A DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED PHASE III TRIAL TO ASSESS THE SAFETY AND EFFICACY OF VIASKIN® PEANUT IN PEANUT-ALLERGIC YOUNG CHILDREN 1-3 YEARS OF AGE

EPITOPE STUDY

Sponsor:	DBV TECHNOLOGIES S.A. 177-181 avenue Pierre Brossolette 92120 Montrouge - FRANCE Tel: PPD Fax:
Clinical Research Organization:	Pharm Research Associates (UK) LTD 500 South Oak Way, Green Park, Reading RG2 6AD, UNITED KINGDOM
Sponsor Protocol No.:	EPITOPE (EPIT in TOddlers with PEanut Allergy) – V712-304
IND No.:	14366
EudraCT No.:	2016-003679-23
Investigational Medicinal Product Name:	DBV712 (Viaskin® Peanut)
Development Phase:	III
Versions and Dates of Protocol:	Version 7.0, 15 November 2019 Version 6.0, 28 August 2018 Version 4.0, 09 November 2017 Version 3.0, 11 September 2017 Version 2.0, 12 May 2017 Version 1.0, 27 September 2016

The study will be conducted according to the protocol and in compliance with Good Clinical Practice (GCP), with the Declaration of Helsinki and with other applicable regulatory requirements.

SIGNATURE PAGE

Declaration of Sponsor or Responsible Medical Officer

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

This study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational product, as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki, [2013] (APPENDIX 1), and the guidelines on Good Clinical Practice.

PPD	PPD	PPD
Chief Medical Officer DBV Technologies S.A.	Signature	Date

Declaration of the Investigator

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

I have read and understood and agree to abide by all the conditions and instructions contained in this protocol.

All documentation for this study that is supplied to me and that has not been previously published will be kept in the strictest confidence. This documentation includes this study protocol, Investigator's Brochure (IB), electronic case report form (CRF), and other scientific data.

The study will not be commenced without the prior written approval of a properly constituted Institutional Review Board (IRB) or Independent Ethics Committee (IEC). No changes will be made to the study protocol without the prior written approval of the Sponsor and the IRB or IEC, except where necessary to eliminate an immediate hazard to the subjects.

Responsible Investigator of the local study center

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Signature Date

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Name (block letters)

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Title (block letters)

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Institution (block letters)

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Phone number

PROTOCOL SYNOPSIS

Title	A double-blind, placebo-controlled, randomized phase III trial to assess the safety and efficacy of Viaskin® Peanut in peanut-allergic young children 1-3 years of age.
Sponsor Study No.	EPITOPE (V712-304)
Phase	III
Sponsor	DBV Technologies S.A.
Study Centers	This is a multicenter study to be conducted in Australia, Europe and North America. Between 50-70 sites from at least 8 countries could participate.
Objective	To verify the safety and local tolerance of the 2 DBV712 doses of 100 and 250 µg and to assess the efficacy and safety of DBV712 to induce desensitization to peanut in peanut-allergic subjects 1 to 3 years of age after a 12-month treatment period by EPicutaneous ImmunoTherapy (EPIT).
Design	In previous clinical studies in peanut allergic children 4 to 11 years old, DBV712 250 µg has been demonstrated as a safe and effective treatment for inducing desensitization to peanut. However, DBV712 has never been assessed in younger children from 1 to 3 years old. The present study is designed to assess in this population the safety of 2 doses of DBV712 in the first part of the study (Part A) and then to demonstrate the efficacy and safety of the selected dose in the second part (Part B). This is a 12-month, double-blind, placebo-controlled, randomized phase III trial to assess the safety and efficacy of DBV712 (doses of 100 µg or 250 µg peanut protein per patch) in peanut-allergic children 1 to 3 years of age. The trial will be conducted in approximately 50-70 sites in at least 8 countries with Investigators and staffs trained and experienced in the diagnosis and the management of peanut allergy and anaphylaxis, and capable of performing Double-Blind, Placebo-Controlled Food Challenges (DBPCFCs) in young children. Peanut allergic children meeting the following key inclusion criteria will be selected: • Physician-diagnosed peanut allergy or high suspicion of peanut allergy as assessed by the physician: child presenting signs, symptoms and a medical and/or a family history putting him/her at high risk of having a peanut allergy and/or history of presence of peanut-specific IgE and/or positive SPT; • Subject currently following a strict peanut-free diet; • Peanut specific IgE (ImmunoCAP system) > 0.7 kU/L; • Positive peanut SPT with a largest wheal diameter ≥ 6 mm; • Positive DBPCFC to peanut, with symptoms meeting the challenge stopping criteria at an ED ≤ 300 mg peanut protein. During the maximum 6-week screening period, subjects will undergo an entry/screening DBPCFC to peanut to confirm their allergy to peanut and to determine their entry or screening peanut ED. The starting dose of the challenge will be 1 mg peanut protein and will escalate up to the highest dose of 300 mg peanut protein. Subjects who react at or below the dose of 300 mg peanut protein are considered eligible. A post-treatment DBPCFC will be performed at Month 12, starting at the dose of 1 mg peanut protein and proceeding up to the highest dose of 2,000 mg peanut protein. The primary efficacy endpoint of this phase III study is the difference between the percentage of treatment responders in the selected DBV712 dose group (250 µg) compared to the placebo group at Month 12, determined on the peanut protein ED during the food challenge. Other efficacy assessments at months 3, 6 and 12, include immunological changes in peanut-specific IgE and IgG4 subtype and SPTs. Key assessments of global safety will be performed at each study visit including skin observation of the patch areas of application, vital signs, physical examinations, clinical laboratory assessments. Atopic dermatitis will also be assessed at baseline and at months 3, 6 and 12 using the SCORing Atopic Dermatitis (SCORAD).

In between visits, occurence of local skin reactions will be specifically solicited and their severity graded on a daily basis by the parents/guardians in a diary, for at least 6 months for part A subjects, and during the whole treatment duration for part B subjects (see thereafter the design of Parts A and B). Any other AEs (including local skin reactions occurring after the first 6 months of treatment for part A subjects), and any concomitant medications will also be reported in the diary by the parents/guardians and this will be reviewed by the site medical staff at each subject visit.

At screening, at Month 12 and at the end of study visit, the subjects' parents/guardians will complete quality of life questionnaires (Food Allergy Quality of Life Questionnaire [FAQLQ] / Food Allergy Independent Measure-parent form [FAIM] / EuroQol-5D-5L (EQ-5D-5L) [part B only, see thereafter for design of Part B]) to assess the impact of DBV712 12-month treatment on their quality of life.

[redacted]

The overall maximum study duration for each subject is approximately 62 weeks (6-week screening period, 12-month treatment period and 4-week follow-up period). The subjects will attend a total of 12 study visits:

- 3 visits during the screening phase,
- 8 visits during the treatment period (+1 additional Visit 7bis for the subjects in Part A in the eventuality of dose switching for safety reason. After interim safety analysis, both doses of DBV712 were shown to be safe, and no dose switching is required. As a consequence, Visit 7bis will be not applicable; see section 3.1.1),
- 1 visit at the end of the follow-up period.

In addition, 5 telephone contacts will be made during the treatment period.

After completion of this 12-month blinded study, eligible subjects will be offered the opportunity to participate in an extension study to receive treatment with DBV712 250 µg for 24 additional months if they were initially randomized in the DBV712 100 µg or 250 µg groups, or for 36 months if they were randomized in the placebo group.

The study will be conducted in 2 parts, A and B.

Study Part A

In the first part, the safety of 2 doses of DBV712, 100 µg and 250 µg was evaluated with a double-blind placebo-controlled design. Fifty subjects were to be randomized either in the placebo arm or in the 2 active arms, with a 1:2:2 ratio, i.e. 10 subjects in the placebo arm and 20 subjects in each of the 2 active arms, DBV712 100 µg and DBV712 250 µg.

A safety analysis was to be performed after the first 3 months of treatment to estimate the safety profiles of the 2 studied doses of DBV712. The safety and tolerability assessment was to be assessed by an independent Data and Safety Monitoring Board (DSMB).

As a result of this tolerability and safety review, 4 situations could have been encountered:

1. Both doses are considered well tolerated with a good safety profile. The 250 µg dose would then be selected for the continuation of the study in Part B. In parallel, all subjects still in Part A at the moment of the decision would remain under the treatment arm they were under until their Month 12 treatment period: subjects under DBV712 250 µg dose in Part A would continue with the same dose up to Month 12, subjects under DBV712 100 µg dose in Part A would continue with the same dose up to Month 12, and subjects under placebo would remain under placebo up to Month 12. There would be no Visit 7bis to perform in this situation.
2. The DBV712 250 µg dose has a better tolerability/safety profile than the 100 µg dose. The 250 µg dose would then be selected for the continuation of the study in Part B. In parallel, all subjects still in Part A at the moment of the decision would come for

the Visit 7bis to receive a new treatment box with the right treatment: subjects under DBV712 250 µg dose in Part A (the safest dose) would receive a new box of DBV712 250 µg so that they could continue with the same safe dose up to Month 12, subjects under DBV712 100 µg dose in Part A (dose considered not safe) would receive a new box of DBV712 250 µg so that they were treated with a safe dose up to Month 12 and subjects under placebo would receive a new box with placebo up to Month 12. It would have been important that all subjects come back for the Visit 7bis to keep the blinding with regard to the subjects who need to change their treatment dose.

3. The highest dose of DBV712 250 µg is not considered as having an acceptable safety profile and only the DBV712 100 µg dose is considered having a favorable safety profile. The DBV712 100 µg dose would be selected for the continuation of the study in Part B. In parallel, all subjects still in Part A at the moment of the decision would come for the Visit 7bis to receive a new treatment box with the right treatment: subjects under DBV712 250 µg dose in Part A (dose considered not safe) would receive a new box of DBV712 100 µg so that they were treated with a safe dose up until Month 12; subjects under DBV712 100 µg dose in Part A (the safe dose) would receive a new box of DBV712 100 µg so that they could continue with the same safe dose up until Month 12, and subjects under placebo would receive a new box with placebo up until Month 12. In this situation too, it would have been important that all subjects come back for the Visit 7bis to keep the blinding with regard to the subjects who need to change their treatment dose.
4. Both doses are considered by the DSMB as having an unfavorable safety profile or tolerability. The study would then be stopped and all subjects would have to stop applying the patches and would be withdrawn from the study.

Hence, the 50 first subjects included in the 3 initial treatment arms in Part A were to continue blindly their assigned treatment until the end of the study (i.e. 12 months of treatment; Situation n°1), or were to stop their treatment prematurely (Situation n°4), or were to switch to the safest DBV712 dose (Situation n°2 or n°3), according to the decision or recommendation made by the DSMB.

Upon review of the 3-month safety data of the 51 subjects actually randomized in part A, the DSMB had no safety concern and considered both doses as well tolerated with a good safety profile (scenario "1" as described above). As a consequence:

- The dose selected for part B is the 250-µg dose;
- All subjects from part A were to remain in their initial randomized treatment arm until the end of 12-month treatment (placebo, DBV712 100 µg or DBV712 250 µg).

