2)	28 (12.9)
Headache	81 (15.2)	24 (11.1)
Application site erythema	74 (13.9)	21 (9.7)
Cough	71 (13.3)	28 (12.9)
Asthma	59 (11.1)	20 (9.2)
Application site eczema	56 (10.5)	12 (5.5)
Vomiting	54 (10.2)	15 (6.9)
Urticaria	50 (9.4)	21 (9.7)
Rhinitis allergic	44 (8.3)	11 (5.1)
Eczema	43 (8.1)	16 (7.4)
Application site swelling	40 (7.5)	2 (0.9)
Viral infection	39 (7.3)	10 (4.6)
Nasal congestion	36 (6.8)	17 (7.8)
Gastroenteritis	36 (6.8)	12 (5.5)
Oropharyngeal pain	34 (6.4)	12 (5.5)
Pharyngitis streptococcal	34 (6.4)	10 (4.6)
Seasonal allergy	33 (6.2)	10 (4.6)
Abdominal pain upper	30 (5.6)	5 (2.3)
Anaphylactic reaction	29 (5.5)	5 (2.3)
Wheezing	28 (5.3)	11 (5.1)
Gastroenteritis viral	28 (5.3)	9 (4.1)
Rash	26 (4.9)	8 (3.7)
Sinusitis	26 (4.9)	5 (2.3)
Influenza	24 (4.5)	11 (5.1)
Ear infection	23 (4.3)	8 (3.7)
Food allergy	22 (4.1)	6 (2.8)
Application site reaction	22 (4.1)	3 (1.4)
Otitis media	22 (4.1)	3 (1.4)
Hypersensitivity	21 (3.9)	7 (3.2)
Conjunctivitis allergic	21 (3.9)	6 (2.8)
Viral upper respiratory tract infection	20 (3.8)	10 (4.6)

Preferred Term	n (%)	n (%)
Diarrhoea	19 (3.6)	3 (1.4)
Application site urticaria	18 (3.4)	1 (0.5)
Abdominal pain	17 (3.2)	8 (3.7)
Allergy to animal	16 (3.0)	6 (2.8)
Pruritus	14 (2.6)	7 (3.2)
Throat irritation	14 (2.6)	7 (3.2)
Eye pruritus	14 (2.6)	6 (2.8)
Conjunctivitis	14 (2.6)	4 (1.8)
Ear pain	14 (2.6)	3 (1.4)
Epistaxis	14 (2.6)	2 (0.9)
Eye swelling	12 (2.3)	1 (0.5)
Arthropod bite	11 (2.1)	8 (3.7)
Nausea	11 (2.1)	4 (1.8)
Pneumonia	11 (2.1)	1 (0.5)
Application site discolouration	11 (2.1)	0
Rhinorrhoea	10 (1.9)	9 (4.1)
Pharyngitis	10 (1.9)	2 (0.9)
Skin papilloma	10 (1.9)	1 (0.5)
Application site dermatitis	10 (1.9)	0
Dyspnoea	9 (1.7)	3 (1.4)
Arthropod sting	9 (1.7)	2 (0.9)
Application site rash	9 (1.7)	1 (0.5)
Erythema	8 (1.5)	6 (2.8)
Bronchitis	8 (1.5)	5 (2.3)
Pain in extremity	8 (1.5) 1	4 (1.8)
Application site irritation	8 (1.5)	2 (0.9)
Respiratory tract infection	8 (1.5)	2 (0.9)
Motion sickness	8 (1.5)	0
Myalgia	8 (1.5)	0
Oral pruritus	7 (1.3)	5 (2.3)
Toothache	7 (1.3)	5 (2.3)
Skin abrasion	7 (1.3)	2 (0.9)
Fatigue	6 (1.1)	3 (1.4)
Anxiety	6 (1.1)	2 (0.9)
Medical device pain	4 (0.8)	4 (1.8)
Sneezing	4 (0.8)	4 (1.8)
Limb injury	3 (0.6)	7 (3.2)

Source: Table 6.8-A

AEs/SAEs related to food challenges and peanut consumptions are excluded.
Events occurring on 1% or more of the subjects (by PT) on the total number of subjects.
n (%) =Number (%) of subjects experiencing at least one event, percentages are based on the number of subjects in each treatment group.
AEs were classified into Preferred Term using Version 20.1 of MedDRA.

Table 37 Recurrence of events (P3PC Pool)

		DBV712 250 µg (N=532)	Placebo (N=217)
Any TEAE	n(%) m	489 (91.9%) 3384	188 (86.6%) 1132
	Number (%) of subjects with:		
	- 1 event	56 (10.5%)	32 (14.7%)
	- 2 events	61 (11.5%)	31 (14.3%)
	- 3 events or more	372 (69.9%)	125 (57.6%)
Application site reactions (1)	n(%) m	192 (36.1%) 585	41 (18.9%) 150
	Number (%) of subjects with:		
	- 1 event	87 (16.4%)	18 (8.3%)
	- 2 events	42 (7.9%)	13 (6.0%)
	- 3 events or more	63 (11.8%)	10 (4.6%)
Urticaria	n(%) m	66 (12.4%) 108	25 (11.5%) 39
	Number (%) of subjects with:		
	- 1 event	45 (8.5%)	17 (7.8%)
	- 2 events	11 (2.1%)	4 (1.8%)
	- 3 events or more	10 (1.9%)	4 (1.8%)
Asthma	n(%) m	61 (11.5%) 138	21 (9.7%) 34
	Number (%) of subjects with:		
	- 1 event	31 (5.8%)	12 (5.5%)
	- 2 events	12 (2.3%)	7 (3.2%)
	- 3 events or more	18 (3.4%)	2 (0.9%)
Anaphylactic reactions including accidental peanut consumption	n(%) m	42 (7.9%) 44	9 (4.1%) 10
	Number (%) of subjects with:		
	- 1 event	41 (7.7%)	8 (3.7%)
	- 2 events	0	1 (0.5%)
	- 3 events or more	1 (0.2%)	0
TEAEs leading to epinephrine intake	n(%) m	28 (5.3%) 32	3 (1.4%) 3
	Number (%) of subjects with:		
	- 1 event	26 (4.9%)	3 (1.4%)
	- 2 events	1 (0.2%)	0
	- 3 events or more	1 (0.2%)	0
Anaphylactic reactions	n(%) m	29 (5.5%) 31	5 (2.3%) 5
	Number (%) of subjects with:		
	- 1 event	28 (5.3%)	5 (2.3%)
	- 2 events	0	0
	- 3 events or more	1 (0.2%)	0

(1) defined as TEAEs with MedDRA High level term equals to « Application and instillation site reactions ».
AE related to food challenges or accidental peanut consumption are excluded, except the analysis for "Anaphylactic reactions including APC".

Adverse Drug Reactions to DBV712 250 µg Identified by the Sponsor

A difference of more than 1% for TEAEs (analysed according to grouped PTs or analysed separately, see Section 2.1, SCS) in the DBV712 250 µg vs placebo groups in the P3PC pool was used to screen for potential adverse drug reactions (ADRs). Medical judgment was then used to decide if a potential ADR qualified as an ADR, considering the frequency of reporting, the frequency in excess compared to placebo, the relevance of the TEAE, the extent to which the AE was consistent with the pharmacology of DBV712 and its route of administration.

The following ADRs were identified: application site reactions and anaphylactic reactions, Table 38.

Table 38 EU Summary of Product Characteristics (EU SPC): Adverse Drug Reactions

System Organ Class	Very Common	Common	Uncommon
Immune system disorders		Anaphylactic reaction	
General disorders and administration site conditions	Application site reaction* Application site eczema	Application site swelling Application site urticaria Application site hyperpigmentation**	Application site excoriation** Application site bleeding** Application site infection Application site pain

*Including, but not exclusively, application site reactions such as pruritus, erythema, macule, papule, irritation.
**LLT term.

Local Application Site Reactions

Table 39 Overview of Local Application Site Reaction TEAEs (P3PC Pool)

	DBV712 250 µg (N=532)	Placebo (N=217)
Local application site reaction TEAEs[a]		
All events	192 (36.1) 585	41 (18.9) 150
Leading to permanent treatment discontinuation	3 (0.6) 6	0
Leading to temporary treatment discontinuation	11 (2.1) 14	0
Leading to use of topical corticosteroids	125 (23.5) 365	22 (10.1) 77
DBV712-induced local TEAEs[b]		
All events	191 (35.9) 580	41 (18.9) 149
Mild	139 (26.1)	37 (17.1)
Moderate	44 (8.3)	3 (1.4)
Severe	8 (1.5)	1 (0.5)

Source: Table 6.1.1-A, Table 6.4.1-A, Table 6.7-A, Table 9.1.1-A, Table 9.1.2-A, Table 10.1.1-A, Table 10.2-A
a: All TEAEs corresponding to the HLT "Application and instillation site reactions".
b: TEAEs considered related to IP by the Investigator and corresponding to the HLT "Application and instillation site reactions". DBV712-induced local TEAEs are presented by maximum severity.

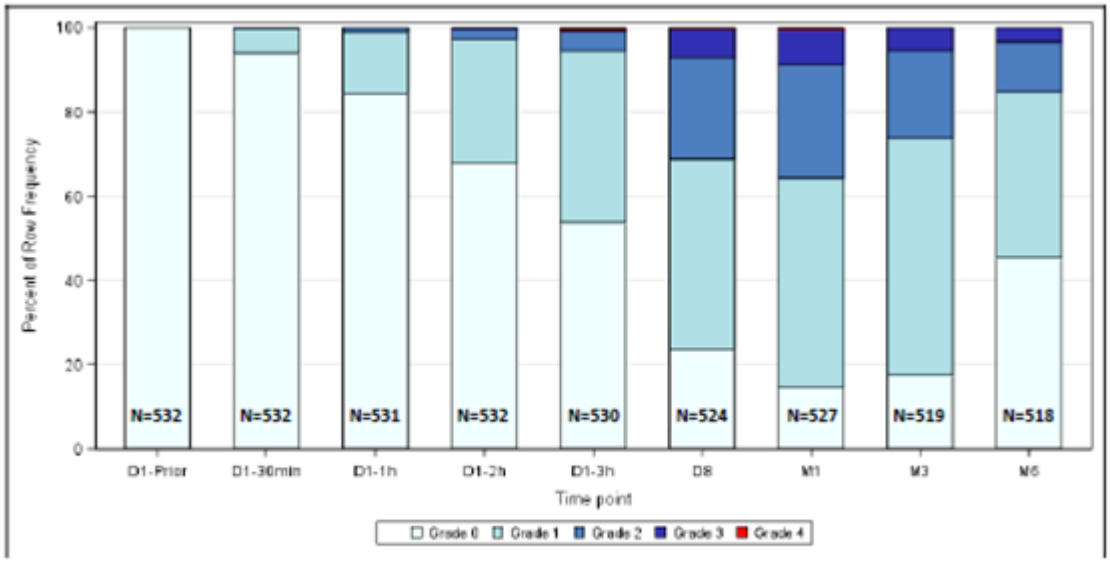
Particular attention was paid to the monitoring of local skin reactions.

By subject diary (during the first 6 months of patch application): local skin reactions graded by the parents/subjects according to a 4-point severity scale (0=none; 1=mild; 2= moderate and 3=severe)

Subject diaries revealed that local skin reactions occurred in a high proportion of subjects in both treatment groups. Among subjects with evaluable diary data from the P3PC pool, all 531 (100%) subjects in the DBV712 250 µg group and 189/216 (87.5%) subjects in the placebo group reported local skin reactions (itching, redness and/or swelling) during the first 6 months of treatment. Subjects in the DBV712 250 µg group and placebo group experienced local skin reactions for a mean percentage of days of 89.4% and 31.3% respectively, during the first 6 months of treatment. In the DBV712 250 µg group, the proportion of days with reactions having a reported maximum intensity of 3 tended to be higher during the first month of treatment compared to the following 5 months.

