CLINICAL STUDY PROTOCOL

A DOUBLE-BLIND, PLACEBO-CONTROLLED RANDOMIZED TRIAL TO STUDY THE VIASKIN MILK EFFICACY AND SAFETY FOR TREATING IgE-MEDIATED COW'S MILK ALLERGY IN CHILDREN (MILES STUDY)

Protocol Number:	MILES (V135-201)
IND Number:	IND 16070
Investigational Product:	Viaskin Milk (DBV135)
Indication:	Immunoglobulin E (IgE)-mediated Cow's Milk Allergy
Phase:	Phase 1/2
Sponsor:	DBV TECHNOLOGIES 177-181 avenue Pierre Brossolette 92120 Montrouge France PPD Internet: www.dbv-technologies.com
Contract Research Organization:	Syneos Health (formerly INC Research, LLC) 3201 Beechleaf Court Suite 600 Raleigh, NC 27604-1547 United States
Protocol Version and Date:	Initial Protocol: Final Version 1.0, 02 June 2014 Amendment 1: Final Version 1.0, 07 November 2014 Amendment 2: Final Version 2.0, 10 July 2015 Amendment 3: Final Version 3.0, 22 September 2016 Amendment 4: Final Version 4.0, 18 December 2017 Amendment 5: Final Version 5.0, 15 May 2018 Amendment 6: Final Version 6.0, 24 June 2019

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PROTOCOL APPROVAL SIGNATURES

Protocol Title: A Double-Blind, Placebo-Controlled Randomized Trial to Study the Viaskin MILk Efficacy and Safety for Treating IgE-Mediated Cow's Milk Allergy in Children (MILES Study)

Protocol Number: MILES (V135-201)

This study will be conducted in compliance with the clinical study protocol (and amendments), ICH guidelines for current Good Clinical Practice and applicable regulatory requirements.

Sponsor Signatories:

PPD

Chief Medical Officer
DBV Technologies

Date PPD

PROTOCOL SYNOPSIS

Protocol Number:	MILES (V135-201)
Title:	A Double-Blind, Placebo-Controlled Randomized Trial to Study the Viaskin MILk Efficacy and Safety for Treating IgE-Mediated Cow's Milk Allergy in Children (MILES Study)
Investigational Product:	Viaskin Milk (DBV135)
Indication:	Immunoglobulin E (IgE)-mediated cow's milk allergy
Number of Study Centres:	Seventeen sites in North America (United States and Canada)
Phase:	Phase 1/2
Objectives:	The objectives of this study are: • To evaluate the safety and efficacy of Viaskin Milk after 12 months of epicutaneous immunotherapy (EPIT) treatment, for desensitizing IgE-mediated cow's milk-allergic children. • To assess the long-term safety and efficacy of up to 48 months of treatment with Viaskin Milk. • To assess the safety and the therapeutic benefit of the most effective tested dose of Viaskin Milk over 24 months of treatment.

Study Design: This is a multi-center, double-blind, placebo-controlled, randomized trial to study the safety and efficacy of Viaskin Milk applied epicutaneously every day to subjects from 2 to 17 years of age with IgE-mediated cow's milk allergy (CMA). Viaskin Milk is a patch containing an extract of cow's milk proteins. Subjects will receive blinded treatment for 1 year at one of the 3 doses of Viaskin Milk: 150 µg, 300 µg, or 500 µg, or placebo. After the first year, all subjects were to switch to the highest dose of Viaskin Milk, 500 µg, and continue treatment in an open-label manner for up to a maximum of 3 additional years.

Following results of the 12-month blinded period, all eligible subjects who wish to continue participation in the study will switch from Viaskin Milk 500 µg to Viaskin Milk 300 µg for 24 months of treatment.

The study will be conducted at 17 sites in the United States and Canada, with selected Investigators and staff experienced in the diagnosis and management of CMA and anaphylaxis, and who are capable of performing a double-blind placebo-controlled food challenge (DBPCFC) in children (2 to 11 years old) and adolescents (12 to 17 years old).

Eligible subjects with confirmed IgE-mediated CMA will perform a first DBPCFC at screening with escalating doses of cow's milk proteins. Subjects showing a positive DBPCFC at screening, defined as the appearance of objective signs or symptoms to an eliciting dose of cow's milk proteins ≤300 mg (approximately 9.4 mL of cow's milk) will be randomized in the study.

The study will be divided into 2 consecutive parts (Part A and Part B) for randomization of the subjects to treatment.

Part A will evaluate the safety of 3 escalating doses of Viaskin Milk (150 µg, 300 µg, and 500 µg of cow's milk proteins) *versus* placebo in successive cohorts of subjects before proceeding to Part B. In each cohort, evaluation of safety will be based on safety data collected and analyzed from subjects treated for 3 weeks. It is to be noted that after these first 3 weeks of treatment, Part A subjects will not discontinue treatment but instead will continue treatment up to Month 12, at which time subjects will undergo a second DBPCFC.

Part B is designed to evaluate the efficacy and safety of the 3 doses of Viaskin Milk (150 µg, 300 µg, and 500 µg of cow's milk protein, assessed to be safe from Part A) *versus* placebo. Subjects will be randomized to receive a 12 month treatment (blinded treatment period), at which time a second DBPCFC will be performed. The efficacy of Viaskin Milk will be assessed based on data pooled from subjects in both Part A and Part B, treated up to Month 12.

After the Month 12 DBPCFC, all subjects from Part A and Part B were to continue treatment for another 12 months in an open-label manner with Viaskin Milk at 500 µg, the highest dose assessed to be safe from the safety data in Part A subjects. Then, a third DBPCFC was to be performed at Month 24.

After Month 24, eligible subjects from Part A or Part B were to be proposed to enter the study extension to receive 2 additional years of EPIT with open-label Viaskin Milk at 500 µg. For subjects entering the study extension, a fourth and fifth DBPCFC were to be performed at Month 36 and Month 48, respectively. Following results of the 12-month blinded period, DBPCFC procedures were stopped while the subjects were still receiving Viaskin Milk 500 µg.

After implementation of Protocol Amendment 5, all subjects will receive Viaskin Milk 300 µg for 24 months, independently of the duration of previous treatment with Viaskin Milk 500 µg. For subjects switching to Viaskin Milk 300 µg, an optional DBPCFC may be performed after 12 and/or 24 months of treatment, at the decision of the Investigator and the subject.

A final End-of-Study (EOS) visit will be performed for all subjects when they complete the study. The EOS visit was to take place 2 weeks after the last DBPCFC at Month 24 for the subjects completing the study at Month 24, or 2 weeks after the last DBPCFC at Month 48, for subjects completing the study extension at Month 48. For subjects switching to Viaskin Milk 300 µg, the EOS visit will take place 2 weeks after the end of the 24-month treatment period at this dose.

During their participation in the study, all subjects will be instructed to remain on a strict cow's milk-free diet with no consumption of dairy products or baked milk products until their EOS visit (except during the DBPCFCs).

Number of Subjects:

Approximately 194 subjects (18 subjects in Part A and 176 subjects in Part B) will be randomized to treatment in this study.

The number of subjects continuing beyond the Month 24 visit and/or in the treatment period with Viaskin Milk 300 µg will depend on the study extension eligibility criteria and the willingness of subjects to continue in the study.

Treatment: Viaskin Milk patches contain a solid deposit of cow's milk proteins (150 µg, 300 µg, and 500 µg). The placebo treatment consists of a Viaskin patch with a similar formulation devoid of cow's milk proteins. Once the patch is applied to the skin, CCI [redacted] must be used each day to cover the Viaskin patch to prevent it from coming off the skin or moving around and to avoid the allergenic proteins spreading over other areas of the skin. The patches will be applied on the inter-scapular area on the back of children and on the inner side of the arms for adolescents and former adolescents who have become adults.

Repeated daily application of the Viaskin patch (active or placebo, as applicable) will be made from Day 1 (Visit 4) for all subjects, with a progressive increase of the daily duration of application as follows: 6 hours of daily application during the first week, 12 hours of daily application during the second week, and for an entire 24-hour daily application from the third week (Day 15) onwards. The patch will be changed every day for the duration of the study.

The subjects will receive blinded Viaskin Milk or placebo patch for the first 12 months at the doses deemed to be safe in Part A (150 µg, 300 µg and 500 µg). Then, from Month 12 to Month 24, all subjects were to receive the active Viaskin Milk patch at 500 µg, the highest dose assessed to be safe from the safety data in Part A subjects. The Viaskin Milk patch at 500 µg was to be continued up to Month 48 for subjects entering the study extension.

After implementation of Protocol Amendment 5, all eligible subjects will switch to Viaskin Milk 300 µg for 24 months of treatment.

Study Duration: The total duration of the study will be approximately 6 years.

The total duration of participation in the study will differ for each individual subject and could be up to approximately 6 years.

Study Population:

The inclusion and exclusion criteria for study entry are listed below.

Inclusion Criteria:

1. Signed Informed Consent Form (ICF) by parent(s)/guardian(s) of subjects and informed assent form (IAF) for subjects ≥7 years, or as per local or country specific guidelines or regulations.
2. Male or female subjects 2 to 17 years old at Visit 1.
3. Documented medical history or physician-confirmed diagnosis of IgE-mediated CMA with systemic symptoms related to ingestion of milk or dairy products.
4. Subjects currently following a strict cow's milk-free diet, with no consumption of dairy or baked milk products.
5. Cow's milk sIgE level at screening ≥10 kU/L
6. Positive Skin Prick Test (SPT) to cow's milk with a largest wheal diameter ≥6 mm.
7. Positive DBPCFC at screening with an eliciting dose ≤300 mg cow's milk proteins (approximately ≤9.4 mL of cow's milk).
8. Negative urine pregnancy test for female subjects of childbearing potential. Female subjects of childbearing potential must agree and commit to use effective medical methods of contraception for the entire duration of their participation in the study. Sexual abstinence will be accepted as an effective method of contraception for girls below 15 years of age.
9. Ability to perform spirometry procedures in accordance with the American Thoracic Society guidelines (2005) for subjects ≥6 years old. Ability to perform peak expiratory flow (PEF) measurements for subjects ≥5 years old. Subjects <8 years of age who have documented inability to adequately perform spirometry can perform only the PEF evaluation. Subjects <5 years of age may be enrolled if they had no clinical features of moderate or severe persistent asthma severity (as defined by the 2007 National Heart, Lung, and Blood Institute [NHLBI] Guidelines) within 1 year before Visit 1.
10. Subjects and/or parents/guardians willing to comply with all study requirements during participation in the study.

Study Population (continued):

Exclusion Criteria:

1. History of severe anaphylaxis to cow's milk resulting in hypotension, hypoxia or neurological compromise (collapse, loss of consciousness or incontinence) or requiring mechanical ventilation.
2. Pregnancy or lactation.
3. Spirometry forced expiratory volume in 1 second (FEV_1) <80% of the predicted value at Visit 1 for subjects ≥6 years and able to perform the spirometry, or PEF <80% of predicted value at Visit 1 for subjects performing only the PEF measurements.
4. Any clinical features of moderate or severe persistent asthma severity (as defined by the 2007 NHLBI guidelines) and high daily doses of inhaled corticosteroids (see Appendix 14.6).
5. Known allergy to the Viaskin patch materials or excipients, or to any of the components of the food challenge formulas other than the cow's milk proteins.
6. Allergy or known history of reaction to [redacted] medical dressing with no possibility to use an alternative adhesive dressing authorized by the sponsor in replacement.
7. Subjects having objective symptoms to the placebo formula leading to stopping the challenge during the screening DBPCFC.
8. Severe reaction during the screening DBPCFC defined as need for intubation, and/or hypotension persisting after epinephrine administration, and/or the need for >2 doses of epinephrine.
9. Symptomatic allergy to pollens with symptoms during the pollen season that might interfere with the symptoms observed during the DBPCFC, if the DBPCFC is performed during the pollen season. Screening of such subjects should be made out of the pollen season.
10. Inability to discontinue short-acting antihistamines for 3 days or long-acting antihistamines for 5 to 7 days (depending on the half-life) before the DBPCFC.
11. Use of systemic long-acting corticosteroids within 12 weeks before Visit 1 and/or use of systemic short-acting corticosteroids within 4 weeks before Visit 1 or use of systemic long-acting or short-acting corticosteroids during screening (unless used to treat symptoms triggered by the DBPCFC or triggered by accidental allergen consumption; in the latter case, DBPCFC must then be scheduled after a minimum of 7 wash-out days).

Study Population (continued):

12. Subjects with asthma conditions meeting 1 or several criteria below:
    - Uncontrolled persistent asthma (as defined by the 2007 NHLBI guidelines) or subject is being treated with a combination therapy of medium or high daily dose of inhaled corticosteroid with a long acting inhaled β2-agonist. Intermittent asthmatic subjects who require intermittent use of inhaled corticosteroids for rescue are permitted.
    - At least 2 systemic corticosteroid courses for asthma within 1 year before Visit 1 or 1 oral corticosteroid course for asthma within 3 months before Visit 1, or during screening (unless used to treat symptoms triggered by the DBPCFC).
    - Prior intubation/mechanical ventilation due to asthma within 2 years before Visit 1, or during screening.
13. Upper respiratory infection or gastroenteritis within 7 days of DBPCFC (DBPCFC must then be rescheduled at least 7 days after resolution of these conditions).
14. Any history of milk immunotherapy (eg, oral immunotherapy, sublingual immunotherapy or specific oral tolerance induction).
15. Prior history of any other food allergen immunotherapy (eg, oral immunotherapy, sublingual immunotherapy or specific oral tolerance induction) within 5 years before Visit 1.
16. Subjects currently under aeroallergen immunotherapy and unwilling or unable to discontinue at the time of Visit 1. Aeroallergen Immunotherapy must be discontinued at the time of Visit 1.
17. Use of any anti-IgE drug (eg, omalizumab), any immunomodulatory therapy, or any biological agent therapy (eg, anti-tumor necrosis factor drugs) within 1 year before Visit 1, or during screening.
18. Generalized dermatologic diseases (eg, severe atopic dermatitis, uncontrolled generalized eczema, icthyosis vulgaris) with no intact zones to apply the Viaskin patch, or urticarial and mast cell disorders such as chronic idiopathic urticaria.

Study Population (continued):

19. Subject and/or subject's parents/guardians with obvious excessive anxiety and unlikely to cope with the conditions of a food challenge.
20. Past or current disease, including but not limited to active eosinophilic gastrointestinal disorders, autoimmune disorders, immunodeficiency, malignancy, uncontrolled disease (hypertension, diabetes, psychiatric disorder, cardiac disease), or other disorders (eg, liver, gastrointestinal, kidney, cardiovascular, pulmonary disease or blood disorder) which in the opinion of the Investigator or the sponsor may affect the subject's participation in the study or place the subject at increased risk.
21. Subjects and/or parents/guardians unable to use the epinephrine auto-injector properly in spite of being adequately trained.
22. Contraindicated condition for the use of epinephrine.
23. Use of any investigational drug or device, or participation in another interventional clinical study within 3 months before Visit 1.
24. Subjects receiving beta-blockers or angiotensin converting-enzyme inhibitors.
25. Subjects unable to follow the protocol requirements.

Eligibility Criteria for Study Extension with Viaskin Milk 500 µg (Months 24 to 48):

The inclusion and exclusion criteria for entry in the study extension up to Month 48 are listed below.

Inclusion Criteria:

1. Signed study extension ICF by parent(s)/guardian(s) of subjects and informed assent form for subjects ≥7 years, or as per local or country specific guidelines or regulations.
2. Subjects who completed the first 2 years in MILES, including a complete documented DBPCFC at Month 24.

   Note: following results of the 12-month blinded period, Month 24 DBPCFC should not be performed anymore. Inclusion criterion #2 becomes “Subjects who completed the first 2 years in MILES”
3. Negative urine pregnancy test at Month 24 for female subjects of childbearing potential. Female subjects of childbearing potential must continue to agree and commit to using effective medical methods of contraception for the entire duration of their participation in the study. Sexual abstinence will be accepted as an effective method of contraception for females below 15 years of age.
4. Subjects must agree to continue following a strict cow’s milk-free diet, with no consumption of dairy or baked milk products during participation in the study (except during the DBPCFCs).
5. Subjects and/or parents/guardians willing to comply with all study requirements during participation in the study extension.

Exclusion Criteria:

1. Any new disorder or disease that may affect the subject’s participation in the study, or place the subject at increased risk, or for which epinephrine use is contraindicated.
2. Poor compliance in patch application (below 80%), defined as patch not applied at all for >73 days (either consecutive or not) during the second year of participation in MILES.

Eligibility Criteria for the switch to Viaskin Milk 300 µg:	**Inclusion Criteria:** 1. Signed ICF by parent(s)/guardian(s) of subjects and informed assent form for subjects ≥7 years, or as per local or country specific guidelines or regulations. 2. Negative urine pregnancy test at Visit Switch 1 for female subjects of childbearing potential. Female subjects of childbearing potential must continue to agree and commit to using effective medical methods of contraception for the entire duration of their participation in the study. Sexual abstinence will be accepted as an effective method of contraception for females below 15 years of age. 3. Subjects must agree to continue following a strict cow's milk-free diet, with no consumption of dairy or baked milk products during participation in the study (except during the DBPCFCs). 4. Subjects and/or parents/guardians willing to comply with all study requirements during participation. **Exclusion Criteria:** 1. Any new disorder or disease that may affect the subject's participation in the study, or place the subject at increased risk, or for which epinephrine use is contraindicated. 2. Poor compliance in patch application (below 80%) during the previous year of participation in MILES.
Primary Endpoint:	The primary efficacy endpoint will be the percentage (%) of subjects who are treatment responders after the first 12 months of EPIT. A treatment responder is defined as a subject who meets at least one of the following criteria: • A ≥10-fold increase in the Cumulative Reactive Dose (CRD) of cow's milk proteins at the Month 12 DBPCFC as compared to baseline value and reaching at least 144 mg of cow's milk proteins (approximately 4.5 mL of milk) • A CRD of cow's milk proteins ≥1444 mg (approximately 45 mL of milk) at the Month 12 DBPCFC.

Secondary Endpoints:

Secondary Efficacy Endpoints up to Month 12 (double-blind, placebo-controlled treatment period):

- The mean and median CRD of cow's milk proteins at Month 12 and change from baseline.
- The change from baseline value in levels of sIgE and allergen-specific immunoglobulin G4 (sIgG4) to cow's milk at all timepoints evaluated up to Month 12.
- The change from baseline value in levels of sIgE and sIgG4 to caseins, α-lactalbumin, and β-lactoglobulin at all timepoints evaluated up to Month 12.
- The change from baseline in SPT wheal at all timepoints evaluated up to Month 12.
- The change in the severity of symptoms elicited during the milk DBPCFC from baseline to Month 12.
- The change from baseline in Quality of Life (QoL) assessments at Month 12.

Endpoints after Month 12 (open-label treatment periods with Viaskin Milk 500 µg up to 48 months and Viaskin Milk 300 µg for 24 months):

- The percentage (%) of subjects who are treatment responders over the course of open-label treatment with Viaskin Milk 500 µg and 300 µg.
- The CRD of cow's milk proteins over the course of open-label treatment with Viaskin Milk 500 µg and 300 µg.
- The levels of sIgE to cow's milk over the course of open-label treatment with Viaskin Milk 500 µg and 300 µg.
- The levels of sIgG4 to cow's milk proteins over the course of open-label treatment with Viaskin Milk 500 µg.
- The levels of sIgE and sIgG4 to caseins, α-lactalbumin, and β-lactoglobulin over the course of open-label treatment with Viaskin Milk 500 µg and 300 µg.
- The SPT wheal over the course of open-label treatment with Viaskin Milk 500 µg and 300 µg.
- The severity of symptoms elicited during the milk DBPCFC over the course of open-label treatment with Viaskin Milk 500 µg and 300 µg
- The QoL assessments over the course of open-label treatment with Viaskin Milk 500 µg and 300 µg.

Safety Endpoints:

- Adverse Events (AEs) and Treatment-Emergent Adverse Events (TEAEs) by system organ class, preferred term, maximum severity, and relatedness to the investigational product.
- Serious Adverse Events (SAEs) and Treatment-Emergent Serious Adverse Events (TESAEs) by system organ class, preferred term, severity, and relatedness to the investigational product.
- TEAEs leading to study discontinuation, and relatedness to the investigational product.
- Incidence, duration, and maximum severity of local cutaneous reactions, as assessed by the subject.
- Severity of local cutaneous reactions, as assessed by the Investigator.
- Adverse Events of Special Interest (AESI) including systemic allergic symptoms and local AESI
- Frequency and severity of symptoms elicited during the DBPCFC.
- Vital signs, physical examinations, and laboratory data.
- Spirometry and PEF data.

Exploratory Endpoints:

- The change from baseline in epigenetic modifications at Month 12, if evaluated
- Epigenetic modifications over the course of open-label treatment with Viaskin Milk 500 µg and 300 µg, if evaluated.
- The relationship between the presence of filaggrin mutations, safety, and response to treatment.
- The change from baseline value in levels of sIgE to peanut, egg, house dust mite, and grass pollen.
- Enumeration and characterization of reactions triggered by accidental consumption of cow's milk (in any form) during the study.
- Analysis of "risk-taking behavior" of subjects (voluntary milk consumption) during the study.
- Planned management of the subject after termination of the study.

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LIST OF ABBREVIATIONS

ACE	=	Angiotensin-Converting Enzyme
AE	=	Adverse Event
AESI	=	Adverse Event of Special Interest
ALT	=	Alanine Aminotransferase
ANCOVA	=	Analysis of Covariance
AST	=	Aspartate Aminotransferase
BDRM	=	Blinded Data Review Meeting
BMI	=	Body Mass Index
BUN	=	Blood Urea Nitrogen
°C	=	Degrees Celsius
CFR	=	Code of Federal Regulations
cGCP	=	Current Good Clinical Practice
CMA	=	Cow's Milk Allergy
CSR	=	Clinical Study Report
CRD	=	Cumulative Reactive Dose
CRO	=	Contract Research Organization
CTD	=	Cumulative Tolerated Dose
DBPCFC	=	Double-Blind Placebo-Controlled Food Challenge
DBV	=	DBV Technologies
DSMB	=	Data and Safety Monitoring Board
eCRF	=	Electronic Case Report Form
EDC	=	Electronic Data Capture
EDS	=	Epicutaneous Drug Delivery System
EOS	=	End-of-Study
EPIT	=	Epicutaneous Immunotherapy
ET	=	Early Termination
FAS	=	Full Analysis Set
FDA	=	Food and Drug Administration
FEV_1	=	Forced Expiratory Volume in 1 Second
FAIM	=	Food Allergy Independent Measure
FAQLQ-CF	=	Food Allergy Quality of Life Questionnaire – Child Form
FAQLQ-PF	=	Food Allergy Quality of Life Questionnaire – Parent Form
FAQLQ-PFT	=	Food Allergy Quality of Life Questionnaire – Parent Form Teenagers
FAQLQ-TF	=	Food Allergy Quality of Life Questionnaire – Teenager Form
FU	=	Follow-up
GMP	=	Good Manufacturing Practice
GSP	=	Global Safety and Pharmacovigilance
h	=	Hour(S)
IAF	=	Informed Assent Form
ICF	=	Informed Consent Form
ICH	=	International Conference on Harmonisation
IgE	=	Immunoglobulin E
IgG4	=	Immunoglobulin G4
IP	=	Investigational Product
IRB	=	Institutional Review Board
ITT	=	Intent-to-Treat Set
i.v.	=	Intravenous
IWRS	=	Interactive Web Response System
LOCF	=	Last Observation Carried Forward
MedDRA	=	Medical Dictionary for Regulatory Activities
MMRM	=	Mixed Model Repeated Measures
n	=	Number of subjects with an observation

N	=	Number of subjects in the dataset or population
NHLBI	=	National Heart, Lung, and Blood Institute
OFC	=	Oral Food Challenge
OLS	=	Open-label Set
PC	=	Placebo Controlled
PEF	=	Peak Expiratory Flow
PPS	=	Per Protocol Set
QA	=	Quality Assurance
QoL	=	Quality of Life
RBC	=	Red Blood Cell
SAE	=	Serious Adverse Event
SAP	=	Statistical Analysis Plan
SD	=	Standard Deviation
sIgE	=	Allergen-Specific Immunoglobulin E
sIgG4	=	Allergen-Specific Immunoglobulin G4
SOC	=	System Organ Class
SOP	=	Standard Operating Procedure
SPT	=	Skin Prick Test
SS	=	Safety Set
SUSAR	=	Suspected Unexpected Serious Adverse Reaction
TEAE	=	Treatment-Emergent Adverse Event
TESAE	=	Treatment-Emergent Serious Adverse Event
WBC	=	White Blood Cell
WHODrug	=	World Health Organisation Drug Dictionary
WMA	=	World Medical Association

1 Introduction

1.1 Background

Food allergies represent a major health problem that can affect up to 6% of young children and 3 to 4% of adults, and appears to have an increasing prevalence.[1,2] Allergic reactions to food can result from different immunologic mechanisms including immunoglobulin E (IgE)-mediated reactions (acute onset), non-IgE cell-mediated reactions (delayed or chronic onset) or a combination of both. Food allergies lead to a large variety of clinical symptoms involving the skin, and/or the gastrointestinal and respiratory tracts, and the cardiovascular system. Of these food allergy symptoms, those described as anaphylactic shock can be life-threatening and require a rapid admission to an emergency room.

Cow's milk allergy (CMA) is the most common food allergy in infants and young children, with an incidence of approximately 2 to 3% in developed countries.[3,4] Several studies have shown that the prognosis for developing tolerance to cow's milk is good, with a majority of patients outgrowing their CMA by the age of 2 to 3 years.[5,6] However, other studies have shown that tolerance might also occur much later, with an increasing number of children whose CMA persists into school age and even into adolescence.[7] Recent studies suggest that the resolution rate of CMA is approximately 50% by 5 years of age.[8,9] The low levels of allergen-specific IgE (sIgE) to cow's milk and milk skin prick test (SPT) wheal size have been shown to be good predictors of resolution, while high levels of cow's milk sIgE have been shown to be predictors of persistence of CMA.[,10] The concomitant presence of both asthma and allergic rhinitis, and the severity of atopic dermatitis have also been shown to be associated with a lower likelihood for developing tolerance.[

To date, the standard of care for management of food allergy is strict avoidance of the responsible allergen(s). This is especially challenging for cow's milk, which is widely included in many dairy products, and also in smaller amounts in other manufactured food products. Consequently, the risk of accidental allergic reactions in children allergic to cow's milk represents a major health concern, and the frequency of accidental exposure, some leading to severe reactions, could reach 40% in children over a 12-month period.[11]

There are no specific approved treatments for IgE-mediated CMA. Several studies have been carried out to investigate the effect of oral immunotherapy or sublingual immunotherapy for the treatment of CMA; these studies have shown some efficacy in increasing the quantity of cow's milk consumed.[12,13] However, occurrences of local adverse events (AEs), as well as systemic, potentially serious reactions during the course of oral immunotherapy are common.[14] In addition to the systemic side effects observed, the clinical desensitization can be lost in some cases within 1 week off therapy. Thus, developing alternative therapies for treating CMA or for improving the natural history of the disease represents a clear unmet medical need.

DBV Technologies (DBV) is developing a novel product for the treatment of CMA. The investigational product, Viaskin Milk (DBV 135) consists of an epicutaneous drug delivery system like a patch (Viaskin delivery system), containing a solid deposit of formulated milk protein extract. Epicutaneous immunotherapy (EPIT), consisting of repeated applications of the patch containing the allergen to intact skin, is a novel method under investigation for the treatment of food allergies.

The rationale for testing EPIT in humans for the treatment of CMA is based on the following:

1. EPIT has shown evidence of clinical benefit in animal and early human studies, especially in the pediatric population with CMA.

2. EPIT provides a ready-to-use and easy-to-administer form of allergen immunotherapy, particularly well-adapted to the pediatric population.

3. EPIT can directly target the immunocompetent cells (such as the Langerhans and Dendritic cells) in a nonvascularized environment (ie, the epidermis).

EPIT is expected to have a better safety profile than the other forms of immunotherapy due to the slow delivery of large allergenic macromolecules in the epidermis that do not appear to pass through the basement membrane and enter the systemic circulation, hence reducing notably the risk of systemic distribution of the allergen. EPIT has been shown to be well tolerated and could represent a very promising approach for the treatment of CMA.

1.2 Nonclinical Studies

Several nonclinical studies support the clinical development of Viaskin Milk. These include an efficacy study in milk-sensitized mice, toxicology studies (including repeat-dose, genotoxicity and tolerance studies), as well as biocompatibility studies performed with the Viaskin alone.

The overall results of the studies support the conclusion that no toxic effects are expected with Viaskin Milk. Details regarding nonclinical studies with Viaskin Milk are available in the Investigator's Brochure.[15]

1.3 Clinical Studies

A brief summary of clinical study information for Viaskin Milk is included below. Refer to the Viaskin Milk (DBV 135) Investigator's Brochure for additional details regarding clinical studies with Viaskin Milk.

A pilot 3-month clinical study entitled "Efficacy of a new epicutaneous desensitization method to induce cow's milk tolerance in children with cow's milk protein allergy: a pilot study" has been completed (study #SV 782). The clinical study report (CSR) of this pilot trial was completed and its results have also been published.[16] This double-blind, placebo-controlled, randomized pilot study evaluated the safety and efficacy of EPIT for the treatment of CMA in highly sensitive IgE-mediated CMA children. This study was performed utilizing an atopy patch test such as the commercially available Diallertest® diagnostic product. Diallertest is a ready-to-use cow's milk allergen atopy patch test that has been made available by DBV Technologies on the French market in June 2004 for the diagnosis of CMA. The Diallertest kit includes one control patch and one allergen patch containing 500 µg of skimmed cow's milk powder (approximately 150 µg cow's milk protein).

Children aged between 3 months to 15 years and with cow's milk protein sIgE >0.35 kU/L and/or a positive SPT to cow's milk protein plus an oral milk challenge were eligible for participation in the study. If the oral cow's milk challenge was positive at a dose <10 mL, the subjects were randomized (1:1) to receive active treatment patch (containing 1 mg of cow's milk powder) or placebo. Each patch was applied on the posterior trunk in the inter-scapular space of the children for 48 hours, 3 times a week. The total duration of the blinded therapy was 3 months, followed by an open-label dosing up to an additional 6 months. The primary efficacy criterion was the maximal cumulative tolerated dose (CTD) of cow's milk (in mL) after 3 months of the blinded treatment.

The mean age ± standard deviation (SD) of the subjects enrolled in this study was 3.82 ± 2 years (range: from 10 months to 7 years and 8 months). A total of 9 children treated with the active patch and 7 children treated with placebo were incorporated in the per protocol analysis. An oral food challenge with cow's milk was performed at baseline (Day 0) and after 3 months (Day 90) of blinded treatment. The maximal CTD of milk increased from a mean ± SD of 1.77 ± 2.98 mL at Day 0 to 23.61 ± 28.61 mL at Day 90 in the active treatment group; in the active group, CTD slightly decreased in 1 patient and increased by >10-fold in 2 patients and >100-fold in 3 patients after the EPIT treatment. The mean CTD did not change in the placebo group (4.36 ± 5.87 mL at Day 0 to 5.44 ± 5.88 mL at Day 90). Although this preliminary study failed to demonstrate a statistically significant improvement of the CTD (likely due to the limited number of subjects and short duration of the treatment period), subjects treated with the active patch demonstrated increased tolerance to milk exposure.

No child required interruption of treatment because of an AE and none received epinephrine. No serious adverse events (SAEs) were reported during the trial. Overall, repeated application of the active patch was safe and well tolerated in this study.

In summary, the results of the pilot study with cow's milk EPIT demonstrated a favorable safety profile, a clear trend toward clinical efficacy, and suggested that longer treatment periods might be appropriate.

1.4 Study Rationale

This study is designed to evaluate the safety and efficacy of repeated doses of Viaskin Milk delivered epicutaneously in pediatric subjects with IgE-mediated CMA. The goals of developing this new treatment are as follows:

- To protect subjects with IgE-mediated CMA from the risk of severe reactions, in particular severe anaphylactic reactions, in case of accidental exposure to cow's milk.
- To permit or accelerate the re-introduction of cow's milk and other dairy products into the diet of cow's milk-allergic subjects.

2 Study Objectives

The objectives of this study are:

1. To evaluate the safety and efficacy of Viaskin Milk to induce desensitization to cow's milk in IgE-mediated cow's milk-allergic children after 12 months of EPIT treatment.

2. To assess the long-term safety and efficacy of up to 48 months of treatment with Viaskin Milk.

3. To assess the safety and the therapeutic benefit of the most effective tested dose of Viaskin Milk over 24 months of treatment.

3 Investigational Plan

3.1 Overall Study Design and Plan

This is a multi-center, double-blind, placebo-controlled, randomized trial to study the safety and efficacy of Viaskin Milk applied epicutaneously every day to subjects from

2 to 17 years of age with IgE-mediated CMA. Viaskin Milk is a patch containing an extract of cow's milk proteins. The placebo treatment will consist of a Viaskin patch containing a similar formulation without cow's milk proteins. The study will be conducted at 17 sites in the United States and Canada, with selected Investigators and staff experienced in the diagnosis and management of CMA and anaphylaxis, and who are capable of performing a double-blind placebo-controlled food challenge (DBPCFC) in children (2 to 11 years old), adolescents (12 to 17 years old).

Eligible subjects with confirmed IgE-mediated CMA will perform a first DBPCFC at screening with escalating doses of cow's milk proteins. Subjects showing a positive DBPCFC at screening, defined as the appearance of objective signs or symptoms to an eliciting dose of cow's milk proteins ≤300 mg (approximately 9.4 mL of cow's milk) will be randomized in the study.

Double-blind, placebo-controlled treatment period up to Month 12

The study was divided into 2 consecutive parts for randomization of the subjects to treatment: Part A and Part B. Part A initially permitted an evaluation of the safety of 3 escalating doses of Viaskin Milk (150 µg, 300 µg, and 500 µg cow's milk proteins) *versus* placebo in successive cohorts of subjects before proceeding to Part B. Part B permitted an evaluation of the efficacy and safety of the 3 safe doses of Viaskin Milk (150 µg, 300 µg and 500 µg of cow's milk protein, as assessed from the safety data in Part A subjects) *versus* placebo. The efficacy of Viaskin Milk was assessed based on data pooled from subjects in both Part A and Part B. Details of subject enrollment and the treatments administered for each part of the study are provided in Section 3.1.2 for Part A and in Section 3.1.3 for Part B.

In both Part A and Part B of the study, subjects were randomized to receive treatment with Viaskin Milk *versus* placebo for 12 months (blinded treatment period), at which time a second DBPCFC was performed. The primary analysis of this study was conducted after data have been collected up to Month 12 visits including both days of the DBPCFC at Month 12. Consequently, results from the safety and efficacy data collected in all Part A and Part B subjects up to and including the Month 12 visits will be reported in the 12-Month CSR.