After all subjects from Part A complete the study, Part A data will be unblinded for analysis.

Study Part B

The second part of the study aims to assess the safety and efficacy of the selected dose after 12-month treatment *versus* placebo. This part was to be initiated after the choice of the highest safe dose upon the DSMB meeting. As from protocol v6.0, the selected highest safe dose for part B upon DSMB recommendation is 250 µg. Additional subjects will be recruited in the active selected dose arm and in the placebo arm, to reach the targeted total number of subjects. In accordance with the calculated sample size for this study, a total of 350 additional subjects will be randomized in the second part (Part B) of the study. These subjects will be randomized with a 2:1 ratio in either the active or placebo arm, 233 subjects in the active arm and 117 subjects in the placebo arm.

An interim analysis to evidence the treatment activity on the immune system of 1 to 3 years old children is planned after the first 50 subjects from part B have received 6 months of active treatment with the selected DBV712 dose of 250 µg (Visit 8). This analysis, encompassing peanut-specific IgE, peanut-specific Immunoglobulin G4 subtype (IgG4), SPT and main safety data, will specifically be conducted on the measurements of the peanut-specific IgG4. The relative change from baseline of the peanut-specific IgG4 levels in the DBV712 250 µg

treatment group at Month 6 will be numerically compared to the relative change from baseline of the peanut-specific IgG4 levels in the placebo group at Month 6. The median relative change in IgG4 of the DBV712 250 µg treatment group is expected to be greater than the median relative change in IgG4 of the placebo treatment group.

In the situation where the median relative change from baseline of the peanut specific IgG4 is equal or lower than the median relative change in the placebo group, the premature stop of the study for lack of evidence of therapeutic benefit will be considered. This unblinded data review will be conducted by the DSMB who will be responsible of issuing the recommendation to the sponsor.

Treatment

The Investigational medicinal Product (IMP), DBV712, is an epicutaneous delivery system (Viaskin® patch) containing a solid deposit of a formulation of peanut protein extrac[redacted]. The Viaskin® patch also includes a hypoallergenic adhesive film that will help prevent the Viaskin® patch from coming off inadvertently.

The placebo treatment will consist of a similar formulation, but devoid of peanut protein.

Only 1 patch is to be applied per day (every 24 hours). Application of the Viaskin® patch at a similar time for each daily application (am or pm) is recommended. A leaflet with safety precautions for using the Viaskin® patch will be given to each subject and parents/guardians.

Duration of treatment

Repeated daily application of a Viaskin® patch is planned for 12 months for all subjects: a blinded 12-month period of treatment with DBV712 *versus* placebo. At the start of treatment, the duration of daily application of the Viaskin® patch will be progressively increased for the first 4 weeks as follows:

- 2 hours (± 30 minutes) per day the 1st week;
- 4 hours (± 30 minutes) per day the 2nd week;
- 8 hours (± 1 hour) per day the 3rd week;
- 12 hours (± 2 hours) per day the 4th week.

From the first day of the 5th week onwards (Day 29), the duration of application will be 24 hours (± 4 hours) for each patch applied daily until the end of the treatment period. However, in case of local unbearable or intense skin reactions, this period of progressive increase duration of daily application of the patch can be extended beyond the 4 weeks described above.

Number of Subjects

The total number of subjects to randomize in EPITOPE will be approximately 400 (see the table below).

Randomized subjects	DBV712 100 µg	DBV712 250 µg	Placebo	Total
Part A	20	20	10	50
Part B	0	233	117	350

In this age population, the estimated screen failure rate could be up to 60% based on previous experience in 4 to 11 years old subject population and site distribution. Therefore, approximately 1,000 peanut-allergic children 1 to 3 years would need to be screened to get the 400 randomized subjects. Details for Part A and Part B are presented below.

Part A

During the first safety part of the study (Part A), 50 subjects (10 placebo subjects, 20 subjects at the 100 µg DBV712 dose, 20 subjects at the 250 µg DBV712 dose) will be randomized. The 20 subjects initially randomized at the dose of DBV712 not retained will continue at that dose up to Month 12 if there are no safety concerns regarding this dose.

After the 3-month safety DSMB analysis, 250 µg was selected as the highest safe dose.

Part B

The sample size for the efficacy part of the study is calculated based on the following assumptions:

- A 2:1 ratio in favor of the DBV712 dose *versus* placebo;
- A 40% response rate for DBV712 (optimal active dose) and a 10% response rate for placebo using missing=failure imputation method (based on a maximum drop-out rate of 15%). This will give a 30% absolute difference for the primary endpoint between active and placebo at 12 months of treatment;
- A lower bound of the 95% confidence interval (CI) of the difference between the selected active treatment and placebo response rates ≥15%;
- Newcombe method is used for the computation of the CI.

Hence, the minimum number of subjects needed to ensure a power of at least 90% is 350 (approximately 233 subjects in total in the selected active DBV712 group [250 µg] and 117 subjects in the placebo group).

Potential sample size reestimation for Part B

The analysis of Part A should provide a more accurate assessment of whether the sample size for Part B is appropriate or whether it needs to be adjusted. The current sample size calculation was done at a time when no data in 1-3 year-old subjects existed for DBV712. Therefore, the unblinded data from Part A is essential in refining the current sample size calculation for Part B.

Sample size adjustment could be proposed based on a combination of (but not limited to):

- a formal computation of probability of success
- a reassessment of placebo response rate assumption

If, for instance, the exact observed percentages of responders in part A are believed to be the "true" rates in the population, then:a higher placebo rate could require a greater sample size, as shown in examples below.

Placebo responder rate	DBV712 250 µg responder rate	Total Sample Size
10%	40%	350
20%	50%	462
30%	60%	519

Regulators and institutional review boards will be informed if any sample size adjustments are needed.

Population

Subjects will be enrolled in this study only if they meet, among others, the following eligibility criteria:

Key inclusion criteria

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

Key exclusion criteria

- Diagnosis of asthma that fulfills any of the following criteria:
  - Uncontrolled asthma (as per Global Initiative for Asthma [GINA] latest guidelines);
  - Asthma requiring controller treatment step 3 or higher (as per GINA latest guidelines: either moderate [double low dose] of inhaled corticosteroid, or association of inhaled corticosteroid with leukotriene receptor antagonist. Long acting beta agonists are not recommended below 5 years)
  - History of 2 or more systemic corticoid courses within the 3 previous months prior to Visit 1 or 1 systemic corticoid course within the 4 weeks prior to Visit 1 for treating a diagnosed asthma.
  - Prior intubation/mechanical ventilation for asthma within one year prior to Visit 1
- Presence of more than 3 episodes of wheezing in the past year (each lasting more than 10 consecutive days, apart from colds) or presence of respiratory symptoms (wheezing, cough, heavy breathing) between these episodes, and/or other respiratory symptoms suggesting either undiagnosed asthma or asthma not controlled by asthma treatment (as per GINA latest guidelines).
- Peanut allergic subjects presenting a medical history of severe anaphylaxis to peanut will be excluded from this study. Severe anaphylaxis is defined by the Grade 3 of the Anaphylaxis Staging System, including:
  - Severe hypoxia, persistent hypotension or more than 20% drop in blood pressure, neurological compromise, or
  - Cyanosis or SpO2 ≤ 92% at any stage, confusion, cardiovascular collapse, loss of consciousness, bradychardia, cardiac arrest.
- Prior history of any immunotherapy to any food (e.g. oral immunotherapy, sublingual immunotherapy, specific oral tolerance induction). Subjects who received a prior oral immunotherapy of less than 1 month-duration which ended at least 3 months before Visit 1 are eligible for inclusion.
- Subjects receiving or planning to receive any immunotherapy (aeroallergens, venoms, anti-infective…) during their participation in the study. These immunotherapies must be discontinued at the time of Visit 1.
- Generalized dermatologic disease (e.g. severe atopic dermatitis, uncontrolled generalized eczema, ichthyosis vulgaris) extending widely on the skin and especially on the back with no intact zones to apply the Viaskin® patches.

Criteria for Evaluation of Efficacy

Primary efficacy endpoint:

The primary efficacy endpoint is the difference between the percentage of treatment responders in the selected active DBV712 group (250 µg) compared to the placebo group after 12 months of EPIT treatment.

A subject is defined as a treatment responder if:

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

OR

- The initial ED was ≤10 mg peanut protein and the ED is ≥300 mg peanut protein at the post-treatment DBPCFC at Month 12.

Secondary efficacy endpoints:

Change from baseline to Month 12 in cumulative reactive dose (CRD) and ED in the selected active DBV712 group (250 µg) *versus* the placebo group.

Other efficacy endpoints:

- The percentage of subjects reaching a cumulative dose ≥1,444 mg peanut protein at the post-treatment DBPCFC at Month 12 in the selected active DBV712 group (250 µg) *versus* the placebo group;
- The percentage of subjects reaching a cumulative dose ≥3,444 mg peanut protein at the post-treatment DBPCFC at Month 12 in the selected active DBV712 group (250 µg) *versus* the placebo group;
- The percentage of subjects unresponsive (those showing no symptoms leading to DBPCFC stop) to the highest dose of peanut protein (2,000 mg peanut protein) in the selected active DBV712 group (250 µg) *versus* the placebo group.
- Change from baseline in peanut-specific IgE and IgG4 at months 3, 6 and 12 in the selected active DBV712 group (250 µg) *versus* the placebo group;
- Change from baseline in peanut SPT at months 3, 6 and 12 in the selected active DBV712 group (250 µg) *versus* the placebo group;
- Description of the quality of life questionnaires (Parent FAQLQ/FAIM) and change from baseline in FAQLQ/FAIM scores at Month 12 (for those countries where the translated and validated questionnaires were available) in the selected active DBV712 group (250 µg) *versus* the placebo group.

Criteria for Evaluation of Safety

The following safety criteria will be evaluated during the study and at the 3-month interim analysis:

- Adverse events and Treatment-Emergent Adverse Events (TEAEs) by System Organ Class (SOC) and Preferred Terms (PTs);
- TEAEs by maximum severity and relatedness to DBV712;
- Incidence, duration and maximum severity of local cutaneous DBV712-induced AEs as assessed by the subjects;
- Incidence and severity of local cutaneous DBV712-induced AEs as assessed by the Investigators;
- Local Adverse Events of Special Interest (AESIs) (i.e., reactions at patch sites potentially leading to skin barrier disruption) and systemic AESIs (i.e. anaphylaxis, or systemic hypersensitivity reactions leading to epinephrine intake), whatever the causal relationship to IMP;
- Serious AEs (SAEs) by SOC, and PTs, maximum severity and relatedness to DBV712;
- Laboratory data, physical examinations and vital signs;

Safety of study procedure:

- Symptoms elicited during DBPCFCs by severity and change in the severity of symptoms in the selected active DBV712 group (250 µg) *versus* the placebo group;
- SAEs elicited during DBPCFCs.

