Statistical Analysis Plan

Sponsor Name:	DBV Technologies
Protocol Number and Title:	MILES 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 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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Investigational Product:	Viaskin Milk (DBV135)
Indication:	Immunoglobulin E (IgE)-mediated Cow's Milk Allergy
Phase:	Phase 1 / 2
Syneos Health Project Code:	CCI
Author:	PPD
SAP Version:	8.0
SAP Version Date:	30 Oct 2020

Syneos

Statistical Analysis Plan

Version: 8.0 **Date: 30 Oct 2020**

I confirm that I have reviewed this document and agree with the content.

APPROVALS		
S neos Health		
PPD Lead Biostatistician	PPD Date (dd-Mmm-yyyy)	
PPD PPD Biostatistician DBV Technolo ies	16-Nov-2020 Date (dd-Mmm-yyyy)	
PPD VP, Head of Biometrics	PPD Date (dd-Mmm-yyyy)	
PPD Chief Medical Officer	12 Nov 2020 Date (dd-Mmm-yyyy)	

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Document History – Version Control

Version	Date	Author	Comment
1.0	30-Oct-2015	PPD	Initial version
2.0	19-Jul-2017		Updates (Amendment 3 of the study protocol)
3.0	19-Dec-2017		Updates after dry-run, Removal of the inferential paragraph in primary endpoint analysis section and addition of the paragraph detailling the dose selection for phase 3
4.0	09-Feb-2018		Systemic/inhaled and Topical Corticosteroids definition update
5.0	07-Dec-2018		Updates (Amendment 5 of the study protocol) including change in study design ofor open-label treatment period and update of AESI definition and retrieval strategies
6.0	02-Apr-2019		AESI retrieval strategy update. Clarification of OL-500 Set
7.0	20-Dec-2019		Updates for OL-300 analyses
8.0	30-Oct-2020		Updates for COVID-19

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1 GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
1-DB	Year 1 of treatment – Double blind treatment period
1-SW	Year 1 of Viaskin Milk 300µg open-label treatment period
1-OLS-300	First year open-label set 300
2-SW	Year 2 of Viaskin Milk 300µg open-label treatment period
2-OLS-300	Second year open-label set 300
AA	Allergen Avoidance
AADR	Allergen Avoidance and Dietary restrictions
AE	Adverse Event
AESI	Adverse Events of Specific Interest
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
BDRM	Blinded Data Review Meeting
BMI	Body Mass index
CI	Confidence Interval
CMA	Cow's Milk Allergy
COVID-19	Corona Virus Disease 2019
CRD	Cumulative Reactive Dose
CRO	Contract Research Organization
CSR	Clinical Study Report
DBPCFC	Double-Blind Placebo-Controlled Food Challenge
DBV	DBV Technologies
DR	Dietary Restrictions
DRM	Data Review Meeting
DSMB	Data and Safety Monitoring Board
EI	Emotional Impact
EOS	End of Study
EPIT	Epicutaneous Immunotherapy

Abbreviation	Description
FA	Food (-related) Anxiety
FAIM	Food Allergy Independent Measure
FAIM-PFC	FAIM Parent Form (Children aged 0-12 years)
FAIM-PFT	FAIM Parent Form (Adolescents aged 13-17)
FAIM-CF	FAIM Child Form (8-12 years)
FAIM-TF	FAIM Teenager Form (13-17 years)
FAQLQ	Food Allergy Quality of Life Questionnaire
FAQLQ-CF	Food Allergy Quality of Life Questionnaire – Child Form
FAQLQ-PF	Food Allergy Quality of Life Questionnaire – Parent Child Form
FAQLQ-PTF	Food Allergy Quality of Life Questionnaire – Parent Teenager Form
FAQLQ-TF	Food Allergy Quality of Life Questionnaire – Teenager Form
FEV_1	Forced Expiratory Volume in 1 Second
FUP	Follow-Up
h	Hour
IgE	Immunoglobulin E
IgG4	Immunoglobulin G4
IP	Investigational Product
ITT	Intent-to-Treat
IWRS	Interactive Web Randomization System
LS-Mean	Least Squares Mean
MI	Multiple Imputation
OFC	Oral Food Challenge
OL	Open Label
OL-500	Viaskin Milk 500µg open-label treatment period
OLS-500	Open Label Set 500
PC	Phone Contact
PEF	Peak Expiratory Flow
PPS	Per Protocol Set

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Abbreviation	Description
PPS-500	Per Protocol Open Label Set 500
PPS-300 year 1	Per Protocol Open Label Set 300 Year 1
PPS-300 year 2	Per Protocol Open Label Set 300 Year 2
PT	Preferred Term
Q1	First Quartile
Q3	Third Quartile
Q no	Question number
QoL	Quality of Life
RAE	Risk of Accidental Exposure
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDL	Social and Dietary Restrictions
SI	Standard International System of Units
sIgE	Allergen-Specific Immunoglobulin E
sIgG4	Allergen-Specific Immunoglobulin G4
SOC	System Organ Class
SOP	Standard Operating Procedure
SPT	Skin Prick Test
SR	Social Restrictions
SS	Safety Set
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
TLF	Table, Listing and Figure
VS1	Switch Visit 1

2 PURPOSE

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables, and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

After the results of the 12-month double-blind treatment period, Viaskin Milk 300µg was shown to be the most effective dose as compared to placebo. Since all subjects were receiving Viaskin Milk 500µg dose following the double-blind period, the decision was made by the Data and Safety Monitoring Board (DSMB) to permit the subjects to switch to Viaskin Milk 300µg dose for a 2-year open-label treatment period (see protocol amendment 5). SAP version 5.0 was created after the protocol amendment 5 in order to describe the analysis to be performed for the Viaskin Milk 500µg open-label treatment period (OL-500).

For traceability, the analyses scheduled in SAP versions 4.0 to 6.0 and run for the double-blind and OL-500 treatment periods are kept in this document (v7.0).

The current SAP (v7.0) will include the description of the analyses to be performed for the Viaskin Milk 300µg open-label treatment periods (OL-300) including:

- the analysis at Year 1 of Viaskin Milk 300µg open-label treatment period
- the analysis at the end (Year 2) of Viaskin Milk 300µg open-label treatment period.

Compared to SAP version 4.0, posterior SAP versions will also present the updated definition of Adverse Events of Specific Interest (AESI) as defined in study protocol amendments from version 5.0. This updated definition leads to an update of AESI retrieval strategies. This updated definition and identification were used for the analysis of Viaskin Milk 500µg open-label treatment periods (OL-500) and will be used for the analyses of Viaskin Milk 300µg open-label treatment periods (OL-300). The initial definition of AESI (see SAP version 4.0) was kept for the analysis of the double-blind period.

2.1 RESPONSIBILITIES

Syneos Health will perform the statistical analyses and is responsible for the production and quality control of all analysis datasets, tables, figures, and listings if not mentioned otherwise in this SAP.

2.2 TIMINGS OF ANALYSES

2.2.1 Primary analysis and subsequent analyses

The primary analysis of safety and efficacy was performed at the end of the double-blind period, after all randomized subjects had completed the Month 12 Double-Blind Placebo-Controlled Food Challenge (DBPCFC), or withdrew.

After month 12, all subjects continued treatment with Viaskin Milk 500µg dose in an open-label manner for up to a maximum of 36 additional months. After the analysis of the double-blind period that showed the best efficacy with the Viaskin Milk 300µg dose, subjects were switched to the 300µg dose and continued treatment for two additional years.

Following the month 12 double-blind period primary analysis, three subsequent analyses will be conducted during the open-label treatment periods:

1. OL-500 period analysis: when all randomized subjects completed the Viaskin Milk 500µg open-label period, or withdrew.

2. OL-300 period Year 1 analysis: when all randomized subjects completed one year of Viaskin Milk 300µg open-label period, or withdrew (see Table 1).

3. OL-300 period (Year 2) final analysis : when all subjects completed the End of Study (EOS) visit, or withdrew. The complete analysis as described in this SAP will be performed.

This current SAP v7.0 describes in particular the analyses that will be done for the first year and at the end of the OL-300 period.

2.2.2 DSMB analyses

The DSMB is responsible for reviewing the data during the study on an independent basis to ensure subject safety at some specific steps. The DSMB will make recommendations concerning the conduct of the study.

Details on DSMB activities are described in the DSMB-Charter and the DSMB-SAP.

3 STUDY 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 Immunoglobulin E (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.

3.1 BRIEF DESCRIPTION

MILES study (V135-201) is a multi-centre, 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. The placebo treatment consists of a Viaskin Milk patch containing a similar formulation without cow's milk proteins.

Subjects received blinded treatment for 1 year at one of the 3 doses of Viaskin Milk: 150µg, 300µg, or 500µg, or placebo. After the first year, all subjects receivedthe highest dose of Viaskin Milk 500 µg, and continued 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 were switched from Viaskin Milk 500 µg to Viaskin Milk 300 µg dose for 24 additional months of treatment.

The study is 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 DBPCFC in children (2 to 11 years old) and adolescents (12 to 17 years old).

Eligible subjects with confirmed IgE-mediated CMA performed 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) were randomized in the study.

The study was divided into 2 consecutive parts for randomization of the subjects to treatment: Part A and Part B. Part A permitted an evaluation of the safety of 3 escalating doses of Viaskin Milk (150µg, 300µg, and 500µg cow's milk proteins) versus placebo in successive cohorts of subjects prior proceeding to Part B. Part B was designed to evaluate the efficacy and safety of the 3 selected safe doses (as determined from Part A) of Viaskin Milk 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 enrolment and the treatments administered for each part of the study are provided in Section 3.4.

Subjects from both Part A and Part B were randomized to receive treatment with Viaskin Milk or placebo for 12 months (randomized double-blind treatment period), after which 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 were reported in the 12-Month Clinical Study Report (CSR).

After the Month 12 DBPCFC, all subjects from Part A and Part B were to continue treatment with active Viaskin Milk 500µg, the highest dose determined to be safe, for up to a maximum of 36 months (DBPCFCs at Month 24, 36 and 48). Following results of the 12-month blinded period, all eligible subjects who wish to continue participation in the study switched from Viaskin Milk 500 µg to Viaskin Milk 300 µg for 24additional months of treatment, as per protocol Amendment 5, independently of the duration of previous treatment (Optional DBPCFC at 12 and/or 24 months after switch to Viaskin Milk 300µg dose).

A final End-of-Study (EOS) visit will be performed for all subjects when they completed or stopped 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.

Three-hundred-and-eight children and adolescent subjects have been screened, 198 were randomized in this study, 18 subjects in Part A and 180 subjects in Part B. In Part B, the randomization was 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).

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

Figure 1 of the study protocol version 6.0 presents a summary of the enrolment process into Part A and Part B of the study, and Figures 2 and 3 present the overview of the study design.

3.2 SUBJECT SELECTION

3.2.1 Inclusion Criteria

Please refer to the respective section of the study protocol version 6.0 for complete information of the inclusion criteria.

3.2.2 Exclusion Criteria

Please refer to the respective section of the study protocol version 6.0 for complete information of the exclusion criteria.

3.2.3 Eligibility Criteria for Study Extension with Viaskin Milk 500 µg

Please refer to the respective section of the study protocol version 6.0 for complete information of the eligibility criteria for study extension with Viaskin milk 500µg. Note: following results of the 12-month blinded period, Month 24 DBPCFC should not be performed anymore.

3.2.4 Eligibility Criteria for the switch to Viaskin Milk 300 µg

Please refer to the respective section of the study protocol version 6.0 for complete information of the eligibility criteria for study extension with Viaskin milk 300µg.

3.3 DETERMINATION OF SAMPLE SIZE

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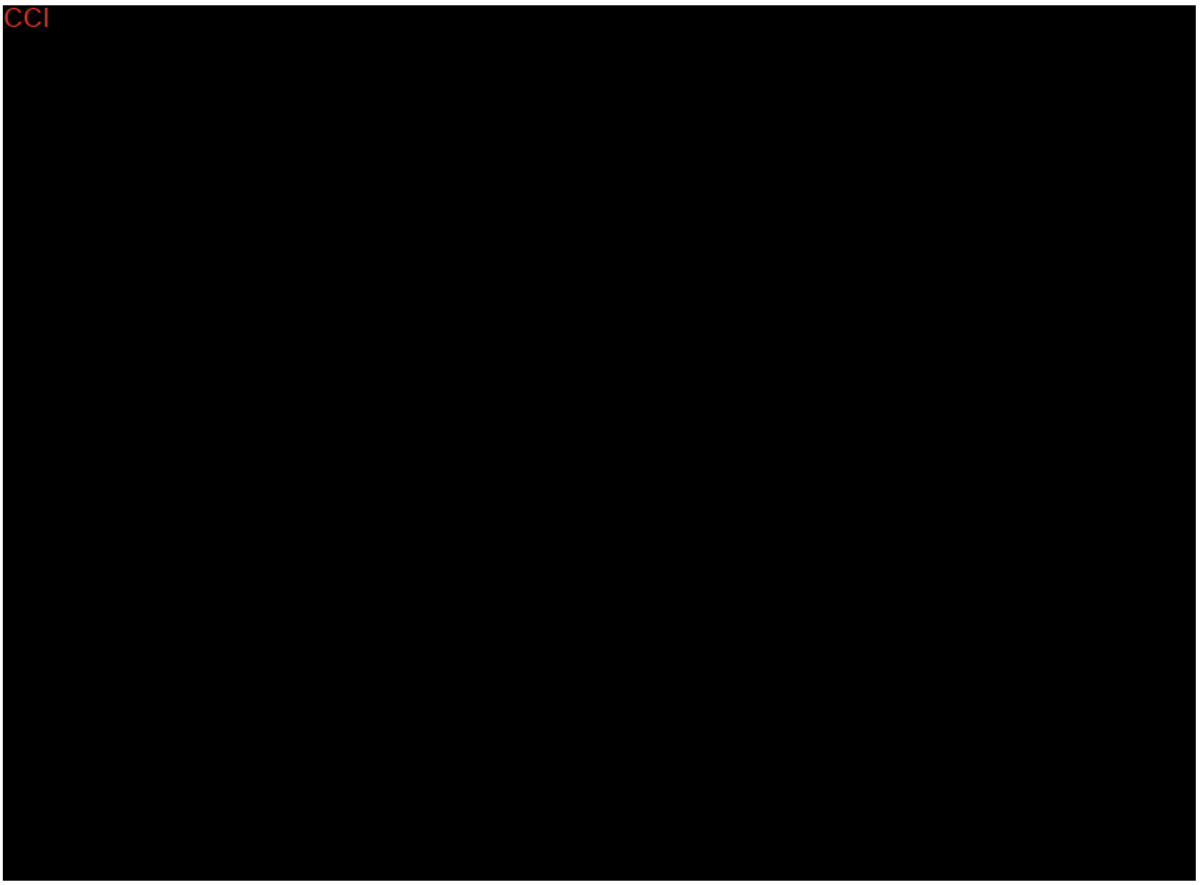

3.4 TREATMENT ASSIGNMENT & BLINDING

3.4.1 Part A

In Part A, subjects were 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 was assessed over a 3-week treatment period for each dose before proceeding to Part B.