Open-label periods with Viaskin Milk 500 µg up to 48 months and Viaskin Milk 300 µg for 24 months

After the Month 12 DBPCFC, all subjects from Part A and Part B were to continue treatment for another 12 months in an open-label manner with active Viaskin Milk at the highest dose selected (500 µg of cow's milk protein), based on safety data in Part A subjects. A third DBPCFC was to be performed at Month 24.

After Month 24, all eligible subjects from Part A and Part B were to be proposed to enter the study extension to receive 2 additional years of EPIT with open-label Viaskin Milk at 500 µg (see eligibility criteria in Section 4.3). For subjects entering the study extension, the fourth and fifth DBPCFCs were to be performed at Month 36 and Month 48, respectively.

Results of the 12-month blinded period showed that the most effective tested dose was the Viaskin Milk 300 µg, and that this dose was safe[1]. Given that all subjects were currently receiving the 500-µg dose, all subjects will switch from Viaskin Milk 500 µg to

[1] Refer to the Investigator's Brochure of Viaskin Milk for details about results of the 12-month blinded period.

Viaskin Milk 300 µg for 24 months, independently of the duration of previous treatment with Viaskin Milk 500 µg.

Subjects will continue to receive Viaskin Milk 500 µg until they can switch to Viaskin Milk 300 µg. No DBPCFCs are to be performed while the subjects are still receiving Viaskin Milk 500 µg. Once the regulatory approvals are received and the Viaskin Milk 300 µg is available at the investigational sites, subjects will come for a switch visit to receive Viaskin Milk 300 µg for 24 additional months. A DBPCFC can be performed after 12 and/or 24 months of treatment with Viaskin Milk 300 µg but will be optional. The subjects who decline to continue in the study to receive Viaskin Milk 300 µg will be discontinued and will perform an EOS or an early termination (ET) visit (see Section 7.2.3.1).

A final End-of-Study (EOS) visit will be performed for all subjects when they complete the study. For subjects who complete the study at Month 24 of the open-label treatment period with Viaskin Milk 500 µg, the EOS visit will take place 14 days ±3 days after Visit 17. For subjects who will switch to Viaskin Milk 300 µg, this EOS follow-up visit will take place 2 weeks after the end of the treatment period.

All safety and efficacy data collected during the entire study will be reported in a final CSR.

Subjects are to remain on a cow's milk-free diet with no consumption of dairy products or baked milk products during their entire participation in the study (except during DBPCFC procedures). An anaphylaxis emergency plan[17] will be designed for this study and provided to the subjects (see Appendix 14.5 for an example). An epinephrine auto-injector CCI [redacted] will also be given to each subject at Visit 4 to be used according the anaphylaxis emergency plan.

The total duration of the study will be approximately 6 years. The total duration of participation in the study will differ for each subject, depending on when they switch to Viaskin Milk 300 µg, and could be up to approximately 6 years.

Flow charts summarizing the process of enrollment into each part of the study and the overall study design are presented in Section 3.1.5.

3.1.1 Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) composed of experts in food allergy and in the methodology of clinical trials will be formed to monitor the safety data for this study. This DSMB will be independent of the sponsor and will review safety data from the study at specified intervals during the study and on an *ad hoc* basis, as deemed necessary by the DSMB Chair or when conveyed by the sponsor. The DSMB will review blinded data, but may have access to unblinded data as deemed necessary by the DSMB members.

The data review by the DSMB members will ensure that safety of Viaskin Milk at a specific dose is assessed before escalating to the next highest dose of Viaskin Milk in Part A of the study. The DSMB members will also review the cumulative safety data collected from all subjects in Part A to determine the Viaskin Milk safety profile at each of the dose levels evaluated in Part A, to help the sponsor in selecting the doses to be used in Part B. The roles, responsibilities, constitution and operations of the DSMB will be described in the DSMB Charter, which will be reviewed and signed by each member of the DSMB.

3.1.2 Part A

In Part A of the study, the safety of 3 escalating doses of Viaskin Milk, 150 µg, 300 µg, and 500 µg cow's milk proteins, will initially be assessed over a 3-week treatment period. Subjects will be randomized into 3 successive cohorts of 6 subjects each to receive either Viaskin Milk or placebo in a 2:1 ratio.

Cohort 1 (150 µg dose group): a total of 6 subjects will be randomized (2:1 ratio) to receive either Viaskin Milk at 150 µg (n=4) or placebo (n=2). Safety data will be collected and analyzed after 3 weeks of treatment. The 3-week safety data will be reviewed by the independent DSMB. If the DSMB considers that the 150 µg dose is safe, then Cohort 2 will open for randomization at the next highest dose of Viaskin Milk.

Cohort 2 (300 µg dose group): the screening of subjects in Cohort 2 may start once the enrollment in Cohort 1 is complete, but no subject will be randomized and treated in this cohort before the review of the DSMB from the previous cohort has been completed and the DSMB recommendation made. The same process as described above for Cohort 1 will be repeated: a total of 6 additional subjects will be randomized (2:1 ratio) to receive Viaskin Milk at 300 µg (n=4) or placebo (n=2). Safety data after 3 weeks of treatment will be collected and analyzed. In parallel, cumulative safety data from the previous Cohort 1 subjects will also be collected and made available for review by the DSMB. If the DSMB considers that the 300 µg dose is safe, then Cohort 3 will open for randomization at the next highest dose of Viaskin Milk.

Cohort 3 (500 µg dose group): the screening of subjects in Cohort 3 may start once the enrollment in Cohort 2 is complete, but no subject will be randomized and treated in this cohort before the review of the DSMB from the previous cohort has been completed and the DSMB recommendation made. The same process as described above for Cohorts 1 and 2 will be repeated: a total of 6 additional subjects will be randomized (2:1 ratio) to receive Viaskin Milk at 500 µg (n=4) or placebo (n=2). Safety data after 3 weeks of treatment will be collected and analyzed. In parallel, cumulative safety data from subjects in the previous Cohorts 1 and 2 will also be collected and made available for review by the DSMB. The DSMB will assess whether this dose of 500 µg is also safe.

All subjects in Part A will continue their blinded treatment at their assigned initial dose of treatment (150 µg, 300 µg, or 500 µg Viaskin Milk or placebo) up to Month 12.

3.1.3 Part B

After the analysis of the cumulative safety data of Part A subjects, the 3 doses of Viaskin Milk (150 µg, 300 µg, and 500 µg of cow's milk protein) were kept to study the efficacy of Viaskin Milk in a placebo-controlled dose-finding Part B of the study.

The screening of subjects in Part B may start after enrollment in Part A is complete; however, none of the subjects screened in Part B can be randomized and treated before the review of the safety data from Part A subjects has been completed by the DSMB and by the US Food and Drug Administration (FDA).

A pause in the randomization will allow for this safety review to occur and recommendations to be released.

In Part B, approximately 176 additional subjects will be randomized (1:1:1:1 ratio) to receive Viaskin Milk 150 µg (n=44), Viaskin Milk 300 µg (n=44), Viaskin Milk 500 µg (n=44), or placebo (n=44) up to Month 12.

3.1.4 Open-label treatment periods with Viaskin Milk 500 µg and Viaskin Milk 300 µg

Treatment period with Viaskin Milk 500 µg

After the Month 12 DBPCFC, all subjects in Part A and in Part B were to continue treatment in an open-label manner for another 12 months up to Month 24 with Viaskin Milk at the highest dose selected (500 µg of cow's milk protein), based on the safety data of Part A subjects.

Subjects who terminated the study at Month 24 were to attend an EOS visit 2 weeks after the Month 24 DBPCFC.

After the first 2 years in the MILES study, depending on the threshold of desensitization achieved at Month 24, a longer treatment period with EPIT may be valuable for some subjects. In contrast, the re-introduction of milk into the diet as early as possible (eg, baked milk products or dairy products) or the initiation of different therapies may be a preferred option for other subjects. For this purpose, all eligible subjects from Part A and Part B (see eligibility criteria in Section 4.3) were proposed to enter into the open-label study extension, to receive 2 additional years of EPIT with Viaskin Milk 500 µg, if deemed appropriate by the Investigator, and depending on the willingness of each individual subject.

Subjects who entered the study extension were to continue their treatment up to Month 48 and to perform additional DBPCFCs at Month 36 and at Month 48.

Following results of the 12-month blinded period, the DBPCFCs that were to be performed at Month 24, Month 36 and Month 48 should not be conducted while the subjects are still receiving Viaskin Milk 500 µg.

Switch to Viaskin Milk 300 µg

Following results of the 12-month blinded period, all eligible subjects will switch from Viaskin Milk 500 µg to Viaskin Milk 300 µg for 24 additional months, independently of the duration of previous treatment with Viaskin Milk 500 µg:

- Subjects who will decline to switch to Viaskin Milk 300 µg will be discontinued from the study and an ET visit or an EOS visit will be performed (see Section 7.2.3);
- Subjects who will switch to Viaskin Milk 300 µg will be treated for 24 additional months:
    - Until Visit S1 is performed and the subjects start with Viaskin Milk 300 µg, they will continue to receive Viaskin Milk 500 µg. No DBPCFC should be performed while the subjects are still receiving Viaskin Milk 500 µg.
    - Subjects will then follow a dedicated study flowchart (see Table 6 and Table 7),
    - Optional DBPCFCs can be performed after 12 and/or 24 months of treatment,

If the decision is made by the Investigator and the subject to perform a DBPCFC, its performance must comply with the standardized methodology defined in Section 7.3.1.1. Standardized milk and placebo food challenge formula and material as well as the Manual of Procedures will be provided to all sites and must be used for conducting the food challenge.

When performed, the results of these food challenge(s) will be documented and reported in the e-CRF.

- The EOS visit will take place 2 weeks after the end of the treatment period.

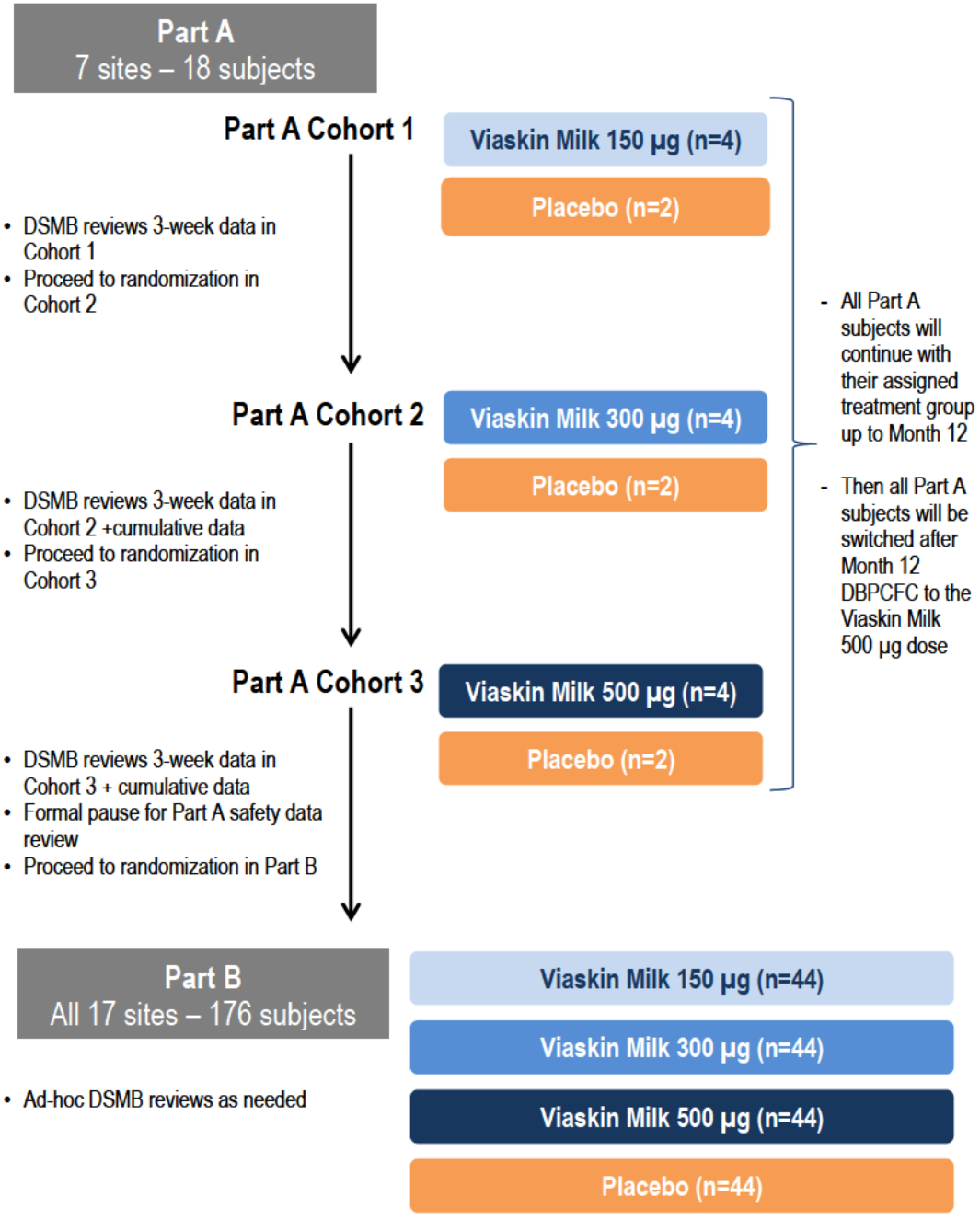
During their participation in the study all subjects will be instructed to remain on a strict cow's milk-free diet with no consumption of dairy products or baked milk products until their final study visit (except during DBPCFC). At the end of participation in the study, the re-introduction of milk products (eg, dairy products or baked milk products) into the subject's diet, or the decision to keep the subject under a strict cow's milk-free diet will be left to the Investigator's discretion.

3.1.5 Summary Study Design Flow Charts

3.1.5.1 Process Summary of Enrollment

Figure 1 presents a summary of the enrollment process into Part A and Part B of the study.

Figure 1: Process Summary of Enrollment



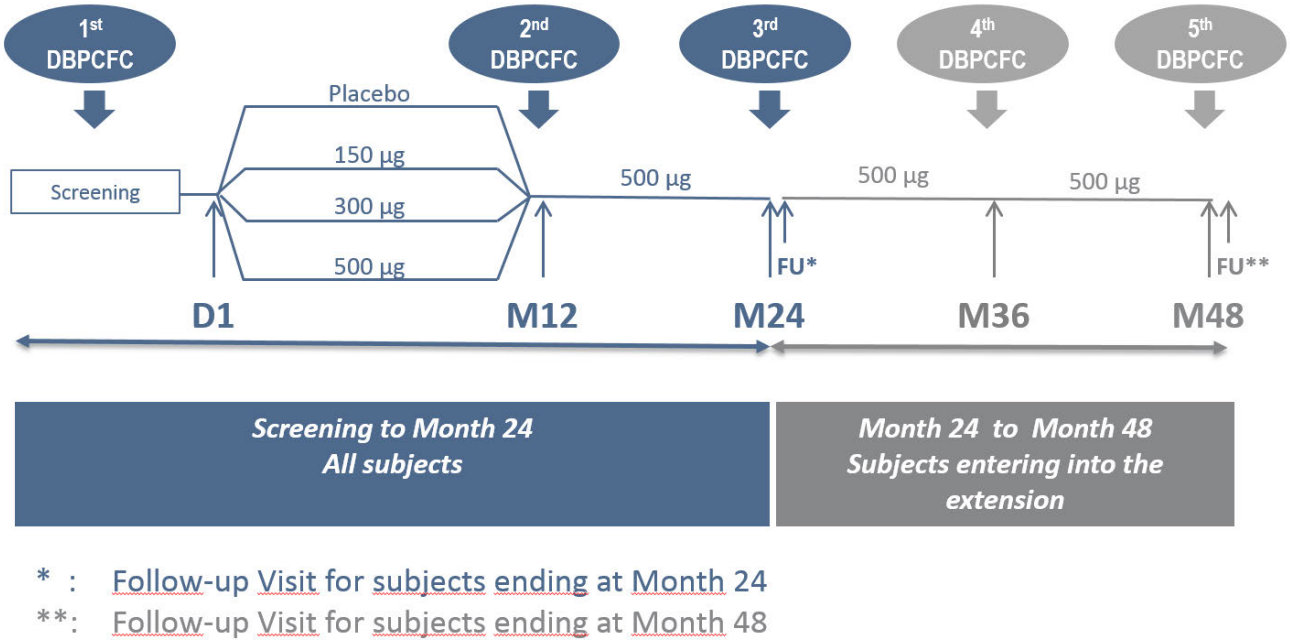
Abbreviations: DBPCFC=double-blind placebo-controlled food challenge; DSMB=data and safety monitoring board

3.1.5.2 Study Design Summary

Figure 2 presents a summary of the overall study design for Part A, Part B and the open-label treatment with Viaskin Milk 500 µg as was planned before Protocol Amendment 5.

Figure 3 presents a summary of the study design for the open-label treatment period with Viaskin Milk 300 µg.

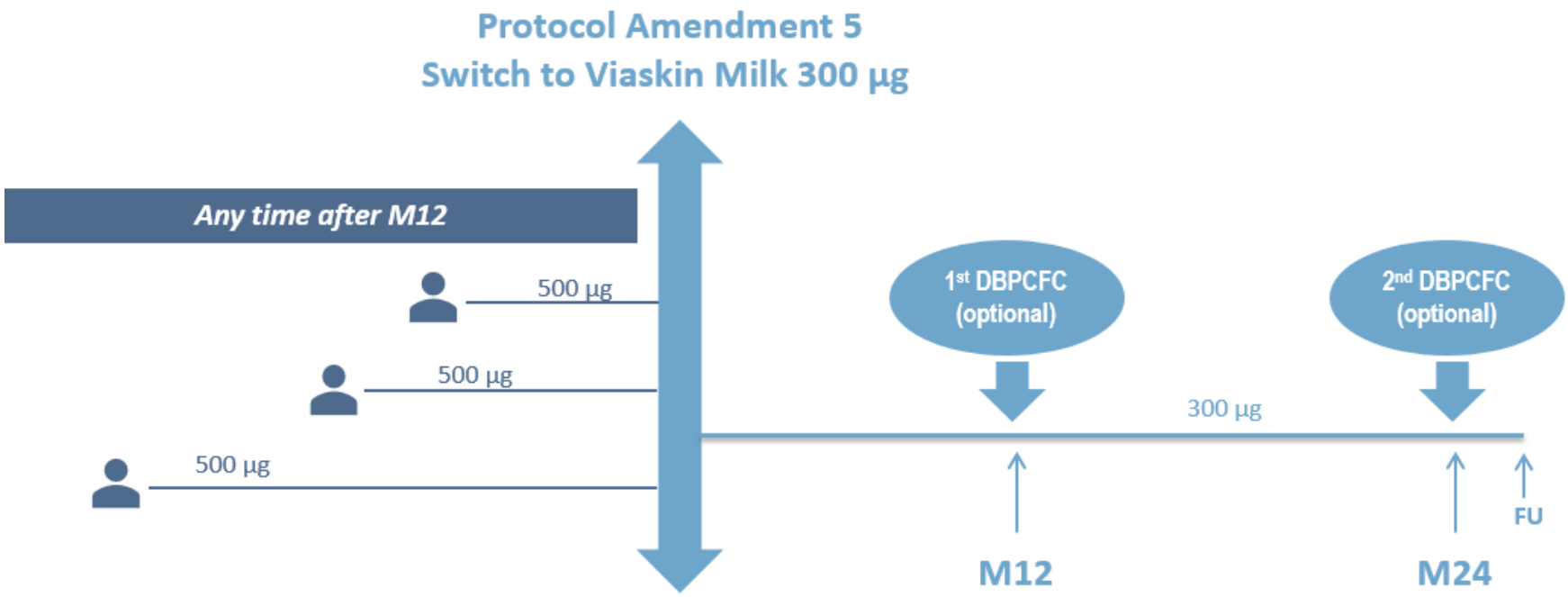
Figure 2: Overview of the Study Design for Part A, Part B and the open-label treatment period with Viaskin Milk 500 µg as was planned before Protocol Amendment 5



Abbreviations: D=day; FU=follow-up; M=month; DBPCFC=Double-Blind Placebo Controlled Food Challenge;

Following results of the 12-month blinded period, Month 24, Month 36 and Month 48 DBPCFCs should not be performed while the subjects are still receiving Viaskin Milk 500 µg.

Figure 3. Overview of study design for the open-label treatment period with Viaskin Milk 300 µg



Abbreviations: FU=follow-up; M=month; DBPCFC=Double-Blind Placebo Controlled Food Challenge.

3.2 Discussion of Study Design

A randomized, double-blind study is considered the most suitable design, and placebo is considered the appropriate control, to evaluate the Viaskin Milk EPIT product in children and adolescent subjects with IgE-mediated CMA. Randomization and double-blinding are used to minimize bias in treatment allocation and in the assessment of both safety and efficacy during the double-blind treatment period. Randomization and double-blinding also minimizes bias arising from the expectations of subjects and/or their parent(s)/guardian(s), the Investigators, and from individuals who collect the study data.

An open-label extension at the highest safe dose based on the safety data collected during the Part A and B was initiated. The selected dose before the availability of efficacy data was the Viaskin Milk 500 µg.

After the efficacy data became available at the end of the 12-month blinded period[2], the most efficacious dose was determined to be the Viaskin Milk 300 µg. This dose was shown to be safe. Consequently, all subjects will switch over to this dose for an additional treatment period of 24 months.

4 Selection of Subjects and Criteria for Withdrawal

4.1 Number of Planned Subjects

Approximately 194 children and adolescent subjects will be randomized in this study, 18 subjects in Part A and 176 subjects in Part B. The screen failure rate is anticipated to be around 35%, therefore approximately 300 subjects may be screened in the study.

4.2 Eligibility Criteria for Study Enrollment

4.2.1 Inclusion Criteria

1. Signed Informed Consent Form (ICF) by parent(s)/guardian(s) of subjects and informed assent form (IAF) for subjects ≥7 years, or as per local or country specific guidelines or regulations.

2. Male or female subjects 2 to 17 years old at Visit 1.

3. Documented medical history or physician-confirmed diagnosis of IgE-mediated CMA with systemic symptoms related to ingestion of milk or dairy products.

4. Subjects currently following a strict cow's milk-free diet, with no consumption of dairy or baked milk products.

5. Cow's milk sIgE level at screening ≥10 kU/L.

6. Positive SPT to cow's milk with a largest wheal diameter ≥6 mm.

7. Positive DBPCFC at screening with an eliciting dose ≤300 mg cow's milk proteins (approximately ≤9.4 mL of cow's milk).

8. Negative urine pregnancy test for female subjects of childbearing potential. Female subjects of childbearing potential must agree and commit to use

[2] Refer to the Investigator's Brochure of Viaskin Milk for details about results of the 12-month blinded period.

effective medical methods of contraception for the entire duration of their participation in the study. Sexual abstinence will be accepted as an effective method of contraception for girls below 15 years of age.

9. Ability to perform spirometry procedures in accordance with the American Thoracic Society guidelines (2005)[18] for subjects ≥6 years old. Ability to perform peak expiratory flow (PEF) measurements for subjects ≥5 years old. Subjects <8 years of age who have documented inability to adequately perform spirometry can perform only the PEF evaluation. Subjects <5 years of age may be enrolled if they had no clinical features of moderate or severe persistent asthma severity (as defined by the 2007 National Heart, Lung, and Blood Institute [NHLBI] Guidelines[19]) within 1 year before Visit 1.

10. Subjects and/or parents/guardians willing to comply with all study requirements during participation in the study.

4.2.2 Exclusion Criteria

1. History of severe anaphylaxis to cow's milk resulting in hypotension, hypoxia or neurological compromise (collapse, loss of consciousness or incontinence) or requiring mechanical ventilation.

2. Pregnancy or lactation.

3. Spirometry forced expiratory volume in 1 second (FEV_1) <80% of the predicted value at Visit 1 for subjects ≥6 years and able to perform the spirometry, or PEF <80% of predicted value at Visit 1 for subjects performing only the PEF measurements.

4. Any clinical features of moderate or severe persistent asthma severity (as defined by the 2007 NHLBI guidelines) and high daily doses of inhaled corticosteroids (see Appendix 14.6).

5. Known allergy to the Viaskin patch materials or excipients, or to any of the components of the food challenge formulas other than the cow's milk proteins.

6. Allergy or known history of reaction to [redacted] medical dressing with no possibility to use an alternative adhesive dressing authorized by the sponsor in replacement.

7. Subjects having objective symptoms to the placebo formula leading to stopping the challenge during the screening DBPCFC.

8. Severe reaction during the screening DBPCFC defined as need for intubation, and/or hypotension persisting after epinephrine administration, and/or the need for >2 doses of epinephrine.

9. Symptomatic allergy to pollens with symptoms during the pollen season that might interfere with the symptoms observed during the DBPCFC, if the DBPCFC is performed during the pollen season. Screening of such subjects should be made out of the pollen season.

10. Inability to discontinue short-acting antihistamines for 3 days or long-acting antihistamines for 5 to 7 days (depending on the half-life) before the DBPCFC.

11. Use of systemic long-acting corticosteroids within 12 weeks before Visit 1 and/or use of systemic short-acting corticosteroids within 4 weeks before Visit 1 or use of systemic long-acting or short-acting corticosteroids during screening (unless used to treat symptoms triggered by the DBPCFC or triggered by accidental allergen consumption; in the latter case DBPCFC must then be scheduled after a minimum of 7 wash-out days).

12. Subjects with asthma conditions meeting 1 or several criteria below:

    - Uncontrolled persistent asthma (as defined by the 2007 NHLBI guidelines) or subject is being treated with a combination therapy of medium or high daily dose of inhaled corticosteroid with a long acting inhaled β2-agonist. Intermittent asthmatic subjects who require intermittent use of inhaled corticosteroids for rescue are permitted.

    - At least 2 systemic corticosteroid courses for asthma within 1 year before Visit 1 or 1 oral corticosteroid course for asthma within 3 months before Visit 1, or during screening (unless used to treat symptoms triggered by the DBPCFC).

    - Prior intubation/mechanical ventilation due to asthma within 2 years before Visit 1, or during screening.

13. Upper respiratory infection or gastroenteritis within 7 days of DBPCFC (DBPCFC must then be rescheduled at least 7 days after resolution of these conditions).

14. Any history of milk immunotherapy (eg, oral immunotherapy, sublingual immunotherapy or specific oral tolerance induction).

15. Prior history of any other food allergen immunotherapy (eg, oral immunotherapy, sublingual immunotherapy or specific oral tolerance induction) within 5 years before Visit 1.

16. Subjects currently under aeroallergen immunotherapy and unwilling or unable to discontinue at the time of Visit 1. Aeroallergen Immunotherapy must be discontinued at the time of Visit 1.

17. Use of any anti-IgE drug (eg, omalizumab), any immunomodulatory therapy, or any biological agent therapy (eg, anti-tumor necrosis factor drugs) within 1 year before Visit 1, or during screening.

18. Generalized dermatologic diseases (eg, severe atopic dermatitis, uncontrolled generalized eczema, icthyosis vulgaris) with no intact zones to apply the Viaskin patch, or urticarial and mast cell disorders such as chronic idiopathic urticaria.

19. Subject and/or subject's parents/guardians with obvious excessive anxiety and unlikely to cope with the conditions of a food challenge.

20. Past or current disease, including but not limited to active eosinophilic gastrointestinal disorders, autoimmune disorders, immunodeficiency, malignancy, uncontrolled disease (hypertension, diabetes, psychiatric disorder, cardiac disease), or other disorders (eg, liver, gastrointestinal, kidney, cardiovascular, pulmonary disease or blood disorder) which in the opinion of the

Investigator or the sponsor may affect the subject's participation in the study or place the subject at increased risk.

21. Subjects and/or parents/guardians unable to use the epinephrine auto-injector properly in spite of being adequately trained.

22. Contraindicated condition for the use of epinephrine.

23. Use of any investigational drug or device, or participation in another interventional clinical study within 3 months before Visit 1.

24. Subjects receiving beta-blockers or angiotensin converting-enzyme (ACE) inhibitors.

25. Subjects unable to follow the protocol requirements.

4.3 Eligibility Criteria for Study Extension (Months 24 to 48)

Not applicable after subjects have switched to Viaskin Milk 300 µg.

4.3.1 Inclusion Criteria

1. Signed study extension ICF by parent(s)/guardian(s) of subjects and informed assent form for subjects ≥7 years, or as per local or country specific guidelines or regulations.
2. Subjects who completed the first 2 years in MILES, including a complete documented DBPCFC at Month 24.

   Note: following results of the 12-month blinded period, Month 24 DBPCFC should not be performed anymore. Inclusion criterion #2 becomes "Subjects who completed the first 2 years in MILES".
3. Negative urine pregnancy test at Month 24 for female subjects of childbearing potential. Female subjects of childbearing potential must continue to agree and commit to using effective medical methods of contraception for the entire duration of their participation in the study. Sexual abstinence will be accepted as an effective method of contraception for females below 15 years of age.
4. Subjects must agree to continue following a strict cow's milk-free diet, with no consumption of dairy or baked milk products during participation in the study (except during the DBPCFCs).
5. Subjects and/or parents/guardians willing to comply with all study requirements during participation in the study extension.

4.3.2 Exclusion Criteria

1. Any new disorder or disease that may affect the subject's participation in the study, or place the subject at increased risk, or for which epinephrine use is contraindicated.
2. Poor compliance in patch application (below 80%), defined as patch not applied at all for >73 days (either consecutive or not) during the second year of participation in MILES.

4.4 Eligibility criteria for the switch to Viaskin Milk 300 µg

The following eligibility criteria apply to the subjects who agree to switch to Viaskin Milk 300 µg.

4.4.1 Inclusion Criteria

1. Signed ICF by parent(s)/guardian(s) of subjects and informed assent form for subjects ≥7 years, or as per local or country specific guidelines or regulations.
2. Negative urine pregnancy test at Visit Switch 1 for female subjects of childbearing potential. Female subjects of childbearing potential must continue to agree and commit to using effective medical methods of contraception for the entire duration of their participation in the study. Sexual abstinence will be accepted as an effective method of contraception for females below 15 years of age.
3. Subjects must agree to continue following a strict cow's milk-free diet, with no consumption of dairy or baked milk products during participation in the study (except during the DBPCFCs).
4. Subjects and/or parents/guardians willing to comply with all study requirements during participation.

4.4.2 Exclusion Criteria

1. Any new disorder or disease that may affect the subject's participation in the study, or place the subject at increased risk, or for which epinephrine use is contraindicated.
2. Poor compliance in patch application (below 80%) during the previous year of participation in MILES.

4.5 Removal of Subjects from Therapy or Assessments

Subjects who are withdrawn from the study will not be replaced. Participation of a subject in this clinical study may be discontinued for any of the following reasons:

- Adverse Event: any SAE, clinically significant AE, or severe laboratory abnormality.
- Subject or parent(s)/guardian(s) decision (consent withdrawal).
- Investigator decision: occurrences of any medical condition or circumstances that expose the subject to substantial risk and/or do not allow the subject to adhere to the requirements of the protocol.
- Pregnancy.
- Noncompliance: subject's failure to comply with protocol requirements or study-related procedures.
- Lost to follow-up: subject's failure to return for scheduled visits despite telephone or written attempts of contact.
- Sponsor or regulatory authority decision: termination of the study by the sponsor, FDA, or other regulatory authorities.
- Death.

Subjects and their parent(s)/guardian(s) are free to withdraw consent from participating in the study at any time without prejudice to further treatment. The reason(s) for withdrawal will be documented. Subjects withdrawing from the study should complete the early termination study procedures (Section 7.2.5).

Reasonable efforts will be made to contact subjects who are lost to follow-up and will be documented in the subject's file.

Subjects who are withdrawn from the study will receive standard of care according to the judgment of the treating physician.

The sponsor has the right to terminate the study under special circumstances that may be related to the investigational product or the company or for any other reason. In these instances, the Investigators and the regulatory authorities and Institutional Review Boards (IRBs) will be informed about the reason of study termination.

Stopping rules for the study are presented in Section 6.7.

5 Investigational Products

5.1 Drug Substance

The drug substance is an unmodified allergen extract that is a lyophilized cow's milk proteins extract. CCI [redacted]

5.2 Investigational Products Administered

The investigational product Viaskin Milk (DBV135) patch consists of an epicutaneous drug delivery system (EDS), with the appearance of a patch, containing a solid deposit of cow's milk proteins. CCI [redacted]

- [redacted]
- [redacted]

Placebo treatment will consist of a Viaskin patch with a similar formulation to Viaskin Milk but devoid of cow's milk proteins. CCI [redacted]

CCI [redacted]

5.3 Investigational Products Storage

The investigational products will be stored in the refrigerator between 2°C to 8°C (35.6°F to 46.4°F); see USP Controlled Room Temperature.

Storage at ambient temperature for short and/or intermittent periods of time, including transportation, is permitted.

5.4 Packaging and Labelling

All packaging and labelling operations will be performed according to GMP for medicinal products and the relevant regulatory requirements. CCI [redacted] One investigational patch will be placed in a pouch and each pouch will be labelled. The labelled pouches will be placed in labelled treatment boxes and several treatment boxes may be inserted into labelled treatment kits. Alternatively, depending upon the schedule of visits, the pouches will be placed directly into the labelled treatment kits, in which case one treatment kit will represent one treatment box. Each treatment kit will be labelled with a kit number. Sites will use the Interactive Web Response System (IWRS) for kit assignment to the subjects, and then site personnel will dispense the individual treatment box to the subjects at each visit, with a sufficient quantity of Viaskin patches to cover the period between two consecutive visits. The labelled and packaged investigational product will be stored according to GMP requirements under the storage conditions established by stability studies.

Upon receipt of a shipment request, the study drug will be shipped to the clinical site. The pharmacist will receive and store the investigational product as instructed (see Section 5.3) until dispensation. At the end of the study, the pharmacist will be responsible for destroying any unused investigational product – either returned by the subjects or not dispensed at all – and will provide a corresponding certificate of destruction.

6 Administration of Study Treatments

6.1 Method of Assigning Subjects to Treatment Groups

All subjects will be assigned an identification number at Visit 1. The IWRS will randomize all eligible subjects and assign the appropriate treatment kit. IWRS will manage the inventory and assignment of treatment to subjects at the kit level. The site pharmacists will dispense the drug product according to the IWRS recommendations. Subjects at each dose level will be randomly assigned to receive either Viaskin Milk or placebo according to a computer-generated randomization code that will be produced by an unblinded study statistician at the Contract Research Organization (CRO) in accordance with the Standard Operating Procedures (SOPs) of the CRO. In addition, the randomization to treatment for subjects randomized in Part B will be stratified by site and by age group (children 2 to 11 years old at the time of Visit 1; adolescents 12 to 17 years old at the time of Visit 1).

6.2 Selection of Doses in the Study

The optimal Viaskin Milk clinical dose could not be anticipated at the start of the study, but the doses to be tested in this study were based on the results obtained from the preclinical toxicity/local tolerance studies that were performed to evaluate the toxicity of

the product, and from the results of the pilot 3-month clinical study (study #SV 782) (see Section 1.3).