DBV712-Induced Local TEAEs (per Investigator's Assessment) – P3PC Pool

Figure 10 (D150 absolute numbers included): Severity of Local Skin Reactions Over Time as Per Investigator Assessment in the DBV712 250 µg Group (P3PC Pool)



Source: Figure ADH05.1

Table 40 Local Skin Reactions as Per Investigator Grading (P3PC Pool)

		DBV712 250 µg (N=532)	Placebo (N=217)
Period/visit-time point	**Skin Grade[a]**		
Overall treatment period	**n**	532	217
	Grade 0	8 (1.5)	110 (50.7)
	Grade 1	187 (35.2)	87 (40.1)
	1A	130 (24.4)	70 (32.3)
	1B	57 (10.7)	17 (7.8)
	Grade 2	236 (44.4)	18 (8.3)
	2A	152 (28.6)	15 (6.9)
	2B	84 (15.8)	3 (1.4)
	Grade 3	96 (18.0)	2 (0.9)
	3A	44 (8.3)	2 (0.9)
	3B	52 (9.8)	0
	Grade 4	5 (0.9)	0
	4A	4 (0.8)	0
	4B	1 (0.2)	0
	Grade ≥1	524 (98.5)	107 (49.3)
Day 1 - 3 hours after application	**n**	530	217
	Grade 0	285 (53.8)	208 (95.9)
	Grade 1	216 (40.8)	8 (3.7)
	Grade 2	25 (4.7)	0
	Grade 3	2 (0.4)	1 (0.5)
	Grade 4	2 (0.4)	0
	Grade ≥1	245 (46.2)	9 (4.1)
Month 1	**n**	527	215
	Grade 0	77 (14.6)	170 (79.1)
	Grade 1	262 (49.7)	40 (18.6)
	Grade 2	142 (26.9)	4 (1.9)
	Grade 3	44 (8.3)	1 (0.5)
	Grade 4	2 (0.4)	0
	Grade ≥1	450 (85.4)	45 (20.9)
	n	518	212

		DBV712 250 µg (N=532)	Placebo (N=217)
Month 6	**Grade 0**	235 (45.4)	177 (83.5)
	Grade 1	204 (39.4)	32 (15.1)
	Grade 2	62 (12.0)	3 (1.4)
	Grade 3	17 (3.3)	0
	Grade 4	0	0
	Grade ≥1	283 (54.6)	35 (16.5)
Month 12	**n**	226	110
	Grade 0	73 (32.3)	90 (81.8)
	Grade 1	107 (47.3)	17 (15.5)
	Grade 2	41 (18.1)	3 (2.7)
	Grade 3	5 (2.2)	0
	Grade 4	0	0
	Grade ≥1	153 (67.7)	20 (18.2)

Source: Table 14.1-A
Percentages are based on the number of subjects with non-missing data for each treatment group.
a: Most severe grade observed during the overall treatment period (excluding timepoint Day 1 - Before application).
Grade if localised under the patch: 1A, 2A, 3A and 4A; grade if extending beyond the patch: 1B, 2B, 3B and 4B.
Subjects are counted once per maximum grade regardless of the localisation.

Table 41 DBV712-Induced Local TEAEs, by PT (P3PC Pool)

	DBV712 250 µg (N=532)	Placebo (N=217)
Preferred Term	**n (%)**	**n (%)**
Any DBV712-induced local TEAE[a]	191 (35.9)	41 (18.9)
Application site pruritus	83 (15.6)	15 (6.9)
Application site erythema	74 (13.9)	21 (9.7)
Application site eczema	54 (10.2)	11 (5.1)
Application site swelling	40 (7.5)	2 (0.9)
Application site reaction	22 (4.1)	3 (1.4)
Application site urticaria	18 (3.4)	1 (0.5)
Application site discolouration	11 (2.1)	0
Application site dermatitis	10 (1.9)	0
Application site rash	9 (1.7)	1 (0.5)
Application site irritation	8 (1.5)	2 (0.9)
Application site oedema	6 (1.1)	1 (0.5)
Application site dryness	4 (0.8)	0
Application site pain	2 (0.4)	1 (0.5)
Application site vesicles	2 (0.4)	1 (0.5)
Application site discomfort	1 (0.2)	1 (0.5)
Application site discharge	1 (0.2)	0
Application site erosion	1 (0.2)	0
Application site haemorrhage	1 (0.2)	0
Application site induration	1 (0.2)	0
Application site inflammation	0	1 (0.5)
Application site papules	0	1 (0.5)

Source: Table 10.1.1-A, Table 10.1.2-A
AEs/SAEs related to food challenges and peanut consumptions are excluded.
DBV712-induced local TEAEs were defined as TEAEs considered as related to IP with a HLT equal to "Application and instillation site reactions".
n (%) = Number (%) of subjects experiencing at least one event, with percentages based on the number of subjects in each treatment group; m = Number of events.
AEs were classified into System Organ Class and Preferred Term using Version 20.1 of MedDRA.
a: General disorder/Administration site conditions = HLT not equal/equal to "Application and instillation site reactions".

Systemic Anaphylactic Reactions

In the P3PC pool, 36 anaphylactic reactions were reported by the Investigators (PT = anaphylactic reaction), none were graded as severe. Anaphylactic reactions were predominantly graded as mild or moderate (8/31 mild and 23/31 moderate in the DBV712 250 µg group, all moderate in the placebo group), and symptoms predominantly included urticaria, cough, wheeze, subjective respiratory symptoms or vomiting.

In the P3PC Pool anaphylactic reactions led to epinephrine/adrenaline administration in 17 (3.2%) subjects in the DBV712 250 µg group compared with 3 (1.4%) subjects in the placebo group. Almost all episodes occurred within the first 6 months of treatment in both treatment groups, with the majority of episodes in the DBV712 250 µg group reported within the first 2 months.

Overall, in the P3PC pool, 22 episodes of anaphylactic reactions in 20 subjects, all in the DBV712 250 µg group, were considered treatment-related by the Investigator (7 related, 8 probably related, 7 possibly related). Next to anaphylactic reactions (3.8%), urticaria (3.9%) and conjunctivitis allergica (1.5%) occurred, which are also considered treatment related. In 9 out of these 22 episodes (41.0%), no epinephrine was administered to the subjects.

Anaphylactic reactions meeting seriousness criteria were infrequent: 5 serious events were reported for 4 subjects (0.8%) in the DBV712 250 µg group (all assessed by the Investigator as possibly/probably related to IP) and 2 serious events were reported for 2 (0.9%) subjects in the placebo group (assessed as not related). All subjects recovered without sequalae.

The course of treatment was generally not hampered by the occurrence of anaphylactic reactions, with temporary discontinuation of DBV712 250 µg following 23 episodes of anaphylactic reaction in 22 subjects (including 2 episodes in 2 placebo subjects). In only one subject was recurrence of an anaphylactic reaction reported after treatment recommenced. Four episodes of anaphylactic reaction in 4 (0.8%) subjects lead to permanent treatment discontinuation in the DBV712 250 µg group (none in the placebo group).

Table 42 Frequent (≥1%) TEAEs Considered Related to IP by the Investigator by PT (P3PC Pool)

	DBV712 250 µg (N=532)	Placebo (N=217)
Preferred Term	**n (%)**	**n (%)**
Application site pruritus	83 (15.6)	15 (6.9)
Application site erythema	74 (13.9)	21 (9.7)
Application site eczema	54 (10.2)	11 (5.1)
Application site swelling	40 (7.5)	2 (0.9)
Application site reaction	22 (4.1)	3 (1.4)
Urticaria	21 (3.9)	4 (1.8)
Anaphylactic reaction	20 (3.8)	0
Application site urticaria	18 (3.4)	1 (0.5)
Application site discolouration	11 (2.1)	0
Application site dermatitis	10 (1.9)	0
Application site rash	9 (1.7)	1 (0.5)
Eczema	8 (1.5)	4 (1.8)
Application site irritation	8 (1.5)	2 (0.9)
Conjunctivitis allergic	8 (1.5)	2 (0.9)

Source: Table 6.9-A
AEs/SAEs related to food challenges and peanut consumptions are excluded.
n (%) = Number (%) of subjects experiencing at least one event, with percentages based on the number of subjects in each treatment group.
AEs were classified into Preferred Term using Version 20.1 of MedDRA.

Table 43 Synthesis of anaphylactic reaction symptoms based on narratives outside of accidental peanut consumption and food challenge (including those retrieved by SMQ algorithm) (P3PC Pool)

Symptoms SOC	Preferred term	Number of occurrences in DBV712 group	Number of occurrences in placebo
Infections and infestations	Conjunctivitis	2	1
Psychiatric disorders	Somnolence	1	
Nervous system disorders	Dizziness	1	
	Lethargy	2	
Vascular disorders	flushing	1	
	Pallor	1	
Respiratory, thoracic and mediastinal disorders	Nasal congestion	2	
	Rhinorrhea	4	
	Oropharyngeal pain	2	
	Throat tightness	1	
	Throat irritation	5	
	Cough	16	6
	Wheezing	12	4
	Dyspnoea	13	2
Gastrointestinal disorders	Oral pruritus	3	1
	Paresthesia oral	2	1
	Lip swelling/oedema	3	
	Swollen tongue	1	
	Nausea	5	1
	Vomiting	5	3
	Abdominal pain	3	1
Skin and subcutaneous tissue disorders	Urticaria	23	5
	Pruritus	2	1
	Hyperhydrosis	1	
	Swelling face	1	
	Rash	3	
	Angioedema	2	1
General disorders and administration site conditions	Chest discomfort	2	
	Chest pain	1	

Serious adverse events and deaths

In the P3PC pool, few subjects experienced serious TEAEs (excluding serious TEAEs related to food challenges and accidental/voluntary peanut consumptions): 10 cases in 9 (1.7%) subjects in the DBV712 250 µg group, and 7 cases in 7 (3.2%) subjects in the placebo group.

Table 44 Serious TEAEs by SOC and PT (P3PC Pool)

	DBV712 250 µg (N=532)	Placebo (N=217)
System Organ Class Preferred term	**n (%)**	**n (%)**
Any SAE	9 (1.7)	7 (3.2)
Immune system disorders	4 (0.8)	2 (0.9)
Anaphylactic reaction	4 (0.8)	2 (0.9)
Respiratory, thoracic and mediastinal disorders	3 (0.6)	0
Bronchospasm	1 (0.2)	0
Throat irritation	1 (0.2)	0
Wheezing	1 (0.2)	0
Infections and infestations	2 (0.4)	1 (0.5)
Appendicitis	1 (0.2)	1 (0.5)
Tonsillitis	1 (0.2)	0
Eye disorders	0	1 (0.5)
Visual impairment	0	1 (0.5)
Gastrointestinal disorders	0	1 (0.5)
Coeliac disease	0	1 (0.5)
Injury, poisoning and procedural complications	0	1 (0.5)
Post procedural haemorrhage	0	1 (0.5)
Nervous system disorders	0	1 (0.5)
Seizure	0	1 (0.5)

Source: Table 8.1.1-A, Table 8.1.2-A
SAEs related to food challenges and peanut consumptions are excluded.
n (%) = number (%) of subjects experiencing at least one event, percentages are based on the number of subjects in each treatment group.
AEs were classified into System Organ Class and Preferred Term using Version 20.1 of MedDRA.

By PT, 5 events of anaphylactic reaction in 4 (0.8%) subjects in the DBV712 250 µg group and 2 events in 2 (0.9%) subjects in the placebo group have been observed in the P3PC pool. Of these anaphylactic reactions had been assessed by the Investigator as related to the IP in 5 events in 4 (0.8%) subjects in the DBV712 250 µg group. Whereas the 2 SAEs in 2 (0.9%) subjects in the placebo group were assessed as unrelated to IP. All events of anaphylactic reactions were assessed as moderate in severity.

Consistent with results for the P3PC and DBPC Pools, by PT, anaphylactic reaction was the most frequently reported serious TEAE in all three treatment groups (rate of 0.9, 1.1, and 2.3 events per 100 SY).

These data emphasise an increased risk of anaphylaxis in patients treated with DBV712 250 µg.

Laboratory findings

There were no clinically relevant differences between DBV712 250 µg treated patients and patients in the placebo group with regard to vital signs, lung function tests, SCORAD. In addition, the pooled analysis of haematology and biochemistry data did not indicate any safety signals associated with DBV712 treatment (data not shown).

Safety in special populations

The applicant declared that no conclusions could be drawn from the results on the subgroup analyses by race (White (420 [78.9%] subjects in the DBV712 250 µg group and 167 [77.0%] in the Placebo group), filaggrin gene mutation status (wild type for filaggrin gene (83.4% and 81.3% in the DBV712 250 µg and placebo groups), or screening ED (ED >10 mg (82.8% and 83.1% in the DBV712 250 µg and placebo groups).