Exploratory Variables

- The change from baseline in total IgE, and in IgE and IgG4 specific to peanut protein components at 3, 6 and 12 months for both DBV712 groups *versus* the placebo group;
- Description of reactions triggered by accidental consumption of peanut during the study and analysis of "Risk-taking behavior" of parents' subjects (voluntary peanut consumption);
- Epigenetic modifications of the promoters of specific genes;

- Sensitization status to some other allergens and their evolution over the study period;
- SCORAD evolution over time
- [redacted]
- Quality of Life analysis using the EQ-5D-5L
- Basophil activation test (BAT) analyses (US eligible sites only)
- CCI [redacted].

Statistical Methods

Analysis populations:

- Safety population:
  All subjects who are randomized and have received at least 1 dose of IMP in Part B. This population will be used to assess comparative safety information.
- Intent-to-treat (ITT) population:
  All subjects who are randomizedin Part B. This population will be used to assess comparative efficacy information.
- Per-protocol (PP) population:
  All subjects in the ITT population who do not have major deviations from the protocol that may affect the primary efficacy endpoint. The PP population will be used to perform robustness analyses of the primary efficacy evaluation.
- Part A population:
  All subjects who are randomized in Part A. This population will be used for descriptive efficacy and safety analyses.

Primary efficacy analysis:

The primary efficacy endpoint in this study is the difference between the percentage of treatment responders in the selected active DBV712 group (250 µg) compared to the placebo group after 12 months of EPIT treatment.

The primary efficacy analysis will be performed on the ITT population using missing=failure imputation method (i.e. subjects with missing DBPCFC peanut ED value at Month 12 will be considered as non-responders).

The primary measure of treatment effect will be the difference in response rates between active and placebo treatment groups. The primary analysis will apply a Wald test at a 2-sided 5% significance level to evaluate a null hypothesis of no difference, and a 2-sided 95% Newcombe CI for the difference in response rates will be calculated. The pre-specified thresold for the primary analysis will be defined by a ≥15% lower CI bound, and this condition will determine whether the primary objective has been successfully met.

A supportive analysis will be performed in subjects randomized in parts A and B, using the same statistical method as for the primary analysis.

Secondary efficacy analyses:

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

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

Safety Analyses:

Adverse Events

TEAEs will be defined as any AEs, regardless of relationship to IMP, which occur during or after the initial patch application or any event already present that worsens in either severity or relationship to DBV712 or placebo.

An overall summary of TEAEs will be provided showing the number and percentage of subjects with any TEAEs, any potentially drug-related TEAEs, any DBV712-induced Local TEAE, any severe DBV712-induced local TEAE, any severe TEAEs, any severe potentially drug-related TEAEs, any serious TEAEs, any potentially drug-related serious TEAEs, any

TEAEs leading to discontinuation and any TEAEs leading to death. The number of events will also be presented.

The number of TEAEs, as well as the number and percentage of subjects who experienced at least one TEAE will be summarized by SOC and PT.

The incidence of the following events will be summarized:

- TEAEs by maximum severity, by duration and by relatedness to Viaskin® patch;
- Local skin reactions at sites of Viaskin® patch application as assessed by the subjects (incidence, duration and severity, 0 to 3 grading scale);
- Local skin reactions at sites of Viaskin® patch application as assessed by the Investigator (severity, 0 to 4 grading scale at each time point);
- SAEs, serious TEAEs and serious potentially IMP-related TEAEs;
- Potentially IMP-related TEAEs;
- TEAEs leading to study treatment discontinuation and TEAEs leading to epinephrine intake;
- Local and systemic AESIs.

Additionally, the proportions of patches during the one-year exposure period that led to mild, moderate or severe TEAE considered related to Viaskin® patches, will be summarized.

All AEs will be listed as well as SAEs and TEAEs leading to an epinephrine intake.

The reactions induced by a DBPCFC because they are expressly provoked, will be differentiated from those AEs occurring outside of a challenge. Objective and subjective symptoms/reactions elicited during a challenge will be summarized separately:

- Symptoms elicited during a peanut food challenge by severity;
- SAEs elicited during a peanut food challenge.

Other safety assessments

Laboratory tests (hematology and biochemistry), vital signs, physical examination [redacted] be summarized and listed by visit.

Interim analyses

End of Part A safety analysis

A safety analysis was to be conducted on the initial first 50 subjects included in the 3 treatment arms, DBV712 100 µg, DBV712 250 µg and placebo after 3 months of patch application. These safety data was to be reviewed by the DSMB and their members were to release their recommendation on the safe dose to select for the study part B. Upon review of the 3-month safety data of the 51 randomized subjects in part A, the DSMB had no safety concern and considered both doses as well tolerated with a good safety profile. The 250-µg dose was selected for part B.

For the subjects in the Part A, depending on the DSMB recommendations, the dose of the 2 DBV712 groups were either to be kept unchanged or adjusted. The study could also be definitively discontinued. Upon DSMB recommendations, all subjects from Part A are to remain in their initially randomized treatment arm.

Interim futility analysis of the IgG4 immunological response at Month 6

This analysis will be conducted when 50 subjects from Part B have reached 6 months of active treatment with the active DBV712 dose selected in the Part A (250 µg). This analysis will be conducted more specifically on peanut specific IgG4 measurements. The median relative change from baseline of the peanut specific IgG4 levels in the selected active DBV712 treatment group (250 µg) will be compared to the median relative change from baseline of the peanut specific IgG4 levels in the placebo group. The median value of the selected active group (250 µg) is expected to be greater than the median value of the placebo group.

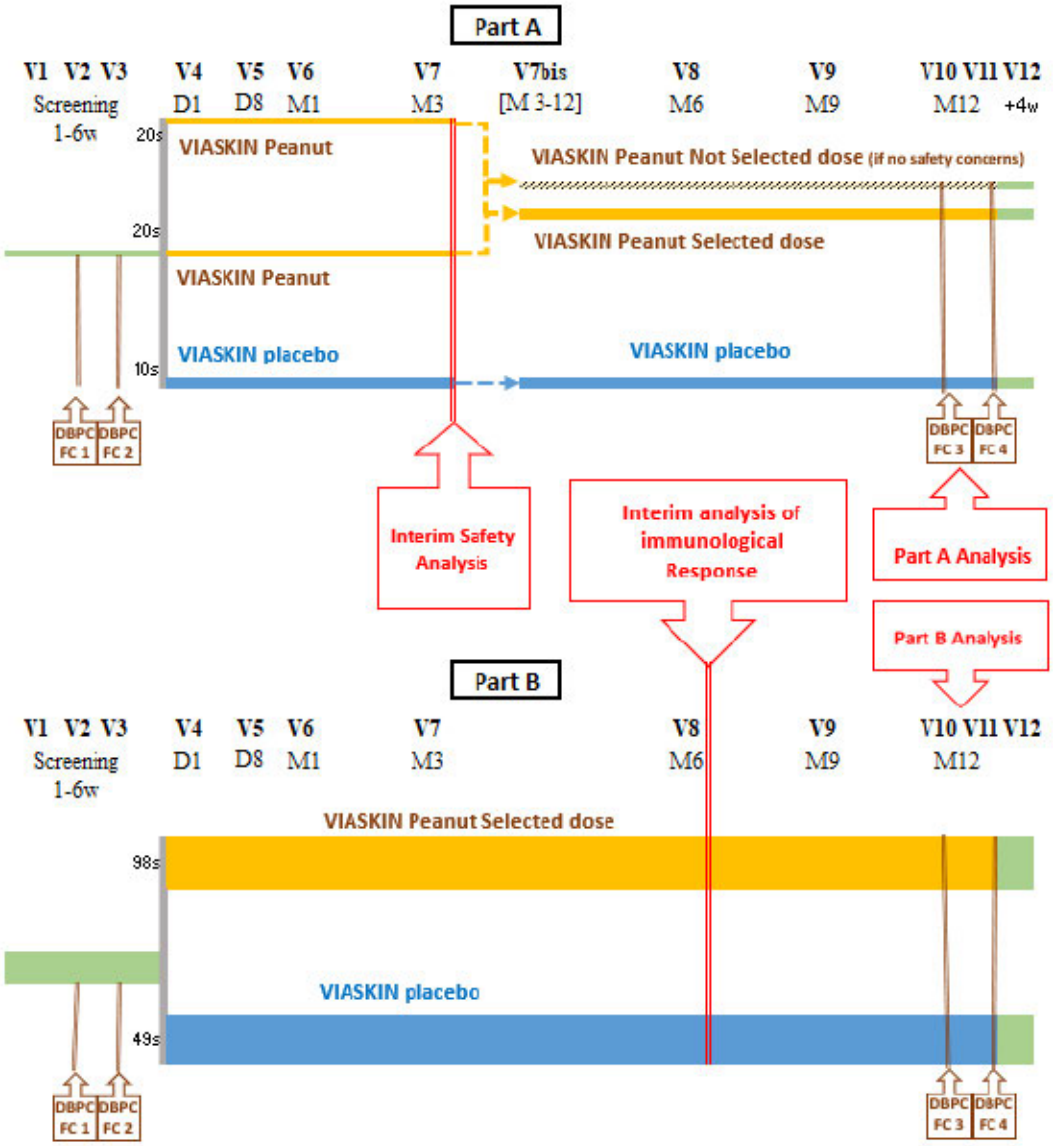
In the situation where the change from baseline of the peanut specific IgG4 is equal to or lower than the change in the placebo group, the premature stop of the study for lack of evidence of treatment activity will be considered. This unblinded data review will be

conducted by the DSMB who will be responsible of issuing the recommendation to the Sponsor.

Part A analysis

An analysis will be conducted when all subjects from Part A will have terminated the study. The aim is to describe the efficacy and safety data among all subjects enrolled in Part A. All analyses will be detailed in a separate interim Statistical Analysis Plan.

Study Design



Based on the Interim Safety Analysis, the DBV712 Selected dose for Part B is 250 µg, and all subjects from Part A are to continue their treatment until the end of the study as per their initially randomized arm (Placebo, DBV712 100 µg or DBV712 250 µg). As a consequence, the Visit 7bis for dose switching in Part A is not applicable.

Abbreviations: D = Day; DBPCFC = Double-blind, placebo-controlled food challenge; M = Month; s= subject; V = Visit; w=weeks.