The analysis of the cumulative safety data allowed the selection of the 3 Viaskin Milk doses (150µg, 300µg, and 500µg of cow's milk protein) for randomization into Part B of the study. The screening of subjects in Part B of the study continued when the enrolment

in Part A was complete, however no subject was 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 Food and Drug Administration. A pause in the randomization allowed for this safety review to occur and recommendations to be released.

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

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

3.4.2 Part B

3.4.2.1 Method of Assigning Subjects to Treatment Groups

In Part B, 180 additional subjects were randomized (1:1:1:1 ratio) to receive Viaskin Milk 150µg, Viaskin Milk 300µg, Viaskin Milk 500µg or placebo up to Month 12.

All subjects were assigned an identification number at Visit 1. The IWRS randomized all eligible subjects and assigned the appropriate treatment kit. IWRS managed the inventory and assignment of treatment to subjects at the kit level. The site pharmacists dispensed the drug product according to the IWRS recommendations. Subjects at each dose level were randomly assigned to receive either Viaskin Milk or placebo according to a computer-generated randomization code that was 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 were 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).

3.4.2.2 Selection of Doses in the Study

Subjects from Part A and Part B continued treatment with active Viaskin Milk for another 12 months in an open-label manner at the highest dose (500µg of cow's milk protein) determined to be safe from Part A. The transition from the blinded to the open-label part of the study was performed keeping the blinding until the results of the first 12-month period were obtained.

The primary analysis that was conducted after the 12-month blinded period showed that the Viaskin Milk 300µg was the most effective tested dose. No safety concern was identified at any of the investigated doses. Therefore, all eligible subjects were proposed to switch to Viaskin Milk 300µg for a further 24 months, independent of the duration of previous treatment with Viaskin Milk 500µg or treatment having received during the blinded initial 12 months of study.

3.4.2.3 Administration of Study Treatments to Subjects

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

The subjects were randomized to receive either Viaskin Milk (150µg, 300µg, 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.

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

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

Following results of the 12-month double-blind treatment period, all eligible subjects were proposed to switch to Viaskin Milk 300µg for additional 24 months, independently of the previous duration of treatment.

3.4.2.4 Daily duration of patch application at the beginning

To increase the safety of subjects at the beginning of the treatment for both double-blind and open-label Viaskin Milk 500µg periods, the daily duration of patch application was 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

The switch to Viaskin Milk 300 µg did not require a progressive increase of application duration, and all subjects were able to start with 24 hours of daily application of Viaskin Milk 300 µg.

3.4.3 DBPCFC

The sequence of food challenge formulas on the first day and the second day of the DBPCFCs will also be randomized. Each site was provided with randomization tables at Screening, Month 12, Month 24, Month 36 and Month 48, as well as at Month 12 and Month 24 after switch to 300µg. The unblinded site personnel in charge of the preparation of the food challenge formula was 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 of the protocol for emergency unblinding procedures). At the end of the second day of the challenge will the order of

the formulas be unblinded to the subject and the assessors.

3.5 ADMINISTRATION OF STUDY MEDICATION

In Section 6 of the study protocol version 6.0 the complete information of the study drug administration is available.

3.6 STUDY PROCEDURES AND FLOWCHART

The planned study assessments are summarized in the study protocol version 6.0 in Section 7.4 "Schedule of assessments":

- Table 2 for the first year of treatment (double-blind period),
- Table 3, 4 and 5 for the second, third and fourth year of treatment with Viaskin Milk 500µg dose (open-label Viaskin Milk 500µg period),
- Table 6 and 7 for first and second year after the switch to Viaskin Milk 300µg dose (open-label Viaskin Milk 300µg period).

4 ENDPOINTS

4.1 PRIMARY EFFICACY ENDPOINT

The primary efficacy endpoint was the percentage (%) of subjects who were treatment responders after the first 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 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 protein (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 cumulative reactive dose (CRD) of cow's milk proteins is entered directly in CRF by the sites and is calculated as the sum up 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).

4.2 SECONDARY EFFICACY ENDPOINTS

4.2.1 Double-blind 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 cow's milk sIgE and sIgG4 at all time points 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 time points evaluated up to Month 12.
- The change from baseline in SPT wheal at all time points evaluated up to Month 12.
- The change in the severity of symptoms elicited during the milk DBPCFC from baseline to Month 12[1].
- The change from baseline in Quality of Life (QoL) assessments at Month 12.

4.2.2 Open-label periods

- 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.

[1] Grading of symptoms will be done using the grading definition in the OFC Symptom Score Sheets.

4.3 SAFETY ENDPOINTS

- 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[2] allergic symptoms and local AESI.
- Frequency and severity of symptoms elicited during the DBPCFC.
- Vital signs, physical examinations, and laboratory data.
- Spirometry and Peak Expiratory Flow (PEF) data.

4.4 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 behaviour" of subjects (voluntary milk consumption) during the study.
- Planned management of the subject after termination of the study.

[2] Events are considered as systemic unless there is evidence in the event term or coding information that the reaction is only extended around the patch area.

5 ANALYSIS SETS

5.1 INTENT-TO-TREAT SET (ITT)

The Intent-to-Treat Set includes all randomized subjects. Subjects will be analyzed according to randomized treatment.

The ITT Set will be used for all analyses of efficacy endpoints during the double-blind period.

5.2 PER PROTOCOL SET (PPS)

The Per Protocol Set includes all subjects from the ITT population who do not have major protocol violations that may affect the primary endpoint. This population will be analyzed according to study treatment that was actually received by the subjects.

Protocol deviations occurring during the randomized blinded treatment period were categorized as either major or minor at the (Blind) Data Review Meetings (BDRM). A corresponding listing was prepared for review in order to determine the subjects to be excluded from the ITT, and hence did not belong in the Per Protocol set. Manual protocol deviations were also collected and considered at the BDRM. BDRM specifications are described in separate specific document. Decisions taken at the BDRM were documented and approved by DBV prior to database lock and unblinding the study.

Protocol deviations may include but are not limited to:

- Informed Consent / Assent
- Inclusion / Exclusion Criteria
- Investigational Product Administration
- Visit Schedule
- Procedures / Tests
- Concomitant Medications
- Adverse Events / Serious Adverse Events
- Food Challenge
- Other

Protocol deviations due to Corona Virus Disease 2019 (COVID-19) are added in 2020:

- Missed or out-of window visits due to COVID-19
- Missed assessments due to COVID-19
- Direct-to-Patient shipment of IMP due to COVID-19

5.3 SAFETY SET (SS)

The Safety Set includes 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 will be determined at the BDRM, on a case-by-case basis.

The safety set will be used for all safety analysis tables and listings, which include the randomized blinded treatment period.

5.4 OPEN-LABEL SET 500 (OLS-500)

The Open-Label Set 500 includes all subjects who entered the open-label treatment period and applied at least one Viaskin Milk 500µg patch during the open-label period.

Analyses of the Viaskin Milk 500µg open-label treatment period was performed on the OLS-500.

5.5 PER PROTOCOL OPEN-LABEL SET 500 (PPS-500)

The Per Protocol Open-Label Set 500 includes all subjects from the OLS-500 population who do not have major protocol violations that may affect the main efficacy endpoint.

Protocol deviations occurring during the Viaskin Milk 500µg open-label treatment period were categorized as either major or minor at the Data Review Meeting (DRM). A corresponding listing was prepared for review in order to determine the subjects to be excluded from the Per Protocol Open-Label Set 500 (PPS-500). DRM specifications were described in separate specific document.

5.6 OPEN-LABEL SET 300 (OLS-300)

The Open-Label Set 300 will include all subjects who entered the open-label treatment period after switch to Viaskin Milk 300µg and applied at least one Viaskin Milk 300µg patch during this open-label period.

Analyses of the Viaskin Milk 300µg open-label treatment period will be run on the OLS-300.

5.7 PER PROTOCOL OPEN-LABEL SET 300 YEAR 1 (PPS-300 YEAR 1)

The Per Protocol Open-Label Set 300 Year 1 will include all subjects from the OLS-300 population who do not have major protocol violations during the first year of Viaskin Milk 300µg open-label treatment period that may affect the efficacy evaluation of the open-label 300µg dose during the first year.

Respective protocol deviations will be categorized as either major or minor at the Data Review Meeting (DRM).

A corresponding listing will be prepared for review in order to determine the subjects to be excluded from Per Protocol Open-Label Set 300 Year 1. DRM specifications are described in separate specific document.

5.8 PER PROTOCOL OPEN-LABEL SET 300 YEAR 2 (PPS-300 YEAR 2)

The Per Protocol Open-Label Set 300 Year 2 will include all subjects from the OLS-300 population who do not have major protocol violations during the second year of Viaskin Milk 300µg open-label treatment period that may affect the main efficacy evaluation of the open-label 300µg dose during the second year.

Respective protocol deviations will be categorized as either major or minor at the Data Review Meeting (DRM).

A corresponding listing will be prepared for review in order to determine the subjects to be excluded from the OLS-300 Year 2. DRM specifications are described in separate specific document.

6 GENERAL ASPECTS FOR STATISTICAL ANALYSIS

6.1 GENERAL METHODS

6.1.1 General

All analyses and summaries will be produced using CCI

Unless otherwise specified, summaries will be presented overall and for each age group, in total and by treatment (placebo/dose level/overall active). "Overall active" is a synonym for "All Doses Viaskin Milk". In the OL-period(s) analyses, it is defined as the subjects who were randomized / treated in one of the 3 Viaskin Milk doses for the double-blinde treatment period.

The secondary and explorative efficacy endpoints, referring to "Change to Baseline" are all analyzed with respect to "Month 0". If not specified otherwise, summaries for changes from baseline indicate summaries relative to "Month 0" as well as relative to "Month 12", see section 6.2.1 for definition.

Unscheduled assessments will not be included in summary tables unless specified otherwise, but will be included in the subject listings.

In case of repeated measurements in the scheduled time-windows, the first measurement will be used for analysis, if not specified otherwise.

Early termination assessments will be analyzed as having occurred at the next scheduled assessment.

All tables, listings and figures will include footers that identify the name of the program that created the item, together with the date and time on which it was created. Headers will include the total number of pages that the presentation contains and, for each page, the number of the page within the presentation.

6.1.2 Presentation of Descriptive statistics

If not stated otherwise continuous variables will be summarized using the number of

subjects with evaluable data (n), mean, standard deviation (SD), median, first and third quartiles (Q1, Q3), minimum and maximum. The same number of decimal places as in the raw data will be presented when reporting minimum, maximum and median. Values rounded to 1 more decimal place than in the raw data will be presented when reporting the mean, and values rounded to 2 more decimal places than in the raw data will be presented when reporting the SD.

Categorical variables will be summarized using the number of observations (n), frequency and percentage of subjects. All percentages will be presented as rounded to one-decimal point, unless otherwise specified. Percentages equal to 100 will be displayed as 100% and percentages will not be presented for zero frequencies.

Unless stated otherwise (e.g. in the respective footnotes), the percentages will be based on the number of non-missing observations (in the respective visit, if applicable). The column header will still contain the number of subjects in the treatment group.

There will be a row for the number of missing observations if there are missings available

The number of subjects on which the percentages rely on is given in the summaries explicitly, if it is different from the numbers given in the column headers. This is mainly applicable

- for the frequency counts with missing values (which will not be used in the calculations)
- for the visit-wise summaries (as the numbers of available subjects per visit might be different to the number of subjects in the respective population displayed in the column header).

6.1.3 Presentation of Statistical Tests

Unless otherwise stated, all formal tests of hypotheses will be conducted at the two-sided level of significance with alpha=0.05.

Any calculated p-values will be rounded to 3 decimal places; p-values less than 0.001 will be presented as '$p < 0.001$' and p-values greater than 0.999 will be presented as '$p > 0.999$'.

6.1.4 Presentation of Listings

All relevant subject data will be included in listings and sorted by dose level at the beginning of treatment, subject's number and visit, as applicable, for all randomized subjects. Subject data will be assigned to randomized blinded vs. open-label or the different periods (Screening, 1-DB, OL500, 1-SW, 2-SW, and Follow-Up), if applicable.

Data from Part A Cohorts 1, 2, and 3 will be clearly identified.

6.2 KEY DEFINITIONS

6.2.1 Baseline, Month 0, Month 12, LV-OL-500 and last value prior to active treatment

"Month 0" is defined as the latest available assessment (scheduled or unscheduled) before first application of any Viaskin patch, whether this patch is active or placebo. Except for efficacy endpoint using information collected during screening DBPCFC, assessments derived throughout the DBPCFC at Screening (vital signs…) will not be considered.

"Baseline" is identical to "Month 0". The later will be used in the statistical outputs for clarification and precision, as the term "Baseline" used in the protocol will sometimes refer to a specific Visit.

"Month 12" is defined as the latest available assessment at Visit 12 or Visit 13 before first application of any Open-Label Viaskin patch, without using the assessments derived throughout any DBPCFC.

"LV-OL-500": The last value during Viaskin Milk 500µg Open-Label treatment period is defined as the latest available assessment (scheduled or unscheduled) during the Viaskin Milk 500µg OL period (OL-500), i.e the one collected during switch to Viaskin Milk 300µg visit (VS1), or during early termination visit, or during any visit earlier (except for the one used to define Month12), whichever is the latest. LV-OL-500 will serve as a baseline value for the OL-300 analyses labelled as "last value prior to switch to Viaskin Milk 300µg" for subjects in OLS-300.