Table 45 Overall Summary of TEAEs by Age Group (P3PC Pool)

Category	Age 4-5 years		Age 6-11 years	
	DBV712 250 µg (N=147) n (%)	Placebo (N=64) n (%)	DBV712 250 µg (N=385) n (%)	Placebo (N=153) n (%)
TEAEs	138 (93.9)	57 (89.1)	351 (91.2)	131 (85.6)
Mild TEAEs	127 (86.4)	52 (81.3)	336 (87.3)	122 (79.7)
Moderate TEAEs	62 (42.2)	21 (32.8)	177 (46.0)	57 (37.3)
Severe TEAEs	3 (2.0)	2 (3.1)	15 (3.9)	1 (0.7)
Serious TEAEs	2 (1.4)	1 (1.6)	7 (1.8)	6 (3.9)
TEAEs considered related to IP[a]	69 (46.9)	13 (20.3)	161 (41.8)	40 (26.1)
Serious TEAEs considered related to IP[a]	1 (0.7)	0	3 (0.8)	0
TEAEs leading to permanent IP discontinuation	4 (2.7)	0	4 (1.0)	0
TEAEs leading to temporary IP discontinuation	23 (15.6)	5 (7.8)	51 (13.2)	13 (8.5)
TEAEs leading to death	0	0	0	0
DBV712-induced local TEAEs[b]	56 (38.1)	11 (17.2)	135 (35.1)	30 (19.6) 5

Source: Table 5.1-A-1
a: Considered related to study treatment when reported as possibly related, probably related or related.
b: DBV712-induced local TEAE are defined as TEAE considered related to IP with a MedDRA HLT equal to "Application and instillation site reactions".
AEs/SAEs related to food challenges and peanut consumptions are excluded.
n (%) = Number (%) of subjects experiencing at least one event, percentages are based on the number of subjects in each treatment group.

Gender

In both groups there were more males than females (313 [58.8%] subjects and 134 [61.8%] subjects were male in the DBV712 250 µg and Placebo groups, respectively). Gender did not show an effect on the overall proportion of subjects with TEAEs when comparing males vs females (in either treatment group).

Atopic dermatitis

Subjects with an ongoing history of eczema/atopic dermatitis reported a higher frequency of application site eczema compared to those without, in both the DBV712 250 µg group (34 [14.0%] subjects vs 22 subjects [7.6%], respectively) and the placebo group (9 [8.7%] subjects vs 3 [2.6%] subjects, respectively) (Table 46). However, in terms of incidence of serious or severe TEAEs, or TEAEs leading to permanent or temporary discontinuations, the treatment safety profile was similar between subjects with and without ongoing history of eczema/atopic dermatitis. Moreover, no meaningful change in the severity of eczema (by Scoring Atopic Dermatitis index) was observed over 12 months of treatment with DBV712 250 µg.

Table 46 Overall Summary of TEAEs by Ongoing History of Eczema (P3PC Pool)

	With Ongoing History of Eczema		Without Ongoing History of Eczema	
Category	DBV712 250 µg (N=243) n (%)	Placebo (N=103) n (%)	DBV712 250 µg (N=289) n (%)	Placebo (N=114) n (%)
TEAEs	224 (92.2)	88 (85.4)	265 (91.7)	100 (87.7)
Mild TEAEs	217 (89.3)	83 (80.6)	246 (85.1)	91 (79.8)
Moderate TEAEs	111 (45.7) 5	39 (37.9)	128 (44.3)	39 (34.2)
Severe TEAEs	5 (2.1)	1 (1.0)	13 (4.5)	2 (1.8)
Serious TEAEs	2 (0.8)	3 (2.9)	7 (2.4)	4 (3.5)
TEAEs considered related to IP[a]	113 (46.5)	34 (33.0)	117 (40.5)	19 (16.7)
Serious TEAEs considered related to IP[a]	1 (0.4)	0	3 (1.0)	0
TEAEs leading to permanent IP discontinuation	4 (1.6)	0	4 (1.4)	0
TEAEs leading to temporary IP discontinuation	32 (13.2)	8 (7.8)	42 (14.5)	10 (8.8)
TEAEs leading to death	0	0	0	0
DBV712-induced local TEAEs[b]	94 (38.7)	26 (25.2)	97 (33.6)	15 (13.2)

Source: Table 5.1-A-7
a: Considered related to study treatment when reported as possibly related, probably related or related.
b: DBV712-induced local TEAE are defined as TEAE considered related to IP with a MedDRA HLT equal to "Application and instillation site reactions".
AEs/SAEs related to food challenges and peanut consumptions are excluded.
n (%) = Number (%) of subjects experiencing at least one event, percentages are based on the number of subjects in each treatment group

Overall, the presence of an ongoing history of asthma did not affect the safety or tolerability of DBV712. The presence or absence of an ongoing history of asthma did not influence the occurrence of anaphylaxis, nor was there a difference in the occurrence of asthma TEAEs reported in asthmatic compared with non-asthmatic subjects. Likewise, the overall summary of TEAEs for subjects with ongoing history of allergy other than peanut was similar to that seen in the overall population.

	P3PC pool - DBV712 250 mcg				
MedDRA Terms	Age 4-55 N=532 n (%)	Age 4-5 N=147 n (%)	Age 6-11 N=385 n (%)	Age 12-18 N=0 n (%)	Age >18 N=0 n (%)
Total TEAEs	489 (91.9)	138 (93.9)	351 (91.2)	Not applicable	Not applicable
Serious TEAEs – Total	9 (1.7)	2 (1.4)	7 (1.8)	-	-
- Fatal	0	0	0	-	-
- Hospitalization/prolong existing hospitalization	6 (1.1)	2 (1.4)	4 (1.0)	-	-
- Life-threatening	0	0	0	-	-
- Disability/incapacity	0	0	0	-	-
- Other (medically significant)	4 (0.8)	0	4 (1.0)	-	-
TEAE leading to drop-out	8 (1.5)	4 (2.7)	4 (1.0)	-	-
Psychiatric disorders	11 (2.1)	2 (1.4)	9 (2.3)	-	-
Nervous system disorders	94 (17.7)	11 (7.5)	83 (21.6)	-	-
Accidents and injuries [1]	86 (16.2)	20 (13.6)	66 (17.1)	-	-
Cardiac disorders	1 (0.2)	0	1 (0.3)	-	-
Vascular disorders	3 (0.6)	0	3 (0.8)	-	-
Cerebrovascular disorders	0	0	0	-	-
Infections and infestations	360 (67.7)	107 (72.8)	253 (65.7)	-	-
Anticholinergic syndrome	0	0	0	-	-
Quality of life decreased	0	0	0	-	-
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures [2]	11 (2.1)	0	11 (2.9)	-	-

TEAE: Treatment-Emergent Adverse Event

AE related to food challenges and peanut consumptions are excluded.

[1] “Accidents and injuries” is not a MedDRA defined SOC. “Injury, poisoning and procedural complications” SOC is presented.

[2] Includes Fall 1 (0.2), Syncope 4 (0.8), Dizziness 6 (1.1). Fractures are included in the “Injury, poisoning and procedural complications” SOC.

	DBPC pool - DBV712 250 mcg				
MedDRA Terms	Age 4-55 N=645 n (%)	Age 4-5 N=153 n (%)	Age 6-11 N=433 n (%)	Age 12-18 N=34 n (%)	Age >18 N=25 n (%)
Total TEAEs	587 (91.0)	143 (93.5)	395 (91.2)	33 (97.1)	16 (64.0)
Serious TEAEs – Total	11 (1.7)	2 (1.3)	7 (1.6)	0	2 (8.0)
- Fatal	0	0	0	0	0
- Hospitalization/prolong existing hospitalization	8 (1.2)	2 (1.3)	4 (0.9)	0	2 (8.0)
- Life-threatening	0	0	0	0	0
- Disability/incapacity	0	0	0	0	0
- Other (medically significant)	5 (0.8)	0	4 (0.9)	0	1 (4.0)
TEAE leading to drop-out	10 (1.6)	4 (2.6)	5 (1.2)	1 (2.9)	0
Psychiatric disorders	13 (2.0)	2 (1.3)	10 (2.3)	0	1 (4.0)
Nervous system disorders	110 (17.1)	11 (7.2)	91 (21.0)	3 (8.8)	5 (20.0)
Accidents and injuries [1]	101 (15.7)	20 (13.1)	72 (16.6)	5 (14.7)	4 (16.0)
Cardiac disorders	1 (0.2)	0	1 (0.2)	0	0
Vascular disorders	4 (0.6)	0	4 (0.9)	0	0
Cerebrovascular disorders	0	0	0	0	0
Infections and infestations	423 (65.6)	112 (73.2)	286 (66.1)	17 (50.0)	8 (32.0)
Anticholinergic syndrome	0	0	0	0	0
Quality of life decreased	0	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures [2]	13 (2.0)	0	13 (3.0)	0	0

TEAE: Treatment-Emergent Adverse Event

AE related to food challenges are excluded in studies V712-301 and V712-201-E. AE related to peanut consumptions are excluded in studies V712-301 and V712-302.

[1] “Accidents and injuries” is not a MedDRA defined SOC. “Injury, poisoning and procedural complications” SOC is presented.

[2] Includes Fall 2 (0.3), Syncope 4 (0.6), Dizziness 7 (1.1). Fractures are included in the “Injury, poisoning and procedural complications” SOC.

	Global pool - DBV712 250 mcg				
MedDRA Terms	Age 4-55 (FSY=1289.1) Rate	Age 4-5 (FSY=228.8) Rate	Age 6-11 (FSY=875.2) Rate	Age 12-18 (FSY=143.0) Rate	Age >18 (FSY=42.1) Rate
Total TEAEs	697.7	779.3	696.4	578.1	685.7
Serious TEAEs – Total	3.2	2.2	2.6	3.5	19.0
- Fatal	0	0	0	0	0
-Hospitalization/prolong existing hospitalization	2.4	1.7	2.2	1.4	14.3
- Life-threatening	0	0	0	0	0
- Disability/incapacity	0.1	0	0.1	0	0
- Other (medically significant)	0.9	0.4	0.6	2.1	4.8
TEAE leading to drop-out	2.0	4.4	1.5	1.4	2.4
Psychiatric disorders	3.3	1.7	3.8	2.1	4.7
Nervous system disorders	31.0	9.6	34.6	34.3	61.7
Accidents and injuries [1]	22.2	20.1	22.6	23.8	19.0
Cardiac disorders	0.1	0	0.1	0	0
Vascular disorders	0.5	0.4	0.6	0	0
Cerebrovascular disorders	0	0	0	0	0
Infections and infestations	158.4	232.5	155.2	78.3	94.9
Anticholinergic syndrome	0	0	0	0	0
Quality of life decreased	0	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures [2]	2.1	0.4	3.0	0	0

TEAE: Treatment-Emergent Adverse Event

AE related to food challenges are excluded in studies V712-301, V712-303 and V712-201-E. AE related to peanut consumptions are excluded in studies V712-301, V712-302 and V712-303.

SY = subject-years. FSY = Follow-up duration in SY.
Rate = 100 x Events count / FSY.

[1] “Accidents and injuries” is not a MedDRA defined SOC. “Injury, poisoning and procedural complications” SOC is presented.

[2] Includes Fall 8 events (0.6), Syncope 5 events (0.4), Dizziness 14 events (1.1). Fractures are included in the “Injury, poisoning and procedural complications” SOC.

Immunological events

SIT induces immunomodulation, the specific changes, e.g. of IgE, IgG4 are addressed in the section of efficacy.

Safety related to drug-drug interactions and other interactions

No specific interaction studies have been conducted. No drug interactions have been reported with the use of DBV712.

Discontinuation due to AES

Data from the P3PC Pool, showed that 8 (1.5%) subjects in the DBV712 250 µg group experienced a total of 11 TEAEs leading to permanent treatment discontinuation. Of these subjects, 3 were discontinued for serious anaphylactic reactions, 1 for a non-serious anaphylactic reaction, 1 for an event of urticaria, and 3 for local application site reaction TEAEs (severe application site pruritus respectively urticaria; application site erythema, pruritus, or swelling, application site discolouration – hypopigmentation). All 11 events were assessed as related to DBV712. None events in the Placebo group were noted.

Table 47 TEAEs Leading to Permanent Treatment Discontinuation by SOC and PT (P3PC Pool)

	DBV712 250 µg (N=532)	Placebo (N=217)
System Organ Class **Preferred term**	**n (%)**	**n (%)**
Any TEAEs leading to permanent treatment discontinuation	8 (1.5)	0
Immune system disorders	4 (0.8)	0
Anaphylactic reaction	4 (0.8)	0
General disorders and administration site conditions	3 (0.6)	0
Administration site conditions[a]	3 (0.6)	0
Application site pruritus	2 (0.4)	0
Application site discolouration	1 (0.2)	0
Application site erythema	1 (0.2)	0
Application site swelling	1 (0.2)	0
Application site urticaria	1 (0.2)	0
Skin and subcutaneous tissue disorders	1 (0.2)	0
Urticaria	1 (0.2)	0

Source: Table 9.1.2-A, Table 9.2.2-A
AEs/SAEs related to food challenges and peanut consumptions are excluded.
n (%) = Number (%) of subjects experiencing at least one event, percentages are based on the number of subjects in each treatment group.
AEs were classified into System Organ Class and Preferred Term using Version 20.1 of MedDRA.
a: HLT equal to "Application and instillation site reactions".