Schedule of Procedures

Study Assessments	Screening (Max 42d; more if DBPCFC postponed[1])				Treatment Period (12 months)												End of Study	Early Term	Unsch. Visit
Visit tags – PC (Phone Call)	V1	V2	V3[2]	V4[2]	PC1	V5	PC2	V6	PC3	V7	PC4	V7bis[3]	V8	PC5	V9	V10	V11	V12	ET	UV[5]
Duration in study	D-42/D-3			D1	D4	D8	D22	M1	M2	M3	M4.5	M3-12	M6	M7.5	M9	M12	M12	M12		
Time Windows	42d (max) before V4	Any-time up to D-2	Within 1 w of V2 up to D-1		±2 d	±3 d	±2 d	±3 d	±3 d	±7 d	±7 d	±7 d	±7 d	±7 d	±7 d	±7 d	Max V10 + 1 w	V11 + 4 w[4]		
Informed consent	X																			
Check eligibility[6] (inclusion/exclusion criteria)	X			X																
Disease/Medical history[7]	X																			
Parental medical history of atopy	X																			
Demographics	X																			
Physical examination[8]	X	X[10]	X[10]	X		X		X		X		X	X		X	X[10]	X[10]	X	X	X
Vital signs[9]	X	X[10]	X[10]	X		X		X		X		X	X		X	X[10]	X[10]	X	X	X
SCORAD	X									X			X			X				
SPT	X									X			X			X			X	
Immunological markers[11]	X									X			X			X			X	
Laboratory tests[12]	X									X			X			X			X	X
FAQLQ/FAIM/EQ-5D-5L[13]	X															X		X		
Epigenetic analyses	X									X			X			X				
BAT[14]	X									X			X			X			X	
DBPCFC[1]		X	X													X	X			
Randomization				X																
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense food sampling kit and instructions				X																
Check for any accidental peanut consumption					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Subject participation card	X																			
Subject diary (dispense/check)				X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Dispense IMP to the subject				X		X		X		X		X	X		X	X				

Study Assessments	Screening (Max 42d; more if DBPCFC postponed[1])				Treatment Period (12 months)													End of Study	Early Term	Unsch. Visit
Visit tags – PC (Phone Call)	V1	V2	V3[2]	V4[2]	PC1	V5	PC2	V6	PC3	V7	PC4	V7bis[3]	V8	PC5	V9	V10	V11	V12	ET	UV[5]
Duration in study	D-42/D-3			D1	D4	D8	D22	M1	M2	M3	M4.5	M3-12	M6	M7.5	M9	M12	M12	M12		
Time Windows	42d (max) before V4	Any-time up to D-2	Within 1 w of V2 up to D-1		±2 d	±3 d	±2 d	±3 d	±3 d	±7 d	±7 d	±7 d	±7 d	±7 d	±7 d	±7 d	Max V10 + 1 w	V11 + 4 w[4]		
Apply 1 Viaskin® patch at site				X																
Check the used/unused IMP						X		X		X		X	X		X	X	X		X	X
[redacted]																				
Check skin reactions under the patch and grading[16]				X		X		X		X		X	X		X	X	X		X	X
Photographs of the back and download the photos taken by subject's parents (if any)				X		X		X		X		X	X		X	X	X		X	X
Dispense epinephrine auto-injector and anaphylaxis emergency action plan (Safety leaflet) / camera or a specific device/hydrocortisone 1%				X																
Review utilization of epinephrine auto-injector and anaphylaxis emergency action plan (when required)						X		X		X		X	X		X	X				
Time under observation before discharge		3 h	3 h	3 h												3 h	3 h			

Abbreviations: BAT = Basophil activation test; D = Day; DBPCFC = Double-blind, placebo-controlled food challenge; d = days; ET = Early termination; FAQLQ/FAIM = Food Allergy Quality of Life Questionnaire/Food Allergy Independent Measure; h = hours; IMP = Investigational medicinal Product; M = Month; PC = Phone contact; SCORAD = Scoring atopic dermatitis; SPT = Skin prick test; UV = Unscheduled Visit; V = Visit.

1 If the subject has a concomitant disease which temporarily contra-indicates the performance of the DBPCFC, the test is to be postponed until at least 7 days after recovery

2 Visit 4 may take place on the same day as Visit 3, but this would result in a very long day for the subject (parents/guardians) as all Visit 4 procedures would then have to take place that same day.

3 The Visit 7bis was to be conducted for Part A subjects only in the eventuality of a dose switching for safety reason. After review of the 3-month safety data,

both doses of DBV712 were considered as safe, and no dose switching is required. As a consequence, Visit 7bis will not be performed.

4 Visit 12 will take place only for subjects not rolling over into the extension follow-up study

5 Unscheduled Visit could be conducted in case of AEs, need for treatment re-supply, etc. Procedures will be optional and performed as deemed necessary by the investigator.

6 At V1, all selection criteria could be verified except for those that depend on the results of the immunological markers testing (peanut-specific IgE) and on the outcome of the entry/screening DBPCFC.

7 Including history of peanut allergy.

8 Including a complete skin examination, body weight and height.

9 Blood pressure, heart rate and respiratory rate.

10 These examinations are to be done before the DBPCFC. Additionally, they can be repeated during the DBPCFC procedure on both days anytime if judged necessary by the Investigator.

11 Peanut-specific IgE, peanut-specific IgG4, peanut-specific IgE and peanut specific IgG4 to Ara h 1, Ara h 2, Ara h 3, and total IgE will be evaluated at Visits 1, 7, 8, 10. Total IgE will be assessed in Part B subjects only. IgE specific to cow's milk, egg white, house dust mites, and grass pollen will be assessed at Visit 1 and Visit 10 only and in case of an early termination visit.

12 Laboratory tests performed centrally. Hematology: hemoglobin, hematocrit, platelets, red blood cells, white blood cells with differential cell count. Biochemistry: aspartate aminotransferase, alanine aminotransferase, total bilirubin, total protein, blood urea nitrogen, creatinine.

13 For both FAQLQ and FAIM, Parental Form will be used. The translated forms of FAQLQ and FAIM will be completed in countries where they are available in local languages. The EQ-5D-5L questionnaire will be completed by parents/guardians for subjects randomized in part B only.

14 BAT performed centrally in US eligible sites only.

[redacted]

16 Check the reaction of the skin on the back of the subject and grade the severity of the local skin reactions. At Visit 4, grading is to be assessed: before patch application, 30 minutes, 1 hour and 2 hours during the patch application and 1h after the patch removal, to document any reaction. Photographs will be taken at each grading time point.

List of Study Personnel

Sponsor	PPD *SVP Global Clinical Development* DBV Technologies S.A. 177-181 avenue Pierre Brossolette 92120 Montrouge - FRANCE Tel: PPD E-mail: PPD PPD *Director Clinical Projects,* DBV Technologies S.A. (same address as above) Tel: PPD E-mail: PPD PPD *Director of Project Management, acting as Clinical Project Manager,* DBV Technologies S.A. (same address as above) Tel: PPD E-mail: PPD PPD *Medical Monitor* DBV Technologies S.A. (same address as above) Tel: PPD E-mail: PPD
Central Laboratory/Kit Supply/Samples Shipment (Biochemistry, Hematology, Immunological Markers)	CCI

TABLE OF CONTENTS

[redacted]

Tables in Text

Figures in Text

List of Appendices

List of Abbreviations and Definitions of Terms

AE	Adverse Event
AESI	Adverse Event of Special Interest
APC	Antigen-Presenting Cells
ATC	Anatomical Therapeutic Chemical (Classification System)
BAT	Basophil Activation Test
CI	Confidence Interval
CRD	Cumulative Reactive Dose
CRO	Contract Research Organization
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DBPCFC	Double-Blind, Placebo-Controlled Food Challenge
DSMB	Data and Safety Monitoring Board
ECG	ElectroCardioGram
e-CRF	Electronic Case Report Form
ED	Eliciting Dose
EDC	Electronic Data Capture
EPIT	EPicutaneous ImmunoTherapy
EQ-5D-5L	EuroQol-5D-5L
FAQLQ/FAIM	Food Allergy Quality of Life Questionnaire/Food Allergy Independent Measure
FDA	Food and Drug Administration
GA^{2}LEN	Global Allergy and Asthma European Network
GCP	Good Clinical Practice
GINA	Global INitiative for Asthma
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IgE, IgG4	Immunoglobulin E, Immunoglobulin G4 subtype
IMP	Investigational Medicinal Product
IND	Investigational New Drug

IRB	Institutional Review Board
ITT	Intent To Treat
IV	Intravenous
IWRS	Interactive Web Response System
LEAP	Learning Early About Peanut Allergy
MedDRA	Medical Dictionary for Regulatory Activities
OIT	Oral ImmunoTherapy
PP	Per-Protocol
PT	Preferred Term
SaO2	Oxygen saturation as measured by blood analysis
SAP	Statistical Analysis Plan
SCORAD	SCORing Atopic Dermatitis
SLIT	SubLingual ImmunoTherapy
SOC	System Organ Class
SpO2	Oxygen saturation as measured by pulse oxymetry
SPT	Skin Prick Test
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-Emergent Adverse Event
US(A)	United States (of America)
WHO	World Health Organization

1 INTRODUCTION

1.1 Background

Peanut allergy is the most common cause of fatal food allergy reactions (1, 2). An estimated 1% of the population of the United States of America (USA), over 3 million people, is allergic to peanuts or tree nuts (3). The prevalence of peanut allergy in children has been increasing over the last 2 decades, as indicated by surveys conducted in the USA and United Kingdom: the rate of peanut allergy in children doubled within a range of 5 to 6 years (4, 5) and more than tripled between 1997 and 2008 with a prevalence of 0.4% in 1997, 0.8% in 2002 and 1.4% in 2008 (3). Studies indicate that peanut allergy might resolve in about 20% of cases (6–9), but may recur in some desensitized individuals, making this allergy a life-long affliction in the vast majority of cases.

A recent randomized study of peanut consumption in infants at high risk of developing peanut allergy, the Learning Early About Peanut Allergy (LEAP) study, has evaluated the strategies of peanut consumption or avoidance at very early ages, between 4 and 11 months of age (10). In the subset of infants at high risk to develop peanut allergy, which were infants with eczema, positive egg Skin Prick Test (SPT), negative or slightly positive peanut SPT, the results of this prospective study demonstrated that early peanut consumption during infancy might be preferable to avoidance for preventing the occurrence of peanut allergy in infants at high risk.

Peanut allergy falls within the Immunoglobulin E (IgE)-mediated category of food allergies, with immediate reactions triggered by circulating allergen-specific IgE upon exposure to the allergen (11). IgE-mediated allergic reactions to foods have a rapid onset, usually within a few minutes following exposure to the allergen. IgE-mediated allergic reactions to peanut provoke characteristic responses in the skin, gastrointestinal tract, upper and lower respiratory tract and cardiovascular system (12). IgE-mediated reactions to food may also trigger generalized reactions, that is anaphylaxis, a severe, potentially fatal, systemic allergic reaction that occurs suddenly after contact with an allergy-causing substance (13).

The complete mechanism of IgE-mediated food allergy remains unknown. However, it is thought that the development of an IgE-mediated response to an allergen is the result of a series of molecular and cellular interactions involving Antigen-Presenting Cells (APCs), T cells and B cells (14, 15). Upon re-exposure to the sensitizing food, the allergen crosslinks the specific IgEs bound on mast cells and basophils, triggering release of vasoactive and inflammatory mediators such as histamine, leukotrienes, prostaglandins, and platelet-activating factor. The massive release of these mediators induces immediate allergic systemic symptoms, including anaphylaxis.

There are no approved treatments available for peanut allergy (16). Currently, the only therapeutic option available for peanut-allergic subjects is strict avoidance. However, since peanut is a ubiquitous ingredient in many foods, strict avoidance is difficult to achieve, and accidental ingestion of peanut by peanut-allergic subjects may result in severe reactions and fatal outcomes (17).

The only available countermeasure in case of severe systemic and/or life-threatening reactions/anaphylaxis to peanuts is injectable epinephrine as recommended by the World

Allergy Organization (18). Epinephrine remains a rescue therapeutic agent and is not designed for a routine use.