Last value prior to active treatment is equivalent to Month 0 for subjects initially randomized to an active treatment group and Month 12 for subjects initially randomized to placebo.

6.2.2 Treatment Periods

The following periods are defined:

Table 1: Treatment periods – start and stop dates

Treatment period Name	Start Date	End Date°
Screening (SC)	Informed Consent	Visit 4 -1 day
Randomized blinded treatment period (1-DB)	Visit 4	Visit 13
Viaskin Milk 500µg open-label treatment period (OL-500)	Visit 13 +1 day	Visit VS1 (switch to Viaskin Milk 300µg)
Viaskin Milk 300µg open-label treatment period year 1 (OL-300 Year 1)	Visit VS1 (switch to Viaskin Milk 300µg) + 1 day	Visit VS3/VS4*
Viaskin Milk 300µg open-label treatment period (OL-300)	Visit VS1 (switch to Viaskin Milk 300µg) + 1 day	Visit VS6/VS7*
Whole treatment period	First treatment	Last treatment
Follow-Up (FUP)	Last scheduled visit +1 day	Last assessment

Whole study period	Informed Consent	Last assessment

° If the date of discontinuation comes earlier than the respective end date visit, then date of discontinuation will be used.

* VS4 and VS7 are applicable only for subjects performing the optional DBPCFC

Adverse Events, concomitant medications and other events or assessments with a start date at Visit 13, but clearly identified as starting after first open-label patch application were excluded from 1-DB period and analyzed in the open-label periods.

Months 0 to 12 - Randomized blinded treatment period (1-DB)

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 were combined and pooled by dose level, as applicable, for the efficacy analyses at Month 12. Randomized blinded treatment period start and stop dates are displayed in Table 1.

Month 12 to VS1 (Switch Visit to Viaskin Milk 300µg) – Viaskin Milk 500µg Open-Label treatment period (OL-500)

All subjects from both Part A and Part B continued in the Viaskin Milk 500µg Open-Label treatment period at highest dose of Viaskin Milk selected (500µg of cow's milk protein).

Open-Label treatment period with Viaskin Milk 500µg start and stop dates are given in Table 1, with end date as the latest end date of Open-Label period with Viaskin Milk 500µg until start of Viaskin Milk 300µg.

Adverse Events, concomitant medications and accidental cow's milk consumption will be considered as occuring during the OL-500 period if they occur up to the day before VS1, i.e. between Visit 13 +1 day (included) and VS1 day (included).

Viaskin Milk 300µg open-label treatment period year 1 (OL-300 Year 1)

Open-Label treatment period with Viaskin Milk 300µg year 1 start and stop dates are given in Table 1.

Adverse Events, concomitant medications and accidental cow's milk consumption will be considered as occuring during the OL-300 Year 1 period, i.e. between Visits VS1 (excluded) and VS3/VS4 day (included). **Viaskin Milk 300µg open-label treatment period (OL-300)**

Open-Label treatment period with Viaskin Milk 300µg start and stop dates are given in Table 1.

Adverse Events, concomitant medications and accidental cow's milk consumption will be considered as occuring during the OL-300 period, i.e. between Visits VS1 (excluded) and VS6/VS7 day (included).

Whole treatment period Start and stop dates are given in Table 1.

Start and stop dates from the whole treatment period, the Follow-Up period (FUP) and the whole study period are also given in Table 1.

6.2.3 Start and Stop Dates of the DBPCFC

Data evaluated during DBPCFC will be summarized by age group, dose level/placebo/all active groups and total for DBPCFCs at Screening and Month 12.

Start and stop dates are displayed in the table below.

Table 2: Food Challenges – start and stop dates

Food Challenges Name	Start Date	End Date°
DBPCFC at Screening	Visit 2	Visit 3
DBPCFC at Month 12	Visit 12	Visit 13
DBPCFC at Month 24#	Visit 16	Visit 17
DBPCFC at Month 36#	Visit 19	Visit 20
DBPCFC at Month 48#	Visit 22	Visit 23
DBPCFC 12 months after switch to Viaskin Milk 300µg §	Visit VS3	Visit VS4
DBPCFC 24 months after switch to Viaskin Milk 300µg §	Visit VS6	Visit VS7

° If the date of discontinuation comes earlier than the respective end date visit, then date of discontinuation will be used.

In amendment 5, DBPCFC at Months 24, 36, and 48 have been removed from study flow chart. Some DBPCFC at Months 24 and 36 had already been performed – but none at Month 48.

§ For subjects switching to Viaskin Milk 300 µg, an optional DBPCFC may be performed after 12 and/or 24 months after switch, at the decision of the Investigator and the subject.

Adverse Events clearly identified as outside the DBPCFC will be dropped from the respective summaries, even if the date of the visit indicates otherwise.

6.3 MISSING DATA

Missing data will not be imputed for the efficacy analyses except for the classification of treatment responders/non-responders for the primary efficacy analysis.

Partial or missing dates of safety data will be imputed according to the most conservative approach. Unless otherwise specified (see Section 9.3), missing day will be imputed as the first day of month for all start dates, and as the last day of the month for all stop dates. Missing month will be imputed as January for all start dates and as December for all stop dates. Completely missing start dates for AEs or concomitant medication will be imputed as the start date of treatment. Actual values will be presented in data listings.

If severity is missing of an AE starting prior to the date of initial patch application, then a severity of “Mild” will be imputed. If severity is missing of an AE starting on or after the date of initial patch application, then a severity of “Severe” will be assigned.

If seriousness is missing of an AE then “Serious” will be assigned.

Imputed values for relationship, severity or onset date will be used for incidence summaries

6.4 VISIT WINDOWS

Visit windows are defined in section 7.4 of the study protocol version 6.0.

Out-of-window visits will be identified, discussed and classified as major or minor protocol violation in the data review meetings (DRMs). The first DRM was blinded and took place after the last randomized subject rolled over in the OL-phase or discontinued, but before database-lock of the 12-months period. Concomitant medications that started in the randomized blinded treatment period and are ongoing or still present in the open-label treatment period will be assigned to both periods.

Adverse Events that started in the randomized blinded treatment period and are ongoing or still present in the open-label treatment period will only be assigned to the period during which they appeared or worsened.

The following time windows during the DB-period are defined for each of the following visits:

Table 3: Time window definition

Visit	Timepoint (authorized window in study protocol)	Target Day	Lower bound	Upper bound
Visit 4	Day 1	1	First patch application	
Visit 5	Day 2	2	2	2
Visit 6	Day 8/ Week 1 (+/- 2 days)	8	3	14
Visit 7	Day 22/ Week 3 (+/- 3 days)	22	15	29
Visit 8	Week 6 (+/- 3 days)	43	30	60
Visit 9	Month 3 (+/- 7 days)	91	61	136
Visit 10	Month 6 (+/- 7 days)	182	137	227
Visit 11	Month 9 (+/- 7 days)	274	228	319
Visit 12	Month 12 (+/-7 days)	365	320	456

At each visit, the number and percentage of subjects respecting the time window defined in Table 3 will be provided.

6.5 POOLING OF CENTRES

There is no planned pooling of centres. However a sensitivity analysis on the primary efficacy endpoint using the country as covariate will be performed (see Section 8.1.5).

6.6 SUBGROUPS

6.6.1 Age Group

There will be 2 age groups to be evaluated:

- 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

For subjects from Part A, the age group is derived from the age at Visit 1.

For subjects from Part B, the age group corresponds to the IVRS randomization strata.

If not specified otherwise, data will be summarized

- Overall and for each age group, in total and by treatment group (placebo/dose level/ overall active) for the randomized blinded treatment period (Months 0 to 12) and
- Overall and for each age group, in total and by initial randomized treatment group (placebo/dose level/overall active) for the Viaskin Milk 500µg open-label treatment period (Months 12 to 48) as described in Section 6.2.

6.6.2 Filaggrin Mutation Group

Some analyses will also be repeated for the 2 filaggrin mutation subgroups (With/without filaggrin mutation).

6.7 METHODS FOR WITHDRAWALS

Subjects who withdraw from the study prematurely will have all data listed and, where relevant, included in any summaries allocated to the next scheduled assessment.

7 DISPOSITION, PROTOCOL DEVIATIONS, DEMOGRAPHIC, OTHER BASELINE CHARACTERISTICS AND MEDICATION

7.1 SUBJECT DISPOSITION AND WITHDRAWALS

7.1.1 Double-blind Month 12 and OL-500 analyses

The number and percentage of subjects in each analysis population (ITT, PPS, and SS) during the randomized blinded treatment period was summarized overall and for each age group, in total and by treatment group (placebo/dose level/ overall active).

The number and percentage of subjects in the randomized blinded treatment period and for the whole study, who completed, discontinued and their corresponding primary reason for early withdrawal was summarized overall and for each age group, in total and by initial randomized treatment group (placebo/dose level/ overall active).

The number and percentage of subjects in OLS-500 was summarized overall and for each age group, in total and by initial randomized treatment (placebo/dose level/ overall active), as well as the number and percentage of subjects entering the Viaskin Milk 300µg open-label period.

The reason for exclusion from each of the analysis sets was displayed in a listing.

The number and percentage of subjects randomized from each country and site was summarized overall and for each age group, in total and by treatment (placebo/dose level/ overall active). This summary was repeated for each age group.

Besides, Part A recruitment was also summarized by site, including only sites with at least one randomized subject.

Enrolment summaries was presented overall and for each age group, in total and by site and country, showing the

- first date of informed consent,
- last study visit exit date among randomized subjects,
- study duration (days)
- number of subjects screened,
- number of subjects randomized
- number of subjects completing the randomized blinded treatment period
- number of subjects treated with Viaskin Milk 500µg
- number of subjects completers at Month 24
- number of subjects entering Viaskin Milk 300µg open-label period

No formal statistical testing was carried out on these data. Subject disposition and study population was listed for all randomized subjects.

Eligibility Criteria for Study Extension at Month 24 was summarized for the OLS-500, overall and for each age group, in total and by initial randomized treatment group (placebo/dose level/ overall active).

7.1.2 OL-300 Analyses

The number and percentage of subjects in OLS-300 will be summarized overall and for each age group, in total and by initial randomized treatment (placebo/dose level/ overall active). The reason for exclusion from each of the analysis sets will be displayed in a listing.

The number and percentage of subjects randomized from each country and site will be summarized overall and for each age group, in total and by treatment (placebo/dose level/ overall active).

Enrolment summaries will be presented overall and for each age group, in total and by site and country, showing the

- first date of informed consent,
- last study visit exit date among randomized subjects,
- study duration (days)
- number of subjects screened,
- number of subjects randomized
- number of subjects completing the randomized blinded treatment period
- number of subjects treated with Viaskin Milk 500µg
- number of subjects completers at Month 24
- number of subjects entering Viaskin Milk 300µg open-label period
- number of subjects completing Viaskin Milk 300µg open-label period at Month 24 after switch

Eligibility Criteria for switch to Viaskin Milk 300 mg/d will be listed for the OLS-500, overall and for each age group, in total and by initial randomized treatment group (placebo/dose level/overall active).

7.2 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

7.2.1 Analysis of Month 12

Demographic and other baseline characteristics were summarized overall and for each age group, in total and by treatment group (placebo/dose level/ overall active) in the ITT, and PP as described in Section 6.1.2., if not specified otherwise.

The following variables will be summarized:

- Age at Visit 1 (years),
- Age group at Visit 1,
- Gender,
- Ethnic origin,
- Ability to tolerate baked milk products,
- Height (cm),
- Weight (kg),
- Body Mass index (BMI, kg/m²),
- Body Surface (m²),
- Weight/height (kg/m),
- SPT largest wheal diameter (mm),
- SPT mean wheal diameter (mm),
- FEV_1 percent predicted (%),
- PEF percent predicted (%),CRD of cow's milk (mg),
- Cow's milk sIgE (kUI/L),
- Cow's milk sIgE (levels),
- Cow's milk sIgG4 (mg/L),
- Filaggrin mutation group (with mutation [heterozygous/homozygous]/without mutation/Type of mutation). Note that in case of several mutations presented by a subject with different status on heterozygous/homozygous, the subject will be considered as homozygous.

The following calculations will be used, if applicable

Age at Visit 1 (years) = integer of (visit 1 date - date of birth + 1) / 365.25
Height (in cm) = height (in inches) * 2.54
Weight (in kg) = weight (in lbs) * 0.4536
BMI (in kg/m²) = weight / height²
Body surface (in m²) = $0.007184 \times \text{height}^{0.725} \times \text{weight}^{0.425}$

The baseline cow's milk specific sIgE levels was calculated with respect to the total number of subjects with respective values available at baseline according to the following classifications.

- Level 1: [minimum-Q1[
- Level 2: [Q1-median[
- Level 3: [median-Q3[
- Level 4: [Q3-maximum]

Medical history (cow's milk allergy, any other food allergy, any non-food allergy, atopic dermatitis, asthma, allergic rhinitis, other) was summarized overall and for each age group, in total and by treatment group (placebo/dose level/overall active) for all subjects in the ITT. In addition, other food allergies were summarized by MedDRA Lowest Level Term, other medical history by MedDRA System Organ Class and Preferred Term.

7.3 MEDICATION

7.3.1 General

Medications (excluding study treatment) will be coded using the World Health Organization Drug Dictionary, by Anatomical Therapeutic Chemical (ATC) term and standard medication name.

The medications will be defined as, prior or concomitant medications throughout the different treatment periods (1-DB, whole treatment period, …), relative to their start- and, if available, stop-date.

Medications administered during DBPCFC, prior and concomitant medications will be listed for all subjects in the ITT or on the OLS, respectively, if applicable.

The sorting of the medications in the listings will be chronologically and in the tables alphabetically by ATC Level 3, and also alphabetically by standard medication name within each ATC Level 3.

7.3.2 Medications administered during DBPCFC

7.3.2.1 Double-blind Month 12 and OL-500 analyses

Medications administered during DBPCFC was tabulated separately for each food challenge overall and for each age group, in total and by (initial randomized) treatment group (dose level/placebo/overall active) for the subjects in the ITT or on the OLS-500.