Likewise, TEAS leading to temporary treatment discontinuation were noted in a higher proportion of subjects in the DBV712 250 µg group than the Placebo group (74 [13.9%] vs 18 [8.3%] subjects, respectively). The most frequent events leading to temporary discontinuation consisted of PTs within the SOC of "Infections and infestations" (in 21 [3.9%] subjects in the DBV712 250 µg group vs 5 [2.3%] in the Placebo group), anaphylactic reactions (20 [3.8%] vs 2 [0.9%] subjects), urticaria (13 [2.4%] vs 3 [1.4%]), and PTs within the HLT of "Application and instillation site reactions" (in 11 [2.1%] vs no subjects). The majority of subjects temporary discontinued treatment ≤15 days.

In line with this observation is the rate of observed TEAEs leading to administration of epinephrine, which were reported in a higher proportion of subjects in the DBV712 250 µg group (28 [5.3%] subjects) compared with the Placebo group (3 [1.4%] subjects), corresponding to an overall rate of 8.4 vs 1.8 events per 100 SY.

The most frequently reported TEAEs leading to epinephrine administration were PTs within the SOC of "Immune system disorders": anaphylactic reaction (reported in 17 [3.2%] subjects in the DBV712 250 µg group vs 3 [1.4%] subjects in the Placebo group). All other TEAEs were each reported in 1 (0.2%) subject in the DBV712 250 µg group only.

Post marketing experience

No post-marketing data are available since DBV712 has not yet been granted approval in any region.

3.3.9. Discussion on clinical safety

For the integrated safety analysis peanut-allergic subjects had been included who received at least one patch application (DBV712 or placebo) during any of 8 clinical studies. Within these studies, five DBV712 dose levels have been tested (20 µg, 50 µg, 100 µg, 250 µg, and 500 µg) for varying treatment durations (minimum 2 weeks (V712-101), maximum 36 month) and numbers of treated subjects per dose (minimum n = 8, V712-101). Focusing on the target group of this MAA, a total of 694 peanut-allergic subjects aged 4-11 years who were exposed to 250 µg are reported of.

For the purpose of analysis, the applicant defined 3 pooled datasets: The key safety population for evaluation of the DBV712 target dose (250 µg) and target population (subjects aged 4-11 years) is presented in the P3PC Pool, which includes 532 unique subjects: n = 238 from V712-301 (PEPITES), and n = 294 from V712-302 (REALISE). Due to the different durations of the blinded, respectively observational periods, it is noted that nearly 45% of included subjects in the P3PC pool are observed for 12 months (PEPITES study), and 55% for 6 months (REALISE study). In consequence, presented Tables and Figures based on the P3PC pool are in parts misleading and require a careful description. According to the applicant, the two groups (active – placebo) in the P3PC Pool were balanced with respect to demographic and baseline characteristics. However, inclusion and exclusion criteria of the REALISE study were slightly different from the PEPITES study. Thus, a comparison of demographics and baseline characteristics of included subjects between studies was provided in the D120 responses and clarified the pooling. Still, due to the different exposure time, all the summary safety tables and figures based on the P3PC pool are to some extent misleading and should be interpreted keeping these different exposure times in mind.

The double-blind placebo-controlled pool (DBPC Pool, n = 854 subjects; 4 to 55 years; all DBV712 doses) summarizes additional safety data from all 6 double-blind, placebo-controlled studies: V712-301, V712-302, V712-202, V712-201-E (6-month double-blind period), V712-204-E (12-month double-blind period) and V712-101 (2-weeks treatment period), along with corresponding placebo groups. The Global Pool finally (n = 948 total), compromises above listed subjects regardless of study period (study V712-203, the open-label period of study V712-201-E (beyond the 6-month DB period), study V712-204-E (beyond 12-month DB period) and study V712-303). Hence, longer-term data up to 36 months is included.

Treatment duration and compliance

In the P3PC pool (main safety population), 532 subjects aged 4-11 years were included to DBV712 250 µg for 378 SY, Mean 260 days (V712-301, PEPITES - 235.8 SY (12 month), and V712-302, REALISE data from the 6-month double-blind period 142.3 SY). The number of subjects aged 4-11 years old receiving the target dose of 250 µg/24 h (±4) and corresponding subject years by duration of exposure was clarified in the D120 response: The exposed patient population in the P3PC pool comprises a total of 531 patients: (238-1) = 237 exposed patients from study V712-301 of whom 223 were exposed for ⩾12 months, and 294 exposed patients from study V712-302 of whom 180 were exposed for ⩾6 months. Overall compliance was high, and similar for both treatments, with a mean (SD) compliance rate of 98.5% (4.48) for DBV712 250 µg and 98.0% (5.09) for placebo. Overall, 36 (10.1%) subjects discontinued; this is within the expected drop-out rate of 15% in the overall population. A total of 49 (13.8%) subjects had a major protocol deviation, and this amount is considered relevant.

In the DBPC pool, 854 subjects were exposed to DBV712 (any dose) for 605 SY, including 645 subjects exposed to DBV712 250 µg for 460 SY. Among the 645 subjects exposed to DBV712 250 µg in the DBPC pool, 586 were subjects aged 4-11 years. In the Global pool, 948 peanut-allergic subjects, aged 4-55 years, had been exposed to DBV712 at doses ranging from 20 to 500 µg (ISS data cutoff of 20 December 2019).

Common adverse events

P3PC pool: Reported adverse events were slightly higher in the DBV712 250 µg group with 489 (91.9%) to 188 (86.6%) subjects in the placebo group. Most TEAEs were mild or moderate in severity. Although the frequency of severe TEAEs was low, it was numerically higher in the DBV712 250 µg group (18 [3.4%] subjects) than the placebo group (3 [1.4%] subjects). Most frequently reported severe events were local application site TEAEs.

Overall, the most frequently reported TEAE by individual PT was upper respiratory tract infection, (23.5% of subjects in the DBV712 250 µg group and 24.4% in the placebo group). Other frequent PTs (reported in ≥10% of subjects in the DBV712 250 µg group) included application site pruritus (16.0% of subjects in the DBV712 250 µg group vs 6.9% in the placebo group), application site erythema (13.9% vs 9.7%), cough (13.3% vs 12.9%), asthma (11.1% vs 9.2%), application site eczema (10.5% vs 5.5%), and vomiting (10.2% vs 6.9%*).* Frequencies of reported PTs related to gastrointestinal symptoms, like vomiting (10.2% vs 6.9%), abdominal pain upper (5.5% vs 2.3%) and diarrhoea (3.6% vs 1.4%) are noticed to be more prominent in the DBV712 250 µg group vs in the placebo group, which is explained by the applicant as being "common symptoms" in childhood. Treatment-emergent AEs considered related to the investigational product (IP) were reported nearly twice as much in the DBV712 250 µg group than the placebo group (230 [43.2%] and 53 [24.4%] subjects), and mainly consisted of application site reactions (191 [35.9%] and 41 [18.9%] subjects).

Systemic Anaphylactic Reactions

In the P3PC pool, 36 anaphylactic, treatment related reactions were reported. Of these, 29 subjects (5.5%) treated with DBV suffered from 31 anaphylactic reactions, versus 5 subjects (2.3%) from the placebo group, thus, nearly twice as much. The same is true, when considering the occurrence of systemic AESI: Rate = 100 x Events count/FSY: 9.4 DBV vs 4.2 Placebo. Regarding the severity of the anaphylactic reaction, most reactions were mild or moderate (n=31): 8 were mild and 23 moderate in the DBV712 250 µg group, versus 5 moderate reactions in the placebo group had been noted. Symptoms predominantly included urticaria, cough, wheeze, subjective respiratory symptoms or vomiting. Anaphylactic reactions meeting seriousness criteria also existed: 5 serious events were reported for 4 subjects (0.8%) in the DBV712 250 µg group (assessed as possibly/probably IP related). Still, TEAEs leading to epinephrine intake were reported by 32 events from 28 (5.3%) children treated with DBV versus 3 events, from 3 (1.4%) children from the placebo group. Correspondingly, the risk for anaphylactic reactions (including potential severe and serious events) related to DBV712 250 µg treatment, compared to the risk for these events in subjects not treated is doubled (new B/R MO). This means that the dermal route of the DBV712-250 µg treatment is not free from systemic anaphylactic reactions related to the IP. Correspondingly, this need to be reflected in the SmPC (LoOI).

Even more, as AEs related to peanut consumption (accidental or voluntary) is excluded in the above listed analysis, it is of importance to note that anaphylactic reactions including accidental peanut consumption again occurred nearly twice as much in DBV712 treated patients: 44 events from 42 (7.9%) subjects versus 10 events from 9 placebo treated children (4.1%) were observed. In this context, it needs to consider that allergic reactions (following peanut consumption) included 5 events of serious TEAE (anaphylactic reaction) in the DBV712 group relative to 1 event in the Placebo group. Allergic reactions (following peanut consumption) occurred in 33 DBV712 treated subjects (6.2%) leading to epinephrine use in 11 (2.1%) children; comparatively, in 10 placebo subjects (4.6%) leading to epinephrine use in 4 (1.8%) subjects.

Almost all episodes occurred within the first 6 months of treatment in both treatment groups (of note: from month 6 to 12 only subjects from the PEPITES study were analysed,). In the P3PC pool the majority of episodes in the DBV712 250 µg group were reported within the first 2 months. This supports a treatment related effect. The applicant declared that a pattern of any specific confounding factors for the risk of anaphylactic reactions during study had not been identified. In episodes of anaphylaxis by preferred term, the time of application of DBV712 to onset of symptoms varied between 1 and 21 hours.

Overall, in the P3PC pool, 22 episodes of anaphylactic reactions in 20 subjects, all in the DBV712 250 µg group, were considered treatment-related and most of them needed epinephrine. It is depicted that

TEAEs leading to epinephrine intake were noticed in 32 events from 28 (5.3%) subjects in the DBV 712 group versus 3 events from 3 (1.4%) children in the placebo group.

23 episodes of anaphylactic reactions lead to temporary discontinuation of DBV712 250 µg in 22 subjects (including 2 episodes in 2 placebo subjects). In only one subject was recurrence of an anaphylactic reaction reported after treatment recommenced. Four episodes of anaphylactic reaction in 4 (0.8%) subjects lead to permanent treatment discontinuation in the DBV712 250 µg group (none in the placebo group). In all, in the P3PC Pool, 8 (1.5%) subjects in the DBV712 250 µg group experienced a total of 11 TEAEs leading to permanent treatment discontinuation, versus no events in the Placebo group (4 discontinued for anaphylactic reactions, 1 for an event of urticaria, and 3 for local application site reaction TEAEs (including severe application site pruritus; urticaria; and erythema swelling, and hypopigmentation)). All 11 events were assessed as related to DBV712.

Consistent with results for the P3PC in the DBPC Pools, by PT, anaphylactic reaction was the most frequently reported serious TEAE in all three treatment groups (rate of 0.9, 1.1, and 2.3 events per 100 SY).

Overall, 80 serious TEAEs (64 in DBV712 group and 16 in placebo group) were reported during the clinical development programme of DBV712 (Global Pool), excluding SAEs related to food challenge or accidental/voluntary peanut consumption (see OC above). The overall rate of serious TEAEs was 3.2, 4.1, and 6.1 events per 100 SY for the DBV712 250 µg, DBV712 All Doses, and Placebo groups.

TEAE by maximum duration. Among subjects who experienced TEAEs within the SOC “Skin and subcutaneous tissue disorders” (145 [27.3%] and 59 [27.2%] subjects in the DBV712 250 µg and Placebo groups, respectively), most subjects experienced events lasting 1-7 days. Within the SOC “Respiratory, thoracic and mediastinal disorders” most subjects experienced events lasting 1-7 days or 8-15 days. However, 3.6% of TEAEs within the SOC “Respiratory, thoracic and mediastinal disorders” lasted for more than 91 days. Within the SOC “Respiratory, thoracic and mediastinal disorders” 3.3% of the patients on the 250 µg experienced a TEAE lasting more than 91 days. These proportions of very long lasting TEAEs are most likely related to the chronic allergic comorbidities in the patient population

Local patch application site reactions
A higher frequency of application site eczema was reported in subjects with an ongoing history of eczema/atopic dermatitis compared to those without, in both the DBV712 250 µg group (34 [14.0%] subjects vs 22 subjects [7.6%], respectively) and the placebo group (9 [8.7%] was reported in subjects vs 3 [2.6%] subjects, respectively). Thus, patients should be informed regarding specific conditions (e.g. primary or secondary skin barrier impairments) or treatments making the patient more susceptible to enhanced application site reactions and others during treatment accordingly (precaution use, SmPC) (LoOI). In addition, these more severe application site reactions were managed (when required) with topical corticosteroids, reduced patch application time, and temporary treatment discontinuation. Thus, the management is reflected as precise as possible in the SmPC. However, the efficacy data in association with “missed patches” and the need of supervision of a health care professional to re-start the treatment should be further precised (LoOI).