The starting dose of 150 µg of cow's milk proteins is similar to the dose of the related drug product, Diallertest. The highest dose of Viaskin Milk tested in this study is 500 µg of cow's milk proteins; ie, the highest dose tested in toxicity/local tolerance animal studies. An intermediate dose of 300 µg of cow's milk proteins will also be evaluated.

In Part A of the study, 3 doses of Viaskin Milk were evaluated *versus* placebo and administered until Month 12. The escalation in the various cohorts occurred as follows:

- Cohort 1 = Viaskin Milk 150 µg of cow's milk proteins *versus* placebo
- Cohort 2 = Viaskin Milk 300 µg of cow's milk proteins *versus* placebo
- Cohort 3 = Viaskin Milk 500 µg of cow's milk proteins *versus* placebo

In Part B of the study, the 3 safe doses of Viaskin Milk (150 µg, 300 µg and 500 µg of cow's milk protein), were used to study the efficacy of Viaskin Milk in a placebo-controlled dose-finding study.

After Month 12, all subjects (Part A and Part B subjects) were to receive the highest safe dose of Viaskin Milk selected for Part B (500 µg of cow's milk protein) assessed from the safety data of Part A subjects, for an additional 12 months up to Month 24. Subjects entering the study extension after Month 24 were to receive Viaskin Milk 500 µg up to Month 48.

The primary analysis that was conducted after the 12-month blinded period showed that the Viaskin Milk 300 µg was the most effective tested dose[3]. No safety concern was identified at any of the investigated doses. Therefore, all eligible subjects will switch to Viaskin Milk 300 µg for 24 months, independently of the duration of previous treatment with Viaskin Milk 500 µg.

6.3 Administration of Study Treatments to Subjects

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

One Viaskin patch only (Viaskin Milk or placebo) will be applied each day on an intact and dry area of the skin. Once the Viaskin patch is applied to the skin, CC [redacted] must be used each day to cover the Viaskin patch to prevent it from coming off the skin or moving around and to avoid the allergenic proteins spreading over other areas of the skin.

Double-blind, placebo-controlled treatment period up to Month 12

The subjects were randomized to receive either Viaskin Milk (150 µg, 300 µg, or 500 µg of cow's milk proteins) or placebo from Day 1 (Visit 4) up to Month 12 (Visit 12) during the double-blind treatment period.

[3] Refer to the Investigator's Brochure of Viaskin Milk for details about results of the 12-month blinded period.

Open-label treatment periods with Viaskin Milk 500 µg and Viaskin Milk 300 µg after Month 12

After the Month 12 DBPCFC, all subjects were to receive Viaskin Milk 500 µg up to Month 24. After the Month 24 DBPCFC, all subjects who entered the study extension were to continue to receive Viaskin Milk 500 µg up to Month 48.

Following results of the 12-month double-blind treatment period, all eligible subjects will switch to Viaskin Milk 300 µg for 24 months.

6.3.1 Blinded Treatment Period

To increase the safety of the patch at the beginning of the treatment, the daily duration of application will be gradually increased for the first weeks of treatment as follows:

- 6 hours of daily application during the first week (from Day 1 to Day 7);
- 12 hours of daily application during the second week (from Day 8 to Day 14);
- 24 hours of daily application from the third week (from Day 15) onwards.

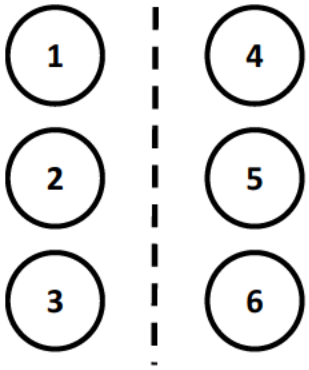
In case of severe local reactions, or if the subject presents an AE considered as a systemic “allergic reaction type” of any severity and related to the study drug, the daily duration of patch application can be adapted/reduced if the Investigator considers this could allow for an optimal management of the safety of the subjects. The daily duration of patch application could then be progressively extended day by day to reach the 24-hours/day application after the AE resolves or stabilizes. In the rare event that Grade 4 local skin reactions occur, subjects should transiently discontinue patch application. Subjects should then visit the site for the next patch application and for adequate examination and treatment of the wounded zone (refer to Section 7.3.2.5, Adverse Events of Special Interest to the Sponsor).

The patches will be applied on the inter-scapular area on the back of the children (2 to 11 years old) and on the inner side of the arms for the adolescents (12 to 17 years old) and former adolescents who become adults (≥18 years old). Children who reach the age of 12 years during their participation in the study may continue to apply the patches on their back, or switch to the arms. For each site of application (arms or back), the specific place where the patch is applied will represent a zone: 6 zones in total will be used and rotated for application of the patches. The application of the patch should start with Zone 1 on Day 1, then Zone 2 on Day 2, then Zone 3 on Day 3…up to Zone 6 on Day 6. Then the patch will be applied back to Zone 1 on Day 7, Zone 2 on Day 8, etc.

- For children (2 to 11 years old), the Zones 1, 2, and 3 will be located on 1 side of the spine and Zones 4, 5 and 6 will be located on the other side of the spine.

- For adolescents (12 to 17 years old) and former adolescents who become adults (≥18 years old), the Zones 1, 2 and 3 will be located on 1 arm and Zones 4, 5, and 6 will be located on the other arm.

Zones for Patch Application



The Viaskin patch should be applied daily, preferably at approximately the same time every day. Application can be in the morning or in the evening, whatever schedule is the most convenient to the subjects and/or parent(s)/guardian(s). If possible, the subjects could take advantage of their shower (or bath) time to change the Viaskin patch. The previous Viaskin patch should be removed before the shower (or bath) and discarded. The new patch should be applied a few minutes after the shower (or bath) and after careful drying of the skin. Once applied to the skin, [redacted] must be used each day to cover the Viaskin patch to prevent it from coming off or moving around, and to avoid the allergenic proteins spreading over other areas of the skin.

When removing a Viaskin patch or in case the Viaskin patch comes off accidentally, it is recommended that the subject or the subject's parent(s)/guardian(s) thoroughly wipe off the zone with a moist disposable napkin or disposable tissue and wash their hands to prevent any accidental transmission of the allergenic proteins. A patch that has been removed prematurely or falls off must not be re-applied. It is not recommended to use any bandage or [redacted] to re-apply and keep on a patch that has been removed. A patch that has been removed prematurely for any reason other than safety reasons or has fallen off inadvertently within 2 hours of being applied can be replaced by another patch and applied at the same location, after thorough wiping of the zone. However, should the patch be removed of fall off after more than 2 hours of application, another patch will not be applied on that same day and the subject will have to wait for the next time of application the following day to apply the subsequent patch.

If the patch was removed or has fallen off prematurely, the daily duration of application of the patch and the reason for early removal will be recorded in the subject diary cards. The duration of the patch application will be recorded every day from Day 1 (Visit 4) up to Month 3 (Visit 9) on the subject diary cards. After Month 3, the subjects will only record the days and time periods when the duration of application did not follow the durations recommended in the protocol. During the period of 24 hours of daily application, flexibility between 20 to 28 hours of daily application is permitted.

The last application of the patch during the blinded treatment period will occur the day before Visit 12 (Month 12). The subject should not apply a patch at Visit 12 and between Visit 12 and Visit 13 of the DBPCFC.

6.3.2 Open-label Treatment Period

After the 2 days of the Month 12 DBPCFC, at Visit 13, all subjects (Part A and Part B) were to continue treatment with Viaskin Milk in an open-label manner, at the highest

dose of Viaskin Milk selected for Part B (500 µg of cow's milk protein), based on safety data of Part A subjects. The Viaskin Milk open-label treatment period was to continue until Month 24 for all subjects and until Month 48 for the subjects who entered the study extension. If a subject experienced reactions after the DBPCFC at Visit 13 that warranted postponing the application of the first patch of the open-label treatment period, it was permitted, at the discretion of the Investigator, to delay the application of the first patch of the open-label treatment up to a maximum of 7 days after Visit 13.

To increase the safety of subjects at the beginning of the open-label treatment period, in particular for subjects crossing over from placebo to the active Viaskin Milk treatment, the daily duration of application was again to be adapted from Visit 13 for the first weeks of treatment as follows:

- 6 hours of daily application during the first week
- 12 hours of daily application during the second week
- 24 hours of daily application from the third week onwards

At the time of Protocol Amendment 5, all subjects were currently receiving active treatment with Viaskin Milk 500 µg. **The switch to Viaskin Milk 300 µg will not require a progressive increase of application duration, and all subjects will be able to start with 24 hours of daily application of Viaskin Milk 300 µg**.

During the open-label treatment periods with Viaskin Milk 500 µg and Viaskin Milk 300 µg, the daily duration of patch application could also be reduced/adapted and progressively extended up over a few days to reach the 24-hours/day application in some specific cases, as described in the previous section, if the Investigator considers this could allow for an optimal management of the safety of the subjects. In the rare event that Grade 4 local skin reactions or other local AESI occur, subjects should transiently discontinue patch application. Subjects should then visit the site for the next patch application and for adequate examination and treatment of the wounded zone. Subjects should remain at the site for 1 hour before being discharged. The site staff should contact the subject via telephone the next day after removal of the patch to ensure that there are no additional local vesicles, blisters or other lesions evocative of skin disruption noted and the treatment with the patch can proceed as planned. The zone with vesicles or lesions should not be used for patch application until the zone has completely healed.

The application of the patch with regard to the location (back or arm) and zones together with the recommendations for applying and removing the patch should continue as described above in the blinded treatment period section (refer to Section 6.3.1).

If the patch was removed or has fallen off prematurely, the daily duration of application of the patch and the reason for early removal will be recorded in the subject diary cards. During the open-label treatment periods with Viaskin Milk 500 µg and Viaskin Milk 300 µg, the subjects will only record the days and time periods when the duration of application did not follow the durations recommended in the protocol. During the period of 24 hours of daily application, flexibility between 20 to 28 hours of daily application is permitted.

For subjects who terminated the study at Month 24, the last patch application was to be the day before the second Month 24 DBPCFC (day before Visit 17). For subjects who entered the study extension after Month 24, the open-label treatment period was to continue with Viaskin Milk 500 µg until Month 48. For those subjects, the last patch application was to be on the day before the second Month 48 DBPCFC (day before

Visit 23). The last application of Viaskin Milk 300 µg will depend upon the participation of the subject in the DBPCFC performed after 24 months of treatment:

- If the subjects perform the DBPCFC, the last patch application will be the day before the second day of the DBPCFC/Visit S7;
- If the subjects do not perform the DBPCFC, the last patch application will be the day before Month 24/Visit S6.

6.4 Blinding

Double-blind, placebo-controlled treatment period up to Month 12

This is a randomized, double-blind study. The subject, Investigator, medical monitor, sponsor, and the entire study processing team will remain blinded to treatment assigned (refer to Section 6.1, Method of Assigning Subjects to Treatment Groups) to the subjects during the 12-month double-blind treatment period and the blinding will remain until all 12-month data are collected.

The appearance of Viaskin Milk and placebo patches will be identical. During the blinded treatment period, an Emergency Code Break procedure will be available to Investigators via IWRS, to allow for unblinding a subject or treatment kit, (ie, informing the Investigator of the treatment group to which the subject has been assigned). The blind for a specific subject can be broken by the Investigator only if the Investigator considers the information indispensable to the safety of the subject. If possible, the medical monitor at the CRO and the sponsor should be consulted before breaking the blind and the Investigator should always assess the relationship of the AE to the investigational product before breaking the blind.

Open-label treatment period with Viaskin Milk 500 µg and Viaskin Milk 300 µg

After the Month 12 DBPCFC and study procedures have been completed (Visit 13), all subjects were to continue treatment until Month 24 with Viaskin Milk in an open-label manner, at the highest dose of Viaskin Milk selected for Part B (500 µg of cow's milk protein), based on safety data of Part A subjects. Treatment with open-label Viaskin Milk 500 µg was to continue until Month 48 for subjects who enter the study extension.

After the switch to Viaskin Milk 300 µg, subjects will receive this treatment in an open-label manner for 24 months.

6.5 Prior and Concomitant Therapy

6.5.1 Prior and Concomitant Therapy Records and Recommendations

All prior medications used within 6 months prior to Visit 1 will be recorded on the electronic case report form (eCRF). All medications taken any time from the study start until the end of the study will be recorded on the eCRF.

Application of a topical corticosteroid to treat any local AE (eczematous lesions, pruritus, edema, etc) is allowed and will be recorded as concomitant medication. A topical medication with 1% hydrocortisone or equivalent will be distributed to each randomized subject at discharge on Day 1 (Visit 4). In case the 1% hydrocortisone topical medication is not sufficient to treat the local reaction, a topical medication containing a more potent corticosteroid can be prescribed and locally applied.

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

Intramuscularly injectable epinephrine CCI [redacted] will be distributed to each subject at discharge on Day 1 (Visit 4) to be used in case of symptoms of anaphylaxis. The Investigator will explain to the subject and/or parent(s)/guardian(s) and document when and how to (self) inject the epinephrine according to the Anaphylaxis Emergency Action Plan (see Appendix 14.5), which will also be given to the subject. The intramuscularly injectable epinephrine will be replaced if used or if it expires. Any use (ie, administration) of injectable epinephrine within 6 months prior to Visit 1 or during the study must be recorded into the eCRF.

The administration of prior/concomitant medications must be recorded in the eCRF to include the medication name, dosage and units, route, schedule, start and stop dates (when applicable), and indication for use. Generic names for concomitant medications should be used or alternatively Trade names should be used in the case of combined medications.

6.5.2 Prohibited Concomitant Treatments and Procedures:

- Any investigational drug or device other than Viaskin Milk or placebo.
- Short-acting antihistamines for 1 to 3 days and long-acting antihistamines for 5 to 7 days before any DBPCFC or SPT procedures (see Appendix 14.7).
- Long-acting β_2 agonists (eg, formoterol) within 36 hours before any DBPCFC.
- Omalizumab or other immunomodulatory agents.
- Biological drugs including but not limited to antibodies, B-cells depleting agents or tumor necrosis factor inhibitors.
- Calcium channel blockers.
- Beta-blockers or ACE inhibitors.
- Any other immunotherapy treatment (eg, food allergen[s] or aeroallergen[s]).
- Before Protocol Amendment 5: Any food challenge to milk (other than required as per this protocol) or to any other food.
- After Protocol Amendment 5: Any food challenge to milk (other than proposed as per this protocol)

6.5.3 Permitted Concomitant Treatments and Procedures:

- Topical corticosteroids to treat any local cutaneous AE (eg, eczema or erythema, pruritus, edema, rash, etc).
- Oral antihistamines and oral or inhaled corticosteroids to treat AEs (see Section 7.3.2.3.3, Rescue Medication). Duration of treatment should be limited and ideally stopped upon AE resolution. An inhalation corticosteroid conversion table is included in Appendix 14.6.
- Intramuscularly injectable epinephrine.

- Treatments (other than those described above) prescribed in case of any AE.
- After Protocol Amendment 5: Any food challenge to any other food than milk required for the subject's medical management will be permitted. Whether the subject's medical condition is still compatible with their participation in the study should be assessed by the Investigator and the Sponsor's medical monitor before the food challenge is performed. Note that the initiation of any other immunotherapy treatment remains prohibited during the participation of the subject in the MILES study (refer to Section 6.5.2).

6.6 Treatment Compliance

Subjects and/or parent(s)/guardian(s) will receive diary cards to record the daily application of Viaskin patches (see Section 7.3.2.12 for further details about diary cards). The duration of the patch application will be recorded every day from Day 1 (Visit 4) up to Month 3 (Visit 9) on the subject diary cards. After Month 3, the subjects will only record the days and time periods when the duration of the patch application did not follow the durations recommended in the protocol. During the period of 24 hours of daily application, flexibility between 20 to 28 hours of daily application is permitted. If a Viaskin patch is removed prematurely or falls off, the daily duration of application of the patch and the reason for early removal will be recorded in the subject diary cards. The data recorded in the diary card by the subject and/or parent(s)/guardian(s) will be collected periodically during the subject's visit at sites and entered into the eCRF or the clinical database.

It is the Investigator's responsibility to correctly instruct subjects and/or parent(s)/guardian(s) on how to store and administer the investigational product. At each visit, prior to dispensing a new investigational treatment box, the compliance of the subject will be assessed by evaluating the number of days the patches were applied (even for a duration that is less than the recommended duration), *versus* the number of days in that time interval. An overall compliance of ≥80% over the treatment period is sought. Subjects exhibiting a poor compliance (<80%) should be counseled on the importance of a good compliance.

The Investigator or designated study personnel will maintain a log of all investigational product dispensed (see Section 10.1, Drug Accountability for details).

6.7 Study Stopping Rules

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

- Any death related to Viaskin dosing;
- More than one Stage 3 anaphylaxis (see Appendix 14.4, Anaphylaxis Staging System) related to Viaskin application (and not occurring during the DBPCFCs);
- More than 3 subjects requiring >1 injection of epinephrine related to Viaskin application (and not occurring during the DBPCFCs).

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

- Accrual into the study may continue without modification;
- Accrual into the study may continue with modifications as recommended by the DSMB;
- Accrual into the study should stop.

7 Study Procedures

7.1 Duration of Treatment

The duration of treatment with the investigational product (Viaskin Milk or placebo) will be 12 months for all subjects in Part A and Part B during the double-blind treatment period, followed by an additional 12 months of active Viaskin Milk treatment during the open-label treatment period. For subjects entering the study extension, open-label treatment with Viaskin Milk 500 µg was to continue for two additional years but will be interrupted consecutive to the switch to Viaskin Milk 300 µg. Switching will allow subjects to receive 2 years of treatment with Viaskin Milk 300 µg.

Consequently, the duration of active Viaskin Milk treatment will differ for each individual subject and could be up to approximately 6 years.

7.2 Study Visits and Assessments

Double-blind treatment period up to Month 12 and open-label treatment period with Viaskin Milk 500 µg

The planned study assessments are summarized in Table 2, Table 3, Table 4, and Table 5 for the first, second, third, and fourth year of treatment, respectively, as described in Section 7.4. A maximum of 24 site visits were planned for subjects in Part A and 23 site visits for subjects in Part B up to Month 48. In addition, a maximum of 15 phone contacts were to be held between scheduled site visits.

Open-label treatment period with Viaskin Milk 300 µg

The planned study assessments are summarized in Table 6 and Table 7 for the first and second years after the switch to Viaskin Milk 300 µg, respectively, as described in Section 7.4. A maximum of 7 site visits are planned, and a maximum of 5 phone calls will be held between scheduled site visits.

The subjects and/or parent(s)/guardian(s) must be instructed that subjects should follow a strict cow's milk-free diet with no consumption of cow's milk, dairy products, or any baked milk products during their entire participation in the study.

7.2.1 Pre-Treatment Screening Period

The screening period will include 3 pre-treatment visits (Visits 1 to 3) for all subjects. The duration of the screening period up to the first day of treatment with the study drug at Visit 4 must be ≤60 days. This gives enough time for the subjects to perform their 3 pre-treatment visits and plan for the Visit 4 based on their schedule and site's availability. The screening period could however be shorter than 60 days. If applicable, subjects with abnormal laboratory assessments due to concomitant transient disease (flu, viral illness, etc) can repeat their laboratory assessments or be rescheduled for laboratory assessment at the discretion of the Investigator.

7.2.1.1 Visit 1 (Screening Visit)

The site staff must go into IWRS to register the subject for Screening.

Subjects will undergo the following procedures at this visit:

Written and signed ICF/IAF will be obtained before any assessments are made.

Written and signed genetic ICF/IAF for optional genetic analysis (epigenetic and filaggrin analysis) may be obtained only if subjects or their parent(s)/guardian(s) agree to participate in these analyses.

All subjects will be assessed for eligibility against the inclusion and exclusion criteria and assigned a subject identification number.

Quality of Life (QoL) Food Allergy QoL Questionnaire (FAQLQ)/Food Allergy Independent Measure (FAIM) forms[20] (Appendix 14.3) will be completed by the subject (when applicable) and parent(s)/guardian(s) before any procedures at this visit are performed. The appropriate QoL questionnaire forms to complete depend on the age of the subject at the time of Visit 1.

The subject's full medical history, including history of CMA and any other type of allergy, if applicable.

Prior medications (received within 6 months prior to Visit 1) and ongoing medications will be documented.

Demographic data, including date of birth, sex, ethnic origin, weight (kg), and height (cm) will be collected.

A physical examination, including a complete skin examination, will be performed and the results documented.

Vital signs (heart rate, systolic and diastolic blood pressure, and respiratory rate) for subjects in a sitting position will be measured.

Spirometry and PEF measurements (depending on the subject's age and ability to perform these tests) will be obtained.

SPT to cow's milk will be performed.

Blood samples for hematology and biochemistry laboratory tests, immunological markers (IgE, immunoglobulin G4 [IgG4]) will be collected.

Only for subjects who signed the genetic ICF/IAF: a blood sample for filaggrin mutations may be collected; only 1 sample for filaggrin mutations is to be collected during the study, either at this visit or at other visits listed in Table 2, Table 3, Table 4, and Table 5.

Only for subjects who signed the genetic ICF/IAF: a blood sample for epigenetic analysis will be collected.

A urine pregnancy test will be performed for female subjects with childbearing potential.

AEs will be recorded from the day of signing the ICF/IAF.

7.2.1.2 Visit 2 (First day of the Screening DBPCFC)

Visit 2 can be scheduled and conducted as soon as the laboratory results from Visit 1 are available and confirm the eligibility criterion related to the cow's milk sIgE (ie, the sIgE must be ≥10 kU/L). This visit 2 corresponds to the first day of the screening DBPCFC.

Subjects will undergo the following procedures at this visit:

A physical examination, including a complete skin examination, will be performed before the DBPCFC and can be repeated anytime during the DBPCFC, as judged necessary by the Investigator.

Vital signs (heart rate, systolic and diastolic blood pressure, and respiratory rate) for subjects in a sitting position will be measured before the DBPCFC and can be repeated anytime during the DBPCFC, as judged necessary by the Investigator.

PEF measurements (depending on the subject's age and ability to perform these tests) will be obtained.

Any AEs that have occurred since the previous visit will be documented and any changes in medications reported.

DBPCFC will be performed and the grading of each symptom will be made using the grading definitions in the Oral Food Challenge (OFC) symptom score sheets (see Appendix 14.2).

A minimum duration of 3 hours observation after the last dose of the food challenge formula has been ingested is required at this visit, before the subject is discharged from the site. The observation period can be extended beyond 3 hours if deemed necessary by the Investigator.

7.2.1.3 Visit 3 (Second day of the Screening DBPCFC)

Visit 3 corresponds to the second day of the screening DBPCFC. Visit 3 will be scheduled within 7 days after Visit 2. However, Visit 3 may be scheduled up to a maximum of 14 days after Visit 2 and documented in the eCRF, if either of the following occur: (1) the subject experiences reactions after the DBPCFC at Visit 2 that require more than 7 days to elapse before the next food challenge, or (2) any intercurrent disease preventing the second day of the challenge to be conducted safely as planned; in this specific condition, the timeframe between the 2 days of challenges might exceed 14 days and must be appropriately documented, or (3) the subject's schedule or site logistics prevent the second day of food challenge to be performed within 7 days of the first day.

Subjects will undergo the following procedures at this visit:

A physical examination, including a complete skin examination, will be performed before the DBPCFC and can be repeated anytime during the DBPCFC, as judged necessary by the Investigator.

Vital signs (heart rate, systolic and diastolic blood pressure, and respiratory rate) for subjects in a sitting position will be measured before the DBPCFC and can be repeated anytime during the DBPCFC, as judged necessary by the Investigator.

PEF measurements (depending on the subject's age and ability to perform these tests) will be obtained.

Any AEs that have occurred since the previous visit will be documented and any changes in medications reported.

DBPCFC will be performed and the grading of each symptom will be made using the grading definitions in the OFC symptom score sheets (see Appendix 14.2).

A minimum duration of 3 hours observation after the last dose of the food challenge formula has been ingested is required at this visit, before the subject is discharged from the site. The observation period can be extended beyond 3 hours if deemed necessary by the Investigator.

After completion of the second day of the food challenge, ie, after the last dose of the challenge has been administered or the challenge stopped because of (a) clear

objective reaction(s) has (have) occurred, the order of the challenge formulas can be unblinded and the results of the challenge will be established as described in Section 7.3.1.1.1 and recorded in the eCRF.

This will be the last criterion to determine whether the subject is eligible to be randomized to treatment or not. If the subject is not eligible for participation in the study, the site staff must go into IWRS to register the subject as Screen Failure. If the subject is eligible for participation in the study, the site staff must go into IWRS to register the subject for randomization once the Cohort or Part is open for randomization. Randomization by IWRS can be performed as soon as the eligibility of the subject is confirmed at the end of Visit 3, and up to the day of Visit 4.

7.2.2 Part A, Part B, 12-month open-label treatment with Viaskin Milk 500 µg and study extension

The following visit schedule applies until Protocol Amendment 5 is approved and the subjects switch to Viaskin Milk 300 µg. However, no further DBPCFC should be conducted while the subjects are still receiving Viaskin Milk 500 µg.

Refer to Section 7.2.3 as soon as the Viaskin Milk 300 µg is available at the study site.

7.2.2.1 Visit 4 (Day 1)

Visit 4 (Day 1) should take place within a maximum of 60 days after Visit 1 (screening visit). This visit corresponds to the first day of treatment.

Subjects will undergo the following procedures at this visit:

Subjects will be reassessed for eligibility against the inclusion and exclusion criteria before proceeding to allocation of a treatment kit. The site staff must login into IWRS to be allocated a randomization treatment kit for the subject.

A physical examination, including a complete skin examination, will be performed.

Vital signs (heart rate, systolic and diastolic blood pressure, and respiratory rate) for subjects in a sitting position will be measured.

Spirometry and PEF measurements (depending on the subject's age and ability to perform these tests) will be obtained.

Any AEs that have occurred since the previous visit will be documented and any changes in medications reported.

One patch will be taken from the Visit 4 treatment box and applied to the subject's skin as described in Section 6.3.

For only Part B subjects, the Visit 4 treatment box will be dispensed to the subject for daily application until the next visit.

Examination, grading, and photography of the area of the skin used for Viaskin patch application will be performed.

Diary card will be dispensed to the subject and instructions will be given for completion.

Epinephrine auto-injector and the Anaphylaxis Emergency Action Plan (Appendix 14.5) will be dispensed and/or their utilization reviewed, as necessary.

Part A subjects will be observed at the site for a minimum duration of 6 hours after application of the patch at this visit.

Part B subjects will be observed at the site for a minimum duration of 3 hours after application of the patch at this visit.

Subjects can then be discharged from the site only after this observation period. This period can be extended beyond 3 or 6 hours if deemed necessary by the Investigator.

Vital signs, PEF measurements, and the examination, grading, and photography of the area of the skin where the Viaskin patch is applied will be performed at the following timepoints: before application of the first patch, then at 30 minutes, 1 hour, 2 hours, 3 hours and 6 hours (when applicable) after application of the patch. Note: for subjects in Part B, the 6-hour timepoint is not required.

Subjects and/or their parent(s)/guardian(s) will be instructed to use the diary card and to bring the card to the site at each subsequent visit. Subjects and/or parent(s)/guardian(s) will be instructed to record any AEs and associated medications on the diary cards and will also be reminded to record the duration of application and reason(s) for early removal of the Viaskin patch, if the patch is removed before the recommended duration of application. Any accidental cow's milk consumption (in any form) must also be documented on the diary cards. At subsequent visits, the diary card will be reviewed and the data will be collected by site personnel.

7.2.2.2 Visit 5 (Day 2) (for Part A Subjects Only)

This visit is required only for subjects enrolled in Part A and will take place the day after Visit 4.

Subjects will undergo the following procedures at this visit:

A physical examination, including a complete skin examination, will be performed.

Vital signs (heart rate, systolic and diastolic blood pressure, and respiratory rate) for subjects in a sitting position will be measured.

PEF measurements (depending on the subject's age and ability to perform these tests) will be obtained.

Any AEs that have occurred since the previous visit will be documented and any changes in medications reported.

Examination, grading, and photography of the area of the skin used for Viaskin patch application will be performed.

A new patch will be taken from the Visit 5 treatment box and applied to the subject's skin as described in Section 6.3.

The Visit 5 treatment box will be dispensed to the subject for daily application until the next visit.

Diary card will be checked and given back to the subject and instructions repeated/reminded if required.

Review/reminder of the utilization of the epinephrine auto-injector and the Anaphylaxis Emergency Action Plan (Appendix 14.5), if required.

Subjects will be observed at site for a minimum duration of 2 hours after application of the patch. The observation period can be extended beyond these 2 hours if deemed necessary by the Investigator.

7.2.2.3 Visit 6 (Day 8/Week 1 ±2 days)

Visit 6 (Day 8/Week 1) will take place 7 days ±2 days after Visit 4 (Day 1).

Subjects will undergo the following procedures at this visit:

A physical examination, including a complete skin examination, will be performed.

Vital signs (heart rate, systolic and diastolic blood pressure, and respiratory rate) for subjects in a sitting position will be measured.

PEF measurements (depending on the subject's age and ability to perform these tests) will be obtained.

Any AEs that have occurred since the previous visit will be documented and any changes in medications reported.

Examination, grading, and photography of the area of the skin used for Viaskin patch application will be performed.

Diary card will be checked and given back to the subject and instructions repeated/reminded, if required.

The treatment box from the previous visit will be collected from the subject and drug accountability/compliance will be assessed.

The Visit 6 treatment box will be dispensed to the subject.

Review/reminder of the utilization of the epinephrine auto-injector and the Anaphylaxis Emergency Action Plan (Appendix 14.5), as necessary.

7.2.2.4 Visit 7 (Day 22/Week 3 ±3 days)

Visit 7 (Day 22/Week 3) will take place 21 days ±3 days after Visit 4 (Day 1).

Subjects will undergo the following procedures at this visit:

A physical examination, including a complete skin examination, will be performed.

Vital signs (heart rate, systolic and diastolic blood pressure, and respiratory rate) for subjects in a sitting position will be measured.

Spirometry and PEF measurements (depending on the subject's age and ability to perform these tests) will be obtained.

Blood samples for hematology and biochemistry laboratory tests, as well as for immunological markers (IgE, IgG4) will be collected.

Only for subjects who signed the genetic ICF/IAF: a blood sample for the analysis of filaggrin mutations may be collected at this visit if not collected at Visit 1.

Any AEs that have occurred since the previous visit will be documented and any changes in medications reported.

Examination, grading, and photography of the area of the skin used for Viaskin patch application will be performed.

Diary card will be checked and given back to the subject and instructions repeated/reminded, if required.

The Visit 6 treatment box will be collected from the subject and drug accountability/compliance will be assessed.

Site staff will login into IWRS to be allocated an initial re-supply kit for the subject. The Visit 7 treatment box will be dispensed to the subject.

Review/reminder of the utilization of the epinephrine auto-injector and the Anaphylaxis Emergency Action Plan (Appendix 14.5) as necessary. The expiry date of the auto-injector will be checked and a new auto-injector should be dispensed to the subject, as necessary.

7.2.2.5 Visit 8 (Week 6 ±3 days)

Visit 8 (Week 6) will take place 6 weeks ±3 days after Visit 4 (Day 1).

Subjects will undergo the following procedures at this visit:

A physical examination, including a complete skin examination, will be performed.

Vital signs (heart rate, systolic and diastolic blood pressure, and respiratory rate) for subjects in a sitting position will be measured.

PEF measurements (depending on the subject's age and ability to perform these tests) will be obtained.

Any AEs that have occurred since the previous visit will be documented and any changes in medications reported.

Examination, grading, and photography of the area of the skin used for Viaskin patch application will be performed.

Diary card will be checked and given back to the subject and instructions repeated/reminded, if required.

The Visit 7 treatment box will be collected from the subject and drug accountability/compliance will be assessed.

The Visit 8 treatment box will be dispensed to the subject.

Review/reminder of the utilization of the epinephrine auto-injector and the Anaphylaxis Emergency Action Plan (Appendix 14.5) as necessary. The expiry date of the auto-injector will be checked and a new auto-injector should be dispensed to the subject, as necessary.

7.2.2.6 Visit 9 (Month 3 ±7 days)

Visit 9 (Month 3) will take place 3 months ±7 days after Visit 4 (Day 1).

Subjects will undergo the following procedures at this visit:

A physical examination, including a complete skin examination, will be performed.

Vital signs (heart rate, systolic and diastolic blood pressure, and respiratory rate) for subjects in a sitting position will be measured.

Spirometry and PEF measurements (depending on the subject's age and ability to perform these tests) will be obtained.

SPT to cow's milk will be performed.

Blood samples for hematology, biochemistry laboratory tests, and immunological markers (IgE, IgG4) will be collected.

Only for subjects who signed the genetic ICF/IAF: a blood sample for the analysis of filaggrin mutations may be collected at this visit if not collected at a previous visit.

Any AEs that have occurred since the previous visit will be documented and any changes in medications reported.

Examination, grading, and photography of the area of the skin used for Viaskin patch application will be performed.

Diary card will be checked and given back to the subject and instructions repeated/reminded, if required.

The Visit 8 treatment box will be collected from the subject and drug accountability/compliance will be assessed.

Site staff will login into IWRS to be allocated an additional re-supply kit for the subject. The Visit 9 treatment box will be dispensed to the subject.

Review/reminder of the utilization of the epinephrine auto-injector and the Anaphylaxis Emergency Action Plan (Appendix 14.5), as necessary. The expiry date of the auto-injector will be checked and a new auto-injector should be dispensed to the subject, as necessary.

7.2.2.7 Visit 10 (Month 6 ±7 days)

Visit 10 (Month 6) will take place 6 months ±7 days after Visit 4 (Day 1).

Subjects will undergo the following procedures at this visit:

Weight (kg) and height (cm) will be measured.

A physical examination, including a complete skin examination, will be performed.

Vital signs (heart rate, systolic and diastolic blood pressure, and respiratory rate) for subjects in a sitting position will be measured.

Spirometry and PEF measurements (depending on the subject's age and ability to perform these tests) will be obtained.

SPT to cow's milk will be performed.

Blood samples for hematology, biochemistry laboratory tests, and immunological markers (IgE, IgG4) will be collected.

Only for subjects who signed the genetic ICF/IAF: a blood sample for the analysis of filaggrin mutations may be collected at this visit if not collected at a previous visit.

Any AEs that have occurred since the previous visit will be documented and any changes in medications reported.

Examination, grading, and photography of the area of the skin used for Viaskin patch application will be performed.

Diary card will be checked and given back to the subject and instructions repeated/reminded, if required.

The Visit 9 treatment box will be collected from the subject and drug accountability/compliance will be assessed.

Site staff will login into IWRS to be allocated an additional re-supply kit for the subject. The Visit 10 treatment box will be dispensed to the subject.