7.3.2.2 OL-300 Analyses

The analysis described in Section 7.3.2.1 will be repeated for the optional DBPCFC 12 month and 24 months after switch to Viaskin milk 300µg on the OLS-300.

7.3.3 Prior Medication

Prior medications are defined as medications started and ended before the date of first dose of study treatment. They were displayed in listings only and provided for the analysis of the DB-period. Medications administered during DBPCFC will not be considered.

7.3.4 Concomitant Medication

7.3.4.1 Double-blind Month 12 and OL-500 analyses

Concomitant medications in the randomized blinded treatment period are defined as medications taken on or after the date of first dose of study treatment, which also include medications ongoing at the date of first dose, up to end of randomized blinded treatment period (1-DB).

Concomitant medications that might be taken to treat an adverse event that would have started on visit 13 and that would be "clearly identified" as starting after first open-label patch application were analyzed in the open-label periods.

Concomitant medications in the randomized blinded treatment were summarized overall and for each age group, in total and by treatment group (placebo/dose level/overall active) for all subjects in the ITT.

Concomitant medications during the whole treatment period will be summarized overall and for each age group, in total and by initial randomized treatment group (placebo/dose level/overall active) for all subjects in the ITT.

Concomitant medications administered during DBPCFC will be analysed separately.

7.3.4.2 OL-300 Analyses

The concomitant medications in the OL-300 period will be summarized overall and for each age group, in total and by initial randomized treatment group (placebo/dose level/overall active) for all subjects in the OLS-300.

Concomitant medications administered during DBPCFC will be analysed separately.

7.4 PROTOCOL DEVIATIONS

7.4.1 Double-blind Month 12 and OL-500 analyses

Major protocol deviations were summarized for the randomized blinded treatment period and the OL-500 for the subjects in the ITT or on the OLS-500, overall and for each age group, in total and by initial randomized treatment (placebo/dose level/ overall active).

7.4.2 OL-300 Analyses

The analysis described in Section 7.4.1 will be repeated for the OL-300 period on the OLS-300.

All protocol deviations and all major protocol deviations due to COVID-19 will be summarized on the OLS-300, overall and for each age group, in total and by initial randomized treatment (placebo/dose level/ overall active).

These protocol deviations will also be listed separatedly.

8 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 PRIMARY EFFICACY ENDPOINT AND ANALYSIS

8.1.1 Primary efficacy endpoint

The primary efficacy endpoint was the percentage (%) of subjects who are treatment responders after 12 months of EPIT treatment (defined in Section 4.1), on the ITT population, using missing = failure imputation method (i.e. subjects with missing observation at Month 12 will be considered as non-responder).

The number and percentage of responders was summarized by treatment group (dose level/placebo).

8.1.2 Primary efficacy analysis

Methods of exact logistic regression was 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 Interval (CI) were presented. A SAS-Code similar to the following was used:

```
PROC LOGISTIC data=<indata>;
        CLASS treat(ref="Placebo" param=ref) agegroup;
        MODEL y=treat agegroup;
        EXACT treat agegroup / estimate=both;
RUN;
```

Following analyses were performed by another CRO.

The primary analysis was performed using model-based analytical approaches which aim to inform the dose selection for phase 3. One of the methods to be used was the MCP-Mod method (Multiple Comparison Procedure – Modelling) [1] that included a first stage of hypothesis testing of candidate models to assess the presence of dose-reponse signal via a trend test (while preserving the family-wise error rate), and a second stage of dose-response modeling of the selected model to obtain inference on adequate doses.

For the first stage of the MCP-Mod approach, the candidate model classes to be considered were linear, Emax, and logistic, but other candidate models were examined as well. More complex models such as sigmod and beta were considered. Prior to model comparison, exploratory analyses were performed in order to determine appropriate initial inputs for model parameters. The most adequate dose-response model within the candidate set was chosen as the one with the most significant contrast. For the second stage of the MCP-Mod approach, one or more candidate models were selected to provide inference on the adequate dose.

The success of this phase 2 study rested on identification of a viable dose, leading to design of a pivotal phase 3 trial.

8.1.3 Sensitivity analysis to statistical method

The pair-wise differences in response rates between each Viaskin Milk treatment group versus placebo were presented with its 2-sided Newcombe 95% confidence interval (CI) stratified on age group. Cochran-Mantel-Haenszel (CMH) method with age group as stratification variable was used to compute a Newcombe 95% CI for the strata-adjusted difference in response rates [2].

8.1.4 Sensitivity to analysis population (supportive analysis)

The analysis described in sections 8.1.2 and 8.1.3 was repeated for subjects in the in the PPS as supportive analysis.

8.1.5 Sensitivity to handling of missing data

Completers:

The analysis described in section 8.1.2 was repeated for subjects in the ITT using observed data (completers as defined by non missing cumulative reactive dose at Month 12) as supportive analysis.

Multiple imputations:

The analysis described in sections 8.1.2 was performed using multiple imputations (MI) instead of missing = failure imputation method on ITT population.

Combined estimate for proportion of responders obtained by averaging out all the imputed proportions of responders. Combined estimate for mean and variability of logarithm of odds ratio obtained by combining the logarithm of odds ratio from logistic regression model analyses of the different imputed data sets, using Rubin's formulae. P-value Viaskin Milk vs. Placebo was presented.

For subjects with missing binary treatment response at Month 12, a response was derived using MI based on placebo group subject's responses. For this monotone missing data pattern, a logistic regression model was used to impute as follows:

Step 1: Select subjects with missing data and subjects on the placebo arm that completed the Month 12 food challenge. The probability distribution that imputes their response relyed only on placebo subjects with a response and so the missing data would mimic placebo response.

Step 2: Use PROC MI to impute missing values of binary treatment responder value using a monotone logistic statement. Additional variables that were included are the baseline CRD, the baseline IgE value and the age group.

Step 3: Combine the imputed data with the non-missing data to achieve a database with all data present. Subjects with non-missing data had their data replicated the same number of iterations as the imputed data prior to recombining with the imputed data.

The seed number is set to 34567, the number of imputation runs to 1000.

Best/worst case scenario:

The best and worst limits of efficacy due to missing data was also presented through analyses described in sections 8.1.2 for:

- Best case scenario, i.e. considering each subject with missing data for primary endpoint as a responder if randomized in any active treatment group; as a non-responder if randomized in placebo group;

- Worst case scenario, i.e. considering each subject with missing data for primary endpoint as a non-responder if randomized in any active treatment group; as a responder if randomized in placebo group.

8.1.6 Sensitivity to (other) covariates

Efficacy endpoint analysis, as described in section 8.1.2, was repeated for subjects in the ITT

- without adjusting for age group
- using country as covariate,
- using baseline cow's milk specific sIgE (categorized as in section 7.1.2) as covariate
- using filaggrin mutation subgroup (With/Without filaggrin mutation) as covariate
- using recruitment part (Part A/Part B)

These analyses were performed without adjusting for age group due to small sample sizes expected.

8.1.7 Subgroup analyses

Efficacy endpoint analysis, as described in sections 8.1.2, (and 8.1.3 for age subgroups only), were repeated for subjects in the ITT for the following subgroups:

- each age groups (age group was not included as covariate; Newcombe confidence interval was not stratified on age group)
- each country (no covariate)
- baseline cow's milk specific IgE (categorized as in section 7.1.2) (no covariate)
- each filaggrin mutation subgroup (With/Without filaggrin mutation) (no covariate)

For descriptive purposes, 90%-CI were provided for the treatment comparisons.

8.2 SECONDARY EFFICACY ENDPOINTS AND ANALYSES

ITT, OLS-500 or OLS-300 (if applicable) will be employed for secondary efficacy analyses. Observed data will be used, no imputation of missing data will be performed.

8.2.1 Treatment Responders

8.2.1.1 OL-500 Analysis

The number and percentage (%) of subjects who were treatment responders or non-responders at Month 24 were summarized overall and in each age-group, in total and by initial randomized treatment group (placebo/dose level/overall active), if applicable.

Response status at each time point (Months 12, 24, 36, 48 if applicable) were listed for subjects with at least one DBPCFC performed during Viaskin Milk 500µg open-label treatment period.

8.2.1.2 OL-300 Analyses

Optional food challenge can be performed after 12 months and/or 24 months of open-label treatment with Viaskin Milk 300µg. No DBPCFC was performed at the end of 500µg period (prior to switch to open-label treatment with Viaskin Milk 300µg).

A responder in the OL-300 analyses is defined as a subject who meets at least one of the following criteria:

- A ≥10-fold increase in the cow's milk proteins CRD at the Month 12 DBPCFC (VS3/VS4) [Month 24 (VS6/VS7)] after switch to Viaskin Milk 300µg as compared to baseline value and reaching at least 144 mg of cow's milk proteins
- A CRD of cow's milk proteins ≥1444 mg at the Month 12 DBPCFC (VS3/VS4) [Month 24 DBPCFC (VS6/VS7)] after switch to Viaskin Milk 300µg

Two types of analyses will be performed, considering different timepoints as baseline:

1. Considering the CRD determined by screening DBPCFC as baseline CRD.
2. Considering the CRD determined by the DBPCFC which was conducted prior to the subject receiving any active treatment as baseline CRD. This refers to Month 12 DBPCFC for subjects randomized to the placebo treatment arm and to screening DBPCFC for subjects randomized to any active treatment arm.

Both types of responders will be summarized overall and in each age-group, in total and by initial randomized treatment group (placebo/dose level/overall active) in the OLS-300.

For the calculation of rates and percentages, only the subjects with DBPCFC at the respective baseline and at Month 12 (VS3/VS4) [Month 24 (VS6/VS7)] after switch will be used.

8.2.2 Cumulative Reactive Dose (CRD) of Cow's Milk Proteins at Months 12 to 48

8.2.2.1 Double-blind Month 12 and OL-500 analyses

The actual value and changes from baseline of CRD of Cow's milk proteins was summarized overall and for each age group, in total and by (initial randomized) treatment group (placebo/dose level/overall active), at each time point until Month 12 on the ITT for the randomized blinded treatment period. This analysis was repeated until Month 48 (if applicable) for the Viaskin Milk 500µg open-label treatment period on the OLS-500 and on PPS-500. Change from Month 12 to each timepoint was also tabulated for the OL-500 period.

An ANCOVA model was built to compare the mean value in log_{10}-transformed CRD at Month 12 between each dose level group and placebo for subjects in the ITT. Treatment group, age group, and baseline log_{10}-transformed CRD were included in the model. The adjusted Least Squares Mean (LS-Mean) differences versus placebo were reported together with associated 95% confidence intervals and corresponding p-values. A SAS code similar to the following was be used.

```
PROC MIXED DATA =<indata>;
        CLASS agegroup treat;
        MODEL aval = base agegroup treat / DDFM=kr;
        LSMEANS treat/cl diff;
RUN;
```

In addition to the analysis of the log_{10}-transformed data, a sensitivity analysis was performed using an appropriate non-parametric test procedure. The treatment effect was estimated using Hodges-Lehmann estimate of the difference in medians of CRD change from month 0. The corresponding 95% confidence interval and the p-value from the hypothesis test of no difference between the treatment groups (Wilcoxon rank-sum test) stratified on age group were presented.

The ANCOVA model and its sensitivity analysis will not be repeated for open-label time points.

Note that only the active milk food challenge will be included, placebo food challenges will not be included.

8.2.2.2 OL-300 Analyses

Descriptive summaries will be presented overall and in each age-group, in total and by initial randomized treatment group (placebo/dose level/overall active) in the OLS-300, using different definitions of baseline values, as described in Section 8.2.1.2

1. Considering the CRD determined by screening DBPCFC as baseline CRD.
2. Considering the CRD determined by the DBPCFC which was conducted prior to the subject receiving any active treatment as baseline CRD.

The absolute CRD values at each timepoint will be presented, in addition with the change from screening and from last value prior any active treatment, taking the different types of baseline into account.

In addition the number (%) of subjects with CRD improvement / stable / deterioration from screening DBPCFC and from last DBPCFC prior any active treatment at each timepoint will be presented, using the following defintions:

- Improvement: CRD at timepoint > CRD at baseline
- Stable: CRD at timepoint = CRD at baseline
- Deterioration: CRD at timepoint > CRD at baseline

with baseline denoting screening DBPCFC or last DBPCFC prior any active treatment, respectively.

8.2.3 Immunological Markers

8.2.3.1 Double-blind Month 12 and OL-500 analyses

Repeated-measures ANCOVA models were built to compare the mean absolute change from baseline value (Visit 1) in

1) Cow's milk specific IgE
2) Cow's milk specific IgG4
3) Specific IgE to caseins
4) Specific IgG4 to caseins
5) Specific IgE to α-lactalbumin
6) Specific IgG4 to α-lactalbumin
7) Specific IgE to β-lactoglobulin
8) Specific IgG4 to β-lactoglobulin

using all time points evaluated up to Month 12 between each dose level group and placebo for subjects in the ITT.

Treatment group, treatment-by-time point interaction, age group, and baseline parameter value were included in the model. The distribution of each parameter was

examined graphically (Bar-Chart) and a natural log transformation of the data was performed to be used in the analysis. The adjusted LS Mean and LS-Mean differences versus placebo and corresponding p-values at each time point (Week 3, Month 3, Month 6, and Month 12) were reported together with associated 95% CI. P-values for treatment effect all time points taken together were also provided. This ANCOVA model will not be repeated for open-label time points.

Actual values and changes from baseline for the immunological markers were summarized overall and for each age group, by (initial randomized) treatment group (dose level/placebo/overall active/total), at each time point until Month 12 for the randomized blinded treatment period.

Same summaries were provided for the Viaskin Milk 500µg open-label treatment period on the OLS-500. Change from Month 12 was also be tabulated for this period, if applicable. Similarily, the last value in the Viaskin Milk 500µg open-label treatment period was summarized.

Actual values and changes from baseline for the immunological markers will be displayed graphically by treatment group in the course of time.

8.2.3.2 OL-300 Analyses

During OL-300 analyses, Cow's milk specific IgG4 were no longer collected and analyzed.

The following values will be summarized for the immunological markers using descriptive statistics overall and for each age group, visit and time point in total and by initial randomized treatment group (placebo/dose level/overall active) on the OLS-300.