It is noted that the severity of local skin reactions over time as per investigator assessment appears to increase from Day 1 up to Month 1, and then tends to decrease over time from Month 3 up to Month 6. The applicant explains that the observed increase in severity of local skin reactions from day 1 to Month 1, followed by decrease in severity from Month 3 to Month 6 reflect the initial rise in peanut-specific IgE levels followed by a decline. However, there seems to be an increase of local reactions >grade 1 between 6 and 12 months. The applicant emphasises this is driven by a small numerical imbalance in grade 2 events, while grade 3 events are balanced and grade 4 events are zero, and the discontinuation rate is very low. However, an increase of application side erythema, pruritus, reactions, swelling and urticaria in the period 6-12 month compared to 0-6 month still needs some explanation

(LoOI). Furthermore, it is noted that the long-term 36-month data from Study V712-303 suggested event rates for PTs related to application site reactions tended to decrease over time and rarely resulted in premature study discontinuation. The rate of DBV712-induced local TEAEs markedly decreased between Year 2 (72.2%) and Year 3 (29.9%) of treatment. The data provided by the applicant indicate a low rate of TEAE-driven discontinuations, overall, and a similar TEAE-frequency in the "completer" group and the "safety".

All observed events of application site hyperpigmentation were reported as mild, 11 were reported as resolved, 6 were reported as unknown outcome and one subject had ongoing hyperpigmentation at study completion.

Interactions and Laboratory results
No direct interactions with other medicinal products are expected with DBV712 nor have been investigated. Nevertheless, starting of this cutaneous peanut SIT is not recommended while undergoing other types or allergen immunotherapy. In 4.4 it now states: "Concomitant allergen immunotherapy: TRADENAME has not been studied in patients who are receiving concomitant allergen immunotherapy. Caution should be exercised when administering this medicinal product in conjunction with other allergen immunotherapies."

Overarching comment on safety analysis
Due to differences in observation time and exposure between performed studies, respectively summarized in suggested safety pools, absolute count data and proportions may not be fully suitable to quantify safety risks correctly. Thus, the applicant provided estimates of exposure-adjusted incidence of adverse events. It was shown that subjects experiencing any TEAE was high and similar in both groups: 91.9% in DBV712 250 µg and 86.6% in Placebo groups. However, TEAEs happened significantly earlier in subjects treated with DBV712 250 µg. The risk of epinephrine intake relating to the investigational product is highest shortly after treatment initiation, with a steep increase of the cumulative hazard function within the first 50 days. However, events evidently continued to occur after that period, and the analysis is restricted to the occurrence of the first of such events. The applicant should further add number(s) of event(s)/subjects of epinephrine intake due to accidental/voluntary peanut consumption and add time point of event for both treatment groups in P3PC Pool (LoOI).

The applicant was asked to explore whether demographic or clinical baseline characteristics (in particular, age, sex, baseline ED, and markers of severity of peanut allergy) are associated with the risk of adverse reactions. Indeed, this seems to be the case. In a very crude approach, interpreting ED, peanut-specific IgE or IgG4, eczema/atopic dermatitis as markers for the same thing (as these markers of allergy severity are likely correlated), it appears that the underlying allergy severity could be associated with an increased risk for any TEAE, anaphylactic reactions, events requiring epinephrine use, application site reactions and asthma. Especially, because of the association with an increased risk for events leading to epinephrine use or anaphylactic reactions (across several definitions of what constitutes an anaphylactic reaction), more accurate parameters of predicting clinical reactions such as Ara h 2 (and Ara h 1, 3, or others) should be included (LoQ).

In addition, it is noted that the applicant has presented comprehensive safety data in children aged 4-5 years. The comparison between subjects 4-5 years vs 6-11 years observed a clear treatment related effect in local and systemic AESI. The applicant state, that no age dependent effect was observed. This is not fully agreed. Risk differences presented for the risk of local AESI suggests that the number needed to harm is approximately 11 in children in aged 4-5 years and approximately 24 in children aged 6-11.

3.3.10. Conclusions on clinical safety

For the purpose of analysis of the safety data, the applicant defined three pooled datasets: the P3PC Pool (n = 532 total; key safety population), the Double-blind placebo-controlled pool (DBPC Pool, n = 854 total)) and the Global Pool (n = 948 total). Especially for the key safety pool, P3PC, due to the different exposure time, all the summary safety tables and figures based on the P3PC pool are to some extent misleading and should be interpreted keeping these different exposure times in mind.

In general, a safety database of 948 patients (children and adults) exposed to peanut EPIT (any tested dose for any tested time), respectively n = 532 in the P3PC pool, is considered adequate for the assessment of the MAA (ICH Topic E 1 Population Exposure: The Extent of Population Exposure to Assess Clinical Safety). The included patients are representative of the general peanut allergic population of EU.

Following Adverse drug reactions were identified: Immune system disorders: common = anaphylactic reactions; General disorders and administration site conditions: very common = application site reaction and eczema; common = application site swelling, urticarial and site hyperpigmentation; uncommon = application site excoriation, bleeding, infection or pain.

Of note, an increased risk of anaphylaxis in patients treated with DBV712 250 µg has been observed.

DBV treated patients suffered nearly twice from anaphylactic reactions, compared to placebo (5.5% vs 2.3%). The number of events of anaphylactic reactions including accidental peanut consumption is also nearly doubled in verum treated subjects (7.9% vs 4.1%). The rate for systemic AESI (rate = 100 x Events count/FSY) is 9.4 vs 4.2, again nearly twice as much. Thus, this points to a treatment related effect. Even more, the finding that anaphylactic reactions (according to PT) occurred mainly in the first 2 months after treatment initiation supports treatment relation.

On the other side, the need for epinephrine following accidental or voluntary peanut consumption seems not to differ between treated or placebo treated subjects, Verum and Placebo treated children needed epinephrine roughly to the same amount/same ratio. Thus, there seem to be no effect of the treatment regarding this measure. Even more, serious anaphylactic reactions had been observed mainly in the DBV treated group (B/R MO).

3.4. Risk management plan

Anaphylactic reaction is the most important topic of the RMP and main focus for pharmacovigilance activities. This is agreed. Warnings in the SmPC regarding the risk of anaphylaxis should be reworked (see comments in the SmPC, especially in 4.4, as well as LoOI).

3.4.1. Safety Specification

Summary of safety concerns

The applicant identified the following safety concerns in the RMP:

Table 48 Summary of the safety concerns

• **Important identified risks**	Anaphylactic reactions
• **Important potential risks**	None
• **Missing information**	Impact on the long-term immune-mediated reactions

Having considered the data in the safety specification the CHMP considers that the following issues should be addressed:

"Possible rebound after discontinuation of treatment" should also be a safety concern (important potential risk)

Please add as important potential risk:

- Possible rebound after discontinuation of treatment

Possible rebound after discontinuation of treatment should be included. Especially as, "thirty-one of 141 subjects (22%) had a decrease in ED from Month 12 to Month 36. Twelve of the 31 subjects still had a higher ED at Month 36 relative to baseline. Of these 31 subjects, 11 were treatment responders at Month 12, but not Month 36."Conclusions on the safety specification

In general, the safety specifications are agreed. However, some issues should be reworked (see above and (LoOI).

3.4.2. Pharmacovigilance Plan

Routine pharmacovigilance activities

The applicant proposes developing targeted questionnaires (TQ) regarding anaphylactic reactions and has submitted an example of a TQ in RMP v. 0.2.

PRAC assessment comment: The applicant agrees to using specific adverse reaction follow-up questionnaires regarding anaphylactic reactions. TQs are, however, classified as *routine* pharmacovigilance activities and not as additional PhV activities as proposed by the applicant. The applicant is requested to list the TQs under *routine PhV activities beyond adverse reactions reporting and signal detection* in the RMP.

Furthermore, the content of the TQ needs to be reworked to better reflect the international definition/guidelines of anaphylactic reactions and anaphylaxis (for example, Brighton criteria with modification as necessary could be used). The information should be tried to be collected at a level that allows for a causality assessment later on (therefore terms such as "extra fast or extra slow heart rate", or inquiring about allergen exposure but ignoring the timeline, as examples, are considered not necessarily helpful). Please refer to, for example, WHO-UMC causality assessment for the type and level of information that will be needed for standardized case causality assessment. Compact, precise, easy to understand and fill-in (tabular) questionnaires are preferred, with the goal of aiding in the collection of as standardized and as complete data as possible.

Finally, the TQ on anaphylactic reactions is primarily aimed for the health care professionals (HCP) since these types of reactions generally require assessment and/or treatment by an HCP, and the HCPs also are generally regarded as the source of most reliable and relevant information in regard to serious reactions such as anaphylaxis. Therefore, providing another TQ for the consumer/parent

is not considered necessary; the applicant is invited to comment on this according to their view. (LoQ).

Summary of additional PhV activities

The applicant does not propose category 1 or 2 additional PhV activities which is agreed. The following category 3 additional PhV activities are proposed by the applicant:

Study	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Study V712-303 (PEOPLE) EudraCT: 2016-002916-42 ClinicalTrials.gov identifier: NCT03013517	To assess the efficacy and safety of DBV712 250 mcg after up to 60 months of EPIT to induce/maintain desensitization to peanut in peanut-allergic children	The important identified risk: anaphylactic reaction The missing information: long term effect of immune-mediated reactions.	DSUR, PSUR and at conclusion of the study completion)	TBD
An epidemiological observational study	To systematically collect the real-world data to assess the natural history of disease in the targeted population as well as longitudinal follow-up for those receiving DBV712	The important identified risk: anaphylactic reaction The missing information: long term effect of immune-mediated reactions.	DSUR, PSUR and at conclusion of the study completion)	TBD
A category 3 PASS	To follow patients longitudinally to evaluate important safety concerns for DBV712.	The important identified risk: anaphylactic reaction The missing information: long term effect of immune-mediated reactions.	DSUR, PSUR and at conclusion of the study completion)	TBD
DSUR = Development safety update report; EPIT = Epicutaneous immunotherapy; PASS = Post-authorisation safety study (PASS); PSUR = Periodic Safety Update Report; TBD = To be determined				

In response to the request that additional PhV activities and/or additional RMMs should be proposed for all safety concerns listed in the RMP summary of safety concerns, the applicant provided the following summary:

1. The applicant will continue to assess the safety data from ongoing and completed clinical studies to further characterize important safety concerns including long-term safety.

2. The applicant plans to systemically collect real-world data in addition to routine and enhanced PhV activities to characterize the important safety concerns. The applicant will also have safety objectives to meet category 3 PASS requirement.

3. The applicant will develop and utilize the TQ as an enhanced PhV activity to further characterize important safety concerns in addition to routine post-authorisation PhV activities.

4. The applicant will develop and utilize the age-appropriate Education Materials in addition to the product labeling and medication guide as risk minimization methods (RMMs) for important safety concerns.

The applicant will use the DSUR/PSUR as milestones to evaluate and present available safety information and update the RMP and other applicable documents, such as product labeling, as appropriate.

PRAC comment: The applicant proposes altogether three category 3 PASS in the RMP PhV plan to address the safety concerns anaphylactic reactions and long-term effect of immune-mediated reactions

- Ongoing V712-303 (PEOPLE study): Open-label follow-up study of the PEPITES study to evaluate the long-term efficacy and safety of DBV712. The PEOPLE study evaluates the clinical benefit of DBV712 250 mcg after up to 5 years of DBV712 250 mcg to induce/maintain desensitization to peanut in peanut-allergic children, and will also aid in evaluating the safety of long-term treatment with DBV712 250 mcg in peanut-allergic children.
- An epidemiological study with observational study design to systematically collect the realworld data to assess the natural history of the disease in the targeted population as well as longitudinal follow-up for those receiving DBV712.
- A PASS with the objective to follow patients longitudinally to evaluate important safety concerns for DBV712.