Review/reminder of the utilization of the epinephrine auto-injector and the Anaphylaxis Emergency Action Plan (Appendix 14.5), as necessary. The expiry date of the

auto-injector will be checked and a new auto-injector should be dispensed to the subject, as necessary.

7.2.2.8 Visit 11 (Month 9 ±7 days)

Visit 11 (Month 9) will take place 9 months ±7 days after Visit 4 (Day 1).

Subjects will undergo the following procedures at this visit:

A physical examination, including a complete skin examination, will be performed.

Vital signs (heart rate, systolic and diastolic blood pressure, and respiratory rate) for subjects in a sitting position will be measured.

PEF measurements (depending on the subject's age and ability to perform these tests) will be obtained.

Any AEs that have occurred since the previous visit will be documented and any changes in medications reported.

Examination, grading, and photography of the area of the skin used for Viaskin patch application will be performed.

Diary card will be checked and given back to the subject and instructions repeated/reminded, if required.

The Visit 10 treatment box will be collected from the subject and drug accountability/compliance will be assessed.

Site staff will login into IWRS to be allocated an additional re-supply kit for the subject. The Visit 11 treatment box will be dispensed to the subject.

Review/reminder of the utilization of the epinephrine auto-injector and the Anaphylaxis Emergency Action Plan (Appendix 14.5) as necessary. The expiry date of the auto-injector will be checked and a new auto-injector should be dispensed to the subject, as necessary.

7.2.2.9 Visit 12 (Month 12 ±7 days; First Day of the Month 12 DBPCFC)

Visit 12 (Month 12) will take place 12 months ±7 days after Visit 4 (Day 1). Visit 12 corresponds to the first day of the Month 12 DBPCFC.

Subjects will undergo the following procedures at this visit:

QoL questionnaire FAQLQ/FAIM forms (Appendix 14.3) will be completed by the subject (when applicable) and parent(s)/guardian(s) before any procedures at this visit are performed. The appropriate QoL questionnaire forms to complete depend on the age of the subject at the time of Visit 1.

Weight (kg) and height (cm) will be measured.

A physical examination, including a complete skin examination, will be performed before the DBPCFC and can be repeated anytime during the DBPCFC, as judged necessary by the Investigator.

Vital signs (heart rate, systolic and diastolic blood pressure, and respiratory rate) for subjects in a sitting position will be measured before the DBPCFC and can be repeated anytime during the DBPCFC, as judged necessary by the Investigator.

Spirometry and PEF measurements (depending on the subject's age and ability to perform these tests) will be obtained.

SPT to cow's milk will be performed.

Blood samples for hematology, biochemistry laboratory tests, and immunological markers (IgE, IgG4) will be collected.

Only for subjects who signed the genetic ICF/IAF: a blood sample for the analysis of filaggrin mutations may be collected at this visit if not collected at a previous visit.

Only for subjects who signed the genetic ICF/IAF: a blood sample for epigenetic analysis will be collected.

A urine pregnancy test will be performed for female subjects with childbearing potential.

DBPCFC will be performed and the grading of each symptom will be made using the grading definitions in the OFC symptom score sheets (see Appendix 14.2).

Any AEs that have occurred since the previous visit will be documented and any changes in medications reported.

Examination, grading, and photography of the area of the skin used for Viaskin patch application will be performed.

Diary card will be checked and given back to the subject and instructions repeated/reminded, if required.

The Visit 11 treatment box will be collected from the subject and drug accountability/compliance will be assessed.

Review/reminder of the utilization of the epinephrine auto-injector and the Anaphylaxis Emergency Action Plan (Appendix 14.5) as necessary. The expiry date of the auto-injector will be checked and a new auto-injector should be dispensed to the subject, as necessary.

A minimum duration of 3 hours observation after the last dose of the food challenge formula has been ingested is required at this visit, before the subject is discharged from the site. The observation period can be extended beyond 3 hours if deemed necessary by the Investigator.

There will be no dispensation of the Investigational product at this visit since it will be the last day of the double-blind treatment period. It is recommended that a patch not be applied on the day of the DBPCFC procedures at Visit 12 and subjects should be instructed to not apply any patch between Visit 12 and Visit 13.

7.2.2.10 Visit 13 (Second day of the Month 12 DBPCFC)

Visit 13 corresponds to the second day of the Month 12 DBPCFC. Visit 13 will take place within 7 days after Visit 12. However, Visit 13 may be scheduled up to a maximum of 14 days after Visit 12 and documented in the eCRF, if either of the following occur: (1) the subject experiences reactions after the DBPCFC at Visit 12 that require more than 7 days to elapse before the next food challenge, or (2) any intercurrent disease preventing the second day of the challenge to be conducted safely as planned; in this specific condition, the timeframe between the 2 days of challenges might exceed 14 days and must be appropriately documented, or (3) the subject's schedule or site logistics prevent the second day of food challenge to be performed within 7 days of the first day.

Subjects will undergo the following procedures at this visit:

A physical examination, including a complete skin examination, will be performed before the DBPCFC and can be repeated anytime during the DBPCFC, as judged necessary by the Investigator.

Vital signs (heart rate, systolic and diastolic blood pressure, and respiratory rate) for subjects in a sitting position will be measured before the DBPCFC and can be repeated anytime during the DBPCFC, as judged necessary by the Investigator.

PEF measurements (depending on the subject's age and ability to perform these tests) will be obtained.

DBPCFC will be performed and the grading of each symptom will be made using the grading definitions in the OFC symptom score sheets (see Appendix 14.2).

Any AEs that have occurred since the previous visit will be documented and any changes in medications reported.

Examination, grading, and photography of the area of the skin used for Viaskin patch application will be performed.

Diary card will be checked and given back to the subject and instructions repeated/reminded, if required.

Site staff will login into IWRS. The treatment kit to be allocated at this Visit 13 should be the first open-label treatment kit for the subject. The Visit 13 treatment box will be dispensed to the subject.

Review/reminder of the utilization of the epinephrine auto-injector and the Anaphylaxis Emergency Action Plan (Appendix 14.5) as necessary. The expiry date of the auto-injector will be checked and a new auto-injector should be dispensed to the subject, as necessary.

A minimum duration of 3 hours observation after the last dose of the food challenge formula has been ingested is required at this visit, before the subject is discharged from the site. The observation period can be extended beyond 3 hours if deemed necessary by the Investigator.

After completion of the second day of the food challenge ie, after the last dose of the challenge has been administered or the challenge stopped because (a) clear objective reaction(s) has (have) occurred, the order of the challenge formulas can be unblinded and the results of the challenge will be established as described in Section 7.3.1.1.2 and recorded in the eCRF.

Visit 13 corresponds to the start date of the open-label treatment period. If the subject experiences reactions after the DBPCFC at Visit 13 that warrant postponing the application of the first patch of the open-label treatment, it is permitted, at the discretion of the Investigator, to delay the application of the first patch of the open-label treatment up to a maximum of 7 days after Visit 13.

7.2.2.11 Visit 14 (21 days ±3 days after Visit 13)

Visit 14 will take place 21 days ±3 days after Visit 13.

Subjects will undergo the following procedures at this visit:

A physical examination, including a complete skin examination, will be performed.

Vital signs (heart rate, systolic and diastolic blood pressure, and respiratory rate) for subjects in a sitting position will be measured.

PEF measurements (depending on the subject's age and ability to perform these tests) will be obtained.

Any AEs that have occurred since the previous visit will be documented and any changes in medications reported.

Examination, grading, and photography of the area of the skin used for Viaskin patch application will be performed.

Diary card will be checked and given back to the subject and instructions repeated/reminded, if required.

The Visit 13 treatment box will be collected from the subject and drug accountability/compliance will be assessed.

The Visit 14 treatment box will be dispensed to the subject.

Review/reminder of the utilization of the epinephrine auto-injector and the Anaphylaxis Emergency Action Plan (Appendix 14.5) as necessary. The expiry date of the auto-injector will be checked and a new auto-injector should be dispensed to the subject, as necessary.

7.2.2.12 Visit 15 (Month 18 ±14 days)

Visit 15 (Month 18) will take place 6 months ±14 days after Visit 13.

Subjects will undergo the following procedures at this visit:

Weight (kg) and height (cm) will be measured.

A physical examination, including a complete skin examination, will be performed.

Vital signs (heart rate, systolic and diastolic blood pressure, and respiratory rate) for subjects in a sitting position will be measured.

Spirometry and PEF measurements (depending on the subject's age and ability to perform these tests) will be obtained.

SPT to cow's milk will be performed.

Blood samples for hematology and biochemistry laboratory tests, as well as immunological markers (IgE, IgG4) will be collected.

Only for subjects who signed the genetic ICF/IAF: a blood sample for the analysis of filaggrin mutations may be collected at this visit if not collected at a previous visit.

Any AEs that have occurred since the previous visit will be documented and any changes in medications reported.

Examination, grading, and photography of the area of the skin used for Viaskin patch application will be performed.

Diary card will be checked and given back to the subject and instructions repeated/reminded, if required.

The Visit 14 treatment box will be collected from the subject and drug accountability/compliance will be assessed.

Site staff will login into IWRS to be allocated a re-supply open-label kit for the subject. The Visit 15 treatment box will be dispensed to the subject.

Review/reminder of the utilization of the epinephrine auto-injector and the Anaphylaxis Emergency Action Plan (Appendix 14.5) as necessary. The expiry date of the auto-injector will be checked and a new auto-injector should be dispensed to the subject, as necessary.

7.2.2.13 Visit 16 (Month 24 ±14 days; First Day of the Month 24 DBPCFC)

Before implementation of Protocol Amendment 5

Visit 16 (Month 24) will take place 12 months ±14 days after Visit 13. Visit 16 corresponds to the first day of the Month 24 DBPCFC. It is recommended that a patch not be applied on that day until all DBPCFC procedures have been completed.

Subjects will undergo the following procedures at this visit:

QoL questionnaire FAQLQ/FAIM forms (Appendix 14.3) will be completed by subjects (when applicable) and parent(s)/guardian(s) before any procedures at this visit are performed. The appropriate QoL questionnaire forms to complete depend upon the age of the subject at the time of Visit 1.

Weight (kg) and height (cm) will be measured.

A physical examination, including a complete skin examination, will be performed before the DBPCFC and can be repeated anytime during the DBPCFC, as judged necessary by the Investigator.

Vital signs (heart rate, systolic and diastolic blood pressure, and respiratory rate) for subjects in a sitting position will be measured before the DBPCFC and can be repeated anytime during the DBPCFC, as judged necessary by the Investigator.

Spirometry and PEF measurements (depending on the subject's age and ability to perform these tests) will be obtained.

SPT to cow's milk will be performed.

Blood samples for hematology and biochemistry laboratory tests, and immunological markers (IgE, IgG4) will be collected.

Only for subjects who signed the genetic ICF/IAF: a blood sample for the analysis of filaggrin mutations may be collected at this visit if not collected at a previous visit.

Only for subjects who signed the genetic ICF/IAF: a blood sample for epigenetic analysis will be collected.

A urine pregnancy test will be performed for female subjects with childbearing potential.

DBPCFC will be performed and the grading of each symptom will be made using the grading definitions in the OFC symptom score sheets (see Appendix 14.2).

Any AEs that have occurred since the previous visit will be documented and any changes in medications reported.

Examination, grading, and photography of the area of the skin used for Viaskin patch application will be performed.

Diary card will be checked and given back to the subject and instructions repeated/reminded, if required.

The Visit 15 treatment box will be collected from the subject and drug accountability/compliance will be assessed.

Site staff will login into IWRS to be allocated a small re-supply open-label kit to cover the period between both days of the DBPCFC. The Visit 16 treatment box will be dispensed to the subject.

Review/reminder of the utilization of the epinephrine auto-injector and the Anaphylaxis Emergency Action Plan (Appendix 14.5), as necessary. The expiry date of the auto-injector will be checked and a new auto-injector should be dispensed to the subject, as necessary.

A minimum duration of 3 hours observation after the last dose of the food challenge formula has been ingested is required at this visit, before the subject is discharged from the site. The observation period can be extended beyond 3 hours if deemed necessary by the Investigator.

After implementation of Protocol Amendment 5

Until the subjects can switch to Viaskin Milk 300 µg, the following will apply:

- The Visit 16 will proceed without the procedures related to the DBPCFC;
- Site staff will login into IWRS to be allocated treatment kits for both Visit 16 and Visit 17;
- Visit 17 will not be conducted.

7.2.2.14 Visit 17 (Second day of the Month 24 DBPCFC) - Not to be conducted after implementation of Protocol Amendment 5

Visit 17 corresponds to the second day of the Month 24 DBPCFC. It is recommended that a patch not be applied on that day until all DBPCFC procedures have been completed.

Visit 17 will take place within 7 days after Visit 16. However, Visit 17 may be scheduled up to a maximum of 14 days after Visit 16 and documented in the eCRF, if either of the following occur: (1) the subject experiences reactions after the DBPCFC at Visit 16 that require more than 7 days to elapse before the next food challenge, or (2) any intercurrent disease preventing the second day of the challenge to be conducted safely as planned; in this specific condition, the timeframe between the 2 days of challenges might exceed 14 days and must be appropriately documented, or (3) the subject's schedule or site logistics prevent the second day of food challenge to be performed within 7 days of the first day.

Subjects will undergo the following procedures at this visit:

A physical examination, including a complete skin examination, will be performed before the DBPCFC and can be repeated anytime during the DBPCFC, as judged necessary by the Investigator.

Vital signs (heart rate, systolic and diastolic blood pressure, and respiratory rate) for subjects in a sitting position will be measured before the DBPCFC and can be repeated anytime during the DBPCFC, as judged necessary by the Investigator.

PEF measurements (depending on the subject's age and ability to perform these tests) will be obtained.

DBPCFC will be performed and the grading of each symptom will be made using the grading definitions in the OFC symptom score sheets (see Appendix 14.2).

Any AEs that have occurred since the previous visit will be documented and any changes in medications reported.

Examination, grading, and photography of the area of the skin used for Viaskin patch application will be performed.

Diary card will be checked and given back to the subject and instructions repeated/reminded, if required.

The Visit 16 treatment box will be collected from the subject and drug accountability/compliance will be assessed.

Review/reminder of the utilization of the epinephrine auto-injector and the Anaphylaxis Emergency Action Plan (Appendix 14.5), as necessary. The expiry date of the auto-injector will be checked and a new auto-injector should be dispensed to the subject, as necessary.

A minimum duration of 3 hours observation after the last dose of the food challenge formula has been ingested is required at this visit, before the subject is discharged from the site. The observation period can be extended beyond 3 hours if deemed necessary by the Investigator.

After completion of the second day of the food challenge ie, after the last dose of the challenge has been administered or the challenge stopped because of (a) clear objective reaction(s) has (have) occurred, the order of the challenge formulas can be unblinded and the results of the challenge will be established as described in Section 7.3.1.1.2 and recorded in the eCRF.

After the second day of the Month 24 DBPCFC, eligible subjects will be proposed to enter the study extension to receive 2 additional years of EPIT with open-label Viaskin Milk 500 µg. Subjects who enter the study extension will undergo the following additional procedures:

Written and signed ICF/IAF to enter study extension will be collected at Visit 17, if not collected previously.

Eligibility criteria to enter study extension will be assessed.

Site staff will login into IWRS to be allocated a re-supply open-label kit for the subject. The Visit 17 treatment box will be dispensed to the subject.

For the subjects who do not enter the study extension, there will be no dispensation of the Investigational Product at this visit. It will be the end of the open-label treatment period. A final EOS follow-up visit will take place 14 days after Visit 17.

7.2.2.15 Visit 18 (Month 30 ±14 days)

For the subjects who enter the study extension, a Visit 18 (Month 30) will take place 18 months ±14 days after Visit 13.

Subjects will undergo the following procedures at this visit:

Weight (kg) and height (cm) will be measured.

A physical examination, including a complete skin examination, will be performed.

Vital signs (heart rate, systolic and diastolic blood pressure, and respiratory rate) for subjects in a sitting position will be measured.

Spirometry and PEF measurements (depending on the subject's age and ability to perform these tests) will be obtained.

SPT to cow's milk will be performed.

Blood samples for hematology and biochemistry laboratory tests, as well as immunological markers (IgE, IgG4) will be collected.

Only for subjects who signed the genetic ICF/IAF: a blood sample for the analysis of filaggrin mutations may be collected at this visit if not collected at a previous visit.

Any AEs that have occurred since the previous visit will be documented and any changes in medications reported.

Examination, grading, and photography of the area of the skin used for Viaskin patch application will be performed.

Diary card will be checked and given back to the subject and instructions repeated/reminded, if required.

The Visit 17 treatment box will be collected from the subject and drug accountability/compliance will be assessed.

Site staff will login into IWRS to be allocated a re-supply open-label kit for the subject. The Visit 18 treatment box will be dispensed to the subject.

Review/reminder of the utilization of the epinephrine auto-injector and the Anaphylaxis Emergency Action Plan (Appendix 14.5) will be provided, as necessary. The expiry date of the auto-injector will be checked and a new auto-injector should be dispensed to the subject, as necessary.

7.2.2.16 Visit 19 (Month 36 ±14 days; First day of the Month 36 DBPCFC)

Before implementation of Protocol Amendment 5

For subjects who entered the study extension, Visit 19 (Month 36) will take place 24 months ±14 days after Visit 13. Visit 19 corresponds to the first day of the Month 36 DBPCFC. It is recommended that a patch not be applied on that day until all DBPCFC procedures have been completed.

Subjects will undergo the following procedures at this visit:

QoL questionnaire FAQLQ/FAIM forms (Appendix 14.3) will be completed by subjects (when applicable) and parent(s)/guardian(s) before any procedures at this visit are performed. The appropriate QoL questionnaire forms to complete depend on the age of the subject at the time of Visit 1.

Weight (kg) and height (cm) will be measured.

A physical examination, including a complete skin examination, will be performed before the DBPCFC and can be repeated anytime during the DBPCFC, as judged necessary by the Investigator.

Vital signs (heart rate, systolic and diastolic blood pressure, and respiratory rate) for subjects in a sitting position will be measured before the DBPCFC and can be repeated anytime during the DBPCFC, as judged necessary by the Investigator.

Spirometry and PEF measurements (depending on the subject's age and ability to perform these tests) will be obtained.

SPT to cow's milk will be performed.

Blood samples for hematology and biochemistry laboratory tests, and immunological markers (IgE, IgG4) will be collected.

Only for subjects who signed the genetic ICF/IAF: a blood sample for the analysis of filaggrin mutations may be collected at this visit if not collected at a previous visit.

Only for subjects who signed the genetic ICF/IAF: a blood sample for epigenetic analysis will be collected.

A urine pregnancy test will be performed for female subjects with childbearing potential.

DBPCFC will be performed and the grading of each symptom will be made using the grading definitions in the OFC symptom score sheets (see Appendix 14.2).

Any AEs that have occurred since the previous visit will be documented and any changes in medications reported.

Examination, grading, and photography of the area of the skin used for Viaskin patch application will be performed.

Diary card will be checked and given back to the subject and instructions repeated/reminded, if required.

The Visit 18 treatment box will be collected from the subject and drug accountability/compliance will be assessed.

Site staff will login into IWRS to be allocated a small re-supply open-label kit to cover the period between both days of the DBPCFC. The Visit 19 treatment box will be dispensed to the subject.

Review/reminder of the utilization of the epinephrine auto-injector and the Anaphylaxis Emergency Action Plan (Appendix 14.5), as necessary. The expiry date of the auto-injector will be checked and a new auto-injector should be dispensed to the subject, as necessary.

A minimum duration of 3 hours observation after the last dose of the food challenge formula has been ingested is required at this visit, before the subject is discharged from the site. The observation period may be extended beyond 3 hours if deemed necessary by the Investigator.

After implementation of Protocol Amendment 5

Until the subjects can switch to Viaskin Milk 300 µg, the following will apply:

- The Visit 19 will proceed without the procedures related to the DBPCFC;
- Site staff will login into IWRS to be allocated treatment kits for both Visit 19 and Visit 20;
- Visit 20 will not be conducted.

7.2.2.17 Visit 20 (Second day of the Month 36 DBPCFC) - Not to be conducted after implementation of Protocol Amendment 5

Visit 20 corresponds to the second day of the Month 36 DBPCFC. It is recommended that a patch not be applied on that day until all DBPCFC procedures have been completed.

For subjects who entered the study extension, Visit 20 will take place within 7 days after Visit 19. However, Visit 20 may be scheduled up to a maximum of 14 days after Visit 19 and documented in the eCRF, if either of the following occurs: (1) the subject experiences reactions after the DBPCFC at Visit 19 that require more than 7 days to

elapse before the next food challenge, or (2) any intercurrent disease preventing the second day of the challenge to be conducted safely as planned; in this specific condition, the timeframe between the 2 days of challenges might exceed 14 days and must be appropriately documented, or (3) the subject's schedule or site logistics prevent the second day of food challenge to be performed within 7 days of the first day.

Subjects will undergo the following procedures at this visit:

A physical examination, including a complete skin examination, will be performed before the DBPCFC and can be repeated anytime during the DBPCFC, as judged necessary by the Investigator.

Vital signs (heart rate, systolic and diastolic blood pressure, and respiratory rate) for subjects in a sitting position will be measured before the DBPCFC and can be repeated anytime during the DBPCFC, as judged necessary by the Investigator.

PEF measurements (depending on the subject's age and ability to perform these tests) will be obtained.

DBPCFC will be performed and the grading of each symptom will be made using the grading definitions in the OFC symptom score sheets (see Appendix 14.2).

Any AEs that have occurred since the previous visit will be documented and any changes in medications reported.

Examination, grading, and photography of the area of the skin used for Viaskin patch application will be performed.

Diary card will be checked and given back to the subject and instructions repeated/reminded, if required.

The Visit 19 treatment box will be collected from the subject and drug accountability/compliance will be assessed.

Site staff will login into IWRS to be allocated a re-supply open-label kit for the subject. The Visit 20 treatment box will be dispensed to the subject.

Review/reminder of the utilization of the epinephrine auto-injector and the Anaphylaxis Emergency Action Plan (Appendix 14.5), as necessary. The expiry date of the auto-injector will be checked and a new auto-injector should be dispensed to the subject, as necessary.

A minimum duration of 3 hours observation after the last dose of the food challenge formula has been ingested is required at this visit, before the subject is discharged from the site. The observation period may be extended beyond 3 hours if deemed necessary by the Investigator.

After completion of the second day of the food challenge ie, after the last dose of the challenge has been administered or the challenge stopped because of (a) clear objective reaction(s) has (have) occurred, the order of the challenge formulas can be unblinded and the results of the challenge will be established as described in Section 7.3.1.1.2 and recorded in the eCRF.

7.2.2.18 Visit 21 (Month 42 ±14 days)

For subjects who entered the study extension, Visit 21 (Month 42) will take place 30 months ±14 days after Visit 13.

Subjects will undergo the following procedures at this visit:

Weight (kg) and height (cm) will be measured.

A physical examination, including a complete skin examination, will be performed.

Vital signs (heart rate, systolic and diastolic blood pressure, and respiratory rate) for subjects in a sitting position will be measured.

Spirometry and PEF measurements (depending on the subject's age and ability to perform these tests) will be obtained.

SPT to cow's milk will be performed.

Blood samples for hematology and biochemistry laboratory tests, as well as immunological markers (IgE, IgG4) will be collected.

Only for subjects who signed the genetic ICF/IAF: a blood sample for the analysis of filaggrin mutations may be collected at this visit if not collected at a previous visit.

Any AEs that have occurred since the previous visit will be documented and any changes in medications reported.

Examination, grading, and photography of the area of the skin used for Viaskin patch application will be performed.

Diary card will be checked and given back to the subject and instructions repeated/reminded, if required.

The Visit 20 treatment box will be collected from the subject and drug accountability/compliance will be assessed.

Site staff will login into IWRS to be allocated a re-supply open-label kit for the subject. The Visit 21 treatment box will be dispensed to the subject.

Review/reminder of the utilization of the epinephrine auto-injector and the Anaphylaxis Emergency Action Plan (Appendix 14.5) as necessary. The expiry date of the auto-injector will be checked and a new auto-injector should be dispensed to the subject, as necessary.

7.2.2.19 Visit 22 (Month 48 ±14 days; First day of the Month 48 DBPCFC)

Before implementation of Protocol Amendment 5

For subjects who entered the study extension, Visit 22 (Month 48) will take place 36 months ±14 days after Visit 13. Visit 22 corresponds to the first day of the Month 48 DBPCFC. It is recommended not to apply a patch on that day until all DBPCFC procedures have been completed.

Subjects will undergo the following procedures at this visit:

QoL questionnaire FAQLQ/FAIM forms (Appendix 14.3) will be completed by subjects (when applicable) and parent(s)/guardian(s) before any procedures at this visit are performed. The appropriate QoL questionnaire forms to complete depend upon the age of the subject at the time of Visit 1.

Weight (kg) and height (cm) will be measured.

A physical examination, including a complete skin examination, will be performed before the DBPCFC and can be repeated anytime during the DBPCFC, as judged necessary by the Investigator.

Vital signs (heart rate, systolic and diastolic blood pressure, and respiratory rate) for subjects in a sitting position will be measured before the DBPCFC and can be repeated anytime during the DBPCFC, as judged necessary by the Investigator.

Spirometry and PEF measurements (depending on the subject's age and ability to perform these tests) will be obtained.

SPT to cow's milk will be performed.

Blood samples for hematology and biochemistry laboratory tests, and immunological markers (IgE, IgG4) will be collected.

Only for subjects who signed the genetic ICF/IAF: a blood sample for the analysis of filaggrin mutations may be collected at this visit if not collected at a previous visit.

Only for subjects who signed the genetic ICF/IAF: a blood sample for epigenetic analysis will be collected.

A urine pregnancy test will be performed for female subjects with childbearing potential.

DBPCFC will be performed and the grading of each symptom will be made using the grading definitions in the OFC symptom score sheets (see Appendix 14.2).

Any AEs that have occurred since the previous visit will be documented and any changes in medications reported.

Examination, grading, and photography of the area of the skin used for Viaskin patch application will be performed.

Diary card will be checked and given back to the subject and instructions repeated/reminded, if required.

The Visit 21 treatment box will be collected from the subject and drug accountability/compliance will be assessed.

Site staff will login into IWRS to be allocated a small re-supply open-label kit to cover the period between both days of the DBPCFC. The Visit 22 treatment box will be dispensed to the subject.

Review/reminder of the utilization of the epinephrine auto-injector and the Anaphylaxis Emergency Action Plan (Appendix 14.5), as necessary. The expiry date of the auto-injector will be checked and a new auto-injector should be dispensed to the subject, as necessary.

A minimum duration of 3 hours observation after the last dose of the food challenge formula has been ingested is required at this visit, before the subject is discharged from the site. The observation period may be extended beyond 3 hours if deemed necessary by the Investigator.

After implementation of Protocol Amendment 5

Until the subjects can switch to Viaskin Milk 300 µg, the following will apply:

- The Visit 22 will proceed without the procedures related to the DBPCFC;
- Visit 23 will not be conducted.

7.2.2.20 Visit 23 (Second day of the Month 48 DBPCFC) - Not to be conducted after implementation of Protocol Amendment 5

Visit 23 corresponds to the second day of the Month 48 DBPCFC. It is recommended that a patch not be applied on that day as it will be the end of the open-label treatment period.

For subjects who entered the study extension, Visit 23 will take place within 7 days after Visit 22. However, Visit 23 may be scheduled up to a maximum of 14 days after Visit 22 and documented in the eCRF, if either of the following occur: (1) the subject experiences reactions after the DBPCFC at Visit 22 that require more than 7 days to elapse before the next food challenge, or (2) any intercurrent disease preventing the second day of the challenge to be conducted safely as planned; in this specific condition, the timeframe between the 2 days of challenges might exceed 14 days and must be appropriately documented, or (3) the subject's schedule or site logistics prevent the second day of food challenge to be performed within 7 days of the first day.

Subjects will undergo the following procedures at this visit:

A physical examination, including a complete skin examination, will be performed before the DBPCFC and can be repeated anytime during the DBPCFC, as judged necessary by the Investigator.

Vital signs (heart rate, systolic and diastolic blood pressure, and respiratory rate) for subjects in a sitting position will be measured before the DBPCFC and can be repeated anytime during the DBPCFC, as judged necessary by the Investigator.

PEF measurements (depending on the subject's age and ability to perform these tests) will be obtained.

DBPCFC will be performed and the grading of each symptom will be made using the grading definitions in the OFC symptom score sheets (see Appendix 14.2).

Any AEs that have occurred since the previous visit will be documented and any changes in medications reported.

Examination, grading, and photography of the area of the skin used for Viaskin patch application will be performed.

Diary card will be checked and given back to the subject and instructions repeated/reminded, if required.

The Visit 22 treatment box will be collected from the subject and drug accountability/compliance will be assessed.

Review/reminder of the utilization of the epinephrine auto-injector and the Anaphylaxis Emergency Action Plan (Appendix 14.5), as necessary. The expiry date of the auto-injector will be checked and a new auto-injector should be dispensed to the subject, as necessary.

A minimum duration of 3 hours observation after the last dose of the food challenge formula has been ingested is required at this visit, before the subject is discharged from the site. The observation period may be extended beyond 3 hours if deemed necessary by the Investigator.

After completion of the second day of the food challenge ie, after the last dose of the challenge has been administered or the challenge stopped because of (a) clear objective reaction(s) has (have) occurred, the order of the challenge formulas can be unblinded and the results of the challenge will be established as described in Section 7.3.1.1.2 and recorded in the eCRF.

All ongoing subjects will terminate the study at Month 48. There will be no dispensation of the Investigational product at this visit since it will be the end of the open-label treatment period for subjects who entered the study extension. A final EOS follow-up visit will take place 14 days after Visit 23.

7.2.2.21 Additional Phone Contacts

In addition to the regular study visits at site, the study personnel will contact the subjects/subjects' guardians or parents by telephone to inquire about AEs, especially skin-related symptoms, and concomitant treatments if any.

- Individual phone contacts (PCs) are designated "PC" followed by the number of the most recent clinic visit (e.g., "9"), followed by the letter "a" for the first phone call after that clinic visit, "b" for the next phone call after that same clinic visit, and so forth). During the first year of treatment, 7 PCs are scheduled at: Month 2 (PC8a)
- Month 4 (PC9a)
- Month 5 (PC9b)
- Month 7 (PC10a)
- Month 8 (PC10b)
- Month 10 (PC11a)
- Month 11 (PC11b).

The dates of these PCs during the first year of treatment will be calculated from the date of Visit 4 (Day 1), with a permitted window of ± 7 days.

During the second year of treatment, 4 additional phone contacts (PCs) are scheduled at:

- Month 14 (PC14a)
- Month 16 (PC14b)
- Month 20 (PC15a)
- Month 22 (PC15b).

The dates of these PCs during the second year of treatment will be calculated from the date of Visit 13 (start date of the open-label treatment period), with a permitted window of ± 7 days.

For the subjects who enter in the study extension, 4 additional phone contacts (PCs) are scheduled at:

- Month 27 (PC17a)
- Month 33 (PC18a)
- Month 39 (PC20a)
- Month 45 (PC21a)

The dates of these PCs during the third and fourth year of treatment will be calculated from the date of Visit 13 (start date of the open-label treatment period), with a permitted window of ±14 days.

7.2.3 Open-label treatment with Viaskin Milk 300 µg

The following study flowchart will apply after the implementation of Protocol Amendment 5 and the subjects can switch to Viaskin Milk 300 µg.

For the subjects not consenting to switch to Viaskin Milk 300 µg, the following procedures should be performed:

- EOS visit procedures (Table 3) if the subject has reached Month 24 of open-label treatment with Viaskin Milk 500 µg,
- ET visit procedures (Table 4 or Table 5) in all other cases.

For the eligible subjects consenting to switch to Viaskin Milk 300 µg, the visit schedule and procedures are described in the sections below. Visit timepoints are in reference to the switch to Viaskin Milk 300 µg (e.g. “Month 6” should be understood as “Month 6 following the switch to Viaskin Milk 300 µg”).

7.2.3.1 Visit S1 (Day 1)

The subject should be contacted to schedule Visit S1 (Day 1).

Signed written ICF/IAF for the switch to Viaskin Milk 300 µg will be obtained before any assessments are made.

QoL questionnaire FAQLQ/FAIM forms (Appendix 14.3) will be completed by subjects (when applicable) and parent(s)/guardian(s) before any procedures at this visit are performed. The appropriate QoL questionnaire forms to complete depend upon the age of the subject at the time of Visit 1.

Site staff will login into IWRS to be allocated open-label 300 µg kits for the subject. Visit S1 treatment boxes will be dispensed to the subject. The treatment box of the previous visit will be collected from the subject and drug accountability/compliance will be assessed.

A physical examination, including a complete skin examination, will be performed.

Vital signs (heart rate, systolic and diastolic blood pressure, and respiratory rate) for subjects in a sitting position will be measured.

Spirometry and PEF measurements (depending on the subject’s age and ability to perform these tests) will be obtained.

SPT to cow’s milk will be performed.

Blood samples for hematology, biochemistry laboratory tests, and immunological markers (IgE, IgG4) will be collected, unless already done within 1 month. In this case, the results of the previous visit may be used for Day 1.

Any AEs that have occurred since the previous visit will be documented and any changes in medications reported.

Examination, grading, and photography of the area of the skin used for Viaskin patch application will be performed.

Diary card will be dispensed to the subject and instructions will be given for completion.

Epinephrine auto-injector and the Anaphylaxis Emergency Action Plan (Appendix 14.5) will be dispensed and/or their utilization reviewed, as necessary. The expiry date of the auto-injector will be checked and a new auto-injector should be dispensed to the subject, as necessary.

Only for subjects who signed the genetic ICF/IAF: a blood sample for epigenetic analysis will be collected.

A urine pregnancy test will be performed for female subjects with childbearing potential.

7.2.3.2 Visit S2 (Month 6 ±14 days)

Visit S2 (Month 6) will take place 6 months ±14 days after Visit S1 (Day 1).

QoL questionnaire FAQLQ/FAIM forms (Appendix 14.3) will be completed by subjects (when applicable) and parent(s)/guardian(s) before any procedures at this visit are performed. The appropriate QoL questionnaire forms to complete depend upon the age of the subject at the time of Visit 1.

Weight (kg) and height (cm) will be measured.

A physical examination, including a complete skin examination, will be performed.

Vital signs (heart rate, systolic and diastolic blood pressure, and respiratory rate) for subjects in a sitting position will be measured.

Spirometry and PEF measurements (depending on the subject's age and ability to perform these tests) will be obtained.

SPT to cow's milk will be performed.

Blood samples for hematology, biochemistry laboratory tests, and immunological markers (IgE, IgG4) will be collected.

Any AEs that have occurred since the previous visit will be documented and any changes in medications reported.

Examination, grading, and photography of the area of the skin used for Viaskin patch application will be performed.

Diary card will be checked and given back to the subject and instructions repeated/reminded, if required.

The Visit S1 treatment boxes will be collected from the subject and drug accountability/compliance will be assessed.