- Absolute values at Month 0, Month 12, last value prior to switch to Viaskin Milk 300µg and all scheduled visits in the analyzed OL-300 period
- Changes from last value prior to any active treatment
- Changes from last value prior to switch to Viaskin Milk 300µg

Actual values for the immunological markers will be displayed graphically by treatment group in the course of time during the analyzed OL-300 period.

8.2.4 Skin Prick Test

8.2.4.1 Double-blind Month 12 and OL-500 analyses

Actual values and change from baseline of SPT mean wheal diameter were summarized at all time points using descriptive statistics overall and for each age group, in total and by randomized treatment group (placebo/dose level/ overall active), on the ITT, for the randomized blinded treatment period. Same summaries were provided on the OLS-500, for the Viaskin Milk 500µg open-label treatment period, if applicable. Similarily, the last value in the Viaskin Milk 500µg open-label treatment period was summarized.

The change in SPT average wheal diameter from baseline was also assessed by looking at the ratio of the average wheal diameter at each time point versus baseline categorized as:

- Significant improvement, if the ratio ≤ 0.75,
- No significant improvement, if the ratio > 0.75.

The number and percentages of subjects with or without significant improvement was then 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 (similar 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 wheal diameter equals to 0 was presented.

Repeated-measures ANCOVA model (same model as for Immunological Markers) was built to compare the change from baseline value in SPT average wheal diameter at all time points evaluated up to Month 12 between each dose level group and placebo for subjects in the ITT. The distribution of the SPT average wheal diameter was examined graphically (bar chart) and a $\log_{10}$-transformation of the data was performed to be used in the analysis. This ANCOVA model will not be repeated for open-label time points.

SPT results were also listed.

8.2.4.2 OL-300 Analyses

The following values will be summarized for the SPT using descriptive statistics overall and for each age group, visit and time point in total and by initial randomized treatment group (placebo/dose level/overall active) on the OLS-300.

- Absolute values at Month 0, Month 12, last value prior to switch to Viaskin Milk 300µg and all scheduled visits in the analyzed OL-300 period
- Changes from last value prior to any active treatment
- Changes from last value prior to switch to Viaskin Milk 300µg

The change in SPT average wheal diameter from both baselines will also be assessed by the ratio of the average wheal diameter at each time point versus baseline categorized as:

- Significant improvement, if the ratio ≤ 0.75,
- No significant improvement, if the ratio > 0.75.

The number and percentages of subjects with or without significant improvement with respect to both baselines will be presented at each timepoint.

The number of subjects with a mean wheal diameter equal to 0 will be presented.

8.2.5 Analysis of Severity during the Milk DBPCFC

8.2.5.1 Double-blind Month 12 and OL-500 analyses

The number of subjects with any objective and subjective allergic reaction during the different DBPCFC for both formulas was summarized overall and for each age group, in total and by (initial randomized) treatment group (placebo/dose level/overall active) for ITT, and OLS-500, respectively.

For the milk formulas only, the number of subjects with the specific objective and subjective allergic reaction during the different DBPCFC were summarized overall and for each age group, in total and by (initial randomized) treatment group (placebo/dose level/overall active) for ITT, and OLS-500, respectively.

The severity of symptoms elicited during the milk DBPCFC were assessed at Screening, Months 12, 24, 36 and 48. Grading of symptoms were done using the grading definition in the Oral Food Challenge (OFC) Symptom Score Sheets. Each symptom (objective and subjective) will be graded once per DBPCFC-Visit.

A total objective severity score was derived as the sum of the severity grades (0, 1, 2 or 3) of the following objective symptoms: pruritus, urticaria/angioedema, rash, sneezing/itching, nasal congestion, rhinorrhea, laryngeal, wheezing, diarrhea, vomiting, cardiovascular and conjunctivitis for DBPCFC with cow's milk formula.

A total subjective severity score was derived as the sum of the severity grades (0, 1, 2 or 3) of the following subjective symptoms: itchy mouth, itchy throat, nausea and abdominal pain for DBPCFC with cow's milk formula.

The total objective and subjective severity score was summarized (absolute and change from baseline) overall and for each age group, in total and by (initial randomized) treatment group (placebo/dose level/overall active), at Screening and Month 12 for subjects on the ITT in the randomized blinded treatment period.

Time-to-first objective symptom at Months 12, was summarized and Kaplan-Meier curves were provided for Month 12, overall and for each age group, in total and by randomized treatment-group (dose level/placebo/overall active). Patients without any objective symptom during the DBPCFC were censored at the time of discharge.

8.2.5.2 OL-300 Analyses

The summaries described in Section 8.2.5.1 for the OL-500 period will be repeated for the OL-300 period using the worst intensity per symptom, subject and visit. The respective listings will present all intensities recorded.

8.2.6 Quality of Life Assessments

8.2.6.1 Food Allergy Quality of Life Questionnaires (FAQLQ)

8.2.6.1.1 General

FAQLQs will be completed by study subjects 8 years old and older (FAQLQ-Child Form (FAQLQ-CF) for age range 8 to 12 years old, FAQLQ-Teenager Form (FAQLQ-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 questionnaire for subjects 0 to 12 years old (FAQLQ-Parent Form (FAQLQ-PF)) and for subjects 13 to 17 years old (FAQLQ-Parent Form Teenagers (FAQLQ-PFT)).

The FAQLQ forms will be completed at baseline, Months 12, 24, 36 or 48 and every 6 months during the Viaskin Milk open-label 300µg. The same questionnaire will be completed throughout the study according to the subject's age at Visit 1.

For the specific questionnaires the following sub-scores as defined in the respective scoring sheets - also available on www.faqlq.com - will be derived:

FAQLQ-CF (8-12 yrs) will be analyzed according to the 4 following domains [3]:

- EI: Emotional impact (Q no: 19-24),
- AA: Allergen avoidance (Q no: 4, 6-10, 15),
- RAE: Risk of accidental exposure (Q no: 11, 13-14, 16-17),
- DR: Dietary restrictions (Q no: 1-3, 5, 12, 18).

FAQLQ-PF (0-12 yrs) will be analyzed according to the 3 following domains [4]:

- EI: Emotional impact (Q no: 2, 6-7, 9-11, 23-28, 30),
- FA: Food-related anxiety (Q no: 1, 4-5, 16-17, 20-21, 29),
- SDL: Social and dietary limitations (Q no: 3, 8, 12-15, 18-19, 22).

The scores are calculated taking the reduced numbers of items for younger children into account: For children between 0-3 years old questions numbers 15 and higher are not applicable and for children aged between 4 and 6 years questions 27 to 30 are not applicable. Age at Visit 1 will be used to define which questions will be applicable during the study for each patient. Questions not needed will be not used for analysis.

These sub-scores rely on different numbers of items according to these age-groups (0-3, 4-6 and 7-12 years old).

FAQLQ-TF (13-17 yrs) will be analyzed according to the 3 following domains [5]:

- EI: Emotional impact (Q no: 5, 12, 19-23),
- RAE: Risk of accidental exposure Q no: 11, 13-15, 17-18),
- AADR: Allergen avoidance and dietary restrictions (Q no: 1-10, 16).

FAQLQ-PTF (13-17 yrs) will be analyzed according to the 4 following domains:

- EI: Emotional impact (Q no: 20-27),
- FA: Food anxiety (Q no: 8-13),
- SR: Social restrictions (Q no: 14-19).
- DR: Dietary restrictions (Q no: 1-7).

For FAQLQ-CF, -TF and PTF total scores will be derived using the completed question directly. The total score from FAQLQ-PF will be calculated as mean of the 3 subscores - without adjusting for age-group.

The scores range from 1 (no problem/impairment) to 7 (maximal problem/impairment). A negative score in the changes to baseline means improvement.

The following instructions from the reference website (www.faqlq.com) will be used for the derivations of (sub-) scales:

1) Each question of the FAQLQ is answered on a 7-point scale (0 to 6) and should be recoded 1 to 7
2) The total FAQLQ-scores (except for FAQLQ-PF) and all sub-scores are calculated by dividing the sum of completed items by the number of completed items
3) If > 20% of items in any (sub-) scale are missing then the respective (sub-) scale is set to missing

8.2.6.1.2 Double-blind Month 12 and OL-500 analyses

The total FAQLQ-scores and the respective sub-scores were summarized overall and for each type of questionnaire, in total and by randomized treatment group (placebo/dose level/overall active) at each time point using absolute value and change from baseline on the ITT for the randomized blinded treatment period.

Same analysis was performed overall and for each type of questionnaire, in total and by initial treatment group at each time point using absolute value and change from baseline on the OLS-500 for the Viaskin Milk 500µg open-label treatment period, if applicable. Similarily, the last value in the Viaskin Milk 500µg open-label treatment period was summarized.

Change from Month 12 was also tabulated at each time point of the Viaskin Milk 500µg open-label treatment period, if applicable.

The change from baseline (Visit 1) in QoL total scores and sub-scores at Month 12 was analyzed using an ANCOVA model for the randomized period. Treatment group and baseline score were included in the model. The adjusted LS-Mean differences versus placebo were reported together with associated 95% CI and p-values for each treatment contrast, i.e. for each pairwise comparison. These ANCOVA models will not be repeated for open-label time points.

8.2.6.1.3 OL-300 Analyses

The following values will be summarized for the total FAQLQ-scores and the respective sub-scores using descriptive statistics overall and for each age group, visit and time point in total and by intial randomized treatment group (placebo/dose level/overall active) on the OLS-300.

- Absolute values at Month 0, Month 12, last value prior to switch to Viaskin Milk 300µg and all scheduled visits in the analyzed OL-300 period
- Changes from last value prior to any active treatment
- Changes from last value prior to switch to Viaskin Milk 300µg

8.2.6.2 Food Allergy Independent Measure (FAIM)

8.2.6.2.1 General

Each question of the FAIM is answered on a 7-point scale (0 to 6) and should be recoded 1 to 7. Total FAIM scores will be calculated by dividing the sum of completed items by the number of completed items. Total FAIM scores range from 1 "low perceived disease severity" to 7 "high perceived disease severity". Calculation of total FAIM scores will be done only when 80% or more of the items are completed.

Some specific items mentioned below have to be reverse coded.

FAIM-CF: Child Form (8-12 years)

This questionnaire consists of 6 items. The mean score will be performed if at least 5 items are completed.

FAIM-PFC: Parent Form (Children aged 0-12 years)

There are 2 sections given in the questionnaire each with the same questions, one from the perspective of the parents (*What chance do you think your child has of.....?*) the other reflecting the thoughts of the child (*What chance does your child think he/she has of.....?*). Both mean scores of the parent's form ("Parent's thoughts" and "Child's thoughts") are calculated as the mean of the single items, only if none of the items is missing. In both scores question 4 needs to be reverse scored.

FAIM-TF: Teenager Form (13-17 years)

This questionnaire is similar to the FAIM-CF and consists of 6 items. The mean score will be performed if a maximum of one item is missing.

FAIM-PFT: Parent Form (Adolescents aged 13-17)

The mean score "Teenager's thoughts" of the parent's form will be created similar to the total scores in FAIM-PFC as the mean of the single items. It will be calculated only if all items are available. Question 4 needs to be reverse scored.

8.2.6.2.2 Double-blind Month 12 and OL-500 analyses

The total FAIM-scores were summarized overall and for each type of questionnaire, in total and by randomized treatment group (placebo/dose level/overall active) at each time point using absolute value and change from baseline until Month 12 on the ITT for the randomized blinded treatment period.

Same analysis was performed overall and for each type of questionnaire, in total and by initial treatment group at each time point using absolute value and change from baseline until Month 48 on the OLS-500 for the Viaskin Milk 500µg open-label treatment period, if applicable. Similarily, the last value in the Viaskin Milk 500µg open-label treatment period was summarized.

Change from Month 12 to each time point was also tabulated for the Viaskin Milk 500µg open-label treatment period, if applicable.

8.2.6.2.3 OL-300 Analyses

The following values will be summarized for the FAIM-scores using descriptive statistics overall and for each age group, visit and time point in total and by initial randomized treatment group (placebo/dose level/overall active) on the OLS-300.

- Absolute values at Month 0, Month 12, last value prior to switch to Viaskin Milk 300µg and all scheduled visits in the analyzed OL-300 period
- Changes from last value prior to any active treatment
- Changes from last value prior to switch to Viaskin Milk 300µg

9 SAFETY

The Safety Set was employed for all safety analyses on the randomized blinded treatment period and on the whole treatment or study period; OLS-500 was used for all safety analyses on the OL-500 period and OLS-300 will be used for the OL-300 period.

Safety analysis will generally be performed on the actual treatments given. In case of wrong dispensation, the subject will be analyzed according to the treatment received the longest.

9.1 EXTENT OF EXPOSURE

9.1.1 General

Extent of exposure was summarized using the exposure duration in the respective period, regardless of temporary interruptions, defined as:

> Date of last patch application in the period - date of first patch application in the period + 1.

Duration of patch application is assessed as recommended or not every day from Day 1 (Visit 4) up to Month 3 (Visit 9) on the subject diary cards. If duration of application is not as recommended, actual duration is recorded in hours and minutes per day. After Month 3 (Visit 9), application not as recommended were registered; actual duration is recorded in hours and minutes per day.Duration will be imputed with the recommended duration (6, 12 or 24 hours) for each day with duration assessed as 'as recommended'.

Reasons for patches not applied per protocol were classified a-posteriori in the randomized blinded treatment period (ITT) and the Viaskin Milk 500µg open-label period (OLS-500). The main reasons for patches not applied as per protocol, were subsequently pre-specified in the subjects' diaries as follows:

- Fell off
- Discomfort
- Personal convenience
- Investigator's decision
- Forgot
- Other

Inconsistencies in the data of diary cards are very common in clinical studies. In general the worst-case principle will be applied. Details of handling the different cases will be documented in a respective note-to-file document.

9.1.2 Double-blind Month 12 and OL-500 analyses

Exposure duration was summarized overall and for each age group, in total by initial treatment group (placebo/dose level/overall active) for the randomized blinded treatment period.

The above analysis was repeated overall and for each age group, in total and by initial treatment group, for the Viaskin Milk 500µg open-label treatment period as well as for the overall treatment period. Exposure duration in the Viaskin Milk 500µg open-label treatment period was summarized overall and for each age group, in total by initial treatment group using the following classes: [0-6[months, [6-12[months, [12-18[months, [18-24[months, [24-30[months, [30-36[months, [36-42[months, [42-48[months.