Various non-specific and food allergen-specific treatment approaches have been under evaluation. Non-specific approaches to food allergy include the use of monoclonal anti-IgE antibodies, which might increase the Eliciting Dose (ED) threshold for the food allergen (19, 20). Food allergen-specific approaches in clinical development include Oral ImmunoTherapy (OIT), SubLingual ImmunoTherapy (SLIT), and EPicutaneous ImmunoTherapy (EPIT) (21). Food-specific approaches may be advantageous as they target the specific foods that cause the severe IgE-mediated anaphylactic reactions (22). Studies on SLIT and OIT have demonstrated some encouraging efficacy results (clinical desensitization), including beneficial immunologic changes (23–26). Oral immunotherapy has shown evidence for inducing desensitization in most subjects, with immunologic changes over time (25–27). These advances are, however, hampered by the significant risk of side effects and occurrence of eosinophilic esophagitis in the context of OIT (28–32). Sublingual immunotherapy for peanut allergy has demonstrated evidence of clinical success, with some subjects showing signs of desensitization with a more satisfactory safety profile compared to OIT and with significant immunologic changes noted during the first year of therapy (24). Despite the evident interest of clinicians to further evaluate these treatment procedures, OIT and SLIT will not likely be applicable across all ages and risk categories of peanut-allergic children and adults. Alternative immunotherapeutic approaches for peanut allergy are therefore needed, with a clinically meaningful benefit and improved safety profile.

The Investigational Medicinal Product (IMP), DBV712 (or Viaskin® Peanut), consists of an epicutaneous delivery system (Viaskin® patch) containing a solid deposit of a formulation of peanut protein extract. The peanut protein allergens are deposited on the backing of an occlusive chamber by electrospraying a liquid formulation of the peanut protein extract. The drug substance is an unmodified, lyophilized peanut extract produced from the extraction and freeze drying of defatted peanut flour, derived from the peanut seed, *Arachis hypogaea*.

Further details can be found in the Investigator's Brochure (IB), which contains comprehensive information on the IMP.

1.2 Rationale

DBV712 is a ready-to-use and easy-to-administer form of allergen immunotherapy, particularly adapted to the pediatric population. It is intended to induce clinical desensitization/tolerization to peanut in subjects allergic to peanut through interaction with the local APCs such as the epidermic Langerhans and dendritic cells. By utilizing the epicutaneous route of administration, DBV712 is able to initiate these immunomodulatory processes while minimizing the potential safety concerns associated with systemic exposure to peanut allergenic proteins.

In the 12-month, Phase IIb VIPES study, among the 3 doses tested (50 µg, 100 µg and 250 µg), the highest dose of 250 µg DBV712 displayed a strong efficacy with the highest magnitude of effect in children with a good safety profile. The efficacy and safety of 12-month treatment with DBV712 at 250 µg were further confirmed in the pivotal Phase III PEPITES study in children aged 4 to 11 years. Additional 6-month safety data from the

interim analysis of the Phase III REALISE study are also consistent with the good tolerability profile of DBV712 250 µg in children.

The children population intended to be studied in this study is younger compared to the one of the previous Phases II and III studies with DBV712. However, even if the skin of infants exhibits distinct anatomical and functional properties, no major differences are reported after 12 months of age in term of thickness of stratum corneum, acting as barrier (air-liquid interface), except for smaller corneocytes suggesting a more rapid turnover of stratum corneum (33). The permeability barrier function becomes adult-like after the first year of life (e.g. trans-epidermal water loss is similar) but some skin characteristics such as capacitance values which are higher in infants/toddlers aged 8 to 24 months, and pH which is less acidic in infant than in the older child/adult, suggest that around 12-24 months of age, the skin is still maturing.

After the age of 2 years, no marked differences with adult are reported in skin structure and characteristics.

More importantly, clinical data of early introduction of allergenic food in the diet of sensitized infant/toddlers or completed and ongoing desensitization studies with food or aeroallergens are encouraging because they suggest that very young children can be desensitized to these allergens, with a higher success as older subjects.

Finally, recently reported differences in immune reactions between adults and children evidencing increased innate immunity in children skin, reinforce the concept of EPIT as a potential well-tolerated, convenient and efficient approach of immunotherapy for food allergic toddler.

Based on these findings, DBV712 at 100 or 250 µg used for EPIT for a duration of 12 months is considered to be suitable doses for treating toddlers/young children with peanut allergy in this study.

1.3 Risk-Benefit Assessment

The primary safety concern for any allergen specific immunotherapy is related to the risk of inducing systemic, severe or life-threatening allergic reactions. DBV712 applied epicutaneously was developed in this sense, which is to reduce the risk of these severe systemic reactions by applying the peanut allergens on the skin and reaching the immune system through the cutaneous Langerhans and dendritic cells.

A comprehensive summary of the safety and efficacy data from non-clinical and clinical studies with DBV712 is available in the IB.

Safety information originating from clinical studies including pediatric subjects have demonstrated a good safety profile for DBV712 up to 250 µg in children as of 4 to 11 years of age. The expected local skin reactions triggered by DBV712 at the site of patch application, which are pruritus, erythema, edema, and urticaria, are in the majority of cases mild or moderate and managed and controlled satisfactorily by the subjects with topical medications containing corticosteroids. As a consequence, a very good compliance was shown in the studies conducted so far.

Furthermore, especially in the Phase IIb VIPES study, DBV712 250 µg has shown a statistically significant effect with up to 53.6% of children responding positively to the treatment *versus* 19.4% for placebo, as per the dose-finding study primary endpoint. In a post-hoc analysis with a higher stringent criterion for the treatment benefit (the same used

for the primary efficacy endpoint in this Phase III EPITOPE study), the magnitude of effect of DBV712 250 µg was even higher (46.5% response rate in the active treatment group *versus* 6.5% response rate for placebo). The efficacy of DBV712 250 µg was further confirmed in the pivotal Phase III PEPITES study, which included 356 peanut-allergic children from 4 to 11 years. In this study, which used the same primary efficacy endpoint than EPITOPE, DBV712 250 µg showed a statistically significant higher responder rate (35.3%) *versus* placebo (13.6%) after 12 months of treatment (between-treatment difference of 21.7%, p<001). Further detail regarding both VIPES and PEPITES studies can be found in the IB.

No particular safety concern arose in young children presenting with filaggrin deficiency during the clinical program indicating a favorable safety profile of the EPIT therapy with regard to this genetic condition jeopardizing skin integrity. The safety assessment made during the CoFAR6 study did not evidence additional adverse events (AEs) in the subjects presenting with atopy (51.4% of the overall study population).

Overall, the available information gathered from several clinical studies conducted in children with DBV712 suggest that DBV712 250 µg dose presents a favorable benefit-risk ratio.

2 STUDY OBJECTIVES

The objective of this study is to verify the safety and local tolerance of the 2 DBV712 doses of 100 and 250 µg and to assess the efficacy and safety of DBV712 to induce desensitization to peanut in peanut-allergic subjects 1 to 3 years of age after a 12-month treatment period by EPIT.

3 OVERALL DESIGN AND PLAN OF THE STUDY

3.1 Overview

This is a 12-month, double-blind, placebo-controlled, randomized phase III trial to assess the safety and efficacy of DBV712 (doses of 100 µg or 250 µg peanut protein per patch) in peanut-allergic children 1 to 3 years of age.

The trial will be conducted in approximately 50-70 sites in at least 8 countries with Investigators and staffs trained and experienced in the diagnosis and the management of peanut allergy and anaphylaxis, and capable of performing Double-Blind, Placebo-Controlled Food Challenges (DBPCFCs) in young children.

Peanut allergic children meeting the following key inclusion criteria will be selected:

- Physician-diagnosed peanut allergy or high suspicion of peanut allergy as assessed by the physician: child presenting signs, symptoms and a medical and/or a family history putting him/her at high risk of having a peanut allergy and/or history of presence of peanut-specific IgE and/or positive SPT;
- Subject currently following a strict peanut-free diet;
- Presence of peanut specific IgE > 0.7 kU/L;
- Positive SPT to peanut with a largest wheal diameter ≥ 6 mm;
- Positive DBPCFC to peanut with symptoms meeting the challenge stopping criteria at an ED ≤ 300 mg peanut protein.

During the maximum 6-week screening period, subjects will undergo an entry/screening DBPCFC to peanut to confirm their allergy to peanut and to determine their entry or screening peanut ED. The starting dose of the challenge will be 1 mg peanut protein and will escalate up to the highest dose of 300 mg peanut protein. Subjects who react at or below the dose of 300 mg peanut protein are considered eligible.

A post-treatment DBPCFC will be performed at Month 12, starting at the dose of 1 mg peanut protein and proceeding up to the highest dose of 2,000 mg peanut protein. The primary efficacy endpoint of this phase III study is the difference between the percentage of treatment responders in the selected DBV712 dose group (250 µg) compared to the placebo group at Month 12, determined on the peanut protein ED during the food challenge.

Other efficacy assessments at months 3, 6 and 12, include immunological changes in peanut-specific IgE and IgG4 subtype and SPTs.

Key assessments of global safety will be performed at each study visit including skin observation of the patch areas of application, vital signs, physical examinations, clinical laboratory assessments. Atopic dermatitis will also be assessed at baseline and at months 3, 6 and 12 using the SCORring Atopic Dermatitis (SCORAD).

In between visits, occurence of local skin reactions will be specifically solicited and their severity graded on a daily basis by the parents/guardians in a diary, for at least 6 months for part A subjects, and during the whole treatment duration for part B subjects (see Sections 3.1.1 and 3.1.2 for design of Parts A and B). Any other AEs (including local skin reactions occurring after the first 6 months of treatment for part A subjects), and any concomitant medications will also be reported in the diary by the parents/guardians and this will be reviewed by the site medical staff at each subject visit.

At screening, at Month 12 and at the end of study visit, the subjects' parents/guardians will complete quality of life questionnaires (Food Allergy Quality of Life Questionnaire [FAQLQ] / Food Allergy Independent Measure-parent form [FAIM] / EuroQol-5D-5L (EQ-5D-5L) [part B only, see Section 3.1.2 for design of Part B]) to assess the impact of DBV712 12-month treatment on their quality of life.

[redacted]

The overall maximum study duration for each subject is approximately 62 weeks (6-week screening period, 12-month treatment period and 4-week follow-up period). The subjects will attend a total of 12 study visits:

- 3 visits during the screening phase,
- 8 visits during the treatment period (+1 additional Visit 7bis for the subjects in Part A in the eventuality of dose switching for safety reason. After interim safety analysis, both doses of DBV712 were shown to be safe, and no dose switching is required. As a consequence, Visit 7bis will be not applicable; see section 3.1.1),
- 1 visit at the end of the follow-up period.

In addition, 5 telephone contacts will be made during the treatment period.

After completion of this 12-month blinded study, eligible subjects will be offered the opportunity to participate in an extension study to receive treatment with DBV712 250 µg for 24 additional months if they were initially randomized in the DBV712 100 µg or 250 µg groups, or for 36 months if they were randomized in the placebo group.