Site staff will login into IWRS to be allocated to be allocated open-label 300 µg kits for the subject. The Visit S2 treatment boxes will be dispensed to the subject.

Review/reminder of the utilization of the epinephrine auto-injector and the Anaphylaxis Emergency Action Plan (Appendix 14.5), as necessary. The expiry date of the auto-injector will be checked and a new auto-injector should be dispensed to the subject, as necessary.

A urine pregnancy test will be performed for female subjects with childbearing potential.

7.2.3.3 Visit S3 (Month 12 ±14 days; First Day of the optional Month 12 DBPCFC)

Visit S3 (Month 12) will take place 12 months ±14 days after Visit S1 (Day 1), for all subjects. Visit S3 corresponds to the first day of the optional Month 12 DBPCFC. Performing Month 12 DBPCFC is optional. If a subject experienced a severe anaphylaxis to cow's milk during the MILES study, whether or not occurring during the DBPCFC, no further DBPCFC should be conducted for this subject.

If the subject decides to perform the DBPCFC, no patch should be applied on that day until all DBPCFC procedures have been completed.

QoL questionnaire FAQLQ/FAIM forms (Appendix 14.3) will be completed by the subject (when applicable) and parent(s)/guardian(s) before any procedures at this visit are performed. The appropriate QoL questionnaire forms to complete depend on the age of the subject at the time of Visit 1.

Weight (kg) and height (cm) will be measured.

A physical examination including a complete skin examination will be performed.

Vital signs (heart rate, systolic and diastolic blood pressure, and respiratory rate) for subjects in a sitting position will be measured.

Spirometry and PEF measurements (depending on the subject's age and ability to perform these tests) will be obtained.

SPT to cow's milk will be performed.

Blood samples for hematology, biochemistry laboratory tests, and immunological markers (IgE, IgG4) will be collected.

Only for subjects who signed the genetic ICF/IAF: a blood sample for epigenetic analysis will be collected.

A urine pregnancy test will be performed for female subjects with childbearing potential.

Any AEs that have occurred since the previous visit will be documented and any changes in medications reported.

Examination, grading, and photography of the area of the skin used for Viaskin patch application will be performed.

Diary card will be checked and given back to the subject and instructions repeated/reminded, if required.

The Visit S2 treatment boxes will be collected from the subject and drug accountability/compliance will be assessed. Site staff will login into IWRS to be allocated open-label 300 µg kits for the subject. The Visit S3 treatment boxes will be dispensed to the subject.

Review/reminder of the utilization of the epinephrine auto-injector and the Anaphylaxis Emergency Action Plan (Appendix 14.5) as necessary. The expiry date of the auto-injector will be checked and a new auto-injector should be dispensed to the subject, as necessary.

Only for subjects performing the DBPCFC: the grading of each symptom will be made using the grading definitions in the OFC symptom score sheets (see Appendix 14.2). Physical examination and vital signs measurements can be repeated anytime during the DBPCFC, as judged necessary by the Investigator.

AEs occurring during the DBPCFC should be collected.

A minimum duration of 3 hours observation after the last dose of the food challenge formula has been ingested is required at this visit, before the subject is discharged from the site. The observation period can be extended beyond 3 hours if deemed necessary by the Investigator.

7.2.3.4 Visit S4 (Second day of the optional Month 12 DBPCFC; only for subjects who performed the first day of the DBPCFC)

Visit S4 will be performed only for subjects who performed the first day of the Month 12 DBPCFC. This visit corresponds to the second day of the Month 12 DBPCFC. No

patch should be applied on that day until all DBPCFC procedures have been completed.

Visit S4 will take place within 7 days after Visit S3. However, Visit S4 may be scheduled up to a maximum of 14 days after Visit S3 and documented in the eCRF, if either of the following occur: (1) the subject experiences reactions after the DBPCFC at Visit S3 that require more than 7 days to elapse before the next food challenge, or (2) any intercurrent disease preventing the second day of the challenge to be conducted safely as planned; in this specific condition, the timeframe between the 2 days of challenges might exceed 14 days and must be appropriately documented, or (3) the subject's schedule or site logistics prevent the second day of food challenge to be performed within 7 days of the first day.

A physical examination, including a complete skin examination, will be performed before the DBPCFC and can be repeated anytime during the DBPCFC, as judged necessary by the Investigator.

Vital signs (heart rate, systolic and diastolic blood pressure, and respiratory rate) for subjects in a sitting position will be measured before the DBPCFC and can be repeated anytime during the DBPCFC, as judged necessary by the Investigator.

PEF measurements (depending on the subject's age and ability to perform these tests) will be obtained.

A urine pregnancy test will be performed for female subjects with childbearing potential.

DBPCFC will be performed and the grading of each symptom will be made using the grading definitions in the OFC symptom score sheets (see Appendix 14.2).

Any AEs that have occurred since the previous visit will be documented and any changes in medications reported.

Examination, grading, and photography of the area of the skin used for Viaskin patch application will be performed.

Diary card will be checked and given back to the subject and instructions repeated/reminded, if required.

Review/reminder of the utilization of the epinephrine auto-injector and the Anaphylaxis Emergency Action Plan (Appendix 14.5), as necessary. The expiry date of the auto-injector will be checked and a new auto-injector should be dispensed to the subject, as necessary.

A minimum duration of 3 hours observation after the last dose of the food challenge formula has been ingested is required at this visit, before the subject is discharged from the site. The observation period can be extended beyond 3 hours if deemed necessary by the Investigator.

After completion of the second day of the food challenge ie, after the last dose of the challenge has been administered or the challenge stopped because of (a) clear objective reaction(s) has (have) occurred, the order of the challenge formulas can be unblinded and the results of the challenge will be established as described in Section 7.3.1.1.2 and recorded in the eCRF.

7.2.3.5 Visit S5 (Month 18 ±14 days)

Visit S5 (Month 18) will take place 18 months ±14 days after Visit S1.

QoL questionnaire FAQLQ/FAIM forms (Appendix 14.3) will be completed by the subject (when applicable) and parent(s)/guardian(s) before any procedures at this visit are performed. The appropriate QoL questionnaire forms to complete depend on the age of the subject at the time of Visit 1.

Weight (kg) and height (cm) will be measured.

A physical examination, including a complete skin examination, will be performed.

Vital signs (heart rate, systolic and diastolic blood pressure, and respiratory rate) for subjects in a sitting position will be measured.

Spirometry and PEF measurements (depending on the subject's age and ability to perform these tests) will be obtained.

SPT to cow's milk will be performed.

Blood samples for hematology and biochemistry laboratory tests, as well as immunological markers (IgE, IgG4) will be collected.

Any AEs that have occurred since the previous visit will be documented and any changes in medications reported.

Examination, grading, and photography of the area of the skin used for Viaskin patch application will be performed.

Diary card will be checked and given back to the subject and instructions repeated/reminded, if required.

The Visit S3 treatment boxes will be collected from the subject and drug accountability/compliance will be assessed.

Site staff will login into IWRS to be allocated open-label 300 µg kits for the subject. The Visit S5 treatment boxes will be dispensed to the subject.

Review/reminder of the utilization of the epinephrine auto-injector and the Anaphylaxis Emergency Action Plan (Appendix 14.5) as necessary. The expiry date of the auto-injector will be checked and a new auto-injector should be dispensed to the subject, as necessary.

A urine pregnancy test will be performed for female subjects with childbearing potential.

7.2.3.6 Visit S6 (Month 24 ±14 days; First Day of the optional Month 24 DBPCFC)

Visit S6 (Month 24) will take place 24 months ±14 days after Visit S1. Visit S6 corresponds to the first day of the optional Month 24 DBPCFC. It is optional to perform Month 24 DBPCFC. If a subject experienced a severe anaphylaxis to cow's milk during the MILES study, whether or not occurring during the DBPCFC, no further DBPCFC should be conducted for this subject.

If the subject decides to perform the DBPCFC, no patch should be applied on that day until all DBPCFC procedures have been completed.

QoL questionnaire FAQLQ/FAIM forms (Appendix 14.3) will be completed by subjects (when applicable) and parent(s)/guardian(s) before any procedures at this visit are performed. The appropriate QoL questionnaire forms to complete depend upon the age of the subject at the time of Visit 1.

Weight (kg) and height (cm) will be measured.

A physical examination, including a complete skin examination, will be performed.

Vital signs (heart rate, systolic and diastolic blood pressure, and respiratory rate) for subjects in a sitting position will be measured.

Spirometry and PEF measurements (depending on the subject's age and ability to perform these tests) will be obtained.

SPT to cow's milk will be performed.

Blood samples for hematology and biochemistry laboratory tests, and immunological markers (IgE, IgG4) will be collected.

Only for subjects who signed the genetic ICF/IAF: a blood sample for epigenetic analysis will be collected.

A urine pregnancy test will be performed for female subjects with childbearing potential.

Any AEs that have occurred since the previous visit will be documented and any changes in medications reported.

Examination, grading, and photography of the area of the skin used for Viaskin patch application will be performed.

Diary card will be checked and given back to the subject and instructions repeated/reminded, if required.

Review/reminder of the utilization of the epinephrine auto-injector and the Anaphylaxis Emergency Action Plan (Appendix 14.5), as necessary. The expiry date of the auto-injector will be checked and a new auto-injector should be dispensed to the subject, as necessary.

There will be no dispensation of the Investigational product at this visit.

Only for subjects performing the DBPCFC: the grading of each symptom will be made using the grading definitions in the OFC symptom score sheets (see Appendix 14.2). Physical examination and vital signs measurements can be repeated anytime during the DBPCFC, as judged necessary by the Investigator.

AEs occurring during the DBPCFC should be collected.

A minimum duration of 3 hours observation after the last dose of the food challenge formula has been ingested is required at this visit, before the subject is discharged from the site. The observation period can be extended beyond 3 hours if deemed necessary by the Investigator.

Only for subjects not performing the DBPCFC: The Visit S5 treatment boxes will be collected from the subject and drug accountability/compliance will be assessed.

7.2.3.7 Visit S7 (Second day of the optional Month 24 DBPCFC; only for subjects who performed the first day of the DBPCFC)

Visit S7 corresponds to the second day of the Month 24 DBPCFC. This visit will be performed only for subjects performed the first day of the DBPCFC. No patch should be applied on that day until all DBPCFC procedures have been completed.

Visit S7 will take place within 7 days after Visit S6. However, Visit S7 may be scheduled up to a maximum of 14 days after Visit S6 and documented in the eCRF, if either of the following occur: (1) the subject experiences reactions after the DBPCFC at Visit S6 that require more than 7 days to elapse before the next food challenge, or (2) any intercurrent disease preventing the second day of the challenge to be conducted

safely as planned; in this specific condition, the timeframe between the 2 days of challenges might exceed 14 days and must be appropriately documented, or (3) the subject's schedule or site logistics prevent the second day of food challenge to be performed within 7 days of the first day.

A physical examination, including a complete skin examination, will be performed before the DBPCFC and can be repeated anytime during the DBPCFC, as judged necessary by the Investigator.

Vital signs (heart rate, systolic and diastolic blood pressure, and respiratory rate) for subjects in a sitting position will be measured before the DBPCFC and can be repeated anytime during the DBPCFC, as judged necessary by the Investigator.

PEF measurements (depending on the subject's age and ability to perform these tests) will be obtained.

A urine pregnancy test will be performed for female subjects with childbearing potential.

DBPCFC will be performed and the grading of each symptom will be made using the grading definitions in the OFC symptom score sheets (see Appendix 14.2).

Any AEs that have occurred since the previous visit will be documented and any changes in medications reported.

Examination, grading, and photography of the area of the skin used for Viaskin patch application will be performed.

Diary card will be checked and given back to the subject and instructions repeated/reminded, if required.

The Visit S5 treatment boxes will be collected from the subject and drug accountability/compliance will be assessed.

Review/reminder of the utilization of the epinephrine auto-injector and the Anaphylaxis Emergency Action Plan (Appendix 14.5), as necessary. The expiry date of the auto-injector will be checked and a new auto-injector should be dispensed to the subject, as necessary.

A minimum duration of 3 hours observation after the last dose of the food challenge formula has been ingested is required at this visit, before the subject is discharged from the site. The observation period can be extended beyond 3 hours if deemed necessary by the Investigator.

After completion of the second day of the food challenge ie, after the last dose of the challenge has been administered or the challenge stopped because of (a) clear objective reaction(s) has (have) occurred, the order of the challenge formulas can be unblinded and the results of the challenge will be established as described in Section 7.3.1.1.2 and recorded in the eCRF.

There will be no dispensation of the Investigational product at this visit since it will be the end of the treatment period. A final EOS follow-up visit will take place 14 days after Visit S7.

7.2.3.8 Additional Phone Contacts

In addition to the regular study visits at site, the study personnel will contact the subjects/subjects' guardians or parents by telephone to inquire about AEs, especially skin-related symptoms, and concomitant treatments if any.

During the first year of treatment with Viaskin Milk 300 µg, 3 PCs are scheduled at Month 1, Month 4 and Month 9, with a permitted window of ± 14 days.

During the second year of treatment with Viaskin Milk 300 µg, 2 PCs are scheduled at Month 15 and Month 21, with a permitted window of ± 14 days.

7.2.4 End-of-Study Follow Up Visit

All subjects will have an EOS follow-up visit when they terminate their participation in the study.

For subjects who complete the study at Month 24 of the open-label treatment period with Viaskin Milk 500 µg, the EOS visit will take place 14 days ±3 days after Visit 17 or after Visit 16 if the DBPCFC is not performed according to Protocol Amendment 5.

For subjects who will switch to Viaskin Milk 300 µg, this EOS follow-up visit will take place:

- If the subject did not perform the DBPCFC at Visit S6: 14 days ±3 days after Visit S6;
- If the subject performed the DBPCFC at Visit S6: 14 days ±3 days after the last day of the DBPCFC.

The site staff must go into IWRS to register the subject for completion.

A physical examination, including a complete skin examination, will be performed.

Vital signs (heart rate, systolic and diastolic blood pressure, and respiratory rate) for subjects in a sitting position will be measured.

PEF measurements (depending on the subject's age and ability to perform these tests) will be obtained.

Any AEs that have occurred since the previous visit will be documented and any changes in medications reported.

Examination, grading, and photography of the area of the skin used for Viaskin patch application will be performed.

Diary card will be collected.

An EOS survey will be completed by the Investigator.

7.2.5 Early Termination Visit

The early termination visit is applicable for subjects withdrawing from the study prematurely. The site staff must go into IWRS to register the subject for early withdrawal.

The following data will be collected from subjects who are withdrawn before completing the study:

QoL questionnaire FAQLQ/FAIM forms (Appendix 14.3) will be completed by the subject (when applicable) and parent(s)/guardian(s) before any procedures at this visit are performed. The appropriate QoL questionnaire forms to complete depend on the age of the subject at the time of Visit 1.

A physical examination, including a complete skin examination, will be performed.

Vital signs (heart rate, systolic and diastolic blood pressure, and respiratory rate) for subjects in a sitting position will be measured.

Spirometry and PEF measurements (depending on the subject's age and ability to perform these tests) will be obtained.

SPT to cow's milk will be performed.

Blood samples for hematology and biochemistry laboratory tests, as well as immunological markers (IgE, IgG4) will be collected.

A urine pregnancy test will be performed for female subjects with childbearing potential.

Any AEs that have occurred since the previous visit will be documented and any changes in medications reported.

Examination, grading, and photography of the area of the skin used for Viaskin patch application will be performed.

Diary card will be collected.

The treatment box from the previous visit is collected from the subject (when applicable) and drug accountability/compliance will be assessed.

An EOS survey will be completed by the Investigator.

7.3 Efficacy and Safety Variables

The timepoints of the planned study assessments are summarized in the Schedule of Assessments (Table 2 to Table 7).

7.3.1 Efficacy Assessments

Efficacy assessments will include the following variables:

- Cumulative Reactive Dose (CRD) of cow's milk proteins during the DBPCFC
- Serum immunology: Levels of sIgE and allergen-specific IgE to cow's milk, caseins, α-lactalbumin, and β-lactoglobulin, levels of specific IgG4 to total cow's milk (not applicable after the switch to Viaskin Milk 300 µg), to caseins, α-lactalbumin, and β-lactoglobulin.
- Severity of symptoms elicited during the milk DBPCFC
- SPT to cow's milk
- QoL assessments

7.3.1.1 Double-Blind Placebo-Controlled Food Challenge to Cow's Milk (DBPCFC)

A detailed Manual of Procedures for the preparation of the challenge formulas and for the conduct of the DBPCFC will be provided to the Investigators and their medical teams as well as to the site personnel that will be dedicated for the preparation of the challenge formulas. This could be dieticians, study nurses, pharmacists, pharmacy technicians, licensed medical assistants, or any other qualified site personnel, as delegated by the Investigator; only the site personnel dedicated to the preparation of the challenge formulas will be unblinded to the order of the formulas administered on the 2 days of the DBPCFCs. An outline of the procedures is specified in this section and the grading of each symptom will be made using the grading definition of the OFC symptom score sheets provided in Appendix 14.2.

The DBPCFC is the gold standard to diagnose and assess food allergy. The subject will be gradually fed with increasing amounts of cow's milk proteins under medical observation. The challenge occurs over two days and must take place under direct medical supervision in a hospital/clinic setting with resuscitation equipment and emergency medications and staff immediately available. It is recommended to have an intravenous (i.v.) line in place prior to challenging the subjects; however, the final decision not to place this i.v. line can be made on a case-by-case basis at the discretion of the Investigator. A local anesthetic cream can be used for establishing this i.v. line, especially for children. If a site prefers to have the subjects come to the hospital the day before the conduct of the DBPCFC, to prepare them for the following day, this is allowed and will not be considered an SAE.

Subjects must be off antihistamines 1 to 7 days (depending of the half-life, see Appendix 14.7) prior to any DBPCFC. Subjects will not be allowed to use long-acting β_2 agonists (eg, formoterol) within 36 hours prior to any DBPCFC. Subjects who received more than a 3-day course of systemic corticosteroids within 4 weeks of a DBPCFC should have the DBPCFC rescheduled to allow for 4 weeks of corticosteroids wash-out. For subjects who require more than 1 day of systemic corticosteroids to treat reactions that occurred during the first day of the DBPCFC, the second day of the DBPCFC can be conducted only from the fourth day onwards.

A DBPCFC will be performed at screening (Visits 2 and 3), at Month 12 (Visits 12 and 13); a DBPCFC was planned at Month 24 (Visits 16 and 17) and for subjects who entered the study extension, at Month 36 (Visits 19 and 20) and Month 48 (Visits 22 and 23), but these food challenges should no longer be performed while the subjects are still receiving Viaskin Milk 500 µg. A DBPCFC can be performed after 12 months (Visits S3 and S4) and/or 24 months (Visits S6 and S7) of treatment with Viaskin Milk 300 µg, at the decision of the Investigator and the subject.

No DBPCFC will be performed while the subjects are still receiving Viaskin Milk 500 µg and until they reach 12 months of treatment with Viaskin Milk 300 µg.

Each DBPCFC will comprise 2 visits: 1 visit for the Placebo Challenge and 1 visit for the Milk Challenge. The order of the 2 formulas is not known to the medical team until the end of the second day of the challenge. The second day of the food challenge should take place within 7 days (one week) after the first day of the food challenge. However, the second day may be scheduled up to a maximum of 14 days after the first food challenge and documented in the eCRF, if any of the following occurs: (1) the subject experiences reactions after the DBPCFC on the first day that require more than 7 days to elapse before the next food challenge, or (2) any intercurrent disease preventing the second day of the challenge to be conducted safely as planned, such as a rhinitis, bronchitis or gastrointestinal infection; in this specific condition and for safety reasons, the timeframe between the 2 days of challenges might exceed 14 days and must be appropriately documented, or (3) the subject's schedule or site logistics prevent the second day of food challenge to be performed within 7 days of the first day.

The order of the food challenge (milk or placebo) will be blinded; it will be determined using a randomization table that will be distributed to site personnel dedicated to the preparation of the challenge formulas (see Section 8.4). After both days of a DBPCFC have been completed, the order of the food challenge (ie, actual visits that the milk and placebo challenges were administered) can be revealed for completion of the eCRF.

The subject should have a light breakfast and may drink water at home at least 2 hours before starting the DBPCFC at the site. During the conduct of the challenge no other food (except for the food challenge formula) should be consumed by the subject. Water should also ideally not be consumed, but limited amount of water will be tolerated

during the challenge. After the last dose of the food challenge, the subject should wait at least 1 hour before ingesting any other food and/or drinking large volumes of water. The contents of the first meal after the food challenge should be light.

All DBPCFCs will consist of administering cow's milk proteins (or placebo) in gradually increasing doses at 20-minute intervals. The Investigator may use clinical judgment to increase the intervals between doses in case there is a suspicion that an objective reaction may be developing (see Section 7.3.1.1.3).

Before implementation of Protocol Amendment 5, DBPCFCs to milk and to other allergens were strictly forbidden. After implementation of Protocol Amendment 5, DBPCFCs to milk (including baked milk, and outside of the one described in this protocol) will still be strictly forbidden as long as the subject is part of the study but performing DBPCFCs to any other food for the subject's medical management will be permitted. Whether the subject's medical condition is still compatible with their participation in the study should be assessed by the Investigator and the Sponsor's medical monitor before the food challenge is performed. If not compatible, the Sponsor may decide to discontinue the subject from the study. Note that the initiation of other immunotherapy treatment remains prohibited during the participation of the subject in the MILES study (refer to Section 6.5.2). **Viaskin Milk patches should not be applied on the day of a food challenge and until all procedures are completed**. Information on food challenges to other allergens than cow's milk will also be recorded in the eCRF.

7.3.1.1.1 DBPCFC at Screening (Visits 2 and 3)

During the screening DBPCFC, the doses of cow's milk proteins to be ingested will be 1 mg, 3 mg, 10 mg, 30 mg, 100 mg, and 300 mg administered at 20-minute intervals. The Investigator may use clinical judgment to increase the intervals between doses in case there is a suspicion that an objective reaction may be developing (see Section 7.3.1.1.3). Very occasionally, the Investigator may use clinical judgment to repeat the same dose (but only once) before administration of the next higher dose and only if there is a suspicion that an objective reaction may be developing (see Section 7.3.1.1.3). The dose and the time of administration of each dose (and of a repeated dose when applicable) will be recorded in the eCRF. The subjects will be kept under observation for an additional 3 hours after the ingestion of the last dose of the challenge formula.

The subjects must react objectively (see Section 7.3.1.1.3) at or below the eliciting dose of 300 mg of cow's milk proteins to be eligible for randomization to treatment. Hence, this screening DBPCFC will be stopped at or below the dose of 300 mg on either day of the challenge (milk or placebo), whether reactions have occurred or not. Subjects who have not reacted objectively at or below the eliciting dose of 300 mg of cow's milk proteins will be considered ineligible for this study.

All subjects should undergo procedures of the DBPCFC on both days. However, in exceptional cases, the DBPCFC on the second day of the challenge might not be performed if the subject had a severe anaphylactic reaction during the first day of the challenge, leaving no doubt about the nature of the formula administered, ie, cow's milk. In this rare case and in this case only, the food challenge formula will be unblinded to confirm that the subject effectively received the milk formula. A severe anaphylactic reaction would involve a >20% drop of blood pressure, cyanosis or Sp02<92%, confusion, collapse, loss of consciousness, 3 doses of epinephrine or more (see Appendix 14.4).

At the end of the second day of the food challenge (Visit 3), the sequence of the 2 formulas (milk or placebo) administered to the subject will be unblinded by the appropriate unblinded staff (eg, dieticians, study nurses, pharmacists, pharmacy technicians, licensed medical assistants, or any other qualified site personnel, as delegated by the Investigator) and revealed to the medical staff. The results of the challenge will then be established and recorded in the eCRF as follows:

1. The subject had objective symptoms to the placebo formula at any dose leading to stopping the challenge. S/He cannot be randomized in the study.

2. The subject had no objective symptoms during the 2 days of the DBPCFC, neither to the placebo nor to the milk formula, even at the highest dose of 300 mg of cow's milk proteins. S/He is considered not allergic enough to cow's milk to participate in this study and cannot be randomized in the study.

3. The subject had no objective symptom when receiving placebo but had an objective reaction (as defined in Section 7.3.1.1.3) at 1 of the doses of the milk formula consumed between 1 mg and 300 mg inclusive. S/He will be randomized in the study as s/he reacted to a dose of milk proteins lower than or equal to 300 mg (eliciting dose).

7.3.1.1.2 DBPCFC at Month 12 (Visits 12 and 13), Month 24 (Visits 16 and 17), Month 36 (Visits 19 and 20), and Month 48 (Visits 22 and 23), and optional DBPCFC after 12 months (Visits S3 and S4) and 24 months (Visits S6 and S7) of treatment with Viaskin Milk 300 µg

No patch should be applied on the day of the DBPCFC until all DBPCFC procedures have been completed.

Following results of the 12-month blinded period, the DBPCFCs that were to be performed at Month 24, Month 36 and Month 48 should not be conducted while the subjects are still receiving Viaskin Milk 500 µg.

After subjects switch to Viaskin Milk 300 µg, the DBPCFCs at 12 months and 24 months will be **optional** and left at the Investigator's and the subject's decision. However, **if a subject experienced a severe anaphylaxis to cow's milk during the MILES study, whether or not occurring during the DBPCFC, no further DBPCFC should be conducted for this subject**.

All DBPCFCs at Month 12 and forward will be conducted using the same procedures that are described for the screening DBPCFC, with the exception that the dosing will continue beyond the 300 mg dose of cow's milk proteins if there are no objective symptoms (see Section 7.3.1.1.3) at the 300 mg dose. The challenge must be continued up to the last dose of 3000 mg of cow's milk proteins or until an objective reaction occurs (as defined in Section 7.3.1.1.3).

For all DBPCFCs at Month 12 and forward, the doses of cow's milk proteins will be 1 mg, 3 mg, 10 mg, 30 mg, 100 mg, 300 mg, 1000 mg, 2000 mg, and 3000 mg administered at 20-minute intervals. The Investigator may use clinical judgment to increase the intervals between doses in case there is a suspicion that an objective reaction may be developing (see Section 7.3.1.1.3). Very occasionally, the Investigator may use clinical judgment to repeat the same dose (only once) before administration of the next higher dose and only if there is a suspicion that an objective reaction may be developing (see Section 7.3.1.1.3). The dose and time of administration of each dose (and of a repeated dose when applicable) will be recorded in the eCRF. The subjects

will be kept under observation for an additional 3 hours after the ingestion of the last dose of the challenge formula.

Subjects should undergo both days of the DBPCFC (milk and placebo). However, in exceptional cases, the DBPCFC on the second day of the challenge might not be performed if the subject had a severe anaphylactic reaction during the first day of the challenge, leaving no doubt about the nature of the formula administered, ie, cow's milk. In this rare case and in this case only, the formula will be unblinded to confirm that the subject effectively received the milk formula. A severe anaphylactic reaction would involve a >20% drop of blood pressure, cyanosis or Sp02<92%, confusion, collapse, loss of consciousness, 3 doses of epinephrine or more (see Appendix 14.4).

At the end of the second day of the food challenge, the sequence of the 2 formulas (milk or placebo) administered will be unblinded by the appropriate unblinded staff (eg, dieticians, study nurses, pharmacists, pharmacy technicians, licensed medical assistants, or any other qualified site personnel, as delegated by the Investigator) and revealed to the medical staff. The results of the challenge will then be established and recorded in the eCRF.

7.3.1.1.3 Criteria for Stopping the DBPCFC

The instructions for each of the DBPCFCs during the double-blind period (Screening, Month 12), the Viaskin Milk 500 µg open-label period (Month 24, Month 36 and Month 48) and the Viaskin Milk 300 µg open-label period (12 and 24 months after the switch) are provided below. Further details are provided in the Manual of Procedures for the DBPCFC.

Only clear-cut OBJECTIVE immediate-type symptom(s) requiring treatment will be considered a permissible reason to stop the DBPCFC and to determine the eliciting dose (highest dose given during the challenge) and the CRD of cow's milk. For the open-label treatment period with Viaskin Milk 300 µg, abdominal complaints will also be considered as a criterion for stopping the challenge (see below). The main objective symptoms to expect are as follows (this list is not exhaustive; also refer to Appendix 14.2, OFC Symptom Score Sheets[21, 22]): local or generalized pruritus, flushing, local or generalized urticaria, hives, swollen lips, swollen tongue, throat tightness, vomiting, diarrhea, dyspnea, rhinorrhea, sneezing, wheezing, conjunctivitis, asthma, drop of the PEF, hypoxia, hypotension, hypotonia, decreased level of consciousness associated with collapse and/or incontinence or other life threatening symptoms.

The stopping rules applying for DBPCFCs performed during the double-blind placebo-controlled period and the open-label treatment period with Viaskin Milk 500 µg were the following:

- There is a >1-point rise in an objective symptom from any category in the OFC Symptom Score Sheets, except only for pruritus, which requires >2-point rise
- There is ≥1-point rise in an objective symptom from ≥2 categories in the OFC Symptom Score Sheets
- There is a 1-point rise in an objective symptom from 1 category in the OFC Symptom Score Sheets, with the following exceptions:
    - Pruritus : 0 to 1 or 0 to 2
    - Urticaria: 0 to 1

- Rash: 0 to 1
- Sneezing/Itching: 0 to 1
- Nasal Congestion: 0 to 1
- Rhinorrhea: 0 to 1
- Laryngeal: 0 to 1 (if explained and not persistent)

The stopping rules applying for DBPCFCs performed during the open-label treatment period with Viaskin Milk 300 µg are the following:

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

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

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

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

* “Laryngeal” means symptoms due to laryngeal oedema and must be differentiated from another cause of cough like pharyngeal transient irritation or lower respiratory symptoms. Transient laryngeal irritation will not be considered as an objective OFC symptom and will not be considered in the stopping rules.
**For emesis/vomiting, the symptoms may result from two different situations: vomiting/spitting-up during the feeding, resulting from subjective intolerance to the food formula or vomiting/emesis resulting from a gastrointestinal allergic reaction to the milk allergen, usually delayed from the feeding. Only the second situation will be considered as an objective OFC symptom and will be considered for the stopping rules.
***Cardiovascular symptoms: hypotension or cardiovascular failure directly related to the systemic allergic reaction. They have to be differentiated from similar symptoms related to another cause, such as a dizziness induced by vomiting.

In case of subjective symptoms, eg, mouth pruritus, throat pruritus, nausea, abdominal pain or any other subjective symptoms at a specific dose, deemed significant enough to question whether an objective symptom could occur, the Investigator can, under these conditions, extend the time between the previous dose and the next dose to see how the subject’s symptom(s) evolve(s). The same dose can be repeated only once, to check whether the subjective symptom(s) reappear(s) or not and with what intensity, and whether (an) objective symptom(s) now clearly appear(s). If (an) objective

symptom appear(s), that would be the end of the food challenge. If only (a) subjective symptom(s) still persist(s) with no appearance of an objective symptom, the next highest dose is then given to the subject, and the challenge should continue until the appearance of a clear objective symptom, at which time the challenge will be stopped.

Complete information of all reactions (objective and subjective symptoms) that occurred during the DBPCFC will be reported in the eCRF, along with information about the doses of cow's milk proteins or placebo administered, time of dose administration, first time of appearance of each symptom, severity grades of each symptom, time of appearance of each severity grade, and medication(s)/treatment(s) given to the subject to treat these symptoms.

7.3.1.1.4 Safety Recommendations During the DBPCFC

As a safety precaution, the objective symptom(s) signalling the end of the DBPCFC will be treated by administration of the best medication(s) to the subject as per the Investigator's judgment. The Investigator and medical staff will use their own clinical judgment for the most effective treatment to give to the subject considering his/her age, the type of the allergic reactions and the severity of the allergic reaction. Also refer to recommendations made by Sampson et al for treating anaphylaxis.

Suggested treatments for the different objective symptoms will be detailed in the Manual of Procedures for the DBPCFC that will be provided to the sites. If there is a need to administer epinephrine to a subject, it should be injected intramuscularly in the anterolateral thigh. Epinephrine should NOT be administered i.v. at the investigative sites to treat the reactions, unless a subject is admitted into the Intensive Care Unit in a hospital setting to treat the severity of the reactions.

Subjects will be kept under observation for an additional 3 hours after the ingestion of the last dose of the challenge formula. Based on the Investigator's judgment, the observation period could be extended beyond 3 hours to ensure that all symptoms have subsided before the subject is discharged. For instance, an overnight stay may be considered necessary by the Investigator if the symptom(s) has (have) not completely resolved within the 3 hours or if the symptoms have been severe or serious and require longer observation periods.

7.3.1.2 Serum Immunology Markers

Blood samples will be collected from subjects to assess levels of sIgE and sIgG4 to cow's milk, caseins, α-lactalbumin, and β-lactoglobulin at the timepoints listed in the Schedule of Assessments (Table 2 to Table 7). Exploratory serum immunology markers are discussed below in Section 7.3.3.

Blood samples for serum immunology markers will be analyzed at a central laboratory designated by the sponsor. Instructions for blood sample collection, storage, and shipment will be provided in the laboratory manual.

7.3.1.3 Skin Prick Test

SPTs will be performed at the visits listed in the Schedule of Assessments (Table 2 to Table 7). SPTs will be performed at all sites using the material recommended by the sponsor CCI to ensure consistency in the results. Cow's milk extract, plus negative control and positive control will be used for the SPT.

The subjects must not take antihistamines for 1 to 7 days (depending on the half-life; see Appendix 14.7) prior to the test. Briefly, a skin lancet is pressed through a small drop of the commercial extract of cow's milk and positive (histamine) and negative controls, into the epidermis of the volar surface of the forearm or back of the forearm. The area is measured for the average wheal diameter after 15 minutes. The average wheal diameter corresponds to the average of the size of the longest diameter and the longest perpendicular diameter. A tracing should be obtained by using a fine ballpoint pen. The tracing will be performed at the demarcation line for the wheal as the skin drops back to flush. Scotch or a clear transport tape should be used to lift the tracing and the tape tracing should be stuck in the subject's dossier.

The SPT should be performed by the same assessor at each visit, if possible, and the results will be recorded on the appropriate page(s) of the eCRF.

7.3.1.4 Quality of Life Questionnaire Forms

The QoL questionnaire FAQLQ/FAIM forms[23] was to be completed by the subjects (when applicable, depending on age) and parents/guardians at Screening Visit 1, at Month 12 and Month 24, and at Month 36 and Month 48 for subjects who entered the study extension (Table 2, Table 3, Table 4, and Table 5). The QoL questionnaire will be completed at the time of the switch and after 6, 12, 18 and 24 months of treatment with Viaskin Milk 300 µg (Table 6 and Table 7). At these visits, the QoL forms must be completed by the subjects (depending on the subject's age at the time of Visit 1) and parents/guardians before any other study procedures are performed on that day.