Mean daily exposure, defined as the total number of hours of application during a period divided by the number of days in that period, was summarized for the first 2 weeks of treatment, from the 3rd week to the Month 3 visit, from the Month 3 to the last patch application during the randomized blinded treatment period (Day 1 – Day 7, Day 8 – Day 14, Day 15 – Month 3, Month 3 - randomized blinded treatment end date).

The above analysis was repeated, overall and for each age group, in total and by initial treatment group for the Viaskin Milk 500µg open label treatment period, as well as for the overall treatment period.

Number of days with patch not applied, defined as the total number of days with null daily duration of application, were summarized as a continuous variable overall and for each age group, in total and by actual treatment group (placebo/dose level/ overall active) for all subjects during the randomized blinded treatment period.

The above analysis was repeated, overall and for each age group, in total and by initial treatment group for the Viaskin Milk 500µg open label treatment period, as well as for the overall treatment period.

Reasons for patches not applied per protocol was summarized overall and for each age group, in total by initial treatment group (placebo/dose level/overall active) for the randomized blinded treatment period.

The above analysis was repeated, overall and for each age group, in total and by initial treatment group for the Viaskin Milk 500µg open label treatment period.

9.1.3 OL-300 Analyses

Exposure duration will be summarized overall and for each age group, in total by initial treatment group (placebo/dose level/overall active) for the analyzed OL-300 period as well as for the overall treatment period for the OLS-300.

Mean daily exposure, defined as the total number of hours of application during the analyzed OL-300 period divided by the number of days in that period, will be summarized for the OLS-300.

Number of days with patch not applied, defined as the total number of days with null daily duration of application, will be summarized as a continuous variable overall and for each age group, in total and by actual treatment group (placebo/dose level/ overall active) for all subjects during the analyzed OL-300 period as well as for the overall treatment period.

Reasons for patches not applied per protocol will be summarized overall and for each age group, in total by initial treatment group (placebo/dose level/overall active) for the analyzed OL-300 period as well as for the overall treatment period for the OLS-300.

9.2 TREATMENT COMPLIANCE

9.2.1 General

The overall compliance, based on the Study Drug Accountability Form, is calculated from the total number of patches dispensed and returned by subject

$$\frac{\text{(number of patches dispensed - number of patches returned)}}{\text{number of days during the corresponding period}}$$

For overall compliance, number of days during the corresponding period is defined as treatment exposure; otherwise, period is defined as the number of days between visit (n) and visit (n-1)

Compliances exceeding 100% will be set to 100%.

9.2.1 Double-blind Month 12 and OL-500 analyses

The number of subjects with a compliance ≥ 80% was presented. An overall compliance of ≥ 80% is defined as good compliance.

Compliance at each visit was calculated during the double blind period in a similar way and summarized.Subjects' compliance overall and by visit was summarized overall and for each age group, in total and by randomized treatment group (placebo/dose level/overall active) for the randomized blinded treatment period (Months 0 to 12).

It was repeated for the Viaskin Milk 500µg open-label treatment period (Months 12 to switch to Viaskin Milk 300µg) and the whole treatment period (Months 0 to switch to Viaskin Milk 300µg).

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 is defined as an exclusion criterion for the extension part of the study and was summarized.

9.2.2 OL-300 Analyses

Compliance will be summarized overall and for each age group, in total by initial treatment group (placebo/dose level/overall active) for the analyzed OL-300 period as well as for the whole treatment period for the OLS-300.

9.3 ADVERSE EVENTS

9.3.1 Definitions

Treatment emergent AEs (TEAEs) are defined as any AEs, regardless of relationship to investigational product which occur during or after the initial patch application (or any event already present that worsens in intensity following exposure to the patch).

AEs with missing or incomplete onset date will be treated as TEAEs and missing onset date will be imputed as date of initial patch application unless there is evidence that the event occurred prior or after the treatment period, e.g. year and month indicate the onset date is before study treatment.

AEs will be considered drug-related if relationship information is definite / probable / possible. If relationship information is missing for a TEAE, the AE will be considered as drug-related.

If the severity is missing of an AE starting prior to the date of initial patch application, then a severity of "Mild" will be assigned. If the severity is missing of an AE starting on or after the date of initial patch application, then a severity of "Severe" will be assigned.

Imputed values for relationship, severity or onset date will be used for incidence summaries, while the actual values will be used in data listings.

9.3.2 General

All AEs and TEAEs were listed and tabulated by Medical Dictionary for Regulatory Activities (version 17.0 or higher) System Organ Class (SOC) and preferred term. Incidence tables will be presented for all TEAEs and TESAEs.

For adverse events analyses, serious adverse events occurring during DBPCFC were not considered, they were described separately (see section 9.3.4).

9.3.3 Double-blind Month 12 and OL-500 analyses

9.3.3.1 Overview tables

An overview of AEs and an overview of TEAEs, occurred in the SS of the randomized treatment period (incl. screening), presented the number of subjects and number of respective events overall and for each age group, in total and by treatment group (placebo/dose level/overall active) with

- Any AE /TEAE,
- Any serious AE/TEAE,
- Any TEAE considered related to the investigational product (IP), and
  - Any TEAE definitely related,
  - Any TEAE probably related,
  - Any TEAE possibly related,
  - Any TEAE unlikely related,
  - Any TEAE not related
- Any TEAE considered not related to IP, and
  - Any TEAE unlikely related,
  - Any TEAE unrelated,
- Any serious TEAE considered related to IP,
- Any TEAE leading to treatment discontinuation,
- Any AE/TEAE leading to death,
- Any mild AE/TEAE,
- Any moderate AE/TEAE
- Any severe AE/TEAE,
- Any severe TEAE considered related to IP.

- Any application site disorder[3] considered related to IP
- Any severe application site disorder considered related to IP
- Any Adverse Events of specific interest (AESI)
- Any local AESI[4]
- Any systemic AESI[5]
  - Considered related to IP
  - Considered unrelated to IP
- Any TEAE leading to an epinephrine intake
  - Considered related to IP
  - Considered unrelated to IP
- Any TEAE leading to systemic or inhaled corticosteroids use
  - Considered related to IP
  - Considered unrelated to IP
- Any TEAE leading to topical corticosteroids use
  - Considered related to IP
  - Considered unrelated to IP

Similar overviews for TEAEs were performed for the whole treatment period as well as for the Viaskin Milk 500µg open-label treatment period, by the initial actual treatment-group.

The overviews of the TEAEs were repeated for the 2 filaggrin mutation subgroups in the Month 12 analysis. These analyses will not be provided for the Viaskin Milk 500µg open-label treatment period analysis.

9.3.3.2 Incidence tables

The following tabulations were produced overall and for each age group, in total and by treatment group (placebo/dose level/overall active) on the SS for the randomized blinded treatment period.

- TEAEs overall and by system organ class and preferred term
- TEAEs by maximum severity, overall and by system organ class and preferred term
- Severity of TEAEs, overall and by system organ class and preferred term
- Severe TEAEs, overall and by system organ class and preferred term
- Severe TEAEs considered related to IP, overall and by system organ class and preferred term

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[3] Application site disorders are AEs with 'Application and instillation site reactions' in their MedDRA-coded HLTs.
[4] Local AESI are identified as detailed in Section 16.1 Appendix 1.
[5] Systemic AESI are identified as detailed in Section 16.2 Appendix 2.

- TEAEs considered related to investigational product (IP), overall and by system organ class and preferred term
- Number of TEAEs considered related to IP by maximum severity, system organ class and preferred term
- TESAEs overall and by system organ class and preferred term
- TESAEs considered related to IP, overall and by system organ class and preferred term
- Adverse Events leading to treatment discontinuation overall and by system organ class and preferred term
- Application site disorders considered related to IP overall and by system organ class and preferred term
- Treatment emergent systemic AESI overall and by system organ class and preferred term
- Treatment emergent systemic AESI considered related to IP overall and by system organ class and preferred term
- Treatment emergent local AESI overall and by system organ class and preferred term

They were repeated overall and for each age group, in total and by initial actual treatment group on the SS for the whole treatment period, and on the OLS-500 for the Viaskin Milk 500µg open-label treatment period :

Additionally, tables showing the number and percentage of subjects who experienced at least one TEAE and the number of events by SOC and PT, summarizing TEAEs leading to:

- Epinephrine use:
  - Standard medication name that contains “EPINEPHRINE” and ATC level 1 = “CARDIOVASCULAR SYSTEM”
- Systemic or inhaled corticosteroid use,
  - ATC code starting with “H02”, “R03AK”, “R03BA”
- Topical corticosteroid use,
  - ATC code starting with “D07”

were presented (exhaustiveness of the above selections, especially regarding the route that can be reported as “Other” with a text field specification, will be checked during the blind data review meeting) on the SS for the randomized blinded treatment period.

They were repeated on the SS for the whole treatment period, and on the OLS-500 for the Viaskin Milk 500µg open-label treatment period.

9.3.3.3 Subject-Year Analysis

A subject-year analysis was performed on the same parameter as described for the overview tables above on the whole treatment period overall and for each age-group for the SS. The subject year analysis should be presented according to treatments received (not randomized). E.g., subject randomized as placebo and treated during one year with Placebo then treated with Viaskin Milk 500µg during 2 years should account for 1 patient-year in Placebo column and 2 patient-year in Viaskin Milk 500µg column.

Additionally, a subject-year analysis presented the total number of subject-years, the number of subjects with a TEAE (respectively a TEAE considered related to IP) per subject-year and the number of TEAEs (respectively TEAEs considered related to IP) per subject-year, for each dose level and by SOC and PT on the whole treatment period overall and for each age-group for the SS.

Separate listings were performed additionally:

- SAEs
- TESAEs
- Adverse events of specific interest (AESI):
    - Local AESIs.

  These local TEAEs of interest will be identified following methodology described in 16.1 Appendix 1.
    - Systemic AESI considered related to IP.
    - Systemic AESI (whether related or not).

  These systemic TEAEs of interest will be identified following methodology described in 16.2 Appendix 2.
- AEs leading to discontinuation
- TEAEs leading to epinephrine intake

9.3.4 OL-300 Analyses

9.3.4.1 Overview tables

An overview of TEAEs occurring in the analyzed OL-300 period will be presented for the OLS-300 overall and for each age group, in total and by initial actual treatment group (placebo/dose level/overall active) as specified in Section 9.3.3.1.

9.3.4.2 Incidence tables

The incidence tables - described in Section 9.3.3.2 - will be repeated overall and for each age group, in total and by initial actual treatment group (placebo/dose level/overall active) on the OLS-300 for the analyzed OL-300 period.

The listings described in Section 9.3.3.2 will include the adverse events starting in OL-300 period.

9.3.4.3 Subject-Year Analysis

Analysis by subject-year will be performed for the OLS-300 equivalently as described in Section 9.3.3.3:

a) The treatment durations and the respective AEs of subjects randomized to Placebo or Viaskin Milk 150µg in the DB-period will be assigned to the treatment arm “Placebo” or “Viaskin Milk 150µg”, respectively.

b) The treatment durations and the respective AEs of subjects randomized to Viaskin Milk 300µg in the DB-period and the whole OL-300 period will be added to the treatment arm “Viaskin Milk 300µg”.

c) The treatment durations and the respective AEs of subjects randomized to Viaskin Milk 500µg in the DB-period and the whole OL-500 period will be added to the treatment arm "Viaskin Milk 500µg".

These treatment durations in days will be divided by 365.25 to get the subject-years. The number of AEs will be divided by the respective subject-years.

9.4 SYMPTOMS ELICITED DURING THE DBPCFC.

9.4.1 Double-blind Month 12 and OL-500 analyses

The symptoms elicited during the DBPCFC (as they are expressly provoked) are differentiated from TEAEs and TESAEs.

SAEs elicited during the DBPCFC were tabulated overall and for each age group, in total and by (initial actual) treatment group (placebo/dose level/overall active), by system organ class and preferred term for each time point of the DBPCFC in the SS, OL-500, respectively - discriminated between Milk- and Placebo-Formula.

SAEs elicited during any DBPCFC were tabulated overall and for each age group, in total and by (initial actual) treatment group (placebo/dose level/overall active), by system organ class and preferred term in the SS - discriminated between Milk- and Placebo-Formula.

Objective and subjective symptoms appearing during the DBPCFCs (which are not reported in the AE form unless they are SAEs) were summarized overall and for each age group, in total and by (initial actual) treatment group (placebo/dose level/overall active) by time point of the DBPCFC and severity in the SS, OL-500, respectively - discriminated between Milk- and Placebo-Formula.

9.4.2 OL-300 Analyses

SAEs elicited during the optional DBPCFC will be tabulated overall and for each age group, in total and by (initial actual) treatment group (placebo/dose level/overall active), by system organ class and preferred term for each time point of the DBPCFC in the analyzed OL-300 Period for the OLS-300. Incidences will be calculated with respect to the number of subjects participating on the respective DBPCFC and discriminated between Milk- and Placebo-Formula.

SAEs elicited during any DBPCFC will be tabulated overall and for each age group, in total and by (initial actual) treatment group (placebo/dose level/overall active), by system organ class and preferred term in the SS - discriminated between Milk- and Placebo-Formula.

Objective and subjective symptoms appearing during the DBPCFCs (which are not reported in the AE form unless they are SAEs) will be summarized overall and for each age group, in total and by (initial actual) treatment group (placebo/dose level/overall active) by time point of the DBPCFC and severity in the OL-300 Period - discriminated between Milk- and Placebo-Formula.

9.5 VITAL SIGNS

9.5.1 General

Vital signs include heart rate (beats/minute), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), and respiratory rate (breaths/minute).

Vital signs of potential clinical significance for children and adolescents are given in Table 4:

Table 4: Vital signs of potential clinical significance for children and adolescents

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 are assessing, whether any of the abnormal values are clinically significant. Clinically significant abnormal values will be recorded as an AE.

9.5.2 Double-blind Month 12 and OL-500 analyses

Observed vital sign values and absolute changes from baseline were summarized using descriptive statistics overall and for each age group, visit and time point in total and by treatment group (placebo/dose level/overall active) on the SS for the randomized blinded treatment period (Months 0 to 12).