No protocols or synopses have been submitted, however, and therefore the proposed studies cannot be assessed nor agreed. In their response to RMP question 3, the applicant describes that "*A feasibility assessment of the availability of existing real-world data sources in Europe has been initiated, and the available observational data can be categorized as either retrospective or prospective. As feasible, available data for consideration will include both administrative data (electronic medical record and claims) and registry data."* The applicant proposes that the study features including duration, sample size, and comparator groups, would be "*finalized upon agreement with the CHMP, with a detailed protocol shared with the CHMP prior to study initiation*". This approach is not supported; more specific information is required for assessment of whether or not the product's PhV plan is sufficient:

- The applicant is requested to clarify the objectives, milestones and due dates of the proposed studies, i.e. synopses or protocols for all proposed PASS should be submitted with the revised RMP v. 0.3. The study plans should include discussion on intended extent of the data, including power calculations as necessary. The study milestones should include timelines for the feasibility step, submission of the full protocol, start of data collection, any progress reports, and submission of the final study report.
- A single Summary table of additional pharmacovigilance activities under RMP III.3 should be added.
- The applicant is also reminded that interpretation of the safety data gathered in the long-term extension study requires a relevant reference group, or reference dataset, to which the observed incidences are compared. Possibilities of utilizing, for example, a registry-based approach, should be discussed.
- The applicant's response should also clarify how each study will add to the characterization of the individual risks of the product and conclude if all three studies are necessary.
- Furthermore, the currently empty RMP Annex 3 should be completed accordingly.
- Finally, the protocols should be submitted as post-authorisation measures (MEA) within 6 months of the EC decision. (LoQ)

The applicant conveys agreement in general to developing additional PhV activities and/or additional RMMs for all safety concerns listed in the RMP summary of safety concerns. While a category 3 PASS and educational materials are generally accepted as an aPhV activity and an aRMM, respectively, the contents of these plans, however, need to be reworked and presented as detailed above in this assessment box and under assessment of the RMMs in section 3.4.4 of this AR. Please note that, as clarified under routine PhV activities above, the TQs are not regarded as additional PhV activities but are routine PhV activities. The TQs regarding anaphylactic reactions should therefore be excluded from the list of aPhV activities.

Since inclusion of some of the risks of the product in the safety specification is yet to be determined (CHMP), the safety specification may still evolve. In the revised RMP v. 0.3, the applicant should propose additional PhV activities and/or additional RMMs for all safety concerns listed in the final RMP summary of safety concerns, as appropriate. Synopses or protocols and milestones should be included in the updated RMP v. 0.3. Based on the final CHMP list of safety concerns, the important potential risks should be linked to PEOPLE-study and/or specific category 3 PASS, and included as safety concerns addressed in table 20 (RMP v.02) under "III.3 Summary table of additional pharmacovigilance activities". Table 25 (RMP v.02) under V.3 "Summary of risk minimisation measures" will need to be revised accordingly. (LoQ)

Additional pharmacovigilance activities to assess the effectiveness of risk minimisation measures

The applicant intends to use the PSUR to report all relevant safety data to assess the effectiveness of routine and additional RMMs with a focus on the safe use of DBV712 in the post-authorisation environment. Additional surveys will be conducted after dissemination of educational materials to assess the understanding of the DBV712 consumers about the important safety information and safety use of DBV712. The survey results will be included in the corresponding PSUR upon the completion of the survey.

PRAC comment: A PSUR is a routine requirement for the MAH and cannot be regarded as an additional PhV activity to assess the effectiveness of additional RMMs (=educational materials).

MAH should clarify and specify what is meant with the planned "additional surveys". A study synopsis or protocol and milestones should be included in the updated RMP v. 0.3. The applicant is reminded, that surveys addressing the effectiveness of additional RMMs are category 3 additional PhV activities, hence the proposed survey should also be included in RMP table 20 (RMP v. 0.2) under "III.3 Summary table of additional pharmacovigilance activities". The target group selection, i.e. parents vs. the prescriber, will also need to be discussed and justified.

Overall conclusions on the PhV Plan

The PRAC, having considered the data submitted, is of the opinion that at present time it is premature to conclude whether or not the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

The PRAC also considered that the applicant should propose a study to monitor the effectiveness of additional RMMs (educational materials) that are considered necessary for the safe and effective use of the product.

3.4.3. Plans for post-authorisation efficacy studies

Summary of Post authorisation efficacy development plan

The applicant proposes no post-authorisation efficacy studies.

3.4.4. Risk minimisation measures

Routine Risk Minimisation Measures

Description of the routine RMMs by the applicant (RMP v.02):

Safety concern	Routine risk minimisation activities
Anaphylactic reactions	Routine risk communication SmPC Sections 4.3 and 4.4 Routine risk minimisation activities recommending specific clinical measures to address the risk SmPC Section 4.2 DBV712 patch should be applied to dry, clean, intact, healthy, non-inflamed skin SmPC Sections 4.3 and 4.4 - Contraindication in case of uncontrolled asthma. - - Consider a temporary discontinuation of TRADENAME if the patient experiences *severe* or uncontrolled asthma. SmPC Section 4.4: - Instruction to strictly maintain the peanut-free diet - Continue to prescribe autoinjectable adrenaline SmPC Section 4.4, Package leaflet - Instruction to educate patients/caregivers to recognize the signs and symptoms of a severe allergic reaction, to remove DBV712 patch and in the proper use of emergency autoinjectable adrenaline - Instruction to educate patients/caregivers to seek immediate medical care upon use of autoinjectable adrenaline SmPC, Package leaflet - Do not use in case of uncontrolled asthma - Continue to practice strictly peanut avoidance - Always carry autoinjectable adrenaline - Instruction in case of signs and symptoms of allergic reactions to remove the DBV712 patch and discuss with health care provider SmPC, Section 4.2, Package leaflet Apply the patch on a skin area that is intact, i.e. free of cuts, scratches. Other routine risk minimisation measures beyond the Product Information Prescription only medicine
SmPC = Summary of Product Characteristics	

Missing information: Impact on long-term immune-mediated reactions	
Risk minimisation measures	Routine risk minimisation measures: - SmPC Section 4.2 Additional risk minimisation measures - None

PRAC comment: The relevant SmPC/PL sections have generally been referenced in the RMP and constitute the routine RMMs. Considering the risks (i.e. anaphylactic reactions in addition to other potential risks determined by the CHMP) associated with the product, it is viewed as essential that the information and instructions in the SmPC and PL are both comprehensive and clear to support the safe use of the product in real life situations, especially when considering the target group of children (as per CHMP final consideration).

Additional technical notes:

Under missing information, the part referring to additional RMMs should be deleted from this section of routine measures

Please provide a single Summary table of routine risk minimisation activities by safety concern under RMP V.1. (LoQ).

Summary of additional risk minimisation measures

Table 49 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern (RMP v. 0.2)

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risk		
Anaphylactic reactions	Routine risk minimisation measures: SmPC Sections 4.2, 4.3, and 4.4 LABELLING AND PACKAGE LEAFLET Sections 2 and 3 Prescription only medicine Additional risk minimisation measures: Patient and parent/caregiver education materials	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities - Targeted Questionnaire for every post-authorisation report of anaphylactic reactions - Effectiveness evaluation of DBV712 educational materials - Ongoing Study V712-303 extension - An epidemiological observational study to systematically collect the real-world data that may include long-term use post authorisation - A post-authorisation safety study to follow patients longitudinally to evaluate important safety concerns

Missing information : Impact on long-term immune-mediated reactions

Impact on long-term immune-mediated reactions	Routine risk minimisation measures: SmPC Section 4.2 Prescription only medicine DBV712 should be applied to dry, clean, intact, healthy, non-inflamed skin Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities - Ongoing Study V712-303 extension - An epidemiological observational study to systematically collect the real-world data that may include long-term use post authorisation - A post-authorisation safety study to follow patients longitudinally to evaluate important safety concerns

In response to the request of key elements for the educational materials in regard to the risk of anaphylactic reactions, the applicant states the following:

Education materials have been used in completed and ongoing clinical studies with DBV712 to guide subjects and their caregivers for safe use of DBV712. Focused age-appropriate education materials are being developed from existing education materials to serve in addition to the product labeling and medication guide as additional RMMs for important safety concerns. An example of the Education Materials for children 7-11 years old is provided in RMP appendix.

PRAC comment: The applicant agrees to developing the required educational materials in regard anaphylactic reactions but has not submitted the requested key elements for them. Please note that the key elements of the educational materials shall be submitted and assessed during the centralised MA assessment while the actual educational materials will be reviewed at the national level at a later stage.

The applicant is re-requested, with regard to 'Anaphylactic reactions', to provide a concise list of the key elements for the educational materials for patients (taking into the account the appropriate reading age of the following groups: 4–6 years and 7–11 years of age) and the parents/caregivers. It is reminded that the educational materials should be concise and focused only on the minimization of the risks of the product. (LoQ)

Regarding the PhV activities listed in the summary table Part V3, please see the detailed assessment under section 3.4.2 of this AR.

The anaphylaxis questionnaire should be listed under *routine pharmacovigilance activities beyond adverse reactions reporting and signal detection*.

Additional technical notes:

- Please delete from this summary table the SmPC text (under missing information, "should be applied to dry, intact…"), it is sufficient to list the SmPC section only here.
- Delete "LABELLING AND PACKAGE LEAFLET" and insert "PL".
- Please provide a single Summary table of pharmacovigilance activities and risk minimisation activities by safety concern under RMP V.3. (LoQ)

Overall conclusions on risk minimisation measures

The PRAC having considered the data submitted was of the opinion that the proposed risk minimisation measures are likely to be sufficient to minimise the risks of the product in the proposed indication(s), but the applicant is requested to provide in regard the risk of anaphylactic reactions:

- a list of the key elements for the educational materials for patients (4–6 years and 7–11 years of age) and their the parents/caregivers

The RMMs may need to be adjusted depending on the final agreed list of safety concerns proposed by the CHMP.

3.4.5. Summary of the risk management plan

Since further RMP revision is required, the Part VI "Summary of activities in the risk management plan by medicinal product" should be revised in line with the issues raised in other parts of the RMP.

PRAC Outcome

The PRAC fully supported the assessment of the pharmacovigilance plan and risk minimisation measures as detailed in the assessment report as well as the suggestions made on the summary of safety concerns. The PRAC also put emphasis on the importance of having a well-detailed synopsis in relation to the planned studies and protocol for the ongoing study that are proposed to be added in the pharmacovigilance plan to ensure they will adequately and sufficiently address the list of safety concerns.

The PRAC agreed that the RMP Abylqis (arachis hypogaea extract) in the proposed indication could be acceptable provided that an update to RMP version 0.2 and satisfactory responses to the questions detailed in the joint CHMP-PRAC D150 overview assessment report (AR) are submitted.

3.4.6. Conclusion on the RMP

The CHMP and PRAC considered that the risk management plan version 0.2 could be acceptable if the applicant implements the changes to the RMP as detailed in the endorsed Rapporteur assessment report and in the list of questions in section 7.4.

3.5. Pharmacovigilance system

Having considered the data submitted in the application, it was not appropriate to conclude on pharmacovigilance system at this time.

Periodic Safety Update Reports submission requirements

The active substance is not included in the EURD list and a new entry will be required. The new EURD list entry uses the {EBD} or {IBD} to determine the forthcoming Data Lock Points. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request an alignment of the PSUR cycle with the international birth date (IBD). The IBD is 14 May 2010.

The applicant should indicate if they wish to align the PSUR cycle with the international birth date (IBD), as applicable (LoQ).

PRAC comment: The applicant has requested to align the PSUR cycle with the IBD, which according to the applicant is 14-May-2010. Please clarify if the date given is in fact DIBD (development IBD), or has the product been authorised somewhere in the world previously (to have an IBD)? EMA advice is requested.

4. Significance/Non-Conformity of paediatric studies

N/A

5. Benefit risk assessment

5.1. Therapeutic Context

5.1.1. Disease or condition

Peanut allergy is one of the most common cause of severe and fatal allergic reactions related to food. In the European Anaphylaxis Registry, collected from 10 European countries between July 2007 and March 2018, anaphylaxis due to peanut was recorded in 459 patients younger than 18 years (median age 5 years). Respiratory (92%, 423) and skin (91%, 418) symptoms were predominant, with the majority of cases (66%, 304) labelled as severe anaphylaxis (grade III-IV according to Ring-Messner classification). There were 3 cases of fatal anaphylaxis (Maris et al, 2019).

The product DBV712 / Abylqis is intended for allergen immunotherapy (AIT). As it utilizes an epicutaneous administration route, it is called: epicutaneous immunotherapy (EPIT). Thus, Abylqis / DBV712 seek marketing authorisation as epicutaneous immunotherapy (EPIT) for the treatment of peanut allergy in children aged 4 to 11 years at the time of treatment initiation. The following wording of the therapeutic indication is given:

TRADENAME is indicated for the treatment of children diagnosed with peanut allergy.

TRADENAME is indicated in children aged 4 to 11 years at the time of treatment initiation. Tradename should be used in conjunction with a peanut-avoidant diet.