The appropriate QoL questionnaire forms to complete depend on the age of the subject at Visit 1, as follows:

- Subjects 8 to 12 years old at the time of Visit 1 will complete the form FAQLQ-CF (Child Form) at Screening (Visit 1) and at Month 12 and Month 24, and at Month 36 and Month 48 for subjects who entered the study extension. Subjects who are 7 years old at the time of Visit 1 may also complete the form FAQLQ-CF at Screening (Visit 1), if their parent(s)/guardians(s) consider they are able to complete these questionnaires, so that when they turn 8 years old at Month 12, they will have a baseline questionnaire available. However, this is not mandatory.

- Subjects 13 to 17 years old at the time of Visit 1 will complete the form FAQLQ-TF (Teenager Form) at Visit 1 and at Month 12 and Month 24, and at Month 36 and Month 48 for subjects who entered the study extension.

- Parents/guardians of subjects 0 to 12 years old at the time of Visit 1 will complete the form FAQLQ-PF at Visit 1 and at Month 12 and Month 24, and at Month 36 and Month 48 for subjects who entered the study extension.

- Parents/guardians of subjects 13 to 17 years old at the time of Visit 1 will complete the form FAQLQ-PFT at Visit 1 and at Months 12 and 24 and at Month 36 and Month 48 for subjects who entered the study extension.

The FAIM is included as a part of the questionnaires listed above. The QoL questionnaire forms are included in Appendix 14.3.

Data collected in the QoL forms must be entered on the appropriate pages of the eCRF. In order to maintain an unbiased assessment, the Investigator or study site

personnel must not influence the subject and/or parent(s)/guardian(s) while they are completing the forms.

7.3.2 Safety Assessments

Safety assessments will include the following:

- AEs (including Viaskin Milk-induced local AEs and SAEs)
- Vital Signs
- Physical examinations (including complete skin examination)
- Clinical laboratory data
- Spirometry and PEF data

7.3.2.1 Adverse Events

7.3.2.1.1 Definitions of an Adverse Event

An AE is defined as any untoward medical occurrence in a clinical study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding or vital sign measurement), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.[24] This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, drug interaction or the significant worsening of the indication under investigation that is not recorded elsewhere in the eCRF under specific efficacy assessments. Note: A procedure is not an AE, but the reason for the procedure may be an AE.

It is the responsibility of the Investigators to document all AEs that occur during the study. AEs will be elicited by asking the subject or his/her parent(s)/guardian(s) a nonleading question, for example, “Are there any new or changed symptoms since we last asked or since your last visit?” AEs should be reported on the appropriate page of the eCRF.

All AEs occurring after the first Viaskin patch application will be considered treatment-emergent AEs (TEAEs). TEAEs will be defined as any AEs, regardless of relationship to Investigational product, which occur during or after the initial Viaskin patch application or any event already present that worsens in either intensity or frequency following exposure to the Viaskin patch. If relationship information is missing for a TEAE, it will be considered drug-related. AEs with missing or incomplete onset date will be treated as TEAEs and missing onset date will be imputed as date of initial Viaskin patch application unless there is evidence that the event occurred before the treatment period.

Assessment of Severity

Each AE will be assigned a category by the Investigator as follows:

Mild	An AE that is easily tolerated by the subject, causes minimal discomfort and does not interfere with everyday activities.
Moderate	An AE that is sufficiently discomforting to interfere with normal everyday activities; intervention may be needed.

Severe	An AE that prevents normal everyday activities; treatment or other intervention may be needed.

If there is a change in severity of an AE, it must be recorded as a separate event.

The severity of anaphylactic reactions, including those reported as part of medical history, will be assessed using the Anaphylaxis Staging System (Appendix 14.4). For anaphylactic reactions occurring during the DBPCFC, only those considered to be a SAE will be assessed for severity.

Assessment of Causality

The relationship between an AE and the investigational product will be determined by the Investigators on the basis of his/her clinical judgment and the following definitions:

Unrelated	Clinical event with an incompatible time relationship to the investigational product administration, and that could be explained by underlying disease or other drugs or chemicals or is incontrovertibly not related to the investigational product.
Unlikely	Clinical event whose time relationship to the investigational product administration makes a causal connection improbable, but that could plausibly be explained by underlying disease or other drugs or chemicals.
Possible	Clinical event with a reasonable time relationship to the investigational product administration, but that could also be explained by concurrent disease or other drugs or chemicals.
Probable	Clinical event with a reasonable time relationship to the investigational product administration, and is unlikely to be attributed to concurrent disease or other drugs or chemicals.
Definite	Clinical event with plausible time relationship to the investigational product administration, and that cannot be explained by concurrent disease or other drugs or chemicals.

All SAEs assessed as “definitely related”, “probably related” and “possibly related” will be categorized as “related” for expedited reporting.

Action Taken

The Investigators will describe the action taken with the drug product in the appropriate section of the eCRF, as follows:

- None: No change in the dose of the study product.
- Discontinued permanently: The study product was permanently stopped.
- Temporarily interrupted: Dosing of the study product was interrupted.
- Other: Specify.

Outcomes of Adverse Events

The Investigators will describe the outcome of the AEs in the appropriate section of the eCRF, as follows:

- Recovered/Resolved: The subject fully recovered from the AE with no residual effect observed.
- Recovered/Resolved with sequelae: The residual effects of the AE are still present and observable.
- Ongoing: The AE itself is still present and observable.
- Death.
- Unknown/Lost to follow up.

Treatment Required

The Investigators will describe if the subject was treated for an AE in the appropriate section of the eCRF, as follows:

- None: No treatment was required.
- Medication required: Prescription and/or over-the-counter medication were required to treat the AE.
- Hospitalization or prolongation of hospitalization required: Hospitalization was required or prolonged due to the AE, whether or not medication was required.
- Other: Specify.

More than one option can be recorded to report all treatments given for each AE.

7.3.2.1.2 Reporting and Follow-up of Adverse Events

AEs will be reported and documented in accordance with the procedures outlined in this section. AEs will be reported from the time of informed consent through to the EOS visit and documented on the appropriate AE pages of the eCRF.

The Investigator will be responsible for ensuring that correct information concerning all AEs is included on the appropriate pages of the eCRF.

The following data should be documented for each AE:

Diagnosis of the event if available and description of the symptom event.

Classification of ‘serious’ or ‘not serious.’

Severity.

Date of first occurrence and date of resolution (if applicable).

Action taken.

Treatment required.

Causal relationship.

Outcome of event (recovered, recovered with sequelae, ongoing, death [with date and cause reported], unknown).

All Investigators should follow up subjects with AEs until the event is resolved or until, in the opinion of the Investigator, the event is stabilized or determined to be chronic. Details of AE resolution must be documented in the eCRF.

Based on the medical judgment of the Investigator, all non-serious AEs (including the abnormal laboratory values identified as AEs by the Investigator) will be followed until

30 days after the removal of the last Viaskin patch. All unresolved, nonserious AEs beyond such date will be recorded as “ongoing” without further follow-up.

7.3.2.2 Serious Adverse Events

7.3.2.2.1 Serious Adverse Event Definition

An SAE is any untoward medical occurrence or effect that, at any dose:

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

  Note: Whereas an anaphylactic reaction is generally considered to be potentially life-threatening, not all anaphylaxes put the subjects at immediate risk of death, if for example appropriate treatments lead to symptoms reduction or disappearance. As per the Anaphylaxis Staging System classification (Appendix 14.4), an anaphylaxis assessed as mild or moderate should not be classified as life-threatening.
- Requires hospitalization (at least overnight stay or inpatient hospital admission) or prolongation of existing hospitalization

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

  1. Evaluation or treatment of a pre-existing (before informed consent signature) and non-exacerbating condition:
     a. The condition existed prior to the subject’s entry into the study and has been recorded in the subject’s disease/medical history and the e-CRF *AND*
     b. The condition has not worsened in severity or frequency during the subject’s exposure to the investigational product *AND*
     c. It has not required a change in treatment management during the subject’s exposure to the investigational product;
  2. Hospitalization for a planned treatment of a pre-existing (before informed consent signature) and non-exacerbating condition;
  3. Hospitalization the day prior to or after the day of DBPCFC for practical reasons and without any AE fulfilling any other seriousness criterion.
- Results in persistent or significant disability/incapacity (an AE is incapacitating or disabling if it results in a substantial and/or permanent disruption of the subject’s ability to carry out normal life functions).
- Is a congenital anomaly/birth defect.

- Is an “**important medical event”** that may not be immediately life-threatening or result in death or hospitalization but that may jeopardize the subject or require intervention to prevent one of the above outcomes. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.
  - An anaphylactic reaction classified as severe using the Anaphylaxis Staging System in Appendix 14.4 (i.e., anaphylactic reaction with cyanosis or SpO2

≤92%, hypotension with >20% drop in blood pressure, confusion, collapse, loss of consciousness or incontinence) or requiring 3 or more epinephrine uses should be reported as an “important medical event”

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

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

All SAEs occurring after the start of Viaskin patch application will also be defined as treatment-emergent SAEs (TESAEs).

7.3.2.2.2 Reporting and Follow Up of Serious Adverse Events

Any SAE must be reported by the Investigator if it occurs during the clinical study (from the time of informed consent through to the EOS visit) or if it occurs within 30 days of receiving the last dose of the investigational product, whether or not the SAE is considered to be related to the investigational product or to any study procedure. An SAE report consists of the SAE form, the AE form, and the concomitant medication form. The DBV Global Safety and Pharmacovigilance (GSP) department will review all incoming SAE reports for accuracy and completeness. The DBV GSP department will provide the forms to the clinical research associate and/or CRO for distribution to the sites. A copy of these forms must be sent by email **immediately and no later than 24 hours** to the attention of the DBV GSP department:

DBV Global Safety and Pharmacovigilance
PPD

For any subject safety concerns, please contact:

Syneos Health Medical Monitor
PPD

Or

DBV Technologies Medical Monitor
PPD

All of these events must also be recorded in the appropriate pages of the eCRF. The Investigator should not wait to receive additional information to document fully the event before notification of a SAE, though additional information may be requested. The minimum information that is required for an initial SAE report is as follows:

- Subject number

- Investigator name and site number
- Event term
- Event onset date
- Serious criteria
- Relationship to study drug

Where applicable, information from relevant laboratory results, hospital case records and autopsy reports should be obtained.

Instances of death, congenital abnormality or an event that is of such clinical concern as to influence the overall assessment of safety, if brought to the attention of the Investigator at any time after cessation of the investigational product administration and linked by the Investigator to this study should be reported to the study monitor.

The sponsor and/or the CRO will promptly notify all relevant Investigators of findings that could adversely affect the safety of subjects, impact on the conduct of the study, or alter the IRB approval/favourable opinion of the study. In addition, the CRO, on behalf of the sponsor, will expedite the reporting to all concerned Investigators, to the DSMB and IRBs, where required, of all adverse reactions that are both serious and unexpected. The sponsor or designee will be responsible to notify the regulatory authorities of any adverse reactions as described above.

Follow-up of all SAEs will be done until the outcome is resolved, has reached a stable condition in the Investigator's opinion, or until the subject is lost to follow-up.

7.3.2.3 Unexpected Adverse Reactions

7.3.2.3.1 Unexpected Adverse Reaction Definition

An unexpected adverse reaction is any untoward and unintended response that is related to the administration of an investigational product at any dose that is not consistent with the applicable product information (eg, Investigator's Brochure for an unauthorized investigational product).

Serious adverse events that are both related (according to the Sponsor and/or the Investigator) to investigational medicinal product(s) and unexpected (according to the Sponsor based on the Reference Safety Information in use) will usually be assessed as reportable by the sponsor to Competent Authorities.

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

All suspected unexpected serious adverse reactions (SUSARs) will be subject to expedited reporting. The CRO and/or the sponsor shall ensure that all relevant information about a SUSAR that is fatal or life-threatening is reported to the relevant competent authorities, Ethics Committees and Investigators within 7 calendar days after knowledge by the sponsor of such a case and that relevant follow-up information is communicated within an additional 8 calendar days. All other SUSARs will be reported to the relevant competent authorities, Ethics Committees and Investigators within 15 calendar days after knowledge by the sponsor of such a case.

Waiver to expedited reporting: In case an anaphylactic reaction is experienced during the DBPCFC and assessed as serious by the Investigator, this event should be reported within 24 hours of awareness by the investigational site as for other SAEs.

Allergic reactions are voluntarily triggered by a food matrix (placebo matrix or allergen protein matrix) during the DBPCFC procedures and anaphylaxis is an expected outcome. These anaphylactic reactions will be considered as expected, except if leading to death (see Appendix 14.9). Serious anaphylactic reactions assessed as related to the DBPCFC (not related to the IP) will not be subject to expedited reporting to relevant Competent authorities or Ethical Committees, unless they have led to death.

All Investigators should follow-up SUSARs until the event is resolved or until, in the opinion of the Investigator, the event is stabilized or determined to be chronic. If Investigators become aware of post-study SUSARs that occur after the subject has completed the clinical study, these events must be reported by the Investigator to the sponsor.

7.3.2.3.2 Warnings and Precautions

Anaphylactic shock is a clinical symptom of food allergies and can be potentially life-threatening. An anaphylaxis emergency action plan, similar to the one provided in Appendix 14.5, will be designed for this study and provided to the sites before initiation. An epinephrine auto-injector (CCI [redacted]) will be given to each subject or parent(s)/guardian(s) at Visit 4 and as needed during the study to be used according to the anaphylaxis emergency action plan. The expiry date of the auto-injector will be checked and a new auto-injector should be dispensed to the subject, as necessary.

Safety precautions to be followed during the DBPCFC are presented in Section 7.3.1.1.4.

7.3.2.3.3 Rescue Medication

Topical corticosteroids, antihistamine medications and oral or inhaled corticosteroids may be used as rescue medications during the study. In the event that antihistamine medication is needed, oral therapy is recommended. The Investigators will determine the best choice of antihistamine and corticosteroid treatment. An inhalation corticosteroid conversion table is included in Appendix 14.6.

7.3.2.4 Pregnancy

The DBV GSP department and medical monitor must be notified of any subject that becomes pregnant while participating in this study. Any subject who becomes pregnant will be withdrawn from the study and must perform an early termination EOS visit. Although pregnancy is not technically an AE, all pregnancies must be followed to conclusion to determine their outcome. This information is important for both drug safety and public health concerns. It is the responsibility of the Investigator, or designee, to report any pregnancy in a subject which occurs during the study by using the Pregnancy Reporting Form.

If any study subject becomes pregnant or has a positive pregnancy test result while receiving the investigational product, or within 30 days of discontinuing the investigational product, the Investigator should contact DBV medical monitor or designee to discuss subject management. Notification of the pregnancy, including the anticipated date of birth, should be submitted on a Pregnancy Reporting Form

immediately and no later than 24 hours and reported to DBV GSP department using the same procedure as described for reporting SAEs (Section 7.3.2.2). If the pregnancy is to be terminated, the anticipated date of termination should be provided.

Follow-up in the Event of a Pregnancy

The sponsor will be informed of all pregnancies in study subjects.

The subject will be asked to provide information on the outcome of the pregnancy, including premature termination should the case arise. Spontaneous miscarriages, ectopic pregnancies and congenital abnormalities will be reported as SAEs. Information on the status of the mother and child will be forwarded to DBV medical monitor and GSP. Generally, follow-up will be in accordance with regulatory guidance and at least 6 to 8 weeks after the estimated delivery date. Any premature termination of the pregnancy will be reported.

7.3.2.5 Adverse Events of Special Interest to the Sponsor

AEs of special interest (AESI) to the sponsor in this study will include:

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

Systemic AESI:

Any acute systemic immediate allergic reactions (rapid onset) after exposure to known or suspected allergen, regardless of the causal relationship to the investigational product and occurring outside the DBPCFCs:

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

7.3.2.6 Accidental Consumption of Cow's Milk

Any reaction triggered by accidental consumption of cow's milk (in any form) during the conduct of the study. This event will be reported in a specific section of the eCRF.

7.3.2.7 Vital Signs

Vital sign measurements will include heart rate, systolic and diastolic blood pressure, and respiratory rate. Measurements will be collected at each visit (see Table 2 to Table 7), before the DBPCFC, and during the DBPCFC at the Investigator's discretion, when applicable.

Vital signs will be measured in a standardized manner, ie, after the subject has rested in the sitting position for 5 minutes and recorded in the eCRF. The criteria to determine clinically significant abnormalities in vital sign measurements are presented in Section 8.1.7.2.

Weight and height measurements will also be collected for each subject at screening and at 6-month intervals during the study (Visits 10, 12, 15, and 16, and for the subjects who entered the study extension at Visits 18, 19, 21, and 22, and for the subjects who will switch to Viaskin Milk 300 µg, at Visits S1 to S7).

7.3.2.8 Physical Examination and Skin Reaction Grading

Physical examination will include, but is not limited to, head, eyes, ears, nose, and throat (HEENT), as well as a complete examination of the skin, and will be performed at each visit (see Table 2 to Table 7), before the DBPCFC, and during the DBPCFC at the Investigator's discretion, when applicable.

Local skin reactions of the area of the skin used for application of the Viaskin patch on the arms (adolescents and former adolescents who become adults) or back (children) will be graded (Table 1) by the same Investigator at each visit if possible, according to the slightly modified recommendations of the EAACI/GA^{2}LEN position paper.[25]

Table 1: Skin Reaction Grading System

Grade	Skin Reaction
Grade 0	Negative
Grade 1	Only erythema, or erythema + infiltration
Grade 2	Erythema, few papules
Grade 3	Erythema, many or spreading papules
Grade 4	Erythema, vesicles

Viaskin patches are transparent and the degree of local reactions can be easily seen through the patch. Grades of local skin reactions on the arms or the back will be recorded in the eCRF when subjects arrive at the site for a visit.

If Grade 4 local skin reactions are observed, patch application should be transiently interrupted and the subject should visit the site for the next application (see Section 6.3.2).

Photographic records will be taken of the site(s) of application of the Viaskin patch and filed in the subject's medical records or source documents and provided to the CRO or sponsor as necessary upon request.

7.3.2.9 Clinical Laboratory Evaluation

Hematology, biochemistry, and any other laboratory tests will be analyzed at a central laboratory(ies) designated by the sponsor. Reference ranges will be supplied and used by the Investigator to assess the laboratory data for clinical significance and pathological changes.

Blood samples will be collected from subjects at the timepoints listed in the Schedule of Assessments (Table 2 to Table 7). Instructions for blood sample collection, storage, and shipment will be provided in the laboratory manual.

The following laboratory tests will be performed using collected samples:

Hematology

Hemoglobin, hematocrit, platelets, red blood cells (RBC), white blood cells (WBC), and differentials.

Biochemistry

Aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, total protein, blood urea nitrogen (BUN), and creatinine.

Total Blood Volume Requirements

The estimated maximum blood volume that will be collected from each subject during a visit will be approximately 15 mL for hematology and biochemistry laboratory tests and efficacy or exploratory assessments (serum immunology markers [Section 7.3.1.2], filaggrin mutations, and epigenetic analyses [Section 7.3.3]), up to Month 48, and approximately 12.5 mL during the treatment period with Viaskin Milk 300 µg.

The estimated maximum total blood volume that will be collected from each subject up to Month 24 will be approximately 80 mL. For subjects who enter the study extension (Month 24 to 48), approximately 50 mL of additional blood will be collected. Consequently, the estimated maximum volume of total blood to be collected from each subject during the whole study (up to Month 48) was to be approximately 130 mL. For subjects who switch to Viaskin Milk 300 µg, up to 57.5 mL of additional blood will be collected within 24 months. The total blood volume requirement does not exceed the recommended sample blood volume of 3 mL/kg and up to 50 mL total within 8 weeks.[26]

7.3.2.10 Other Laboratory Variables

For female subjects of childbearing potential, a urine sample will be collected to screen for pregnancy (urine β-HCG) at the visits listed in Table 2 to Table 7.

7.3.2.11 Spirometry and Peak Expiratory Flow

Spirometry, measured as FEV1, will be performed for subjects ≥6 years old (unless they have documented inability to adequately perform spirometry) and the PEF will be assessed for subjects ≥5 years old at the timepoints listed in Table 2 to Table 7. PEF will not be collected for subject <5 years. Spirometry and/or PEF data (depending on the subject's age and ability to perform these tests) will be documented on the appropriate pages of the eCRF.

FEV_1 will be measured on a standardized calibrated spirometer following the American Thoracic Society (ATS) guidelines. At least 3 acceptable maneuvers will be obtained

and the highest values will be recorded in the eCRF. For subjects who are too young or who have documented inability to adequately perform the spirometry according to the ATS, only PEF values will be used. Again, at least 3 acceptable maneuvers will be obtained and the highest value will be recorded in the eCRF.

7.3.2.12 Subject Diary Cards

Diary cards will be dispensed to the subjects at Visit 4 and as needed during the study. At each subsequent visit after Visit 4, the diary card will be reviewed by appropriate personnel at the site and the data in the card will be collected for entry into the eCRF or into the clinical database.

Subjects or their parent(s)/guardian(s) will be instructed how to use the diary card from Visit 4 (Day 1) and to bring the card to the site at each subsequent visit. Subjects or their parent(s)/guardian(s) will be instructed to record on their diary cards any AEs/medical events and associated medications, the duration of application and reason for removal of the Viaskin patch, if the patch is removed before the recommended duration in addition to any information regarding cow's milk consumption (including dairy products or any baked milk product) during their participation in the study.

At the clinical site, upon review of the diary cards, the investigative staff will interview the subject to know whether the milk consumption was either accidental or voluntary. This will be useful for the Investigators to assess whether there has been any risk-taking behavior and collect as much information as possible about those cases.

7.3.3 Exploratory Assessments

Blood samples will be collected from subjects to assess levels of sIgE to peanut, egg, house dust mite and grass pollen at the timepoints listed in the Schedule of Assessments (Table 2 to Table 7). Blood samples for serum immunology markers will be analyzed at a central laboratory designated by the sponsor. Instructions for blood sample collection, storage, and shipment will be provided in the laboratory manual.

For the analysis of the mutations in the filaggrin gene, blood samples will be collected from subjects only after the genetic ICF/IAF are signed. Blood samples will be collected at the time of Visit 1. If not collected at Visit 1, blood samples for filaggrin analysis can be collected at any subsequent visit where blood is drawn (see Table 2, Table 3, Table 4, and Table 5), but only 1 sample collection for filaggrin is required during the study. No blood sample will be drawn for filaggrin analysis during the 24-month treatment period with Viaskin Milk 300 µg. The genetic screening of the mutations of the filaggrin gene will be performed at a central laboratory designated by the sponsor.

For epigenetic analyses, blood samples will be collected from subjects only after the genetic ICF/IAF are signed. Blood samples will be collected at the visits specified in the Schedules of Assessments (Table 2 to Table 7). The sample will be stored and may be used to assess any epigenetic modifications such as DNA methylation in some allergy-related genes that could play a role in the development of immune tolerance. These tests will be done at a central laboratory designated by the sponsor.

Instructions for the collection, storage, and shipment of samples collected for the filaggrin and/or epigenetic analyses will be provided in the laboratory manual.

An EOS survey will be completed by the Investigator for each individual subject when their participation in the study is terminated (see Table 2 to Table 7). This survey will

allow assessment of the planned management of the subject after termination of the study.

7.4 Schedule of Assessments

Table 2: Schedule of Assessments During the First Year of Treatment

Study Period	Screening[1]			Treatment Period (first year)																EOS Early Term[2]
Visit Number	V1	V2	V3	V4[4]	V5[5]	V6	V7	V8	PC 8a	V9	PC 9a	PC 9b	V1 0	PC 10a	PC 10b	V1 1	PC 11a	PC 11b	V12	V13	ET
Visit Day/Month (Allowance days)	Up to D-60		Within 7 D after V2 (+7)[3]	D1	D2	D8/ W1 (±2)	D22/ W3 (±3)	W6 (±3)	M2 (±7)	M3 (±7)	M4 (±7)	M5 (±7)	M6 (±7)	M7 (±7)	M8 (±7)	M9 (±7)	M10 (±7)	M11 (±7)	M12 (±7)	Within 7 D after V12 (+7)[3]	
Min duration of observation at site[6]		3h	3h	3h or 6h[6]	2h														3h	3h	
Study Assessments:																					
Informed Consent	X																				
Genetic Informed Consent[7]	X																				
Medical History[8]	X																				
Demography[9]	X												X[9]						X[9]		
Check Eligibility Criteria[10]	X			X[10]																	
Physical Examination[11]	X	X[12]	X[12]	X	X	X	X	X		X			X			X			X[12]	X[12]	X
Vital Signs[13]	X	X[12]	X[12]	X[4]	X	X	X	X		X			X			X			X[12]	X[12]	X
FAQLQ/FAIM[14]	X																		X		X
Spirometry (FEV_1)[15]	X			X			X			X			X						X		X
Peak Expiratory Flow[15]	X	X	X	X[4]	X	X	X	X		X			X			X			X	X	X
Skin Prick Test	X									X			X						X		X
Laboratory tests[16]	X						X			X			X						X		X
Immunological Markers[17]	X						X			X			X						X		X
Filaggrin[18] (collected at 1 visit only)	X[18]						X[18]			X[18]			X[18]						X[18]		
Epigenetic Analyses[19]	X																		X		
Urine Pregnancy Test[20]	X																		X		X
DBPCFC		X	X																X	X	
Phone Contact									X		X	X		X	X		X	X			
Adverse Event[21]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior/Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Period	Screening[1]			Treatment Period (first year)																EOS Early Term[2]
Visit Number	**V1**	**V2**	**V3**	**V4[4]**	**V5[5]**	**V6**	**V7**	**V8**	**PC 8a**	**V9**	**PC 9a**	**PC 9b**	**V1 0**	**PC 10a**	**PC 10b**	**V1 1**	**PC 11a**	**PC 11b**	**V12**	**V13**	**ET**
Visit Day/Month (Allowance days)	Up to D-60		Within 7 D after V2 (+7)[3]	D1	D2	D8/ W1 (±2)	D22/ W3 (±3)	W6 (±3)	M2 (±7)	M3 (±7)	M4 (±7)	M5 (±7)	M6 (±7)	M7 (±7)	M8 (±7)	M9 (±7)	M10 (±7)	M11 (±7)	M12 (±7)	Within 7 D after V12 (+7)[3]	
Min duration of observation at site[6]		3h	3h	3h or 6h[6]	2h														3h	3h	
Dispense/Check Diary Card				X	X	X	X	X		X			X			X			X	X	X
IP Dispensation to the Subject				X	X	X	X	X		X			X			X				X	
IP Accountability						X	X	X		X			X			X			X		X
Application of Viaskin Patch at the Site				X	X																
Examination, Grading and Photography of Skin Where Patches Are/Were Applied				X[4]	X	X	X	X		X			X			X			X	X	X
Dispense/Review Epinephrine Auto-Injector and the Anaphylaxis Emergency Action Plan[22]				X	X	X	X	X		X			X			X			X	X	
End-of-Study Survey																					X

Table 3. Schedule of Assessments During the Second Year of Treatment (applicable only until the switch to Viaskin Milk 300 µg)

Study Period	Treatment Period (second year)								EOS FU	EOS Early Term[2]
Visit Number	**V14**	**PC14a**	**PC14b**	**V15**	**PC15a**	**PC15b**	**V16**	**V17 NA under Amendment 5**	**FU[24]**	**ET**
Visit Day/Month (Allowance days)	21 D after V13 (±3)	M14 (±7)	M16 (±7)	M18 (±14)	M20 (±7)	M22 (±7)	M24 (±14)	Within 7 D after V16 (+7)[3]	14 D after V16 or V17 (±3)	
Min duration of observation at site[6]							3h	3h		
Study Assessments:										
Demography[9]				X[9]			X[9]			
Physical Examination[11]	X			X			X[12]	X[12]	X	X
Vital Signs[13]	X			X			X[12]	X[12]	X	X
FAQLQ/FAIM[14]							X			X
Spirometry (FEV_1)[15]				X			X			X
Peak Expiratory Flow [15]	X			X			X	X	X	X
Skin Prick Test				X			X			X
Laboratory tests[16]				X			X			X
Immunological Markers[17]				X			X			X
Filaggrin[18] (collected at 1 visit only)				X[18]			X[18]			
Epigenetic Analyses[19]							X			
Urine Pregnancy Test[20]							X			X
DBPCFC							X[27]	X[27]		
Phone Contact		X	X		X	X				
Adverse Event[21]	X	X	X	X	X	X	X	X	X	X
Prior/Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Dispense/Check Diary Card	X			X			X	X	X	X
IP Dispensation to the Subject	X			X			X	X[23]		
IP Accountability	X			X			X	X		X
Examination, Grading, and Photography of Skin Where Patches Are/Were Applied	X			X			X	X	X	X
Dispense/Review Epinephrine Auto-Injector and the Anaphylaxis Emergency Action Plan[22]	X			X			X	X		
Informed Consent for Study Extension[25]								X[25]		

Study Period	Treatment Period (second year)								EOS FU	EOS Early Term[2]
Visit Number	V14	PC14a	PC14b	V15	PC15a	PC15b	V16	V17 NA under Amendment 5	FU[24]	ET
Visit Day/Month (Allowance days)	21 D after V13 (±3)	M14 (±7)	M16 (±7)	M18 (±14)	M20 (±7)	M22 (±7)	M24 (±14)	Within 7 D after V16 (+7)[3]	14 D after V16 or V17 (±3)	
Min duration of observation at site[6]							3h	3h		
Eligibility Criteria for Study Extension[26]								X		
End-of-Study Survey									X	X

Table 4: Schedule of Assessments During the Third Year of Treatment (applicable only until the switch to Viaskin Milk 300 µg)

Study Period	Treatment Period (third year)					EOS Early Term[2]
Visit Number	PC17a[28]	V18[28]	PC18a[28]	V19[28]	V20[28] NA under Amendment 5	ET
Visit Day/Month (Allowance days)	M27 (±14)	M30 (±14)	M33 (±14)	M36 (±14)	Within 7 D after V19 (+7)[3]	
Min duration of observation at site[6]				3h	3h	
Study Assessments:						
Demography[9]		X[9]		X[9]		
Physical Examination[11]		X		X[12]	X[12]	X
Vital Signs[13]		X		X[12]	X[12]	X
FAQLQ/FAIM[14]				X		X
Spirometry (FEV_1)[15]		X		X		X
Peak Expiratory Flow [15]		X		X	X	X
Skin Prick Test		X		X		X
Laboratory tests[16]		X		X		X
Immunological Markers[17]		X		X		X
Filaggrin[18] (collected at 1 visit only)		X[18]		X[18]		
Epigenetic Analyses[19]				X		
Urine Pregnancy Test[20]				X		X
DBPCFC				X[27]	X[27]	
Phone Contact	X		X			
Adverse Event[21]	X	X	X	X	X	X
Prior/Concomitant Medications	X	X	X	X	X	X
Dispense/Check Diary Card		X		X	X	X
IP Dispensation to the Subject		X		X	X	
IP Accountability		X		X	X	X
Examination, Grading, and Photography of Skin Where Patches Are/Were Applied		X		X	X	X
Dispense/Review Epinephrine Auto-Injector and the Anaphylaxis Emergency Action Plan[22]		X		X	X	
End-of-Study Survey						X

Table 5: Schedule of Assessments During the Fourth Year of Treatment (applicable only until the switch to Viaskin Milk 300 µg)

Study Period	Treatment Period (fourth year)					EOS FU	EOS Early Term[2]
Visit Number	PC20a[28]	V21[28]	PC21a[28]	V22[28]	V23[28] NA under Amendment 5	FU[24]	ET
Visit Day/Month (Allowance days)	M39 (±14)	M42 (±14)	M45 (±14)	M48 (±14)	Within 7 D after V22 (+7)[3]	14 D after V22 or V23 (±3)	
Min duration of observation at site[6]				3h	3h		
Study Assessments:							
Demography[9]		X[9]		X[9]			
Physical Examination[11]		X		X[12]	X[12]	X	X
Vital Signs[13]		X		X[12]	X[12]	X	X
FAQLQ/FAIM[14]				X			X
Spirometry (FEV_1)[15]		X		X			X
Peak Expiratory Flow [15]		X		X	X	X	X
Skin Prick Test		X		X			X
Laboratory tests[16]		X		X			X
Immunological Markers[17]		X		X			X
Filaggrin[18] (collected at 1 visit only)		X[18]		X[18]			
Epigenetic Analyses[19]				X			
Urine Pregnancy Test[20]				X			X
DBPCFC				X[27]	X[27]		
Phone Contact	X		X				
Adverse Event[21]	X	X	X	X	X	X	X
Prior/Concomitant Medications	X	X	X	X	X	X	X
Dispense/Check Diary Card		X		X	X	X	X
IP Dispensation to the Subject		X		X			
IP Accountability		X		X	X		X
Examination, Grading, and Photography of Skin Where Patches Are/Were Applied		X		X	X	X	X
Dispense/Review Epinephrine Auto-Injector and the Anaphylaxis Emergency Action Plan[22]		X		X	X		
End-of-Study Survey						X	X

Table 2/Table 3/ Table 4/ Table 5: (Continued) Schedule of Assessments Legend

1. Screening period, between V1 and V4 should be within 60 days. V2 (first day of food challenge) can be scheduled as soon as the laboratory results from V1 are available.
2. End-of-Study Early Termination Visit is applicable only for subjects withdrawing from the study prematurely.
3. Visit may be scheduled up to a maximum of 14 days after previous visit and documented in the eCRF.
4. V4 is the first dosing visit. For subjects in Part A, procedures marked ([4]) should be performed at the site at the following timepoints: before the first Viaskin patch application, then 30 min, 1h, 2h; 3h and 6h after the first patch is applied. For subjects randomized in the Part B, the procedures should be performed at the same timepoints, except the 6h timepoint.
5. V5 is applicable only for subjects randomized in Part A.
6. Six (6) hours of observation for Part A subjects after the patch is applied at V4; 3h of observation for Part B subjects after the patch is applied at V4. At visits when a DBPCFC is performed, a minimum of 3h of observation after the last dose of the food challenge formula has been ingested.
7. Genetic Informed Consent for filaggrin and epigenetic analyses is optional.
8. Including history of cow's milk allergy and any other types of allergy if applicable.
9. Including date of birth, sex, ethnic origin, weight (kg) and height (cm). At V10, V12, V15, V16, and at V18, V19, V21, and V22 for subjects who entered in the study extension, only the subject's weight and height will be collected.
10. Eligibility criteria must be checked and confirmed at V4 (Day 1).
11. Including, but not limited to, head, eyes, ears, nose, and throat (HEENT), and a complete examination of the skin.
12. Physical examination and vital sign measurements must be performed before the DBPCFC and can be repeated anytime during the DBPCFC, as judged necessary by the Investigator.
13. Vital signs measured in a sitting position include heart rate, systolic and diastolic blood pressure and respiratory rate.
14. FAQLQ/FAIM: Quality of Life questionnaire forms to be completed must correspond to each subject's age at V1. The questionnaires must be completed before any procedures at all visits when QoL forms are completed.
15. Spirometry and/or peak expiratory flow measurements, depending upon the subject's age and ability to perform these tests.
16. Laboratory tests include **Hematology:** hemoglobin, hematocrit, platelets, red blood cells, white blood cells and differentials; **Biochemistry:** aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, total protein, blood urea nitrogen (BUN) and creatinine.
17. Immunological markers include: sIgE and sIgG4 to whole cow's milk proteins, caseins, α-lactalbumin, and β-lactoglobulin; and sIgE to peanut, egg, house dust mite, and grass pollen.
18. Sample for the analysis of filaggrin mutations will be collected only once: this could be at V1 or at any of the visits mentioned. This is optional. Samples will be collected only after the genetic ICF/IAF is signed.
19. This is optional. Samples will be collected only after the genetic ICF/IAF is signed.
20. Only for female subjects of child-bearing potential. Additional pregnancy testing may be repeated during the study at the discretion of the Investigator.
21. AEs are collected from the day of signing the ICF/IAF.
22. The epinephrine auto-injector and the Anaphylaxis Emergency Action Plan are dispensed and their utilization explained at V4; epinephrine auto-injector training must be appropriately documented in the source documents. At subsequent study visits, utilization will be reviewed whenever necessary. Expiry date will be checked and a new auto-injector provided as necessary.
23. IP Dispensation at V17 and beyond is applicable only to subjects who enter the study extension.
24. Subjects will perform only one FU visit, 14 days after V16 or V17 for subjects ending at Month 24, or 14 days after V22 or V23 for subjects who were in the study extension up to Month 48. For subjects who do not consent to switch to Viaskin Milk 300 µg and who just reached V16, the EOS FU visit should take place within 14 days of V16.
25. Signed Informed Consent/Assent to enter study extension will be obtained no later than at V17.
26. Eligibility criteria will be assessed at V17 before subjects enter the study extension.
27. Following results of the 12-month blinded period, the DBPCFCs that were to be performed at Month 24, Month 36 and Month 48 should not be conducted while the subjects are still receiving Viaskin Milk 500 µg. Visits V17, V20 and V23 are no longer applicable.
28. Visits and phone contacts during the third and fourth years are applicable only to subjects who entered the study extension after V17.