Same analysis was performed overall and for each age group, visit and time point in total and by initial actual treatment group on the OLS-500 for the Viaskin Milk 500µg open-label treatment period (Months 12 to switch to Viaskin Milk 300µg). Similarily, the last value in the Viaskin Milk 500µg open-label treatment period was summarized.

Values that are potentially clinically significant will be flagged in the vital signs listings.

9.5.3 OL-300 Analyses

The following vital signs values will be summarized using descriptive statistics overall and for each age group, visit and time point in total and by initial actual treatment group (placebo/dose level/overall active) on the OLS-300.

- Absolute values at Month 0, Month 12, last value prior to switch to Viaskin Milk 300µg and all scheduled visits in the analyzed OL-300 period
- Changes from last value prior to any active treatment
- Changes from last value prior to switch to Viaskin Milk 300µg

Values that are potentially clinically significant will be flagged in the vital signs listings.

9.6 PHYSICAL EXAMINATION

9.6.1 General

Physical examination results are categorized in normal, abnormal, and not done.

9.6.2 Double-blind Month 12 and OL-500 analyses

Physical examination results, including complete observation of the skin were summarized overall and for each age group, visit and time point in total and by treatment group (placebo/dose level/overall active) on the SS for the randomized blinded treatment period.

Same analysis was performed overall and for each age group, visit and time point in total and by initial actual treatment group on the OLS-500, for the Viaskin Milk 500µg open-label treatment period. Similarily, the last value in the Viaskin Milk 500µg open-label treatment period was summarized.

Respective shift tables with respect to Month 0 were produced, if applicable.

9.6.3 OL-300 Analyses

Physical examination results, including complete observation of the skin will be summarized overall and for each age group, visit and time point in total and by initial actual treatment group (placebo/dose level/overall active) on the OLS-300 for the analyzed OL-300 period.

9.7 PATCH SITE SKIN EXAMINATION

9.7.1 General

Examination of the skin at the site of patch application is graded from Grade 0 (negative) up to Grade 4 (erythema, vesicles).

9.7.2 Double-blind Month 12 and OL-500 analyses

These results were summarized using descriptive statistics and presented overall and for each age group and visit in total and by treatment group (placebo/dose level/overall active) on the SS for the randomized blinded treatment period.

These analyses were repeated overall and for each age group and visit in total and by initial actual treatment group on the OLS-500, for the Viaskin Milk 500µg open-label

treatment period. Similarily, the last value in Viaskin Milk 500µg open-label treatment period were summarized.

Worst grades reported for any treatment period will also be tabulated.

9.7.3 OL-300 Analyses

The grades will be summarized using descriptive statistics and presented overall and for each age group and visit in total and by initial actual treatment group (placebo/dose level/overall active) on the OLS-300 for the analyzed OL-300 period.

9.8 CLINICAL LABORATORY TESTS

9.8.1 General

Clinical laboratory test results will be presented in Standard International (SI) units unless otherwise specified.

9.8.2 Double-blind Month 12 and OL-500 analyses

Clinical laboratory tests were summarized overall and for each age group, in total and by time point and treatment group (placebo/dose level/ overall active) for both absolute values and absolute changes from baseline on the SS for the randomized blinded treatment period.

These analyses were repeated overall and for each age group, in total and by time point and initial actual treatment on the OLS-500 for the Viaskin Milk 500µg open-label treatment period. Similarily, the last value in Viaskin Milk 500µg open-label treatment period should be summarized.

Shift tables were generated overall and for each age group, in total and by treatment group (placebo/dose level/overall active) of test abnormalities comparing baseline values to the values collected at Months 12.

Same analysis were performed overall and for each age group, in total and by initial actual treatment group of test abnormalities comparing baseline value (Month 0) to the last value in the Viaskin Milk 500µg open-label treatment period.

Listed data values that are outside the reference range were flagged (low or high), if applicable.

Urine pregnancy test results were listed only.

9.8.3 OL-300 Analyses

Clinical laboratory values will be summarized using descriptive statistics overall and for each age group, visit and time point in total and by initial actual treatment group (placebo/dose level/overall active) on the OLS-300.

- Absolute values at Month 0, Month 12, last value prior to switch to Viaskin Milk 300µg and all scheduled visits in the analyzed OL-300 period
- Changes from last value prior to any active treatment
- Changes from last value prior to switch to Viaskin Milk 300µg

Listed data values that are outside the reference range were flagged (low or high), if applicable.

Urine pregnancy test results were listed only.

9.9 SPIROMETRY AND PEAK EXPIRATORY FLOW

9.9.1 General

Spirometry (FEV_1) and peak expiratory flow (PEV) will be assessed as absolute values and percentage relative to the predicted values.

Collected values will be listed.

9.9.2 Double-blind Month 12 and OL-500 analyses

FEV_1 and PEF results as % predicted values (actual values and change from baseline) were summarized overall and for each age group, visit and time point in total and by treatment group (placebo/dose level/ overall active) using descriptive statistics on the SS for the randomized blinded treatment period.

Same analysis was performed overall and for each age group, visit and time point in total and by initial actual treatment group on the OLS-500 for the Viaskin Milk 500µg open-label treatment period. Similarily, the last value in the Viaskin Milk 500µg open-label treatment period was summarized.

9.9.3 OL-300 Analyses

The following FEV_1 and PEF results as % predicted values will be summarized using descriptive statistics overall and for each age group, visit and time point in total and by initial actual treatment group (placebo/dose level/overall active) on the OLS-300.

- Absolute values at Month 0, Month 12, last value prior to switch to Viaskin Milk 300µg and all scheduled visits in the analyzed OL-300 period
- Changes from last value prior to any active treatment
- Changes from last value prior to switch to Viaskin Milk 300µg

9.10 OTHER SAFETY

9.10.1 Body characteristics

9.10.1.1 General

Weight and height will be reported every six months during the study. From these the Body Mass index (BMI, kg/m²), Body Surface (m²), and weight/height (kg/m) will be derived.

9.10.1.2 Double-blind Month 12 and OL-500 analyses

Absolute values and changes from baseline were summarized overall and for each age group and visit, in total and by treatment group (placebo/dose level/overall active) as well as the respective derived values BMI (kg/m²), Body Surface (m²), and weight/height (kg/m) on the SS for the randomized blinded treatment period.

Same analyses were performed overall and for each age group and visit, in total and by initial actual treatment group, on the OLS-500 for the Viaskin Milk 500µg open-label treatment period, if applicable. Similarily, the last value in the Viaskin Milk 500µg open-label treatment period were summarized.

9.10.1.3 OL-300 Analyses

The following values will be summarized for weight, height, BMI, Body Surface and weight/height using descriptive statistics overall and for each age group, visit and time point in total and by initial actual treatment group (placebo/dose level/overall active) on the OLS-300.

- Absolute values at Month 0, Month 12, last value prior to switch to Viaskin Milk 300µg and all scheduled visits in the analyzed OL-300 period
- Changes from last value prior to any active treatment
- Changes from last value prior to switch to Viaskin Milk 300µg

9.10.2 Safety diary card data

Data derived from the diaries of the first 3 months of treatment were summarized overall and for each age group, in total and by actual treatment group (placebo/dose level/overall active) on the SS. This was done over the whole 3 months period and for 14-days intervals.

The number of days of itching, redness and swelling by severity was displayed. The most severe grades of itching, redness and swelling, documented in the diary card, were summarized. The maximum grade of local reaction reported (itching, redness or swelling) during the first 3 months was also tabulated.

The proportion of evaluations was tabulated by grade taken into account the maximum grade of itching, redness or swelling.

After Month 3, these data are already collected and summarized as AE.

10 EXPLORATORY

10.1 EPIGENETIC MODIFICATIONS AT MONTHS 12, 24, 36 AND 48

Epigenetic analysis will be performed separately. Analysis details will not be described here.

10.2 FILAGGRIN GENE MUTATIONS

Filaggrin gene mutations was assessed from a blood sample collected at Screening and the results were summarized overall and for each age group, in total and by treatment group (placebo/dose level/overall active), whether no mutation, a heterozygous or a homozygous mutation was identified. Five different mutations are expected: R501X, 2282del4, R2447X, S3247X, 3702delG and will be included in the summary.

The relationship between the presence of filaggrin mutations (with/without), safety (SS) and response to treatment (ITT) was only investigated during the double-blind period (see Section 8.1.7 and 9.2.2).

10.3 ADDITIONAL IMMUNOLOGICAL MARKERS

10.3.1 General

Immunological markers are also available for Peanut, Egg White, House Dust Mite and Grass Pollen.

10.3.2 Double-blind Month 12 and OL-500 analyses

Actual values and changes from baseline for the additional immunological markers were summarized overall and for each age group, in total and by treatment group (placebo/dose level/overall active), for each time point until Month 12 for the randomized blinded treatment period in the ITT.

Same analyses were repeated overall and for each age group, in total and by initial randomized treatment group on the OLS-500 for each time point of the Viaskin Milk 500µg open-label treatment period. Similarily, the last value in the Viaskin Milk 500µg open-label treatment period were summarized.

Repeated-measures ANCOVA models were built to compare the mean absolute change from baseline value (Visit 1) during the randomized blinded treatment period in

1) Specific IgE Peanut
2) Specific IgE Egg White
3) Specific IgE House Dust Mite D. Pter
4) Specific IgE Timothy Grass Pollen

similar to the analysis of the immunological markers (Section 8.2.3).

The distribution of each parameter was examined graphically (Bar-Chart) a natural log transformation of the data was performed to be used in the analysis.

These ANCOVA models were not repeated for open-label time points.

10.3.3 OL-300 Analyses

The following values of the additional immunological parameters will be summarized using descriptive statistics overall and for each age group, visit and time point in total and by initial actual treatment group (placebo/dose level/overall active) on the OLS-300.

- Absolute values at Month 0, Month 12, last value prior to switch to Viaskin Milk 300µg and all scheduled visits in the analyzed OL-300 period
- Changes from last value prior to any active treatment
- Changes from last value prior to switch to Viaskin Milk 300µg

10.4 ACCIDENTAL CONSUMPTION OF COW'S MILK

10.4.1 General

Accidental consumption of cow's milk is reported on a specific forms in the CRF, containing frequency, description of reaction(s) (if any) and medication(s) (if any).

10.4.2 Double-blind Month 12 and OL-500 analyses

Frequency of accidental consumption of cow's milk (in any form) was summarized overall and for each age group, in total and by treatment group (placebo/dose level/overall active) on the SS during the randomized blinded treatment period.

Number of allergic reactions and use of treatment for allergic reactions resulting from presumed accidental consumption of cow's milk, were summarized overall and for each age group in total and by treatment group (placebo/dose level/ overall active) on the SS during the randomized blinded treatment period.

Same descriptions were performed overall and for each age group, in total and by initial actual treatment group on the OLS-500 for the Viaskin Milk 500µg open-label treatment period.

The quantity of food consumed, details of symptoms and treatment of allergic reaction were presented in listings. Adverse events corresponding to these accidental consumption of cow's milk were listed.

10.4.3 OL-300 Analyses

Frequency of accidental consumption of cow's milk protein (in any form) will be summarized overall and for each age group, in total and by initial actual treatment group (placebo/dose level/overall active) on the OLS-300 in the analyzed OL-300 period.

Number of allergic reactions and use of treatments for allergic reaction resulting from presumed accidental consumption of cow's milk, will be summarized overall and for each age group in total and by initial actual treatment group (placebo/dose level/ overall active) on the OLS-300 in the analyzed OL-300 period.

10.5 RISK TAKING BEHAVIORS

10.5.1 General

Deliberate consumption is defined as cow's milk consumption documented on the accidental cow's milk consumption form, which is not confirmed to be accidental.

10.5.2 Double-blind Month 12 and OL-500 analyses

Frequency of deliberate consumption of cow's milk (in any form) was summarized overall and for each age group in total and by treatment group (placebo/dose level/overall active) on the SS during the randomized blinded treatment period.

Same analysis were performed overall and for each age group in total and by initial actual treatment group on the OLS-500 for the Viaskin Milk 500µg open-label treatment period.

10.5.3 OL-300 Analyses

Frequency of deliberate consumption of cow's milk (in any form) will be summarized overall and for each age group in total and by initial actual treatment group (placebo/dose level/overall active) on the OLS-300 in the analyzed OL-300 period.

10.6 END OF STUDY SURVEY

10.6.1 General

An EOS survey will be completed by the Investigator for each individual subject when their participation in the study is terminated.

10.6.2 Double-blind Month 12 and OL-500 analyses

Frequencies of the recommendations and estimations regarding the diet / consumption of milk products were summarized overall and for each age group in total and by treatment group (placebo/dose level/overall activel) in the ITT during the randomized blinded treatment period.

10.6.3 OL-300 Analyses

Same analysis will be repeated in the OLS-300 for the OL-300 and in the ITT for the whole study period.

10.7 DBPCFC OTHER THAN MILK

Additional food challenges other than milk (for clinical care) are permitted during the OL-300 treatment period. The results will be listed.

11 INTERIM ANALYSES AND DSMB

11.1 INTERIM ANALYSIS

There are no interim efficacy analyses planned for this study.

A 12-month analysis was conducted after all subjects from Part A and Part B have received 12 months of treatment and completed the Month 12 DBPCFC (both days). A data transfer was performed after the data are cleaned, coded, and reconciled with SAE and laboratory data. The database was locked and treatment unblinded. SDTM and ADaM datasets prepared for 12-month analysis excluded visits posterior to Visit 13; as well as concomitant medications, adverse events and accidental cow's milk consumption occuring after Visit 13.

The study data were analyzed as described in the previous sections of the SAP, version 4.0 dated 09-Feb-2018 and the results were reported in the 12-month CSR.

After the Month 12 DBPCFC, subjects continued treatment with active Viaskin Milk patch in an open-label manner at the highest dose (500µg) assessed to be safe based on safety data of Part A subjects. Following the results of the 12-month analysis, protocol was amended to switch the subjects from Viaskin Milk 500µg to Viaskin Milk 300µg for 24 months.

The study data will be analyzed as described in the previous sections of the SAP one year after switch to Viaskin Milk 300µg and two years after switch to Viaskin Milk 300µg.

11.2 DSMB

Besides the organizational meeting, three DSMB-meetings for Part A, and six for Part A+B are planned. Additional, unscheduled DSMBs will be performed if deemed necessary.