3.1.1 Study part A

In the first part, the safety of 2 doses of DBV712, 100 µg and 250 µg was evaluated with a double-blind placebo-controlled design. Fifty subjects were to be randomized either in the placebo arm or in the 2 active arms, with a 1:2:2 ratio, i.e. 10 subjects in the placebo arm and 20 subjects in each of the 2 active arms, DBV712 100 µg and DBV712 250 µg.

A safety analysis was to be performed after the first 3 months of treatment to estimate the safety profiles of the 2 studied doses of DBV712. The safety and tolerability assessment was to be assessed by an independent Data and Safety Monitoring Board (DSMB).

As a result of this tolerability and safety review, 4 situations could have been encountered:

1. Both doses are considered well tolerated with a good safety profile. The 250 µg dose would then be selected for the continuation of the study in Part B. In parallel, all subjects still in Part A at the moment of the decision would remain under the treatment arm they were under until their Month 12 treatment period: subjects under DBV712 250 µg dose in Part A would continue with the same dose up to Month 12, subjects under DBV712 100 µg dose in Part A would continue with the same dose up to Month 12, and subjects under placebo would remain under placebo up to Month 12. There would be no Visit 7bis to perform in this situation.
2. The DBV712 250 µg dose has a better tolerability/safety profile than the 100 µg dose. The 250 µg dose would then be selected for the continuation of the study in Part B. In parallel, all subjects still in Part A at the moment of the decision would come for the Visit 7bis to receive a new treatment box with the right treatment: subjects under DBV712 250 µg dose in Part A (the safest dose) would receive a new box of DBV712 250 µg so that they could continue with the same safe dose up to Month 12, subjects under DBV712 100 µg dose in Part A (dose considered not safe) would receive a new box of DBV712 250 µg so that they were treated with a safe dose up to Month 12 and subjects under placebo would receive a new box with placebo up to Month 12. It would have been important that all subjects come back for the Visit 7bis to keep the blinding with regard to the subjects who need to change their treatment dose.
3. The highest dose of DBV712 250 µg is not considered as having an acceptable safety profile and only the DBV712 100 µg dose is considered having a favorable safety profile. The DBV712 100 µg dose would be selected for the continuation of the study in Part B. In parallel, all subjects still in Part A at the moment of the decision would come for the Visit 7bis to receive a new treatment box with the right treatment: subjects under DBV712 250 µg dose in Part A (dose considered not safe) would receive a new box of DBV712 100 µg so that they were treated with a safe dose up until Month 12; subjects under DBV712 100 µg dose in Part A (the safe dose) would receive a new box of DBV712 100 µg so that they could continue with the same safe dose up until Month 12, and subjects under placebo would receive a new box with placebo up until Month 12. In this situation too, it

would have been important that all subjects come back for the Visit 7bis to keep the blinding with regard to the subjects who need to change their treatment dose.

4. Both doses are considered by the DSMB as having an unfavorable safety profile or tolerability. The study would then be stopped and all subjects would have to stop applying the patches and would be withdrawn from the study.

Hence, the 50 first subjects included in the 3 initial treatment arms in Part A were to continue blindly their assigned treatment until the end of the study (i.e. 12 months of treatment; Situation n°1), or were to stop their treatment prematurely (Situation n°4), or were to switch to the safest DBV712 dose (Situation n°2 or n°3), according to the decision or recommendation made by the DSMB.

Upon review of the 3-month safety data of the 51 subjects actually randomized in part A, the DSMB had no safety concern and considered both doses as well tolerated with a good safety profile (scenario "1" as described above). As a consequence:

- The dose selected for part B is the 250-µg dose;
- All subjects from part A were to remain in their initial randomized treatment arm until the end of 12-month treatment (placebo, DBV712 100 µg or DBV712 250 µg).

After all subjects from Part A complete the study, Part A data will be unblinded for analysis.

3.1.2 Study part B

The second part of the study aims to assess the safety and efficacy of the selected dose after 12-month treatment *versus* placebo. This part was to be initiated after the choice of the highest safe dose upon the DSMB meeting. As from protocol v6.0, the selected highest safe dose for part B upon DSMB recommendation is 250 µg. Additional subjects will be recruited in the active selected dose arm and in the placebo arm, to reach the targeted total number of subjects.
In accordance with the calculated sample size for this study, a total of 350 additional subjects will be randomized in the second part (Part B) of the study. These subjects will be randomized with a 2:1 ratio in either the active or placebo arm, 233 subjects in the active arm and 117 subjects in the placebo arm.

An interim analysis to evidence the treatment activity on the immune system of 1 to 3 years old children is planned after the first 50 subjects from part B have received 6 months of active treatment with the selected DBV712 dose of 250 µg (Visit 8). CCI [redacted]

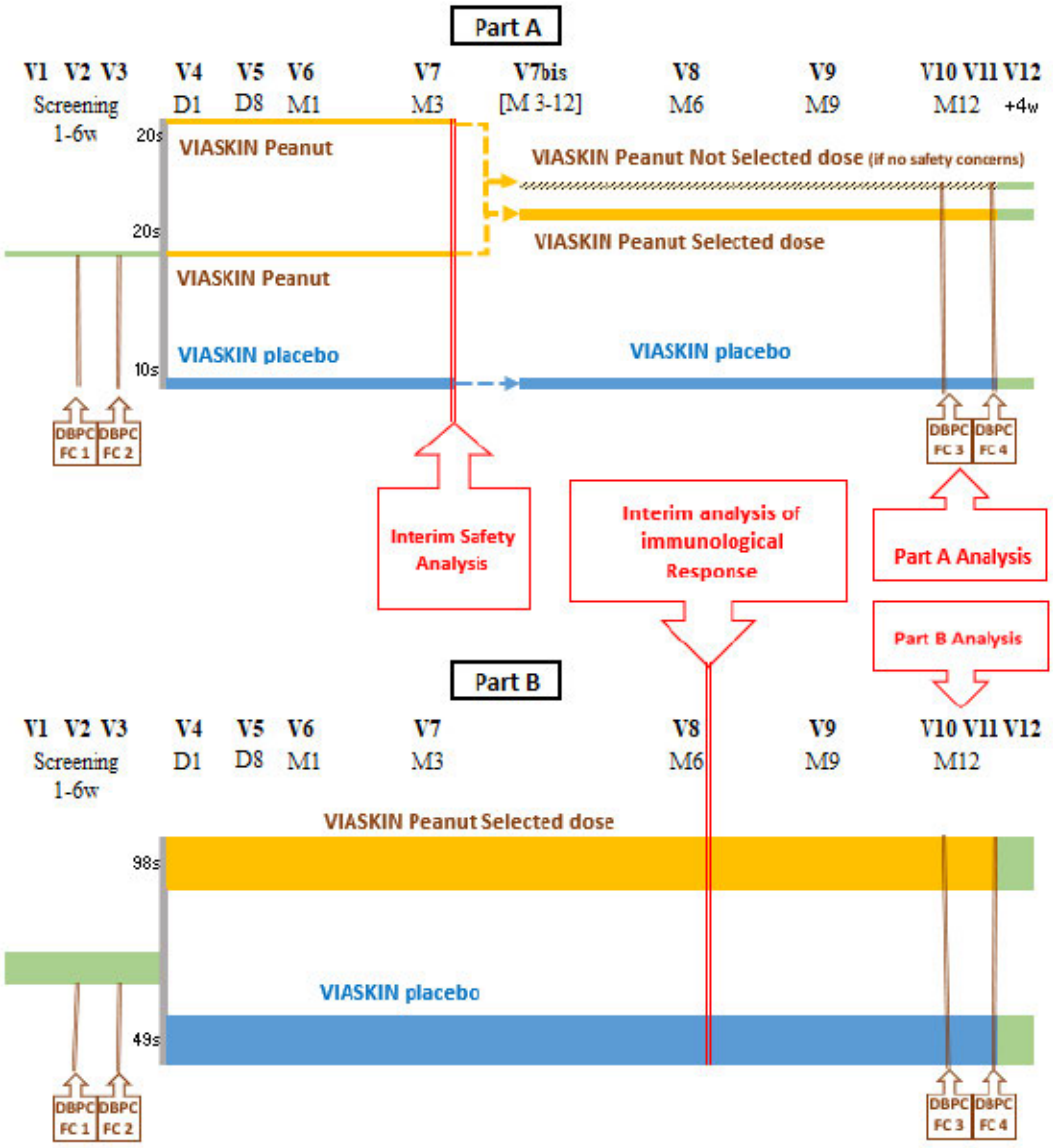
In the situation where the median relative change from baseline of the peanut specific IgG4 is equal or lower than the median relative change in the placebo group, the premature stop

of the study for lack of evidence of therapeutic benefit will be considered. This unblinded data review will be conducted by the DSMB who will be responsible of issuing the recommendation to the sponsor.

3.2 Study Schematic Diagram

The Schedule of visits and procedures is presented in page 15 and the study design is presented in Figure 1.

Figure 1: Study Design



Based on the Interim Safety Analysis, the DBV712 Selected dose for Part B is 250 µg, and all subjects from Part A are to continue their treatment until the end of the study as per their initially randomized arm (Placebo, DBV712 100 µg or DBV712 250 µg). As a consequence, the Visit 7bis for dose switching in Part A is not applicable.

Abbreviations: D = Day; DBPCFC = Double-blind, placebo-controlled food challenge; M = Month; s = subject; V = Visit; w = weeks.

3.3 Criteria for Evaluation of the Study

3.3.1 Efficacy Criteria

3.3.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the difference between the percentage of treatment responders in the selected active DBV712 group (250 µg) compared to the placebo group after 12 months of EPIT treatment. A subject is defined as a treatment responder if:

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

3.3.1.2 Secondary Efficacy Endpoints

The following secondary efficacy endpoints will be analyzed:

- Change from baseline to Month 12 in Cumulative Reactive Dose (CRD) in the selected active DBV712 group (250 µg) *versus* the placebo group;
- Change from baseline to Month 12 in ED in the selected active DBV712 group (250 µg) *versus* the placebo group;

3.3.1.3 Other Efficacy Endpoints

- The percentage of subjects reaching a cumulative dose ≥1,444 mg peanut protein at the post treatment DBPCFC at Month 12 in the selected active DBV712 group (250 µg) *versus* the placebo group;
- The percentage of subjects reaching a cumulative dose ≥3,444 mg peanut protein at the post-treatment DBPCFC at Month 12 in the selected active DBV712 group (250 µg) *versus* the placebo group;
- The percentage of subjects unresponsive (those showing no symptoms leading to DBPCFC stop) to the highest dose of peanut protein (2,000 mg of peanut protein) in the selected active DBV712 group (250 µg) *versus* the placebo group.
- The change from baseline in peanut-specific IgE and IgG4 at months 3, 6 and 12 in the selected active DBV712 group (250 µg) *versus* the placebo group;
- The change from baseline in peanut-specific IgG4 at month 6 in the selected active DBV712 group (250 µg) *versus* the placebo group will be the main criteria of the interim 6-month analysis of the first 50 subjects treated with the selected dose of DBV712;
- The change from baseline in peanut SPT average wheal diameters at months 3, 6 and 12 in the selected active DBV712 group (250 µg) *versus* the placebo group,
- Description of the quality of life questionnaires (FAQLQ/FAIM) and change from baseline in FAQLQ/FAIM scores at Month 12 in the selected active DBV712 group (250 µg) *versus* the placebo group (for those countries where the translated and validated questionnaires are available and used).