Abbreviations: D=Day; DBPCFC=Double-Blind Placebo-Controlled Food Challenge; EOS=End-of-Study; ET=Early Termination; FAIM=Food Allergy Independent Measure; FAQLQ=Food Allergy Quality of Life Questionnaire; FEV_1=Forced Expiratory Volume in 1 second; FU=Follow-up; Ig=Immunoglobulin; IP=Investigational Product; M=Month; Min=Minimum; NA=Not Applicable; PC=Phone Contact; V=Visit; W=Week.

Table 6. Schedule of assessments during the first year after the switch to Viaskin Milk 300 µg

Study Period	Treatment Period (1st year after switch to Viaskin Milk 300 µg)							EOS Early Term[1]
Visit Number	**VS1**	**PCS1**	**PCS2**	**VS2**	**PCS3**	**VS3**	**VS4** *Only for subjects with DBPCFC performed at VS3*	**ET**
Visit Day/Month (Allowance days)	D1	M1 (±14)	M3 (±14)	M6 (±14)	M9 (±14)	M12 (±14)	Within 7 D after VS3 (+7)[2]	
Min duration of observation at site[3]						3h	3h	
Study Assessments:								
Informed Consent for switch to Viaskin Milk 300 µg	X							
Eligibility criteria for switch to Viaskin Milk 300 µg	X							
Demography: weight and height	X			X		X		
Physical Examination[4]	X			X		X[5]	X[5]	X
Vital Signs[6]	X			X		X[5]	X[5]	X
FAQLQ/FAIM[7]	X			X		X		X
Spirometry (FEV_1)[8]	X			X		X		X
Peak Expiratory Flow [8]	X			X		X	X	X
Skin Prick Test	X			X		X		X
Laboratory tests[9]	X[10]			X		X		X
Immunological Markers[11]	X[10]			X		X		X
Epigenetic Analyses[12]	X[10]					X		
Urine Pregnancy Test[13]	X			X		X	X	X
DBPCFC[14]						X	X	
Phone Contact		X	X		X			
Adverse Event	X	X	X	X	X	X	X	X
Prior/Concomitant Medications	X	X	X	X	X	X	X	X
Dispense/Check Diary Card	X			X		X	X	X
IP Dispensation to the Subject	X			X		X		
IP Accountability	X			X		X		X
Examination, Grading, and Photography of Skin Where Patches Are/Were Applied	X			X		X	X	X
Dispense/Review Epinephrine Auto-Injector and the Anaphylaxis Emergency Action Plan[15]	X			X		X	X	
End-of-Study Survey								X

Table 7. Schedule of assessments during the second year after the switch to Viaskin Milk 300 µg

Study Period	Treatment Period (2nd year after switch to Viaskin Milk 300 µg)					EOS FU	EOS Early Term[1]
Visit Number	**PCS4**	**VS5**	**PCS5**	**VS6**	**VS7** *Only for subjects with DBPCFC performed at VS6*	**FU**	**ET**
Visit Day/Month (Allowance days)	M15 (±14)	M18 (±14)	M21 (±14)	M24 (±14)	Within 7 D after VS6 (+7)[2]	14 D after VS7 if VS7 performed (±3) 14 D after VS6 otherwise (±3)	
Min duration of observation at site[3]				3h	3h		
Study Assessments:							
Demography: weight and height		X		X			
Physical Examination[4]		X		X[5]	X[5]	X	X
Vital Signs[6]		X		X[5]	X[5]	X	X
FAQLQ/FAIM[7]		X		X			X
Spirometry (FEV_1)[8]		X		X			X
Peak Expiratory Flow [8]		X		X	X	X	X
Skin Prick Test		X		X			X
Laboratory tests[9]		X		X			X
Immunological Markers[11]		X		X			X
Epigenetic Analyses[12]				X			
Urine Pregnancy Test[13]		X		X	X		X
DBPCFC[14]				X	X		
Phone Contact	X		X				
Adverse Event	X	X	X	X	X	X	X
Prior/Concomitant Medications	X	X	X	X	X	X	X
Dispense/Check Diary Card		X		X	X	X	X
IP Dispensation to the Subject		X					
IP Accountability		X		X[16]	X[16]		X
Examination, Grading, and Photography of Skin Where Patches Are/Were Applied		X		X	X	X	X
Dispense/Review Epinephrine Auto-Injector and the Anaphylaxis Emergency Action Plan[15]		X		X	X		
End-of-Study Survey						X	X

Legend for Table 6 and Table 7:

1. End-of-Study Early Termination Visit is applicable only for subjects withdrawing from the study prematurely.
2. Visit may be scheduled up to a maximum of 14 days after previous visit and documented in the eCRF.
3. At visits when a DBPCFC is performed, a minimum of 3h of observation after the last dose of the food challenge formula has been ingested.
4. Including, but not limited to, head, eyes, ears, nose, and throat (HEENT), and a complete examination of the skin.
5. Physical examination and vital sign measurements must be performed before the DBPCFC and can be repeated anytime during the DBPCFC, as judged necessary by the Investigator.
6. Vital signs measured in a sitting position include heart rate, systolic and diastolic blood pressure and respiratory rate.
7. FAQLQ/FAIM: Quality of Life questionnaire forms to be completed must correspond to each subject's age at V1. The questionnaires must be completed before any procedures at all visits when QoL forms are completed.
8. Spirometry and/or peak expiratory flow measurements, depending upon the subject's age and ability to perform these tests.
9. Laboratory tests include **Hematology:** hemoglobin, hematocrit, platelets, red blood cells, white blood cells and differentials; **Biochemistry:** aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, total protein, blood urea nitrogen (BUN) and creatinine.
10. If performed within 1 month of VS1, the collection of blood for laboratory tests, immunological markers and epigenetic analyses is optional at VS1.
11. Immunological markers include: sIgE to whole cow's milk proteins, caseins, α-lactalbumin, and β-lactoglobulin; sIgG4 to caseins, α-lactalbumin, and β-lactoglobulin; sIgE to peanut, egg, house dust mite, and grass pollen.
12. For subjects who signed the genetic ICF/IAF.
13. Only for female subjects of child-bearing potential. Additional pregnancy testing may be repeated during the study at the discretion of the Investigator.
14. DBPCFC is optional and left at the Investigator's and the subject's decision
15. Review of utilization of the epinephrine auto-injector and the Anaphylaxis Emergency Action Plan whenever necessary. Expiry date will be checked, and a new auto-injector provided as necessary.
16. IP accountability will be performed at Visit S6 if the subject does not perform the DBPCFC at Visit S6. IP accountability will be performed at Visit S7 if the subject performs the DBPCFC at Visit S6.

Abbreviations: D=Day; DBPCFC=Double-Blind Placebo-Controlled Food Challenge; EOS=End-of-Study; ET=Early Termination; FAIM=Food Allergy Independent Measure; FAQLQ=Food Allergy Quality of Life Questionnaire; FEV_1=Forced Expiratory Volume in 1 second; FU=Follow-up; Ig=Immunoglobulin; IP=Investigational Product; M=Month; Min=Minimum; PC=Phone Contact; V=Visit; W=Week.

8 Statistical Methods

8.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to database lock. The SAP will ensure that the study data listings, summary tables, and figures that will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

8.1.1 Datasets or Populations Analyzed

The Safety Set (SS) will include all subjects who applied at least 1 Viaskin patch. Subjects will be analyzed according to treatment received. In case of wrong dispensation, the subject will be analyzed according to the treatment received the longest, or as it will be determined at the Blind Data Review Meeting (BDRM), on a case-by-case basis. The SS will be used for all safety analysis tables and listings.

The Intent-to-Treat Set (ITT) will include all randomized subjects. Subjects will be analyzed according to randomized treatment. The ITT Set will be used for all analyses of efficacy endpoints.

The Per Protocol Set (PPS) will include all subjects from the ITT population who do not have major protocol violations that may affect the primary endpoint. Major protocol deviations will be defined in the SAP.

Protocol deviations will be categorized as either major or minor and discussed during the blinded data review meeting (BDRM). Decisions taken at the BDRM will be documented and approved by DBV prior to database lock and unblinding the study.

The Open-label Sets (OLS) will include all subjects from the ITT who entered the open-label treatment period (ie, who applied at least one Viaskin Milk patch during the open-label treatment period) and will be described in the SAP.

The Open-label Set 300 µg (OLS_300) will include all subjects who switched to Viaskin Milk 300 µg and will be described in the SAP.

8.1.2 General Considerations

There will be 2 age groups considered for the statistical analyses:

- Children: 2 to 11 years of age at the time of Visit 1
- Adolescents: 12 to 17 years of age at the time of Visit 1

Data will be summarized by age group, dose level, and pooled placebo group for the randomized blinded treatment period (Months 0 to 12) as follows:

Part A and Part B: Viaskin Milk 150 µg, 300 µg, 500 µg of cow's milk proteins, and placebo.

Part A and Part B subjects will be combined and pooled by dose level, as applicable, for the efficacy analyses at Month 12.

In general, categorical data will be summarized using counts and percentages, and continuous variables will be summarized using the number of subjects with evaluable

data (n), mean, standard deviation, median, first and third quartiles (Q1, Q3), minimum and maximum.

All hypothesis tests will be in scope of dose-response or longitudinal analyses.

Listings of raw subject data will be sorted by dose level, randomization number and visit, as applicable, for all randomized subjects. For subjects in Part A, data from Cohorts 1, 2, and 3 will be presented separately in the listings.

8.1.3 Subject Disposition

The number and percentage of subjects in each analysis population (ITT, PPS, SS, OLS and OLS_300) will be summarized overall and by treatment group (dose level/placebo).

Subject disposition will be summarized for all subjects in the ITT. The number and percentage of subject completed, discontinued, and the primary reason for early withdrawal from the study will be tabulated by dose level and placebo group.

8.1.4 Demographic and Other Baseline Characteristics

For continuous demographic variables and baseline characteristics (including age, height, weight, body mass index (BMI, kg/m²), body surface (m²), weight/height (kg/m), SPT mean wheal diameter, FEV_1 percent predicted [spirometry], PEF percent predicted, CRD of cow's milk, and milk sIgE), descriptive will be generated for each dose level and placebo group at Visit 1 for all subjects in the ITT.

For categorical demographic variables and baseline characteristics (including sex, ethnic origin, and medical history), the number and percent of subjects in each category will be tabulated for each dose level and placebo group at Visit 1 for all subjects in the ITT.

The same descriptive summaries will be repeated at the entry of the Open-Label period and at the entry of the switch to Viaskin Milk 300 µg.

Individual subject demographic and baseline characteristics data will be listed.

8.1.5 Concomitant Medications

Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODrug). A summary of concomitant medications by the second level Anatomical Therapeutic Chemical (ATC) term and preferred term will be produced overall and by age group, for each dose level and placebo group on the ITT for the randomized blinded treatment period (Months 0 to 12).

Concomitant medications during the open-label treatment periods after Month 12 will be described. Details will be provided in the SAP.

8.1.6 Efficacy

Missing data will not be imputed for the efficacy analyses except for the classification of treatment responders / non responders for the primary efficacy analysis.

8.1.6.1 Primary Efficacy Endpoint and Analysis

The primary efficacy endpoint will be the percentage (%) of subjects who are treatment responders after 12 months of EPIT treatment.

A treatment responder is defined as a subject who meets at least one of the following criteria:

- A ≥10-fold increase in the CRD of cow's milk proteins at the Month 12 DBPCFC as compared to baseline value and reaching at least 144 mg of cow's milk proteins (approximately 4.5 mL of milk).
- A CRD of cow's milk proteins ≥1444 mg (approximately 45 mL of milk) at the Month 12 DBPCFC.

The CRD of cow's milk proteins is entered directly in CRF by the sites and is calculated as the sum of all doses of cow's milk proteins given during the challenge, including repeat doses if applicable, and exact quantity of the last dose given (if not given in totality).

The percentage of subjects who are treatment responders after 12 months of EPIT treatment will be calculated on the ITT population using missing = failure imputation method (ie, subjects with missing observation at Month 12 will be considered as non-responders).

The number and percentage of responders will be summarized overall and by age group, for each pooled dose level (Part A and Part B) and placebo group, for the blinded treatment period (Months 0 to 12).

Methods of exact logistic regression will be used to compare the proportion of treatment responders at Month 12 in each dose level to placebo, adjusting for age group, and including the treatment group as fixed effect, for subjects in the ITT population. P-values, odds ratios together with associated 95% Confidence Intervals (95% CI) will be presented.

The primary efficacy endpoint of this study, together with additional exploratory analyses, will assess the dose-response relationship and aim to inform the dose selection for phase 3. Model-based analytical approaches of exploratory dose finding (e.g., MCP-Mod) will be used to evaluate the dose-response relationship and estimate target dose(s).

Further details of the statistical methodology and considerations for the approaches to be used in the analysis will be specified in the SAP.

8.1.6.1.1 Sensitivity analyses on Primary efficacy criteria

Sensitivity analyses will be performed in order to evaluate the impact of the primary efficacy criteria to the results and interpretation of study results. The analysis described above will be repeated for subjects in the ITT using observed data and in the PPS. A similar analysis will be performed on ITT population using multiple imputation instead of missing = failure imputation method. Multiple imputation method will be further described in the SAP.

Other covariates of interest including baseline IgE (by levels) and country will be explored.

Finally, the primary efficacy analysis will be repeated for each age group as well as for each filaggrin mutation group (With filaggrin mutation / Without filaggrin mutation). Within subgroup, the treatment group comparisons will be conducted at a two-sided 10% significance level.

8.1.6.2 Secondary Efficacy Endpoints and Analysis

The secondary endpoints for the double-blind, placebo-controlled treatment period up to Month 12 are:

- The mean and median CRD of cow's milk proteins at Month 12 and change from baseline.
- The change from baseline value in levels of sIgE and allergen-specific immunoglobulin G4 (sIgG4) to cow's milk at all timepoints evaluated up to Month 12.
- The change from baseline value in levels of sIgE and sIgG4 to caseins, α-lactalbumin, and β-lactoglobulin at all timepoints evaluated up to Month 12.
- The change from baseline in SPT wheal at all timepoints evaluated up to Month 12.
- The change in the severity of symptoms elicited during the milk DBPCFC from baseline to Month 12.
- The change from baseline in Quality of Life (QoL) assessments at Month 12.

The endpoints after Month 12 for the open-label treatment periods with Viaskin Milk 500 µg up to 48 months and Viaskin Milk 300 µg for 24 months are:

- The percentage of subjects who are treatment responders over the course of open-label treatment with Viaskin Milk 500 µg and 300 µg.
- The CRD of cow's milk proteins over the course of open-label treatment with Viaskin Milk 500 µg and 300 µg.
- The levels of sIgE to cow's milk over the course of open-label treatment with Viaskin Milk 500 µg and 300 µg.
- The levels of sIgG4 to cow's milk proteins over the course of open-label treatment with Viaskin Milk 500 µg.
- The levels of sIgE and sIgG4 to caseins, α-lactalbumin, and β-lactoglobulin over the course of open-label treatment with Viaskin Milk 500 µg and 300 µg.
- The SPT wheal over the course of open-label treatment with Viaskin Milk 500 µg and 300 µg.
- The severity of symptoms elicited during the milk DBPCFC over the course of open-label treatment with Viaskin Milk 500 µg and 300 µg
- The QoL assessments over the course of open-label treatment with Viaskin Milk 500 µg and 300 µg.

8.1.6.2.1 Treatment Responders

Treatment responders during the open-label treatment periods after Month 12 will be explored. Details will be provided in the SAP.

8.1.6.2.2 Cumulative Reactive Dose (CRD) of Cow's Milk Proteins

The CRD and changes from baseline will be summarized overall and by age group, dose level group (Part A and Part B pooled), and timepoint on the ITT for the randomized blinded treatment period (Months 0-12).

CRD during the open-label treatment periods after Month 12 will be explored. Details will be provided in the SAP.

8.1.6.2.3 Immunological Markers

All analyses will be carried out on the ITT population.

Absolute values and changes from baseline for the immunological markers were to be summarized overall and by age group, dose level and placebo groups, and timepoint for the randomized blinded treatment period (Months 0 to 12).

Longitudinal analyses will be explored for each of the following parameters:

- cow's milk sIgE and sIgG4 (cow's milk sIgG4 will not be collected after the switch to Viaskin Milk 300 µg)
- sIgE and sIgG4 to
    - caseins,
    - α-lactalbumin, and
    - β-lactoglobulin.

Details will be provided in the SAP.

Immunological markers during the open-label treatment periods after Month 12 will be explored. Details will be provided in the SAP.

8.1.6.2.4 Skin Prick Test

SPT at all timepoints evaluated will be summarized using descriptive statistics overall and by age group, dose level and placebo group on the ITT for the randomized blinded treatment period (Months 0 to 12).

The change from baseline (Visit 1) will be assessed using the ratio of the average wheal diameter at each time point *versus* baseline, derived as improvement (if the ratio of the average wheal diameter ≤ 0.75) / no significant improvement (if the ratio of the average wheal diameter > 0.75) and will be compared between each dose level group and placebo, at each respective visit up to Month 12 using the chi-square test or exact logistic regression (same model as for the primary criteria) in case of low sample sizes (at least one theoretical frequency lower than 5).

The number of subjects with a mean weal diameter equals to 0 will be presented.

Longitudinal analyses will be explored for SPT average wheal diameter. Details will be provided in the SAP.

SPT during the open-label treatment periods after Month 12 will be explored. Details will be provided in the SAP.

8.1.6.2.5 Analysis of Severity During the Milk DBPCFC

The change in the severity of symptoms elicited during the milk DBPCFC from baseline will be assessed at Month 12. Grading of symptoms will be done using the grading definition in the OFC Symptom Score Sheets.[1] Each symptom (objective and subjective) will be graded 0, 1, 2 or 3. A total symptom score will be derived for objective symptoms. The total summary score (absolute and change from baseline) will be summarized overall and by age group, dose level and placebo group on the ITT for the randomized blinded treatment period (Months 0 to 12).

A second severity score will be derived to assess the change from Baseline in the severity of symptoms elicited during the milk DBPCFC at comparable cow's milk proteins dose. The calculation of this severity score at comparable cow's milk proteins dose will be further described in the SAP. This score will be summarized overall and by age group, dose level and placebo group, and timepoint on the ITT for the randomized blinded treatment period (Months 0 to 12).

Longitudinal analyses will be explored for severity score. Details will be provided in the SAP.

Time-to-first objective symptom at Month 12 will be summarized and Kaplan-Meier curves will be provided. Patients without any objective symptom during the DBPCFC will be censored at the time of discharge.

Analysis of severity of symptoms during the open-label treatment periods after Month 12 will be explored. Details will be provided in the SAP.

8.1.6.2.6 Quality of Life Assessments

FAQLQ QoL questionnaires will be completed by study subjects who are 8 years old and older (CF for age range 8 to 12 years old, TF for age range 13 to 17 years old). Subjects who are 7 years old at the time of Visit 1 may also complete the form FAQLQ-CF at Screening (Visit 1), if their parent(s)/guardians(s) consider they are able to complete these questionnaires, so that when they turn 8 years old at Month 12, they will have a baseline questionnaire available. However, this is not mandatory. Parents will also complete a FAQLQ for subjects 0 to 12 years old (PF) and for subjects 13 to 17 years old (PFT). The same questionnaire will be completed throughout the study according to the subject's age at Visit 1.

Each questionnaire type will be summarized by dose level and placebo at each visit using absolute value and change from baseline on the ITT for the randomized blinded treatment period (Months 0 to 12). The summary scores presented will be those derived for the respective questionnaire. No attempt will be made to combine questionnaire types.

Longitudinal analyses will be explored for QoL assessments. Details will be provided in the SAP.

QoL questionnaires during the open-label treatment periods after Month 12 will be explored. Details will be provided in the SAP.

8.1.7 Safety Variables

Safety endpoints will include the following:

- AEs and TEAEs by system organ class, preferred term, maximum severity, and relatedness to the investigational product.
- SAEs and TESAEs by system organ class, preferred term, severity, and relatedness to the investigational product.
- TEAEs leading to study discontinuation, and relatedness to the investigational product.
- Incidence, duration, and maximum severity of local cutaneous reactions, as assessed by the subject.
- Severity of local cutaneous reactions, as assessed by the Investigator.
- AESI including systemic allergic symptoms and local AESI
- Frequency and severity of symptoms elicited during the DBPCFC.
- Vital signs, physical examinations, and laboratory data.
- Spirometry and PEF data.

In all safety presentations, imputation of missing data will take the option of the most conservative outcome, so that, for example, missing relatedness for a TEAE will be assumed to be related and missing severity will be assumed to be severe if the severity is missing for an AE starting on or after the date of initial Viaskin Milk patch application and mild if the severity is missing for an AE starting prior to the date of initial Viaskin Milk patch application.

8.1.7.1 Adverse Events

For adverse events analyses, serious adverse events elicited during DBPCFC will not be considered, they will be described separately.

All AEs and TEAEs will be listed and tabulated separately by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term. Incidence tables will be presented for all TEAEs and TESAEs for the reporting period as defined in Section 7.3.2.1. The following tabulations will be produced overall and by age group, dose level and pooled placebo group on the Safety Set (SS) for the randomized blinded treatment period (Months 0 to 12):

- AEs and TEAEs overall and by system organ class and preferred term
- AEs and TEAEs by maximum severity, overall and by system organ class and preferred term
- TEAEs considered related to investigational product (IP), overall and by system organ class and preferred term
- Number of TEAEs and number of TEAEs considered related to IP by severity
- SAEs and TESAEs overall and by system organ class and preferred term
- SAEs and TESAEs by maximum severity, overall and by system organ class and preferred term
- TESAEs considered related to IP, overall and by system organ class and preferred term

- Viaskin Milk-induced local AEs overall and by system organ class and preferred term

In order to give an indication of longer term safety, a summary of AEs will be produced for a subset of subjects who received the highest safe dose determined during the study from Months 0 to 48. A subject-year analysis will present the total number of subject-years, the number of subjects with a TEAE (and respectively, a TEAE considered related to IP) per subject-year, and the number of TEAEs (and respectively, TEAEs considered related to IP) per subject-year, for each dose level.

Separate listings and tabulations will summarize:

- Systemic AESI whatever the causal relationship with IP.
- Local AESI.
- Severity of symptoms elicited during the DBPCFC.
- Discontinuations due to AEs will also be summarized.

Local and systemic AESI will be identified using systematic retrieval strategies that will be detailed in the SAP.

Adverse events occurring during the open-label treatment periods after Month 12 will be described. Details will be provided in the SAP.

8.1.7.2 Vital Signs

Vital signs will include heart rate, systolic blood pressure, diastolic blood pressure, and respiratory rate. Observed vital sign values and changes from baseline will be summarized using descriptive statistics overall and by age group, visit, timepoint and dose level/placebo group on the SS for the randomized blinded treatment period (Months 0 to 12). Listings of values that are potentially clinically significant will be presented by subject and by test, where applicable.

Vital signs of potential clinical significance for children and adolescents are defined as follows:

Vital Sign	Criteria for Clinically Significant Abnormalities
Heart rate	>120 beats per minute or an increase from pre-dosing of >20 beats per minute, or <50 beats per minute or a decrease from pre-dosing of >20 beats per minute
Systolic blood pressure	> 140 mmHg or an increase from pre-dosing of >40 mmHg, or < 90 mmHg or a decrease from pre-dosing of >30 mmHg
Diastolic blood pressure	> 90 mmHg or an increase from pre-dosing of > 30 mmHg, or < 50 mmHg or a decrease from pre-dosing of > 20 mmHg

The Investigators will assess whether any of the abnormal values are clinically significant. Clinically significant abnormal values will be recorded as an AE.

Vital signs measured during the open-label treatment periods after Month 12 will be described. Details will be provided in the SAP.

8.1.7.3 Physical Examination and Patch Site Examination

Physical examination results, including complete observation of the skin will be listed and summarized overall and by age group, visit, timepoint, and dose level/placebo group on the SS for the randomized blinded treatment period (Months 0 to 12).

Physical examination during the open-label treatment periods after Month 12 will be described. Details will be provided in the SAP.

In addition, examination of the skin at the site of Viaskin patch application will be graded from Grade 0 (negative) up to Grade 4 (erythema, vesicles). These results will be summarized using descriptive statistics and presented overall and by age group, visit, dose level and placebo group in the SS for the randomized blinded treatment period (Months 0 to 12). Worst grade reported by subject for blinded treatment period and open-label treatment period will also be tabulated.

Examination of skin at patch site during the open-label treatment periods after Month 12 will be described. Details will be provided in the SAP.

8.1.7.4 Clinical Laboratory Tests

Clinical laboratory test results will be presented in Standard International (SI) units unless otherwise specified and will be summarized overall and by age group, dose level and placebo group, and timepoint for both absolute values and changes from baseline for the randomized blinded treatment period (Months 0 to 12).

Shift tables will be generated to compare baseline values to the values collected at Month 12. Listed data values that are outside the reference range will be flagged.

Clinical laboratory test results assessed during the open-label treatment periods after Month 12 will be described. Details will be provided in the SAP.

Urine pregnancy test results will be listed.

8.1.7.5 Spirometry and Peak Expiratory Flow

Spirometry (FEV_1) and PEF results as % predicted values will be summarized overall and by age group, dose level and placebo group, and timepoint using descriptive statistics on the SS for the randomized blinded treatment period (Months 0 to 12).

Spirometry and PEF results assessed during the open-label treatment periods after Month 12 will be described. Details will be provided in the SAP.

Spirometry and PEF results will also be listed.

8.1.7.6 Subject Diary Card Data

Diary card data will be listed. Data derived from the diaries (eg, number of days of itching, redness and swelling [with associated grades], worst grades of itching, redness and swelling documented by the subjects, compliance of treatment and duration of patch application) will be summarized.

8.1.8 Exploratory Variables

Exploratory endpoints include the change from baseline value in level of sIgE to peanut, egg, house dust mite, and grass pollen at all timepoints.

Exploratory endpoints will also include the change from baseline in epigenetic modifications at Month 12 and after Month 12 if evaluated.

The above analyses will be defined in the SAP.

Filaggrin gene mutations will be assessed from a blood sample collected at 1 visit and the results will be listed. The relationship between the presence of filaggrin mutations, safety and response to treatment will also be investigated. This analysis will be defined in the SAP.

Exploratory endpoints will also include the enumeration and characterization of reactions triggered by accidental consumption of cow's milk (in any form) and the analysis of "risk-taking behavior" of subjects (or voluntary milk consumption as assessed by the Investigators) during the study. Both pieces of information (accidental consumption and reactions triggered by consumption) will be collected from subject Diary Cards and voluntary or accidental consumption will be assessed by the investigative staff while interviewing the subjects.

Frequency of accidental consumption of cow's milk (in any form), conditions around the accidental consumption, estimated quantity consumed at each occurrence, and associated reactions and severity of reactions will be analyzed separately.

Risk-taking behaviors: frequency of deliberate consumption of cow's milk (in any form), conditions around the consumption, estimated quantity consumed at each occurrence and associated reactions with these consumptions will be analyzed separately. Relatedness to the subject's age category will also be analyzed.

End-of-study surveys completed by the investigators will be analyzed to assess the planned management of each subject after termination of the study.

8.2 Interim Analyses

There are no interim efficacy analyses planned for this study, however a report will be provided based on the safety data collected from Part A subjects, and analysis of the safety data by treatment groups as described in the SAP.

After all subjects from Part A and Part B have received 12 months of treatment with Viaskin patch and completed the Month 12 DBPCFC, a data transfer will be performed after the data are cleaned, coded, and reconciled with SAE and laboratory data. The database will be put on hold (ie, no updates will be performed) during the time of the analysis. The study data will be analyzed as described in the SAP and the results will be reported in the 12-month CSR.

After the Month 12 DBPCFC, subjects were to continue treatment with active Viaskin Milk patch in an open-label manner at the highest dose (500 µg), assessed to be safe based of safety data of Part A subjects, until Month 48, but will be switched to Viaskin Milk 300 µg for 24 months before Month 48. The study data will be analyzed as described in the SAP and the results will be reported in the final CSR.

8.3 Determination of Sample Size

CCI

8.4 Randomization Procedures

Up to approximately 194 subjects will be randomized in the study (18 subjects in Part A and 176 subjects in Part B).

In Part A, subjects will be randomized in 3 successive cohorts of 6 subjects each to receive Viaskin Milk or placebo in a 2:1 ratio. The safety of the 3 doses of Viaskin Milk will be assessed over a 3-week treatment period for each dose before proceeding to Part B with the 3 safe doses. The analysis of the cumulative safety data permitted the selection of the 3 Viaskin Milk doses (150 µg, 300 µg, and 500 µg of cow's milk proteins) for randomization into Part B of the study. The screening of subjects in Part B of the study may continue when the enrollment in Part A is complete, however no subject will be randomized into, or treated in, Part B before the review of the safety data from Part A has been completed by both the DSMB and the FDA. A pause in the randomization will allow for this safety review to occur and recommendations to be released.

In Part B, approximately 176 additional subjects will be randomized (1:1:1:1 ratio) to receive Viaskin Milk 150 µg (n=44) or Viaskin Milk 300 µg (n=44) or Viaskin Milk 500 µg (n=44) or placebo (n=44) until Month 12. Randomization in Part B will be stratified by site and by the following age categories: children 2 to 11 years old and adolescents 12 to 17 years old, based on the subject's age at Visit 1.

Subjects will be randomized to the dose level group or placebo in accordance with the randomization schedule generated by the CRO using [redacted]. An external IWRS will be used to allocate subjects to the dose level group or placebo, as applicable.

Random Sequencing of the Challenge Formulas During the DBPCFC

The sequence of food challenge formulas on the first day and the second day of the DBPCFCs will also be randomized. Each site will be provided with a randomization table at Screening, Months 12, 24, 36, and 48. The unblinded site personnel in charge of the preparation of the food challenge formula will be given a password-protected table. For each subject to be challenged, the unblinded site personnel will enter the

subject information and the table will populate automatically to determine which formula (Milk or placebo) is given on the first day of the food challenge and which formula (Milk or placebo) will be given the second day of the challenge. The subject and the assessors will remain blind to the formulas' order during the conduct of the challenge on both days (see Section 7.3.1.1 for emergency unblinding procedures). Only at the end of the second day of challenge will the order of the formulas be unblinded to the subject and the assessors.

9 Quality Assurance and Quality Control

9.1 Audit and Inspection

Study sites and study documentation will be subject to quality assurance (QA) audit during the course of the study by the sponsor and the CRO representatives. In addition, inspections may be conducted by regulatory authorities at their discretion. The Investigator must permit direct access to all study-related documents during the audits.

9.2 Monitoring

The study data for each subject will be recorded in the eCRF. Data collection must be completed for each subject who is administered the investigational product and for their parent(s)/guardian(s), as applicable, who sign(s) an ICF/IAF.

In accordance with current Good Clinical Practice (cGCP) and ICH guidelines, the clinical monitor of the CRO will perform source document verification at regular intervals to ensure that the data collected in the eCRF are accurate and reliable. The frequency of monitoring visits will be determined by the rate of subject recruitment.

The following will be reviewed at these visits:

- Compliance with the protocol.
- Consent procedures.
- AE collection procedures.
- Regulatory/Essential Document maintenance.
- Storage and accountability of materials.

The monitoring visits also provide the sponsor with the opportunity to ensure the Investigator's obligations and all applicable ICH or health authority regulation requirements are being fulfilled. The Investigator must permit the monitor, the IRB, the sponsor's internal auditors, and representatives from regulatory authorities direct access to all study-related documents and pertinent hospital or medical records for confirmation of data contained within the eCRFs. Subject confidentiality will be protected at all times.

9.3 Data Management and Coding

The CRO will be responsible for activities associated with the data management of this study. This will include setting up a relevant database and electronic data capture (EDC) system ([redacted]) and data transfer mechanisms, along with appropriate validation of data and resolution of queries. Data generated within this clinical study will be handled according to the relevant SOPs of the data management and biostatistics departments of the CRO.

All data that are not available in electronic format (eg, diary cards) will be double-entered into the data management system, if these data have to be entered by the CRO personnel. Following data verification (completion of second data entry and further verification of the entries), the audit trail will be switched on (ie, a computerized log of all subsequent changes to the data will be recorded). Automated checks will be made against the data to ensure completeness and consistency. The database and check programs will be validated before implementation.

MedDRA will be used to code concomitant diseases and AEs and the WHODrug will be used for concomitant medications.

Missing or inconsistent data will be queried in writing to the Investigator for clarification. Subsequent modifications to the database will be documented.

The sites will enter data directly into the EDC system by completing the eCRF via a secure internet connection. The CRO will provide training on how to use the system to the Investigators at each site. Data entered into the eCRF must be verifiable against source documents at the site. Data to be recorded directly in the eCRF (without prior written or electronic record) will be identified and the eCRF will be considered the source document. Any changes to the data entered into the EDC system will be recorded in the audit trail and is FDA CFR 21 Part 11 compliant.

Data entered into the eCRF will be validated as will be defined in the data validation specification. External data checks will be programmed where appropriate (eg for laboratory data) as well as for cross table checking between eCRF's (eg AE and concomitant medication forms).