5.1.2. Available therapies and unmet medical need

Current therapy consists of symptomatic treatment of allergic reactions. Since peanut is ubiquitous in many foods and meals, and undeclared contamination of foods with peanut is common, strict avoidance is difficult to achieve and accidental exposure to peanut remains a common issue. Peanut allergy imposes an adverse psychosocial impact on patients and caregivers, leading to frustration, stress, and isolation. Unlike some food allergies, peanut sensitivity commonly lasts throughout adult life and does not fade (Filder, 2019). It is generally a lifelong condition, with up to 80% of allergic children likely to remain allergic for their entire life (Ho et al, 2008).

On 21st December 2020 first AIT for peanut allergy (Palforzia) was approved by the European Commission for Europe. The medicinal product Palforzia is intended for desensitising children and adolescents to peanut allergy by oral allergen administration (maintenance 300 mg/day), thus it is called oral immunotherapy (OIT). It has been shown that this oral treatment, requires good compliance and a close interaction with (educated) patients and the treating physician (shared decision making), due to safety concerns. Thus, in general a need for an alternative treatment possibly by utilizing an alternative route of administration of peanut allergen, might be helpful.

5.1.3. Main clinical studies

The objective of the pivotal Phase 3 study V712-301 and most of the (supportive) Phase 2 studies (V712-202, V712-201-E, V712-204-E) was to assess the potential of DBV712 to induce clinical desensitisation to peanut after 12 months (6 months for study V712-201-E) of treatment in subjects with documented peanut allergy. A double-blind placebo-controlled food challenge (DBPCFC) was performed at screening as well as at study end to analyse the eliciting does/ the threshold dose of peanut protein in mg at which study participants react. The DBPCFC is the current diagnostic gold standard and is utilized in food immunotherapy studies to reflect the primary endpoint.

The one completed pivotal phase 3 study, V712-301(PEPITES), was a randomised, placebo-controlled, multicentre trial, performed in Europe (Germany and Ireland), Australia, the United States, and Canada. 238 subjects aged 4-11 years were treated with DBV712 250 µg for 12 month. Data from the open-label extension study, V712-301 (PEOPLE) is partially available.

At baseline, the ED of peanut protein during the entry/screening DBPCFC was capped to 300 mg, this means that subjects had to have objective IgE-mediated symptoms to peanut leading to stopping the challenge at ⩽300 mg peanut protein. The patients were randomised 2:1 to receive either active DBV712, consisting of a cutaneous patch containing microgram quantities (250 µg) of a formulated peanut allergen extract, or placebo. The patch is described as an epicutaneous delivery system (Viaskin), which is applied once per day on intact skin. The daily duration of patch application was progressively increased from 6 hours per day (1. week) to 24 hours application (day 15 onwards) for in all 12 months. At the end of the study, the efficacy of this peanut EPIT was evaluated by an exit DBPCFC. The primary efficacy endpoint for the pivotal Phase 3 study V712-301 was the difference in the percentage of treatment responders between the active DBV712 250 µg group and the placebo group in the overall population. A subject was defined as a treatment responder
a) when the initial ED was ⩽10 mg peanut protein (Screening ED subgroup 1) and the ED was ⩾300 mg peanut protein at the Month 12 DBPCFC or
b) when the initial ED was >10 mg peanut protein (Screening ED subgroup 2) and the ED was ⩾1000 mg peanut protein at the Month 12 DBPCFC.

The data set is supplemented by supportive data from a (dose-finding) phase 2 study, V712-202 (VIPES, including a subgroup of 28 children aged 6-11 treated with DBV712 250 µg), and its extension V712-203 (OLFUS-VIPES), as well as from the phase 2b study V712-204-E (CoFAR6; 18 subjects 4-11 yrs treated with DBV712 250 µg). The studies have been conducted in the US, Canada, Australia and across Europe to assess the potential of DBV712 to induce clinical desensitisation to peanut after 12 months of treatment in subjects with documented peanut allergy. In the pilot-study V712-201-E (ARACHILD) a treatment with DBV712 100 µg was tested (V712-201-E).

A total of 284 subjects aged 4-11 years who were initially exposed to DBV712 250 µg have double blind efficacy outcomes.

5.2. Favourable effects

The approach of an epicutaneous immunotherapy (EPIT) to utilize the immunomodulatory capacity of Langerhans cells for the treatment of peanut allergy is - so far - unique. However, methodological studies to proof this concept are lacking. The study V712-301 was completed with an overall rather high treatment compliance (PEPITES: compliance rate (SD) of 98.45% (4.293): 98.65% (3.886) in the DBV712 250 µg group and 98.05% (5.008) in the placebo group). After 12 months of treatment, a larger proportion of subjects in the DBV712 250 µg group (84/238 (35.3%) subjects) were defined as treatment responders compared to the placebo group (16/118 [13.6%] subjects), this corresponds to a risk difference of 21.7%, 95% confidence interval (12.4%, 29.8%), p<0.001 (primary endpoint). The

response rates were numerically higher in treated patients than in controls, overall and in the presented subgroups defined by screening ED > vs. ≤ 30 mg. More subjects treated with DBV712 250 µg reached the highest ED levels of 300 mg (31.9%), 1000 mg (18.1%) and 2000 mg (13.4%) compared with subjects who received placebo: 300 mg (20.3%), 1000 mg (6.8%); 2000 mg (3.4%).

Values of specific IgE, IgG4 as well as SPT diameters support immunomodulatory capacities of DBV712. As an example: in the DBV712 250 µg group, the median (Q1, Q3) peanut-sIgG4 levels increased throughout the 12 months of treatment: from 0.69 mg/L (0.28, 1.39) at baseline to 1.65 mg/L (0.86, 3.28) at Month 3, 2.94 mg/L (1.44, 4.96) at Month 6 and 4.19 mg/L (2.48, 7.65) at Month 12.

Supportive studies are consistent with these observations: modest increase in efficacy /eliciting dose, changes of immunoglobulins and SPT according to typically observed changes according to SIT.

Of note, seen effects are accompanied with in general rather mild safety concerns and limited observations of systemic anaphylactic reactions. Even more, first data indicate that also subjects with a history of severe anaphylaxis, did not develop enhanced treatment related AEs (nearly 7% of subjects with a history of severe anaphylaxis were included in the REALISE study).

5.3. Uncertainties and limitations about favourable effects

With the phase I and phase II data of clinical development the applicant documented that in principle an immunomodulatory effect is obtained by treatment with DBV712. However, uncertainties remain regarding the “best” dose, regarding treatment duration as well as the choice/characteristics of the target population. In addition, manifold questions remain on the functionality, respectively limitations (confounding factors and factors influencing efficacy or safety) of the presented patch system for EPIT. It is speculative, how and if the presented patch system for EPIT is beneficial compared to allergen delivery “systems” with e.g. direct skin contact (like transdermal application, intradermal applications or others). Thus, the claimed superiority of EPIT versus other delivery routes via skin remains hypothetical. Subsequently, the phase III data needs to provide compelling evidence that the benefit–risk is positive for the selected regimen. But this evidence is questioned to be compelling.

To that effect, the submitted one pivotal study V712-301 (PEPITES) did not demonstrate robust and compelling evidence of efficacy, as would be required for a marketing authorization based on a single pivotal study (CPMP/EWP/2330/99). The 95% confidence interval for the risk difference for response (12.4%; 29.8%) did not exclude the pre-specified threshold of 15% which was included “to determine, whether the primary objective was successfully met”. Consequently, no formal confirmatory claims can be based on the hierarchical analysis of secondary endpoints, which required prior rejection of the 15% threshold for clinical relevance. However, these analyses could be considered supportive, and indeed further analyses were requested from the applicant to address clinical relevance.

Uncertainties remain whether the primary responder criterion is sufficiently meaningful (see below), and the applicant confirmed that the predefined threshold for clinical relevance (15%) was not justified but was based on a request from the FDA. However, no good justification was presented for a lower threshold.

In addition, there is uncertainty on the consistency of the effect, and results may be questioned to be robust: Subgroup analyses indicate heterogeneity associated with age, indicating that older children may not have a meaningful benefit, but replication with independent data is currently missing. Further subgroup findings (Asian race, study site) are most likely due to chance, but do not provide reassurance of a substantial effect. It seems rather unlikely to randomly observe effect estimates around or below zero in such subgroups if the effect was well away from zero.

A substantially greater treatment effect was expected in stratum 1 (low eliciting dose) as compared to stratum 2 (high eliciting dose), but this could not be confirmed by the study, as point estimates in the two strata are similar. Post-hoc analyses of eliciting dose as a continuous outcome indicate a statistically significant interaction between eliciting dose and treatment, but its extent does not seem meaningful. The applicant confirmed that the expectation on the treatment effect in stratum 1 was overly optimistic, it is evident that the basis for planning of a pivotal study was not optimal.

The appropriateness of the choice of the primary endpoint requires a critical discussion Please be aware that the requirement of an absolute reactivity threshold of at least 300 mg peanut protein to be reached by subjects with low baseline ED (1 to 10 mg) after 12 months of treatment means not that patients tolerate 300 mg, it means that they react by 300 mg.

In this context fits the observation from Patel et al. 2021 (A systematic review with individual participants data meta-analysis): “In participants who react to low-level peanut exposures (e.g., <50 mg of peanut protein), there can be up to a 10-fold increase in threshold of because of this intrinsic variability rather than because of a specific treatment effect”. This is relevant to Stratum 1 and in parts Stratum 2 and supports the CHMP concern. It is to consider that a threshold measured in course of a DBPCFC in the (artificial) clinical setting, following a precise schedule only when the subject is free from “objective” co-factors (e.g. no current infections, no / clear defined medications, no exercise in parallel etc.) might not be transferred 1:1 into daily life situations. As such, the influence of numerous intrinsic and extrinsic factors (of which the majority may be not known at time of allergen consumption), which are known to reduce the individual threshold level of (accidental) allergic reactions are not covered for “real life situations”.

The “prerequisites for one pivotal study applications” require among others that “the estimated size of treatment benefit must be large enough to be clinically valuable”. Thus, it remains uncertain, if an eliciting dose with a geometric mean (GM) of 277.62 mg after 12 months treatment is large enough to be clinically valuable (GM ED of 117.1 mg was analysed in subgroup 1 (baseline ED of 1, 3 and 10 mg of peanut protein, n=41) and a GM ED of 338.6 mg was observed in patients of subgroup 2 (baseline ED of 30 mg, 100 mg or 300 mg, n=197).

It should be kept in mind that the studie’s entry criterion was defined as ≤300 mg peanut protein as correspondent patients are “considered to be at high risk of allergic reactions as a result of accidental peanut exposure“.

Besides, the individual benefit was varying: 37.0% (n = 88) tolerated 300 mg; of which 16.8% (n = 40) tolerated 1000 mg but 63% did not tolerate 300 mg peanut protein at all after 12 month of treatment (ITT population). Moreover, around 6.7% of patients, respectively 7.8% showed a worsening relative to baseline ED after 12, respectively 36 month of treatment. Considering both subgroups, 4.6 patients must be treated in order to have one patient who meet a responder criterion. Thus, this data describe that only 20% of treated patients are responders, which is not assessed as a convincing rate.

Of note, in the recently approved AIT for peanut allergy (Palforzia) the maintenance dose was 300 mg/day (meaning patients tolerated 300mg/day, this would roughly reflect an ED of 1000 mg considering the efficacy criteria in V712-301).

Efficacy data of prolonged treatment is regarded with reservation. The GM ED at Month 12 of the pivotal trial V712-301 in those patients of the verum group who proceeded and completed in the open-follow-up study V712-303 is about 100 mg higher, suggesting that especially “responders” continued in the follow-up study. After two more treatment years, a GM ED of 425 mg is reached but probably mainly triggered by 13.5% (19/141) subjects with a cumulative reactive dose (CRD) of 5444 g suggesting natural tolerance development. Moreover, 22% (31/141) of subjects having a decrease in

ED from Month 12 to Month 36 and at least 13.5 % (19/141) even reacted at the same or a lower ED relative to baseline (PP population).

Information is missing on characteristics and possible predictors of responders, respectively non-responders after 12 months and after 36 months, and on subjects whose response decreased within the observed time period(s). First data is presented on sustained unresponsiveness (after 2-month off-treatment), with a limited number of subjects (n = 18).

There are indications for an age effect in the response to EPIT with younger patients of having a more pronounced treatment benefit. However, the age cut-off of 4-5 years was not pre-specified as most relevant cut-off, thus, these assumptions was made post-hoc. There are uncertainties regarding efficacy in older children, especially in those of age 8 years and above an efficacious effect is questioned.