Details of the assessment of each of the efficacy endpoints are provided in Section 6.1 and details of the corresponding statistical analysis are provided in Section 8.5.

3.3.2 Safety Criteria

The following IMP safety criteria will be evaluated:

- AEs and treatment-emergent adverse events (TEAEs) by System Organ Class (SOC) and Preferred Terms (PTs);
- TEAEs by maximum severity and relatedness to DBV712;
- Incidence, duration and maximum severity of local cutaneous DBV712-induced AEs as assessed by the subject;
- Incidence and severity of local cutaneous DBV712-induced AEs as assessed by the Investigator;
- Local adverse events of special interest (AESIs) (i.e., reactions at patch sites potentially leading to skin barrier disruption) and systemic AESIs (i.e. anaphylaxis, or systemic hypersensitivity reactions leading to epinephrine intake),whatever the causal relationship to the IMP;
- SAEs by SOC and PTs, and relatedness to DBV712;
- Laboratory data, physical examinations and vital signs;

In addition, the following study procedure safety criteria will be evaluated:

- Symptoms elicited during the entry/screening DBPCFC and post-treatment DBPCFC at Month 12 by severity;
- Change in severity of symptoms elicited during the DBPCFC from baseline to Month 12 in the selected active DBV712 group (250 µg) *versus* the placebo group;
- SAEs elicited during the entry/screening DBPCFC and post-treatment DBPCFC at Month 12.

Details of the assessment of each of the safety criteria are provided in Section 6.2 and details of the corresponding statistical analysis are provided in Section 8.6.

3.3.3 Exploratory Criteria

The following exploratory criteria will be evaluated:

- The change from baseline in IgE and IgG4 specific to peanut protein components at 3, 6 and 12 months for both DBV712 groups *versus* the placebo group;
- The change from baseline in total IgE at 3, 6 and 12 months for both DBV712 groups versus the placebo group;
- Enumeration and characterization of reactions triggered by accidental consumption of peanut during the study and analysis of "risk-taking behavior" of parents' subjects (voluntary peanut consumption) during the study;
- Epigenetic modifications of the promoters of some specific genes;
- Sensitization status to some other allergens and their evolution over the study period;
- SCORAD evolution over time;
- [redacted]
- Quality of Life analysis using the EQ-5D-5L;

- Basophil activation test (BAT) analyses (US eligible sites only);
- CCI [redacted]

Details of the assessment of each of the exploratory criteria are provided in Section 6.4 and details of the corresponding statistical analysis are provided in Section 8.7.

3.4 Justification of the Study Design

This study is designed to assess the efficacy and safety of DBV712 at either 100 µg or 250 µg in children aged 1 through 3 years compared to placebo.

Randomized, double-blind and placebo controlled design was chosen to prevent bias in treatment allocation and in the assessment of both safety and efficacy.

The use of a placebo group in this study is justified to obtain reliable scientific evidence for the evaluation of this new medicinal product.

The first part of the study (Part A) is designed to assess the safety and tolerability of the two doses of DBV712 patches, 100 µg or 250 µg, in this pediatric population. At the time of initiation of EPITOPE study, these two DBV712 doses had been previously tested in several clinical studies in very young children: PEP01.09 study with children from 6 years of age, ARACHILD study with children from 5 years of age, Phase IIb VIPES study with children from 6 years of age and CoFAR6 study with subjects from 4 years of age (34).

No dose-dependent difference regarding the patches local tolerance was identified on the peanut protein doses range 50 to 250 µg. High incidences of local skin reactions from any grade of severity (1 to 3) are reported: 90% to 98%, with very low incidence leading to treatment discontinuation (1.2% in VIPES Study). No difference in local tolerance was identified between the age groups.

Since no children less than 4 years old was treated by DBV712, two doses were selected for this study: the 250 µg dose selected as the therapeutic dose for children aged from 6 to 12 years old, and the lower dose of 100 µg, to deal with possible poor tolerance to the 250 µg dose in younger children.

The safety and tolerability evaluation and dose selection was to be performed after 3 months of active treatment. In the previous Viaskin® clinical studies, a vast majority of the local tolerance issues has emerged within the first month of treatment. The analysis after 3 months of treatment should allow a reliable assessment of the local tolerability and to confirm the tolerance of the two doses (Upon review of the 3-month safety data, both doses were considered as safe by the DSMB, and the highest [250-µg] dose was selected for Part B).

Peanut allergic children will be randomized based on the following key inclusion criteria: peanut allergy with the presence of peanut-specific IgE > 0.7K U/L and a SPT to peanut extract with the largest wheal diameter ≥ 6 mm and a positive DBPCFC with a peanut ED ≤ 300 mg of peanut protein.

A DBPCFC will be performed as it is the "gold standard" to diagnose and assess the food allergies (35). Since it carries a risk of inducing potentially severe allergic reactions, subjects will be appropriately selected and managed for the challenges, based on their clinical history and peanut-specific IgE test results.

The ED of peanut protein, that is the dose of peanut protein administered to subjects during the food challenge procedure, which triggers allergic reactions leading the challenge stop, is capped to 300 mg for the baseline food challenge, with the starting dose of 1 mg. Although the average amount of peanut consumed in an accidental exposure has not been accurately quantified, it is generally believed to be no more than 1 to 2 peanut kernels, or the equivalent of approximately 300 to 600 mg of peanut protein (24, 36, 37). Thus, this study will enroll subjects who will react at or below 300 mg peanut protein.

The second part of the study (Part B) is designed to assess the efficacy, the safety and tolerability of the selected dose of DBV712 patches, 100 µg or 250 µg, in this pediatric population (as from protocol v6.0, the selected dose for part B upon DSMB recommendation is 250 µg). The primary efficacy endpoint will rely on the difference *versus* placebo in the response to the peanut DBPCFC after 12-months of treatment.

The primary endpoint will be assessed at Month 12 based on positive results of previous clinical studies showing evidence of desensitization with peanut EPIT after 12 months of treatment.

An interim analysis will be conducted when 50 subjects from Part B will have reached 6 months of active treatment with the active dose selected in the Part A.

This interim analysis will assess the presence of an immunological reaction to the peanut allergen exposure through the skin, evidenced by an increase of the peanut specific IgG4. In all previous clinical studies, the peanut specific IgG4 levels have consistently risen from baseline in the subjects treated by DBV712 patches. We defined this assessment as a stopping criterion, since the absence of peanut specific IgG4 increase would be a sign of a lack of exposure or a lack of response of the children's immune system, compromising a desensitization to peanut.

The dosing duration escalation is increased in this study in young children from a 2-week period used in the previous Viaskin® studies to a 4-week treatment initiation period in the present study. This extension is justified by the higher difficulty to assess the local tolerance in young children. A slower increase in the duration of the dosing escalation should reduce the local discomfort for the most reactive subjects.

The study design follows the International Conference on Harmonization (ICH) guideline on general considerations for clinical studies (38).

4 STUDY POPULATION

The study population will consist of children 1 to 3 years of age with peanut allergy. Study participation will require consent from a legally authorized representative. Subjects must meet all the inclusion criteria and none of the exclusion criteria.

All parents/guardians will continue with their usual peanut-free diet and label reading of food products to avoid as much as possible any accidental peanut consumption for the duration of the study.

4.1 Inclusion Criteria

Subjects will be enrolled only if they meet all of the following criteria:

1. Male or female from 1-3 years of age at Visit 1.
2. Physician-diagnosed peanut allergy or high suspicion of peanut allergy as assessed by the physician: child presenting signs, symptoms and a medical and/or a family history putting him/her at high risk of having a peanut allergy and/or history of presence of peanut-specific IgE and/or positive SPT.
3. Subject currently following a strict peanut-free diet.
4. Signed informed consent of parent(s)/guardian(s) of the children aged 1-3 years.
5. Peanut-specific IgE level (ImmunoCAP system) > 0.7 kU/L.
6. Positive peanut SPT with a largest wheal diameter ≥ 6 mm.
7. Positive DBPCFC to peanut, with symptoms meeting the challenge stopping criteria at an ED ≤300 mg peanut protein.
8. Parents/guardians and subjects willing to comply with all study requirements during their participation in the study.

4.2 Exclusion Criteria

Subjects will be enrolled only if they meet none of the following exclusion criteria:

1. Peanut allergic subjects presenting a medical history of severe anaphylaxis to peanut will be excluded for this study. Severe anaphylaxis is defined by the Grade 3 of the Anaphylaxis Staging System (APPENDIX 4), including:
   - Severe hypoxia, persistent hypotension or more than 20% drop in blood pressure, neurological compromise, or
   - Cyanosis or SpO2 ≤ 92% at any stage, confusion, cardiovascular collapse, loss of consciousness, bradychardia, cardiac arrest.
2. Severe reaction during the entry/screening DBPCFC, defined as any of the following:
   - Need for intubation
   - Hypotension persisting after epinephrine administration
   - Need for three doses or more of systemic epinephrine.
3. Subject with reactions to the placebo formula during the screening DBPCFC (with reactions deemed to stopping the challenge).
4. Subjects who fail to complete the entry food challenge due to any reason including clear aversion to the food formula matrix,
5. Subject with any clinically significant abnormality identified at the time of screening such as major infantile infectious diseases (pox, measles) which in the judgment of the Investigator can preclude safe participation or strict compliance to the protocol procedures. Subjects can be considered for the study after recovery from these diseases.
6. Viral upper respiratory infection or gastroenteritis or any severe disease within 7 days of food challenge (challenge must be rescheduled at least after 7 days upon recovery).

7. Hypersensitivity to any of the Viaskin® patch components (except to peanut protein), including the adhesive film.
8. Hypersensitivity to any component of the food challenge formula (except to peanut protein) or a known history of apple allergy.
9. Inability to discontinue short-acting antihistamines or long-acting antihistamines for the minimum wash-out periods required (depending on half-lives and specified in APPENDIX 3) prior to the skin prick testing or the food challenges.
10. Diagnosis of asthma that fulfills any of the following criteria:
    - Uncontrolled asthma (as per Global Initiative for Asthma [GINA] latest guidelines; see APPENDIX 8)
    - Asthma requiring controller treatment step 3 or higher (as per GINA latest guidelines: either moderate [double low dose] of inhaled corticosteroid, or association of inhaled corticosteroid with leukotriene receptor antagonist [see APPENDIX 8]. Long acting beta agonists are not recommended below 5 years)
    - History of 2 or more systemic corticoid courses within the 3 previous months prior to Visit 1 or 1 systemic corticoid course within the 4 weeks prior to Visit 1 for treating a diagnosed asthma.
    - Prior intubation/mechanical ventilation for asthma within one year prior to Visit 1.