10 Records and Supplies

10.1 Drug Accountability

On receipt of the investigational product (including placebo product, as applicable), the Investigator (or deputy) will conduct an inventory of the supplies and verify that the investigational product supplies are received intact and in the correct amounts before completing a supplies receipt. The Investigator will retain a copy of this receipt at the site and return the original receipt to the study monitor. The investigational product will be shipped by the depot to a designated person at the study site and must be stored in a locked and secured storage facility, accessible only to those individuals authorized by the Investigator. The inventory of supplies at each study site may be checked at any time during the study by the monitor.

It is the responsibility of the study monitor to ensure that the Investigator (or deputy) has correctly documented the amount received, dispensed and returned of the investigational product on the dispensing log that will be provided. A full product accountability log will be maintained at the site at all times. The study monitor will arrange regular collection of unused investigational product that was returned by the subject. The study monitor will also perform an inventory of investigational product at the close-out visit to the study site. All discrepancies must be accounted for and documented.

At the end of the study, the sites will be responsible for destroying unused investigational product and providing a corresponding certificate of destruction.

10.2 Financing and Insurance

Financing and insurance of this study will be outlined in a separate agreement between the CRO and the sponsor.

11 Ethics

11.1 Institutional Review Board

Before initiation of the study at each study site, the protocol, all protocol amendments, ICFs, IAFs, the subject information sheet and any other relevant study documentation will be submitted to the appropriate IRBs. Written approval of the study and all relevant study information must be obtained before the study sites can be initiated or the investigational product is released to the Investigators. Any necessary extensions or renewals of the IRB approval must be obtained, in particular, for changes to the study such as modification of the protocol, the ICFs, IAFs, the written information provided to subjects and/or parent(s)/guardian(s), and/or other procedures.

The Investigator will report promptly to the IRB any new information that may adversely affect the safety of the subjects or the conduct of the study. The Investigator will submit written summaries of the study status to the IRB annually, or more frequently if requested by the IRB. On completion of the study, the sponsor will notify the IRB that the study has ended.

11.2 Ethical Conduct of the Study

This study will be conducted in accordance with applicable laws and regulations including, but not limited to, the ICH guidelines for Good Clinical Practice (ICH E6)[27], the ethical principles from the declaration of Helsinki[28] (Appendix 14.7), and applicable local regulatory requirements. The IRB must review and approve the protocol and ICFs/IAFs before any subjects are enrolled into the study. Each subject and/or parent(s)/guardian(s) must sign and date the IRB-approved ICFs/IAFs, before any protocol-required procedures are performed.

11.3 Subject Information and Consent

The Investigator is responsible for ensuring that no subject undergoes any study-related examination or activity before the subject's parent(s)/guardian(s) has given written informed consent. Subjects ≥7 years old (or as per local or country specific guidelines or regulations) will be encouraged to sign the IAF to participate in the study. The written ICF/IAF must be given by the subject and/or his/her parent(s)/guardian(s), after detailed information about the study has been given by appropriate personnel at the site and in accordance with any national provisions on the protection of clinical study subjects. The verbal explanation will cover all the elements specified in the written information provided for the subject and/or parent(s)/guardian(s).

The Investigator or designated personnel will inform the subject and/or parent(s)/guardian(s) of the objectives, methods, anticipated benefits and potential risks and inconveniences of the study. The subject and/or parent(s)/guardian(s) should be given every opportunity to ask for clarification of any points he/she does not understand and, if necessary, for more information. At the end of the interview, the subject and/or parent(s)/guardian(s) will be given time to consider the study, if needed, or if the subject and/or parent(s)/guardian(s) requests more time. Parent(s)/guardian(s) will be required to sign and date the ICF(s). After signatures are obtained, the ICF(s)/IAF(s) will be kept and archived by the Investigator in the Investigator's study file for possible inspection by regulatory authorities, the IRB, and the CRO personnel.

It should be emphasized to the subject and/or parent(s)/guardian(s) that he/she is at liberty to withdraw from the study at any time. Subjects and/or parent(s)/guardian(s)

who refuse to give or who withdraw written informed consent should not be included or continue participation in the study.

11.4 Subject Confidentiality

All personal data collected and processed for the purposes of this study should be managed by the Investigator and his/her staff with adequate precautions to ensure confidentiality of those data, and in accordance with the Health Insurance Portability and Accountability Act[29], applicable to national and/or local laws and regulations on personal data protection.

Monitors, auditors, and other authorized agents of the sponsor and/or its designee, the ethics committees approving this research, and the FDA, as well as those of any other applicable agency, will be granted direct access to the study subjects' original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subjects to the extent permitted by the law and regulations. In any presentations of the results of this study or in publications, the subjects' identity will remain confidential.

12 Study Administration, Reporting and Publication, Including Archiving

12.1 Study Administration

International Coordinating Investigator:

PPD

DBV Technologies Personnel

VP, Head of Biometrics

PPD

SVP Global Regulatory Affairs

PPD

SVP Clinical Operations

PPD

Director Clinical Projects

PPD

Clinical Project Manager

PPD

Medical Monitor

PPD

Safety and Pharmacovigilance Officer
DBV Global Safety and Pharmacovigilance Department

PPD

Syneos Health (formerly INC Research) Personnel

The CRO, Syneos Health (formerly INC Research) is conducting this clinical study on behalf of the sponsor, DBV Technologies.

Medical Monitor

PPD

Clinical Drug Supply and Central Laboratories

CCI will manufacture both the active Viaskin Milk and placebo patches.

Central and other laboratories will be designated by the sponsor, DBV Technologies, and appropriate contact information and laboratory manuals will be provided to the sites.

12.2 Reporting and Publication, Including Archiving

Essential documents are those documents that individually and collectively permit evaluation of the study and quality of the data produced. After completion of the study, all documents and data relating to the study will be kept in an orderly manner by the Investigator in a secure study file. This file will be available for inspection by the sponsor or its representatives. Essential documents should be retained for 2 years after the final marketing approval in an ICH region or for at least 2 years since the discontinuation of clinical development of the investigational product. It is the responsibility of the sponsor to inform the study site of when these documents no longer need to be retained. The Investigator must contact the sponsor before destroying any study related documentation. In addition, all subject medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution or medical practice.

The sponsor must review and approve any results of the study or abstracts for professional meetings prepared by the Investigator(s). Published data must not compromise the objectives of the study. Data from individual study sites in multi-center studies must not be published separately.

13 References

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14 Appendices

14.1 Investigator Signature Page

Protocol Title: A Double-Blind, Placebo-Controlled Randomized Trial to Study the Viaskin MILk Efficacy and Safety for Treating IgE-Mediated Cow's Milk Allergy in Children (MILES Study)

Protocol Number: MILES

Confidentiality and cGCP Compliance Statement

I, the undersigned, have reviewed this protocol, including appendices, and I will conduct the study as described in compliance with this protocol, GCP, and relevant ICH guidelines.

Once the protocol has been approved by the IRB, I will not modify this protocol without obtaining prior approval of DBV Technologies and of the IRB. I will submit the protocol modifications and/or any ICF/IAF modifications to DBV Technologies and the IRB, and approval will be obtained before any modifications are implemented.

I understand that all information obtained during the conduct of the study related to the subjects' state of health will be regarded as confidential. No subjects' names will be disclosed. All subjects will be identified by assigned numbers on all eCRFs, laboratory samples or source documents forwarded to the sponsor. Clinical information may be reviewed by the sponsor or its agents or regulatory agencies. Agreement must be obtained from the subject before disclosure of subject information to a third party.

Information developed in this clinical study may be disclosed by DBV Technologies, to other clinical Investigators, regulatory agencies, or other health authority or government agencies, as required.

_____ _____

Investigator Signature Date

_____

Printed Name

_____

Institution

14.2 Oral Food Challenge Symptom Score Sheets

I. SKIN

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

	1-4 years old	5-8 years old	9-12 years old	≥13 years old
Head	17%	16%	12%	4.5%
Neck	2%	2%	2%	1%
Anterior trunk	16%	14%	14%	18%
Posterior trunk	16%	18%	18%	18%
Leg (1)	15%	15%	17%	18%
Arm (1)	9.5%	10%	10%	9%

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

II. UPPER RESPIRATORY/OCCULAR

	Stopping rules: minimal # of grade increase	
	Alone	**Associated**
A. Sneezing/Itching	**+3**	**+2**
0 = Absent		
1 = Mild: rare bursts		
2 = Moderate: bursts <10, intermittent rubbing of nose / eyes / external ear canals		
3 = Severe: continuous rubbing of nose / eyes, periocular swelling and/or long bursts of sneezing		
B. Nasal Congestion	**+3**	**+2**
0 = Absent		
1 = Mild: some hindrance to breathing		
2 = Moderate: nostrils feel blocked, breathing through mouth most of time		
3 = Severe: nostrils occluded		

C. Rhinorrhea	**+3**	**+2**
0 = Absent		
1 = Mild: occasional sniffling		
2 = Moderate: frequent sniffling, requires tissues		
3 = Severe: nose runs freely despite sniffling and tissues		
D. Laryngeal (only symptoms due to laryngeal edema)	**+2**	**+1**
0 = Absent		
1 = Mild: throat clearing, occasional cough		
2 = Moderate: hoarseness, frequent dry cough		
3 = Severe: inspiratory stridor		
E. Conjunctivitis (see example below)	**+3**	**+2**
0 = Absent		
1 = Mild:		
2 = Moderate:		
3 = Severe:		

Grade 1 Grade 2 Grade 3

III. LOWER RESPIRATORY

	Stopping rules: minimal # of grade increase	
	Alone	**Associated**
A. Wheezing (including cough due to bronchospasm)	**+1**	**+1**
0 = Absent		
1 = Mild: expiratory wheezing to auscultation		
2 = Moderate: dyspnea, inspiratory and expiratory wheezing		
3 = Severe: dyspnea, use of accessory muscles, audible wheezing		

IV. GASTROINTESTINAL

	Stopping rules: minimal # of grade increase	
	Alone	**Associated**
A. Subjective Complaints	**+3**	**+2**
0 = Absent		
1 = Mild: itchy mouth/throat, c/o nausea, abdominal pain, no change in activity		
2 = Moderate: frequent c/o nausea or abdominal pain, decreased activity		
3 = Severe: patient in bed; crying, notably distressed		
B. Objective Complaints	**+1**	**+1**
0 = Absent		
1 = Mild: 1 episode of emesis* or diarrhea		
2 = Moderate: 2-3 episodes of emesis* or diarrhea or 1 of each		
3 = Severe: >3 episodes of emesis* or diarrhea or 2 of each		

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

V. CARDIOVASCULAR/NEUROLOGIC

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

14.3 Quality of Life Questionnaire Forms

14.3.1 Food Allergy Quality of Life Questionnaire-Child Form (FAQLQ-CF)

FAQLQ-CF

Food Allergy Quality of Life Questionnaire – Child Form (8-12 years)

To cite this questionnaire:
Flokstra-de Blok BMJ, DunnGalvin A, Vlieg-Boerstra BJ, Oude Elberink JNG, Duiverman EJ, Hourihane JO, Dubois AEJ. Development and validation of a self-administered Food Allergy Quality of Life Questionnaire for children. Clin Exp Allergy 2009 Jan;39(1):127-137.

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

not barely a little bit fairly quite very extremely

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

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

How *frightened* are you because of your food allergy …	
19	of an allergic reaction?
20	of eating the wrong food by accident?
21	to eat something you have never eaten before?

Answer the following questions:	
22	How *concerned* are you that you will never get rid of your food allergy?
23	How *disappointed* are you when people don’t take your food allergy into account?
24	How *disappointed* do you feel because you have a food allergy?

Food Allergy Independent Measure – Child Form (8-12 years)

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

0	1	2	3	4	5	6
never (0% chance)	**very small chance**	**small chance**	**fair chance**	**big chance**	**very big chance**	**always (100% chance)**

How big do you think the chance is that you …		**0**	**1**	**2**	**3**	**4**	**5**	**6**
1	will accidentally eat something to which you are allergic?	☐	☐	☐	☐	☐	☐	☐
2	will have a severe reaction if you accidentally eat something to which you are allergic?	☐	☐	☐	☐	☐	☐	☐
3	will die if you accidentally eat something to which you are allergic?	☐	☐	☐	☐	☐	☐	☐
4	can **not** do the right things for your allergic reaction should you accidentally eat something to which you are allergic?	☐	☐	☐	☐	☐	☐	☐

5. How many foods are you unable to eat because of your food allergy?	**6.** Everyone does things with other people, such as; - playing with friends, - going to a birthday party, - visiting, - staying over with someone for a meal or eating out. **How much does your food allergy affect things you do with others?**
☐ almost none	☐ so little I don't actually notice it
☐ very few	☐ very little
☐ a few	☐ little
☐ some	☐ moderately
☐ many	☐ a good deal
☐ very many	☐ a great deal
☐ almost all	☐ a very great deal

14.3.2 Food Allergy Quality of Life Questionnaire-Teenager Form (FAQLQ-TF)

FAQLQ-TF

Food Allergy Quality of Life Questionnaire – Teenager Form (13-17 years)

To cite this questionnaire:
Flokstra-de Blok BMJ, DunnGalvin A, Vlieg-Boerstra BJ, Oude Elberink JNG, Duiverman EJ, Hourihane JO, Dubois AEJ. Development and validation of the self-administered Food Allergy Quality of Life Questionnaire for adolescents. J Allergy Clin Immunol 2008 Jul;122(1):139-144.

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

0	1	2	3	4	5	6
not	barely	slightly	moderately	quite	very	extremely

	How *troublesome* do you find it, because of your food allergy, that you …	**0**	**1**	**2**	**3**	**4**	**5**	**6**
1	must always be alert as to what you are eating?	☐	☐	☐	☐	☐	☐	☐
2	are able to eat fewer products?	☐	☐	☐	☐	☐	☐	☐
3	are limited as to the products you can buy?	☐	☐	☐	☐	☐	☐	☐
4	must read labels?	☐	☐	☐	☐	☐	☐	☐
5	have the feeling that you have less control of what you eat when eating out?	☐	☐	☐	☐	☐	☐	☐
6	are less able to spontaneously accept an invitation to stay for a meal?	☐	☐	☐	☐	☐	☐	☐
7	are less able to taste or try various products when eating out?	☐	☐	☐	☐	☐	☐	☐
8	must check yourself whether you can eat something when eating out?	☐	☐	☐	☐	☐	☐	☐
9	hesitate eating a product when you have doubts about it?	☐	☐	☐	☐	☐	☐	☐
10	must refuse treats at school or work?	☐	☐	☐	☐	☐	☐	☐
11	must be careful about touching certain foods?	☐	☐	☐	☐	☐	☐	☐
12	must carry an epinephrine auto injector [redacted]? (If you don't have an epinephrine auto injector mark an 'x' here ☐)	☐	☐	☐	☐	☐	☐	☐

0	1	2	3	4	5	6
not	barely	slightly	moderately	quite	very	extremely

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

How *frightened* are you because of your food allergy …		**0**	**1**	**2**	**3**	**4**	**5**	**6**
19	of an allergic reaction?	☐	☐	☐	☐	☐	☐	☐
20	of accidentally eating the wrong food?	☐	☐	☐	☐	☐	☐	☐
21	to eat something you have never eaten before?	☐	☐	☐	☐	☐	☐	☐

Answer the following questions:		**0**	**1**	**2**	**3**	**4**	**5**	**6**
22	How *discouraged* do you feel during an allergic reaction?	☐	☐	☐	☐	☐	☐	☐
23	How *disappointed* are you when people don't take your food allergy into account?	☐	☐	☐	☐	☐	☐	☐

Food Allergy Independent Measure – Teenager Form (13-17 years)

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

0	1	2	3	4	5	6
never (0% chance)	very small chance	small chance	fair chance	great chance	very great chance	always (100% chance)

How great do you think the chance is that you …		0	1	2	3	4	5	6
1	will accidentally eat something to which you are allergic?	☐	☐	☐	☐	☐	☐	☐
2	will have a severe reaction if you accidentally eat something to which you are allergic?	☐	☐	☐	☐	☐	☐	☐
3	will die if you accidentally eat something to which you are allergic?	☐	☐	☐	☐	☐	☐	☐
4	can **not** effectively deal with an allergic reaction should you accidentally eat something to which you are allergic?	☐	☐	☐	☐	☐	☐	☐

5. How many products must you avoid because of your food allergy?	**6. How great is the impact of your food allergy on your social life?**
☐ almost none	☐ negligibly small
☐ very few	☐ very small
☐ a few	☐ small
☐ some	☐ moderate
☐ many	☐ great
☐ very many	☐ very great
☐ almost all	☐ extremely great

14.3.3 Food Allergy Quality of Life Questionnaire – Parent Form for Children (FAQLQ-PF)

FAQLQ-PF

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

To cite this questionnaire:
DunnGalvin A, Flokstra-de Blok BMJ, Burks AW, Dubois AEJ, Hourihane JO. Food allergy QoL questionnaire for children aged 0-12 years: content, construct, and cross-cultural validity. Clin Exp Allergy 2008 Jun;38(6):977-986.

Food Allergy Quality of Life Questionnaire-Parent Form (FAQoL-PF) Children aged 0-12 years

Instructions to Parents

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

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

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

All information given is completely confidential.
This questionnaire will only be identified by a code number.

- If your child is aged **0 to 3 years**, please answer **Section A**.
- If your child is aged **4 to 6 years**, please answer **Section A & Section B**.
- If your child is aged **7 years and over**, please answer **Section A, Section B & Section C**.

SECTION A

Because of food allergy, my child feels…	**Not at all → Extremely** 0	1	2	3	4	5	6
1 Anxious about food	☐	☐	☐	☐	☐	☐	☐
2 Different from other children	☐	☐	☐	☐	☐	☐	☐
3 Frustrated by dietary restrictions	☐	☐	☐	☐	☐	☐	☐
4 Afraid to try unfamiliar foods	☐	☐	☐	☐	☐	☐	☐
5 Concerned that I am worried that he/she will have a reaction to food	☐	☐	☐	☐	☐	☐	☐

Because of food allergy, my child…	**Not at all → Extremely** 0	1	2	3	4	5	6
6 Experiences physical distress	☐	☐	☐	☐	☐	☐	☐
7 Experiences emotional distress	☐	☐	☐	☐	☐	☐	☐
8 Has a lack of variety in his/her diet	☐	☐	☐	☐	☐	☐	☐

Because of food allergy, my child has been negatively affected by…	**Not at all → Extremely** 0	1	2	3	4	5	6
9 Receiving more attention more attention than other children of his/her age	☐	☐	☐	☐	☐	☐	☐
10 Having to grow up more quickly than other children of his/her age	☐	☐	☐	☐	☐	☐	☐
11 His/her environment being more restricted than other children of his/her age	☐	☐	☐	☐	☐	☐	☐

Because of food allergy, my child's social environment is restricted because of limitations on…	**Not at all → Extremely** 0	1	2	3	4	5	6
12 Restaurants we can safely go to as a family	☐	☐	☐	☐	☐	☐	☐
13 Holiday destinations we can safely go to as a family	☐	☐	☐	☐	☐	☐	☐

Because of food allergy, my child's ability to take part has been limited…	**Not at all → Extremely** 0	1	2	3	4	5	6
14 In social activities in other people's houses (*sleepovers, parties, playtime*)	☐	☐	☐	☐	☐	☐	☐

- If your child is aged **0 to 3 years**, please now go to **Section D.**
- If your child is aged **4 to 12 years**, please now answer **Section B.**

SECTION B

	Not at all → Extremely						
Because of food allergy, my child's ability to take part has been limited…	**0**	**1**	**2**	**3**	**4**	**5**	**6**
15 In preschool/school events involving food *(class parties/treats/lunchtime)*	☐	☐	☐	☐	☐	☐	☐

	Not at all → Extremely						
Because of food allergy, my child feels…	**0**	**1**	**2**	**3**	**4**	**5**	**6**
16 Anxious when going to new places	☐	☐	☐	☐	☐	☐	☐
17 Concerned that he/she must always be cautious about food	☐	☐	☐	☐	☐	☐	☐
18 'Left out' in activities involving food	☐	☐	☐	☐	☐	☐	☐
19 Upset that family social outings (eating out, celebrations, days out) have been limited by food allergy	☐	☐	☐	☐	☐	☐	☐
20 Anxious about accidentally eating an ingredient to which he/she is allergic	☐	☐	☐	☐	☐	☐	☐
21 Anxious when eating with unfamiliar adults/children	☐	☐	☐	☐	☐	☐	☐
22 Frustrated by social restrictions	☐	☐	☐	☐	☐	☐	☐

	Not at all → Extremely						
Because of food allergy, my child…	**0**	**1**	**2**	**3**	**4**	**5**	**6**
23 Is more anxious in general than other children of his/her age	☐	☐	☐	☐	☐	☐	☐
24 Is more cautious in general than other children of his/her age	☐	☐	☐	☐	☐	☐	☐
25 Is not as confident as other children of his/her age in social situations	☐	☐	☐	☐	☐	☐	☐
26 Wishes his/her food allergy would go away	☐	☐	☐	☐	☐	☐	☐

- If your child is aged **6 years and under**, please now go to **Section D**.
- If your child is aged **7 years and older**, please answer **Section C**.

SECTION C

Because of food allergy, my child feels…	**Not at all → Extremely** 0	1	2	3	4	5	6
27 Worried about his/her future (opportunities, relationships)	☐	☐	☐	☐	☐	☐	☐
28 That many people do not understand the serious nature of food allergy	☐	☐	☐	☐	☐	☐	☐
29 Concerned by poor labelling on food products	☐	☐	☐	☐	☐	☐	☐
30 That food allergy limits his/her life in general	☐	☐	☐	☐	☐	☐	☐

SECTION D

Please answer the following questions with reference to the 7-point scale on the right

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

Q1. What chance **do you think** your child has of ….?

	Question	**7-point Scale** 0	1	2	3	4	5	6
1	……accidentally ingesting the food to which they are allergic?							
2	……having a severe reaction if food is accidentally ingested?							
3	……dying from his/her food allergy following ingestion in the future?							
4	……effectively treating him/herself, or receiving effective treatment from others (including Epipen administration), if he/she accidentally ingests a food to which he/she is allergic?							

Q2. What chance **does your child think** he/she has of ……?

	Question	**7-point Scale** 0	1	2	3	4	5	6
1	……accidentally ingesting the food to which they are allergic?							
2	……having a severe reaction if food is accidentally ingested?							
3	……dying from his/her food allergy following ingestion in the future?							
4	……effectively treating him/herself, or receiving effective treatment from others (including Epipen administration), if he/she accidentally ingests a food to which he/she is allergic?							

14.3.4 Food Allergy Quality of Life Questionnaire – Parent Form for Teenagers (FAQLQ-PFT)

FAQLQ-PFT

Food Allergy Quality of Life Questionnaire – Parent Form – Adolescents aged 13-17

To cite the original English questionnaire:
Knibb et al., unpublished

To cite the Dutch translated questionnaire:
van der Velde JL, Flokstra-de Blok BMJ, Hamp A, Knibb RC, Duiverman EJ, Dubois AEJ. Adolescent-parent disagreement on quality of life of food allergic adolescents; Who makes the difference? Allergy. 2011

Food Allergy Quality of Life Questionnaire – Parent Form - Adolescents Aged 13-17

Instructions for participants

- The following are all scenarios that parents have told us affect their adolescent's quality of life because of food allergy.
- Please indicate how much of an impact each scenario has on your teenager's quality of life by placing a tick or a cross in one of the boxes number 0-6.
- If you believe the scenario has no impact please choose 0 (not at all). It is important that you answer all the questions to help us understand the impact of food allergy on the quality of life of teenagers.

Response choice
0 = not at all

1 = barely

2 = slightly

3 = moderately

4= quite a bit

5 = very much

6 = extremely

- **All information given is confidential**
- **The questionnaire will only be identified by a code number**

		Response choice						
	Question	**0**	**1**	**2**	**3**	**4**	**5**	**6**
		Not at all	Barely	Slightly	Moderately	Quite a bit	Very much	Extremely
1.	My teenager always eats the same foods because of food allergy							
2.	My teenager has a restricted diet because of food allergy							
3.	My teenager cannot experiment with different foods on holiday because of food allergy							
4.	My teenager misses out because of food allergy							
5.	My teenager is more cautious generally because of food allergy							
6.	My teenager sticks to foods he/she knows							
7.	My teenager has to be more sensible that his/her peers because of food allergy							
8.	My teenager takes more of an interest in food because of food allergy							
9.	My teenager reads the label on everything he/she eats							
10.	My teenager is frustrated about food labelling							
11	My teenager is more wary of situations because of food allergy							
12.	My teenager feels different because he/she cannot eat what his/her friends can eat							
13.	My teenager feels anxious in restaurants							
14.	My teenager finds it difficult to ask about food ingredients in restaurants							
15.	My teenager avoids telling people about his/her food allergy until he/she knows them well							
16.	My teenager gets irritated by his/her food allergy							
17.	My teenager worries as he/she always has to carry a bag because of his/her medication							

	Question	0	1	2	3	4	5	6
		Not at all	Barely	Slightly	Moderately	Quite a bit	Very much	Extremely
18.	School trips away are not easy for my teenager							
19.	My teenager worries that he/she can only eat in a limited range of restaurants							
20.	My teenager has been really scared by having a reaction							
21.	My teenager feels nervous around the food they are allergic to because of food allergy							
22.	My teenager gets frightened about food allergy							
23.	I feel my teenager has had to grow up more quickly because of food allergy							
24.	My teenager has to be more responsible than other teenagers							
25.	My teenager has been teased because of food allergy							
26.	My teenager gets frustrated because of food allergy							
27.	My teenager feels different to other teenagers because of food allergy							

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

0 = extremely unlikely

1 = very unlikely

2 = somewhat unlikely

3 = likely

4 = quite likely

5 = very likely

6 = extremely likely

	Question	7-point Scale						
		0	**1**	**2**	**3**	**4**	**5**	**6**
1.	What chance do you think your teenager has of accidentally ingesting the food to which they are allergic?							
2.	What chance do you think your teenager has of having a severe reaction if food is accidentally ingested?							
3.	What chance do you think your teenager has of dying from his/her food allergy following ingestion in the future?							
4.	What chance do you think your teenager has of effectively treating him/herself or receiving effective treatment from others (including Epipen administration) if he/she accidentally ingests a food to which he/she is allergic?							

14.4 Anaphylaxis Staging System

Anaphylaxis is a generalized allergic reaction that is rapid in onset and may progress to death. The stages of severity for anaphylaxis reactions are presented below.

Staging System of Severity of Anaphylaxis

Stage	**Defined By**
1. Mild (skin and subcutaneous tissues, Gastrointestinal, and/or mild respiratory)	Flushing, urticaria, periorbital or facial angioedema; mild dyspnea, wheeze or upper respiratory symptoms; mild abdominal pain and/or emesis.
2. Moderate (mild symptoms + features suggesting moderate respiratory, cardiovascular or Gastrointestinal symptoms)	Marked dysphagia, hoarseness, and/or stridor; shortness of breath, wheezing & retractions; crampy abdominal pain, recurrent vomiting and/or diarrhea; and/or mild dizziness.
3. Severe (hypoxia, hypotension, or neurological compromise)	Cyanosis or $SpO_2 \leq 92\%$ at any stage, hypotension, confusion, collapse, loss of consciousness; or incontinence.

14.5 Anaphylaxis Emergency Action Plan

Example Form: ANAPHYLAXIS EMERGENCY ACTION PLAN

NAME: **AGE:**

ALLERGY TO:

Asthma: ☐ **Yes** ***(high risk for severe reaction)*** ☐ **No**

Other health problems besides anaphylaxis:

Concurrent medications, if any:

SYMPTOMS OF ANAPHYLAXIS INCLUDE:

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

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

WHAT TO DO:
1. **INJECT EPINEPHRINE IN THIGH USING** ***(specify injector provided and dose):***

Other medication/dose/route:

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

2. **CALL 911 or RESCUE SQUAD (BEFORE CALLING CONTACTS)!**

3. **EMERGENCY CONTACTS**

Emergency contact #1:	**home**	**work**	**cell**
Emergency contact #2:	**home**	**work**	**cell**
Emergency contact #3:	**home**	**work**	**cell**

DO NOT HESITATE TO GIVE EPINEPHRINE!

COMMENTS:

Health's Care Provider Signature / Date:

Parent(s)/Guardians(s)'Signature / Date
(for individuals under age 18 yrs)

14.6 Inhalation Corticosteroid Dose Conversion Table by Age Category

Children ≤4 years of age	Low Daily Dose	Medium Daily Dose	High Daily Dose
Beclomethasone HFA 40 or 80 mcg/puff	NA	NA	NA
Budesonide DPI 90, 180, or 200 mcg/inhalation	NA	NA	NA
Budesonide Inhaled Inhalation suspension for nebulization	0.25-0.5 mg	>0.5-1.0 mg	>1.0 mg
Flunisolide 250 mcg/puff	NA	NA	NA
Flunisolide HFA 80 mcg/puff	NA	NA	NA
Fluticasone HFA/MDI 44, 110, or 220 mcg/puff	176 mcg	>176-352 mcg	>352 mcg
DPI 50, 100, or 250 mcg/inhalation	NA	NA	NA
Mometasone DPI 200 mcg/inhalation	NA	NA	NA
Triamcinolone acetonide 75 mcg/puff	NA	NA	NA
Children 5 to 11 years of age	**Low Daily Dose**	**Medium Daily Dose**	**High Daily Dose**
Beclomethasone HFA 40 or 80 mcg/puff	80–160 mcg	>160–320 mcg	>320 mcg
Budesonide DPI 90, 180, or 200 mcg/inhalation	180–400 mcg	>400–800 mcg	>800 mcg
Budesonide Inhaled Inhalation suspension for nebulization	0.5 mg	1.0 mg	2.0 mg
Flunisolide 250 mcg/puff	500–750 mcg	1,000–1,250 mcg	>1,250 mcg
Flunisolide HFA 80 mcg/puff	160 mcg	320 mcg	≥640 mcg
Fluticasone HFA/MDI 44, 110, or 220 mcg/puff	88–176 mcg	>176–352 mcg	>352 mcg
DPI 50, 100, or 250 mcg/inhalation	100–200 mcg	>200–400 mcg	>400 mcg
Mometasone DPI 200 mcg/inhalation	NA	NA	NA
Triamcinolone acetonide 75 mcg/puff	300–600 mcg	>600–900 mcg	>900 mcg

Abbreviations: DPI=dry powder inhaler; HFA=hydrofluoroalkane; MDI=metered-dose inhaler; NA=not approved and no data available for this age category

14.6 (Continued) Inhalation Corticosteroid Dose Conversion Table by Age Category

Adolescents ≥12 years of age and Adults	Low Daily Dose	Medium Daily Dose	High Daily Dose
Beclomethasone HFA 40 or 80 mcg/puff	80–240 mcg	>240–480 mcg	>480 mcg
Budesonide DPI 90, 180, or 200 mcg/inhalation	180–600 mcg	>600–1,200 mcg	>1,200 mcg
Budesonide Inhaled Inhalation suspension for nebulization	NA	NA	NA
Flunisolide 250 mcg/puff	500–1,000 mcg	>1,000–2,000 mcg	>2,000 mcg
Flunisolide HFA 80 mcg/puff	320 mcg	>320–640 mcg	>640 mcg
Fluticasone HFA/MDI 44, 110, or 220 mcg/puff	88–264 mcg	>264–440 mcg	>440 mcg
DPI 50, 100, or 250 mcg/inhalation	100–300 mcg	>300–500 mcg	>500 mcg
Mometasone DPI 200 mcg/inhalation	200 mcg	400 mcg	>400 mcg
Triamcinolone acetonide 75 mcg/puff	300–750 mcg	>750–1,500 mcg	>1,500 mcg

Abbreviations: DPI=dry powder inhaler; HFA=hydrofluoroalkane; MDI=metered-dose inhaler; NA=not approved and no data available for this age category

14.7 Wash-Out Periods for Short-Acting and Long-Acting Antihistamines Based on Terminal Elimination Half-Life

Short-Acting Antihistamines	Terminal Elimination Half-Life (h)	Minimum Wash-Out Days Before Skin-Prick Tests or Oral Food Challenges (days)
Oral		
acrivastine[a]	2-4	1[c] or ideally 3
cetirizine[a]	6.2-10	Must be 5[d]
cimetidine[a]	1.4	1[c] or ideally 3
diphenhydramine[a]	2-8	1[c] or ideally 3
famotidine[a]	0.8-5.8	1[c] or ideally 3
fexofenadine[a]	14.4	3
hydroxyzine[a]	4.8-9.4	Must be 5[d]
levocetirizine[a]	6	3
nizatadine[a]	1-2	1[c] or ideally 3
mizolastine[b]	12.9	3
ranitidine[a]	2.5-3	1[c] or ideally 3
rupatadine[b]	13	3
Intranasal/Ophthalmic		
emedastine[a]	3-4	1[c] or ideally 3
epinastine[a]	12	3
olopatadine[a]	8-12	3

Long-Acting Antihistamines	Terminal Elimination Half-Life (h)	Wash-Out Period Before Skin-Prick Tests or Oral Food Challenges (days)
Oral		
desloratadine[a]	27	7
ebastine[b]	19.3	5
chlorpheniramine[a]	6.3-23.1	6
ketotifen[a]	21	5
loratadine[a]	28	7
Intranasal/Ophthalmic		
azelastine[a]	22-25	6
ketotifen[a]	21	5
levocabastine[a]	35-40	7

[a] Lexicomp Online®, In: UpToDate, Waltham, MA. (Accessed on November 17, 2015.)

[b] Derived from: Allergy: Principles and Practice (Middleton, 7th Edition) in the form of Table 87.4 (authored by FER Simons and C Akdis).

[c] If the antihistamine is used the day prior to an oral food challenge, a Skin Prick Test must be performed before the initiation of the challenge and the result must be positive (ie, a genuine wheal with the histamine positive control must be obtained before the challenge is effectively initiated). If not, postpone the challenge.

[d] Wash-out period extended beyond 3 days based on actual clinical experience.

14.8 Declaration of Helsinki

WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects

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

Preamble

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

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

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

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words,

"The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

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

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

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

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

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

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

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

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

12. Medical research involving human subjects must be conducted only by

individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

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

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

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

Risks, Burdens and Benefits

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

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

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

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

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

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

Vulnerable Groups and Individuals

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

All vulnerable groups and individuals should receive specifically considered protection.

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

Scientific Requirements and Research Protocols

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

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

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

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

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and

standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

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

Privacy and Confidentiality

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

Informed Consent

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

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

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

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

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

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

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

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

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

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain

for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

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

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

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

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

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

Post-Trial Provisions

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

Research Registration and Publication and Dissemination of Results

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

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made

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publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

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

14.9 Reference Safety Information for the Cow's Milk Food Challenge in the MILES study

In the context of DBV135 (Viaskin Milk) clinical development, a formulated recipe of food challenge has been developed by DBV for the conduct of the Double-Blind Placebo-Controlled Food Challenge (DBPCFC) procedure in clinical trials.

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

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

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

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