5.4. Unfavourable effects

A greater proportion of subjects treated with DBV712 250 µg were reported to have application site reactions (98.5%) compared with the placebo group (49.3%). Subject diaries revealed in the DBV712 250 µg group and placebo group the experience of local skin reactions for a mean percentage of days of 89.4% and 31.3% respectively, during the first 6 months of treatment.

Treatment-emergent AEs considered related to the investigational product (IP) were reported nearly twice as much in the DBV712 250 µg group than in the placebo group (230 [43.2%] and 53 [24.4%] subjects), and mainly consisted of application site reactions (191 [35.9%] and 41 [18.9%] subjects).

The frequency of anaphylactic reactions was higher in the DBV712-250 µg arm than in the placebo arm: 29 (5.5%) vs. 5 (2.3%). Of these, 23 episodes of anaphylactic reaction in 22 subjects (including 2 episodes in 2 placebo subjects) led to temporary discontinuation. Of these, 20 (3.8%) in the DBV712 250 µg arm vs. 0 in the placebo arm were considered related to the IP by the investigator. Four episodes of anaphylactic reaction in 4 (0.8%) subjects were followed by permanent treatment discontinuation in the DBV712 250 µg group (none in the placebo group). IP related urticaria was observed in 21 (3.9%) cases in the DBV group (which led to permanent discontinuation in 1 case) versus 4 (1.8%) in the placebo group.

TEAEs leading to epinephrine intake were observed in 32 events from 28 (5.3%) subjects' in the DBV712 group versus 3 event in 3 (1.4%) subjects in the placebo arm placebo.

This means that the dermal route of the DBV712-250 µg treatment is not free from systemic anaphylactic reactions related to the IP.

Even more, the number of events of anaphylactic reactions including accidental peanut consumption is also nearly twice as high in verum treated subjects (7.9% vs 4.1%). Of note, AEs related to peanut consumption (accidental or voluntary) were excluded from the other anaphylactic reactions (preferred terms) in determining DBV712 event rates. Even more, allergic reactions (following peanut consumption), including 5 events of serious TEAE (anaphylactic reaction) in the DBV712 group relative to 1 event in the Placebo group, was observed in 33 DBV712 subjects (6.2%) leading to epinephrine use in 11 (2.1%) of them and in 10 placebo subjects (4.6%) leading to epinephrine use in 4 (1.8%) of those subjects.Permanent treatment discontinuation was observed in 3 (0.6%) subjects in the DBV712 250 µg group due to application site disorders like pruritus, erythema, swelling or discolouration, none in the Placebo group (P3CP pool). 36 (10.1%) subjects discontinued in the overall population.

5.5. Uncertainties and limitations about unfavourable effects

For the purpose of analysis of the safety data, the applicant defined three pooled datasets: the P3PC Pool (n = 532 total, from the pivotal study V712-301 and from the phase 3 safety only study V712 302; key safety population), the Double-blind placebo-controlled pool (DBPC Pool, n = 854 total, comprising all ages from 4 to 55 years and all tested DBV712 doses) and the Global Pool (n = 948 total, compromises above listed subjects regardless of (open-label) study periods). The key safety P3PC pool consists of two populations with different exposure time, all the summary safety tables and figures based on the P3PC pool are to some extent misleading and should be interpreted keeping these different exposure times in mind. An identification of candidates, which suffer more from adverse reactions in order to define what makes a patient more susceptible, or in opposite, , what makes patients to “none”/ or “bad”-responders” is not possible, mainly due to limited power.

The data (P3PC Pool) suggest a clear effect of treatment related anaphylactic reaction, however a mechanistic explanation is lacking. One central element within these considerations is thought to be associated with the patch per se: general factors influencing the function of the patch (including permeability issues of the skin with its own characteristics (thickness barrier impairments, immune cells etc.), factors influencing patch adhesion but also solubilisation of the peanut protein (time, activity, temperature), or the applied peanut protein dose in correspondence, raise questions as only being examined to a limited extent.

Moreover, prior data showed that some subjects (7.8 % (n=11)) lost their treatment effect after 36 months of treatment. Thus, these patients might be at higher risk for reactions. In addition, as the reached treatment effect after 12 month and even after 36 months is low and only about 63% responder were noted according to the pre-defined criteria, patients and families might expect a higher threshold margin, and get more incautious with e.g. reading labels or want to try if they now tolerate more peanut protein. However, anaphylactic reactions, respectively serious SAEs related to accidental/voluntary peanut consumption are excluded in the safety analyses of the patch. A separate analysis of serious SAEs related to accidental/voluntary peanut consumption also depicts more anaphylactic reactions in the DBV712 treated group compared to placebo. On the other side, the need for epinephrine following accidental or voluntary peanut consumption seems not to differ between DBV712 treated or placebo treated subjects, thus there seem to be no effect of the treatment regarding this measure.Even more, serious anaphylactic reactions had been observed mainly in the DBV treated group.

In general, it is noticed that it might be difficult to distinguish between treatment related anaphylactic reactions or reactions based on accidental peanut consumption. Difficulties might be especially related to the fact that the patch is administered for 24hours/day. However, at least two-fold higher rates of anaphylactic reactions/systemic reactions had been observed in DBV treated patients compared to placebo (due to the patch per se, or as well due to other peanut intake.

5.6. Effects Table

Table 50 Effects Table for Abylqis / DBV712 (data cut-off: 20 December 2019)

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Threshold in DBPCFC	Percentage of treatment responders at month 12 in the overall population	%	N = 238 84 (35.3%) 29.5, 41.6	N = 118 16 (13.6%) 8.5, 20.9	Pre-specified clinical success criterion (Two-sided Newcombe 95% CI <15%) was not achieved (12.4%, 29.8) Thus, no further results in the hierarchical procedure can be considered statistically significant.	Clinical AR
Unfavourable Effects						
TEAEs (P3Pc pool)	Considered related to IP		230 (43.2%)	53 (24.4%)	Exposure-adjusted incidence of adverse events are asked for, to precise pooled data analysis.	Clinical AR
	Leading to permanent discontinuation		8 (1.5%)	0		Clinical AR
	Leading to temporary discontinuation		74 (13.9%)	18 (8.3%)		Clinical AR
Anaphylactic reaction (P3Pc pool)	Anaphylactic reactions		29 (5.5%)	5 (2.3%)		Clinical AR
	…..including accidental peanut consumption		44 events from 42 subjects (7.9%)	10 events from 9 subjects (4.1%)		D120 response
	TEAs leading to epinephrine intake		32 events from 28 subjects (3.2%)	3 events from 3 subjects (1.4%)		Clinical AR
	Systemic AESI	100 x Events count/FSY:	9.4	4.2		D120 response
Local TEAE (P3PC pool)	Induced by IP		191 (35.9%)	41 (18.9%)		Clinical AR

Abbreviations:
Notes:

5.7. Benefit-risk assessment and discussion

5.7.1. Importance of favourable and unfavourable effects

Although DBV712 250 µg treatment is associated with an overall numerically higher response rate in treated patients than in controls after 12 months of treatment, the criterion for the lower bound of the CI to be ≥ 15%, which was included "to determine, whether the primary objective was successfully met", was not reached. The study V712-301 (PEPITES) did not meet the pre-specified criterion for clinical relevance, which was planned to demonstrate robust and compelling evidence of efficacy.

The study entry criterion, was defined as ≤300 mg peanut protein as correspondent patients are "considered to be at high risk of allergic reactions as a result of accidental peanut exposure". In the ITT population, the geometric mean of the eliciting dose (ED) in the double-blind placebo-controlled food challenge (DBPCFC) at 12 months was 277.62 mg in the group treated with DBV712 250 µg , which is higher compared to placebo (Month 12 81.80 mg). However, it is still below the study entry criterion and subjects benefit was varying and even a worsening of ED was noticed.

The efficacy data, respectively the GM ED, was analysed within the trials with a DBPCFC under controlled, clinical conditions. However, cofactors like exercise, sleep deprivation and others play a role in influencing the reactions threshold to a relevant degree in real life situations. Thus, taking this GM ED at Month 12 of 277.62 mg gained in the pivotal study (data from the open-label follow-up study where "selected participants continued" are inappropriate), it is not agreed with the applicant that "an assumed reduction in ED (up to 45%) due to cofactors in subjects treated with DBV712 would on average still be a sufficient "buffer" to cover an accidental peanut exposure in real life". The direct applicability of an amount of 125 (34-177) mg as "threshold margin" is questioned and lack any clinical verification. This amount of peanut protein was analysed within the MIRABEL study, a study in the context of precautionary allergen labelling (PAL) – thus, focused on a different issue. Accidental reactions on open, (non-prepacked) products are excluded and variations between responses are not reflected.

Unfortunately, "the impact of cofactors has not been precisely defined in the context of accidental peanut exposure". However especially the combination of

1. uncertainties with regard to the nature of "accidental intake" per se,

2. the amount of ingested protein (MIRABEL data are not regarded as presenting the correct "threshold margin"),

3. the situation (cofactors) attending individual accidental exposure

4. Very limited data on factors influencing the patch (see OC 4) and

5. Sparse efficacy data (stratum 1 n = 41; stratum 2 n = 197; only one pivotal study which failed is predefined success criterion)

recommends a careful evaluation.

With relevance to higher sensitive patients, Patel et al. 2021 remarks on controlled OFC results based on a systematic review with individual participants data meta-analysis: "In participants who react to low-level peanut exposures (e.g., <50 mg of peanut protein), there can be up to a 10-fold increase in threshold of because of this intrinsic variability rather than because of a specific treatment effect". This needs consideration and supports the CHMP concern of "ED being not "cut in stone," especially with regards to lower provocation levels within the OFC. The applicant himself discusses the "desensitization effect" critically, by presenting the hypothesis that "DBV712 could be used in the highly sensitive patient population (…), to increase the ED to a level that significantly reduces the risks associated with

initiation of OIT." However, correspondent data is not submitted and such an approach is not covered with the current MAA. This idea suggest that the applicant himself is of the opinion that the patch application alone might not suffice to protect these patients.

As stated above, the majority of children did not tolerate 300 mg peanut protein after 12 month of treatment. Thus, they would still be "eligible" for study inclusion/study start. Moreover, around ¼ of patients even showed a decrease of ED compared to baseline - after 36 month of treatment. In opposite, patients and families seem to feel "more safe" because they are under treatment. This may lead to severe allergic reactions in real world – as being indicated already: allergic reactions subsequent to accidental or voluntary peanut consumption were reported in 33 DBV712 subjects (6.2%) and led to epinephrine use in 11 (2.1%) of subjects. There were in total 6 events of even serious TEAE (anaphylactic reaction). Thus, the "important" feeling of peanut allergic children to be cautious might be disguised. Moreover in real world treatment normally no OFC would be performed to "adjust" this mismatch

5.7.2. Balance of benefits and risks

Based on study data, the gained "desensitization" effect is small (GM ED after 12 month of treatment still below study entry criteria) and not considered sufficient for true reduction of accidental reactions. The majority of subjects did not respond according to the predefined definition, and up to ¼ of subjects even had a decrease below BL ED over time. In addition, the one pivotal study did not meet the pre-specified criterion for clinical relevance.

Moreover, systemic absorption seems possible as anaphylactic reactions, the rate for systemic AESI, and TEAEs leading to epinephrine intake, occurred more than twice in the verum group compared to placebo.

This observation suggest even more that patient's feel more save due to treatment (as indicated in improvement of QoL) and consequently do not follow peanut avoidance as strict as before. This may lead to severe allergic reactions in real world – as already indicated: allergic reactions subsequent to accidental or voluntary peanut consumption were reported in 6.2% DBV712 subjects and led to epinephrine use in 2.1% of subjects. There were in total 6 events of serious TEAE (anaphylactic reaction). Thus, the "important" feeling of peanut allergic children to be cautious might be disguised. Moreover, in real world treatment normally no OFC would be performed to "adjust" this mismatch.

In addition, data on clinical development of the patch, including information on factors influencing efficacy, function and safety of the patch, is spare and insufficient.

Even more, the assessment of responses at D120 confirmed some of the uncertainties pertaining the limitations of the data to currently conclude a substantial effect. Of particular relevance seems the observation of a potential age-dependent treatment effect, suggesting that older children may not have a meaningful benefit. However, with replication from another phase 3 study missing, this finding remains uncertain.

Therefore, considering the low desensitization rate combined with higher rates of anaphylactic reactions (due to the patch per se, as well as due to voluntary/accidental intake of peanut protein) the B/R ratio is unfavourable.

5.7.3. Additional considerations on the benefit-risk balance

Not applicable at this stage of the procedure.

5.8. Conclusions

The overall B/R of Abylqis is unfavourable.

6. Biosimilarity assessment

Not applicable