11.2.1 DSMB – Part A

The DSMB members reviewed the safety data collected from all subjects in Part A.

The listings produced for DSMB review are presented as follows:

- Adverse Events
- Demography
- Prior/Concomitant Medications
- Medical History
- Laboratory Data (in particular Haematology, Biochemistry and IgE)
- Vital signs
- Physical Examination
- Spirometry and Peak Expiratory Flow
- Patch site Skin Examination
- Diaries data (local skin reactions)
- Double-Blind Placebo-Controlled Food Challenge (DBPCFC)
- Objective Symptoms DBPCFC
- Subjective Symptoms DBPCFC
- Accidental Cow's Milk Consumption

Further details are described in the DSMB charter and in the DSMB SAP Part A.

11.2.2 DSMB – Part A+B

The DSMB members reviewed the safety data collected from all subjects in Part A and B up to the timelines given.

Further details are described in the DSMB charter and DSMB SAP Part A+B.

12 CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

12.1 AMENDMENT 1: FINAL VERSION 07 NOVEMBER 2014

No change

12.2 AMENDMENT 2: FINAL VERSION 2.0, 10 JULY 2015

a) Protocol amendment 2: 7.2.2.10 - Visit 13 (Second day of the Month 12 DBPCFC)

   Visit 13 corresponds to the start date of the open-label treatment period.

   is replaced by

   Open-Label treatment period start date will be the date of the first patch application of the Open-Label treatment.

b) Protocol amendment 2: Section 8.1.1.2 - General considerations

   Listings of raw subject data will be sorted by dose level, randomization number and visit, as applicable, for all randomized subjects.

is replaced by

All relevant subject data will be included in listings and sorted by dose level at the beginning of treatment, subject's number and visit, as applicable, for all randomized subjects.

c) Protocol amendment 2: 8.1.1.7 - Safety Variables

- *AEs and TEAEs by system organ class, preferred term, severity, and relatedness to the investigational product.*
- *SAEs and TESAEs by system organ class, preferred term, severity, and relatedness to the investigational product.*

Is replaced by

- *TEAEs by system organ class, preferred term, severity, and relatedness to the investigational product.*
- *TESAEs by system organ class, preferred term, severity, and relatedness to the investigational product.*

12.3 AMENDMENT 3: FINAL VERSION 3.0, 22 SEPTEMBER 2016

Following changes from analyses scheduled in protocol amendment 3, dated 22 september 2016 have been implemented in this Statistiscal Analysis Plan:

d) In order to homogenize analyses strategy with DBV Technologies' statistical analysis plans, main efficacy analysis set is ITT, instead of FAS

e) In order to homogenize analyses strategy with DBV Technologies' statistical analysis plans, FAS definition has been modified from 8.1.1.1 Datasets or Populations Analyzed

- *Protocol amendment 3: The Full Analysis Set (FAS) will include all randomized subjects who applied at least 1 Viaskin patch. The FAS will be used for all analyses of efficacy endpoints and for the presentation of subjects in all data listings. Subjects will be analyzed according to the randomized treatment.*

Is replaced by:

- *The Full Analysis Set will be comprised of all subjects who are randomized and have performed DBPCFC at Month 12. This population will be analyzed according to study treatment that was actually received by the subjects.*

f) In order to homogenize analyses strategy with DBV Technologies' other sponsor statistical analysis plans and to address regulatory authorities comments, wording of primary criterion has been modified: suppression of LOCF reference

in 8.1.1.6.1 Primary Efficacy Endpoint:

- *Protocol amendment 3: The percentage of subjects who are treatment responders after 12 months of EPIT treatment will be calculated on the ITT population using Last Observation Carried Forward (LOCF) imputation method (ie, subjects with missing data at Month 12 will be considered as non-responders).*

Is replaced by:

- *The primary efficacy endpoint will be the percentage (%) of subjects who are treatment responders after 12 months of EPIT treatment (defined in Section 4.1), on the ITT population, using Missing = failure imputation method (i.e. subjects with missing observation at Month 12 will be considered as non-responder).*

g) *In order to avoid overlapping periods, open-label period has been modified:*

- *Protocol amendment 3: The percentage of subjects who are treatment responders after 12 months of EPIT treatment will be calculated on the ITT population using Last Observation Carried Forward (LOCF) imputation method (ie, subjects with missing data at Month 12 will be considered as non-responders).*

Is replaced by:

- *The primary efficacy endpoint will be the percentage (%) of subjects who are treatment responders after 12 months of EPIT treatment (defined in Section 4.1), on the ITT population, using Missing = failure imputation method (i.e. subjects with missing observation at Month 12 will be considered as non-responder).*

h) *In order to homogenize analyses strategy with DBV Technologies' other sponsor statistical analysis plans and pharmacovigilance definition, adverse event of specific interest (=Systemic allergic symptoms) identification is modified:*

- *Protocol amendment 3: The initial list of MedDRA-coded PT (Generalized hives (urticarial), Wheezing, Vomiting, Respiratory distress, Shock, Hypotension, Altered mental status, anaphylaxis) will be reviewed before or at BDRM*

Is replaced by:

- *These systemic allergic TEAEs of interest will be identified through the algorithm of the Anaphylactic Reaction Standardized MedDRA queries (SMQ) (methodology described in section 16.1 - Appendix 1)*

i) *It was clarified that in general efficacy analysis in the open label period(s) will be*

summarized by initially randomized treatment arms, whereas safety analysis will be performed on initial actual treatment received.

12.4 AMENDMENT 4: FINAL VERSION 4.0, 18 DECEMBER 2017

Following changes from analyses scheduled in protocol amendment 4, dated 18 December 2017 have been implemented in this Statistiscal Analysis Plan (version 3.0):

a) *In order to homogenize analyses strategy with DBV Technologies' other statistical analysis plans, early termination assessments will be analyzed as having occurred at the next scheduled assessment.*

b) *Visit time windows have been defined for the main visits occurring during the randomized blinded treatment period. Number and percentage* of subjects respecting the time window defined in Table 3 will be provided.

c) *Clarification has been provided in case of several filaggrin mutations presented by subject in order to define the subject's homozygous/heterozygous status.*

d) *In order to homogenize analyses strategy with DBV Technologies' other statistical analysis plans, sensitivity analysis on primary endpoint presenting relative risks has been removed and replaced by presenting difference of responder rate and its Newcombe 95% confidence interval stratified on age group.*

e) *Sensitivity analyses on primary endpoint have been added:*

- *On missing data handling: analysis using observed data, analysis of best case scenario and of worst case scenario*
- *On covariates: analyses adjusted on recruitement part of the study (Part A / Part B)*

f) *Sensitivity analyses on cumulative reactive dose using an appropriate non-parametric test procedure. The treatment effect will be estimated using Hodges-Lehmann estimate of the difference in medians of CRD change from month 0. The corresponding 95% confidence interval and the p-value from the hypothesis test of no difference between the treatment groups (Wilcoxon rank-sum test) stratified on age group will be presented.*

g) *In order to comply with requests from FDA on another project, serious adverse events occurring during DBPCFC will not be considered for adverse events analyses; they will be described separately.*

12.5 AMENDMENT 5: FINAL VERSION 5.0, 15 MAY 2018

Following study design change implemented in protocol amendment 5, dated 15 May

2018, to allow all study subjects to switch from Viaskin Milk 500µg to Viaskin Milk 300µg for a 24 months treatment period, no change beetween applicable protocol and current SAP version.

12.6 AMENDMENT 6: FINAL VERSION 24 JUNE 2019

No change

13 REFERENCE LIST

[1] Bornkamp, Björn, et al. "Innovative approaches for designing and analyzing adaptive dose-ranging trials." Journal of biopharmaceutical statistics 17.6 (2007): 965-995 "Innovative approaches for designing and analyzing adaptive dose-ranging trials." Journal of biopharmaceutical statistics 17.6 (2007): 965-995.

[2] Yeonhee Kim, WA Seunghyun Won. Adjusted proportion difference and confidence interval in stratified randomized trials. PharmaSUG 2013 - Paper SP04.

[3] Flokstra-de Blok BM, DunnGalvin A, Vlieg-Boerstra BJ et al. Development and validation of a self-administered Food Allergy Quality of Life Questionnaire for children. Clin Exp Allergy 2009; 39(1):127-137.

[4] DunnGalvin A, de BlokFlokstra BM, Burks AW, Dubois AE, Hourihane JO. Food allergy QoL questionnaire for children aged 0-12 years: content, construct, and cross-cultural validity. Clin Exp Allergy 2008;38(6):977-986.

[5] Flokstra-de Blok BM, DunnGalvin A, Vlieg-Boerstra BJ, Oude Elberink JN, Duiverman EJ, Hourihane JO et al. Development and validation of a self-administered Food. Allergy Quality of Life Questionnaire for children Clin ExpAllergy 2009;39:127-137.

14 PROGRAMMING CONSIDERATIONS

All tables, data listings, figures (TLFs), and statistical analyses will be generated using CCI CCI). Computer-generated table, listing and figure output will adhere to the following specifications.

14.1 GENERAL CONSIDERATIONS

- One SAS program can create several outputs or a separate SAS program can be created for each output at statistical programmer's discretion.
- Each output will be stored in a separate file.
- Output files will be delivered in Word format / rtf format.

- Numbering of TLFs will follow the International Conference on Harmonization E3 guidance.

14.2 TABLE, LISTING, AND FIGURE FORMAT

14.2.1 General

- All TLFs will be produced in landscape format, unless otherwise specified.
- All TLFs will be produced using the Courier New font, size 8.
- The data displays for all TLFs will have a 1.5-inch binding margin on top of a landscape oriented page and a minimum 1-inch margin on the other 3 sides.
- Headers and footers for figures will be in Courier New font, size 8.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TLFs will be in black and white (no colour), unless otherwise specified.
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TLFs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TLFs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., µ). Certain subscripts and superscripts (e.g., cm^2, C_{max}) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.
- For figures, DBV's graphic chart will be applied whenever possible.

14.2.2 Headers

- All output will have the following header at the top left of each page:
  DBV Technologies
  Protocol Number: MILES

- All output will have Page n of N at the top or bottom right corner of each page. TLFs will be internally paginated in relation to the total length (i.e., the page number appears sequentially as page n of N, where N is the total number of pages in the table).
- The date (date output was generated) will appear along with program name as the last footer on each page.

14.2.3 Display Titles

The title of each TLF is centred. The analysis set will be identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning

the margins will separate the display titles from the column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
Analysis Set

14.2.4 Column Headers

- Column headings are displayed immediately below the solid line described above in initial upper-case characters.
- For numeric variables, the corresponding units are included in column or row heading when appropriate.
- Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings if applicable). This is distinct from the 'n' used for the descriptive statistics representing the number of subjects in the analysis set.

14.2.5 Body of the Data Display

Data in columns of a table or listing will be formatted as follows:

- alphanumeric values are left-justified;
- whole numbers (e.g., counts) are right-justified; and
- numbers containing fractional portions are decimal aligned.

14.2.6 Table Conventions

- Units will be included where available.
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category are presented in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
severe	0
moderate	8
mild	3

  Where percentages are presented in these tables, zero percentages will not be presented and so any counts of 0 will be presented as 0 and not as 0 (0%).

- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 subject represented in one or more groups will be included.

- An Unknown or Missing category should be added to any parameter for which information is not available for 1 or more subjects.
- Unless otherwise specified, the estimated mean for a set of values will be rounded and printed out to 1 more significant digit than the original values, and standard deviations will be rounded and printed out to 2 more significant digits than the original values. The median, minimum and maximum report the same significant digits as the original values. For example, for systolic blood pressure:

N	XX
Mean	XXX.X
Std Dev	X.XX
Minimum	XXX
Q1	XXX
Median	XXX
Q3	XXX
Maximum	XXX

- P-values will be output in the format: "0.xxx", where xxx is the value rounded to 3 decimal places. Any p-value less than 0.001 will be presented as < 0.001. If the p-value should be less than 0.0001 then present as < 0.0001. If the p-value is returned as > 0.999 then present as > 0.999
- Percentage values will be printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Values that round down to 0.0 will be displayed as '< 0.1', or as appropriate with additional decimal places. Unless otherwise noted, for all percentages, the number of subjects in the analysis set for the treatment group who have an observation will be the denominator. Percentages after zero counts will not be displayed and percentages equating to 100% will be presented as 100%, without any decimal places.

The percentage of subjects is normally calculated as a proportion of the number of subjects assessed in the relevant treatment group (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of subjects exposed.

14.2.7 Listing Conventions

- Listings will be sorted for presentation in order of treatment groups as above, subject number, visit/collection day, and visit/collection time.
- Missing data will be represented on subject listings as either a hyphen ("-") with a corresponding footnote ("-=unknown or not evaluated"), or as "N/A", with the footnote "N/A=not applicable", whichever is appropriate.
- Dates will be printed in CCI DATE9.format ("DDMMMYYYY": 01JUL2000). Missing portions of dates will be represented on subject listings as dashes (--JUL2000).

Dates that are missing because they are not applicable for the subject are output as "N/A", unless otherwise specified.

- All observed time values will be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.
- Units will be included where available.

14.2.8 Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- The last line of the listing footnote section will be a standard source line that indicates the name of the program used to produce the data display, date and time the program was run, and the date of database extractions

  (Listing Generation: DD/MMM/YYYY HH:MM Program: xxx.sas Database Extraction Date: DDMMMYYYY
- For Tables additionally the listing source will be included where appropriate
  (Table Generation: DD/MMM/YYYY HH:MM Program: xxx.sas Listing source: Listing xxx Database Extraction Date: DDMMMYYYY)
- If the respective footnotes cover more than 10 lines, they will be displayed only at the beginning of each listing on a separate page.

15 QUALITY CONTROL

SAS programs are developed to produce clinical trial output such as analysis data sets, summary tables, data listings, figures or statistical analyses. Syneos Health Standard Operating Procedure (CCI provide an overview of the development of such SAS programs.

Syneos Health CCI describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the proper clinical trial output by checking for their logic, efficiency and commenting and by review of the produced output.

16 APPENDICES

Listing Mock-ups and Table Mock-ups are separate documents.

Statistical Analysis Plan

CCI