    Asthmatic subjects with the following treatment options **are eligible**:
    - No controller treatment (GINA Step 1),
    - Controller treatment monotherapy (GINA Step 2):
        - with daily or short-term course (intermittent) **low dose** inhaled corticosteroid,
        - or with leukotriene receptor antagonist.
11. Presence of more than 3 episodes of wheezing in the past year (each lasting more than 10 consecutive days, apart from colds) or presence of respiratory symptoms (wheezing, cough, heavy breathing) between these episodes, and/or other respiratory symptoms suggesting either undiagnosed asthma or asthma not controlled by asthma treatment (as per GINA latest guidelines, see APPENDIX 8).
12. Generalized dermatologic disease (e.g. severe atopic dermatitis, uncontrolled generalized eczema, ichthyosis vulgaris) extending widely on the skin and especially on the back with no intact zones to apply the Viaskin® patches.
13. Diagnosis of mast cell disorders including mastocytosis or urticaria pigmentosa as well as hereditary or idiopathic angioedema;
14. Prior history of any immunotherapy to any food (e.g. oral immunotherapy, sublingual immunotherapy, specific oral tolerance induction). Subjects who received a prior oral immunotherapy of less than 1 month-duration which ended at least 3 months before Visit 1 are eligible for inclusion.
15. Subject receiving or planning to receive any immunotherapy (aeroallergens, venoms, anti-infective…) during their participation in the study. These immunotherapies must be discontinued at the time of Visit 1.

16. Symptomatic seasonal allergies that may interfere with the conduct of a DBPCFC. These subjects could be screened at a time when such allergies are asymptomatic (for example outside of the culprit season);
17. Subject receiving β-blocking agents, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, calcium channel blockers or tricyclic antidepressant therapy.
18. Subject who received anti-tumor necrosis factor drugs or anti-IgE drugs (such as omalizumab), any biologic immunomodulatory therapy, cyclosporine or other immunosuppressive drugs within one year prior to Visit 1 or during screening period. Topical calcineurin inhibitors are permitted.
19. Subject who received systemic long-acting corticosteroids within 2 weeks prior to Visit 1 (or within 4 weeks prior to Visit 1 if used for treating asthma), and/or systemic short-acting/intermediate-acting corticosteroids for more than 3 days within 2 weeks prior to Visit 1 or during screening (unless used for DBPCFC symptoms) (see list of corticosteroids in APPENDIX 2).
20. Any disorder in which epinephrine is contraindicated such as congenital cardiac malformation, uncontrolled hypertension, or serious ventricular arrhythmias.
21. Current participation in another clinical trial or participation in another clinical trial in the last 3 months prior to Visit 1,
22. Subjects having any sibling already randomized in any study involving DBV712, including in this EPITOPE study;
23. Subjects or parent(s)/guardian(s) of subjects with obvious excessive anxiety and unlikely to cope with the conditions of a food challenge or unable to follow the protocol requirements.
24. Past or current disease(s) which, in the opinion of the Investigator or the Sponsor may affect the subject's participation in this study or place the subject at increased risk during participation in the study, including but not limited to past or active eosinophilic gastrointestinal disorders, autoimmune disorders, immunodeficiency, malignancy, uncontrolled diseases (e.g. hypertension, psychiatric, neurologic, cardiovascular), or other disorders (e.g. liver, gastrointestinal, kidney, pulmonary disease or blood disorders).
25. Subjects being in any relationship or dependency with the sponsor and/or the investigator or the study staff.

4.3 Patient Withdrawal and Replacement

4.3.1 Subjects Stopping Rules

Subjects must be withdrawn from the **study treatment** under the following circumstances:

- Severe anaphylaxis (stage 3 anaphylaxis, see APPENDIX 4) related to Viaskin® patch application (either peanut or placebo patch);
- More than 2 intramuscular epinephrine injections for an AE related to Viaskin® patch application (either peanut or placebo patch), and not occurring during the DBPCFC nor related to an accidental food allergen consumption.

Subjects may be required to be withdrawn from the study treatment or study after discussion with the Investigator and/or Sponsor for the following reasons:

- AE(s);
- Severe "maculo-papular rash" or severe generalized atopic "dermatitis" outside of patch application area, which failed to be controlled by adequate corrective treatments (including topical corticosteroids) and in spite of several study treatment interruptions;
- At the discretion of the Investigator, if she/he decides that it is in the subject's best interest to be withdrawn from the study;
- The subject is unwilling to continue in the study (consent withdrawal);
- Lack of compliance with protocol requirements and procedures;
- The subject fails to return to the clinic for scheduled visits and does not respond to telephone or written attempts at contact (lost to follow-up);

4.3.2 Study Stopping Rules

The safety of DBV712 is continuously monitored by the DBV medical monitor and the independent DSMB. However, the study will be suspended pending an expedited safety review by the independent DSMB if any of the following occur:

1. Any death related to DBV712 patch dosing;
2. More than 3 cases of severe anaphylaxis (stage 3 anaphylaxis, see APPENDIX 4) related to DBV712 patch application (not occurring during the DBPCFC);
3. More than 5 subjects requiring more than 2 injections of intrasmuscular epinephrine for an AE related to the DBV712 patch application, and not occurring during the DBPCFC nor related to an accidental food allergen consumption.

Upon safety review, the DSMB will recommend 1 of the following outcomes:

- The study may continue without modification;
- The study may continue with modifications as prescribed by the DSMB;
- The study should be discontinued.

The study will be prematurely stopped if the Sponsor, Regulatory Authorities, or Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) for any reason, request to stop the study.

4.3.3 Replacement of Withdrawn Subjects

Subjects who withdraw prematurely after having been randomized and having received at least one dose of the IMP will not be replaced.

4.3.4 Data Collection and Follow-up after Withdrawal

If a subject is prematurely withdrawn from the IMP for any reason before completing all study visits, the Investigator must make every effort to perform the evaluations described for the Early Termination Visit (see Section 7.2.12). The Investigator must furthermore complete all appropriate subject diary and e-CRF pages, providing the date and explanation for the subject's withdrawal/discontinuation. When indicated, the Investigator must

arrange for appropriate follow-up and/or alternative medical care of the discontinued subject.

If the subject fails to attend a scheduled End of Study Visit, there will be at least two documented attempts to contact the subject's parents/guardians via telephone and written communication. If no reply is received, the subject will be considered as lost to follow-up.

4.4 Planned Sample Size and Number of Study Centers

It is planned to randomize 400 subjects at 50 to 70 centers in at least 8 countries for this study. In the event the sample size would need to be adjusted, the number of centers would be adapted accordingly. See Section 8.10 for a discussion of sample size including a potential reassessment.

In the part A, 50 subjects will be randomized in the 3 treatment arms. In the part B, 350 subjects will be randomized in the 2 treatment arms.

4.5 Subject Identification and Randomization

4.5.1 Subject Identification

At screening, each subject will receive a unique, 4-digit, screening number. Screened subjects who drop out of the study before randomization will retain their screening number. The screening number for each subject will be a combination of the 2-digit site number plus the 2-digit number assigned to the subject according to her/his chronological order of screening at that site. The screening number will be used as the subject identifier throughout the study.

4.5.2 Randomization Scheme

An Interactive Web Response System (IWRS) will randomize subjects and assign the appropriate treatment number or kit number. In the part A of the study, subjects will be randomized on a 2:2:1 ratio to DBV712 100 µg, DBV712 250 µg *versus* placebo.

In the part B, the randomization scheme will be on a 2:1 ratio to DBV712 at the selected dose (250 µg).

Randomization will be stratified by center and managed centrally for both parts A and B. The randomization scheme will ensure that the ratio of active treatments to placebo is maintained

The randomization codes will be maintained by IWRS.

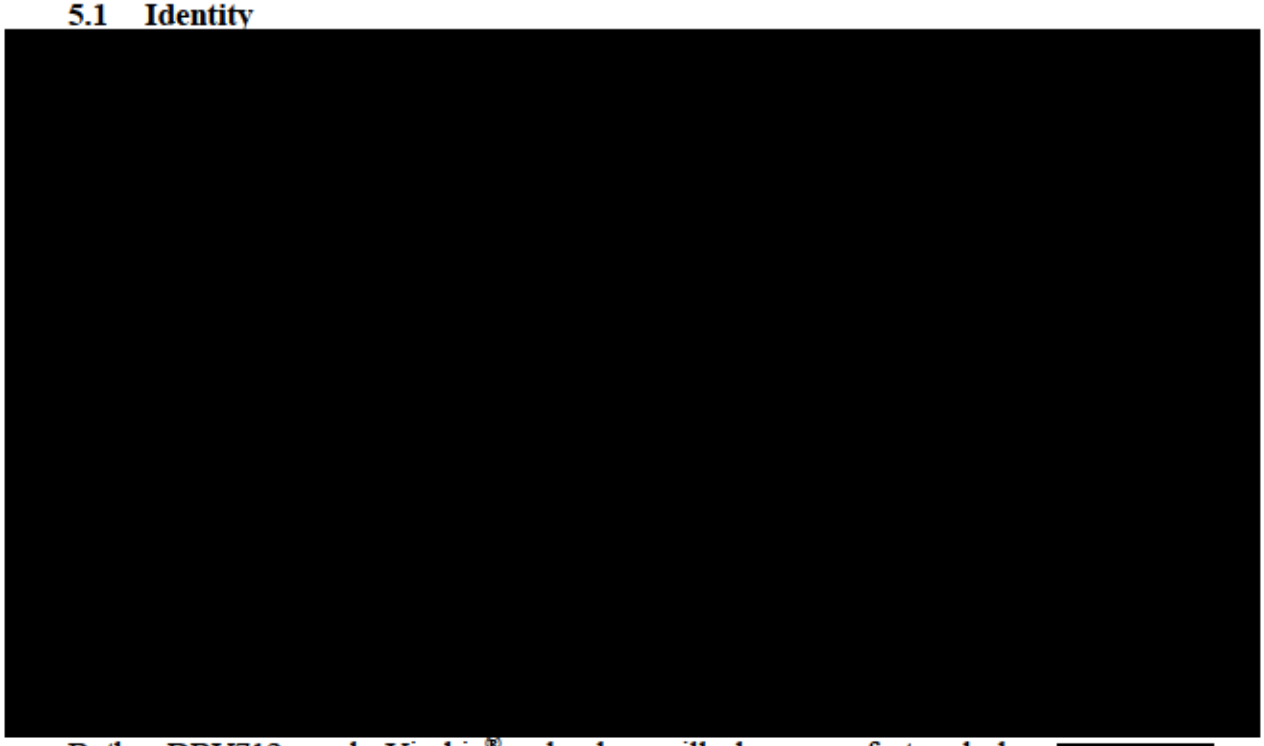
Blinding and breaking the blind procedures are described in Section 5.4.

4.5.3 Allocation/Randomization of Subjects to Treatment

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

5 INVESTIGATIONAL MEDICINAL PRODUCT

5.1 Identity



Both, DBV712 and Viaskin® placebo will be manufactured by CCI and labeled, packaged and released for clinical use by CCI, in accordance with the requirements of Good Manufacturing Practices.

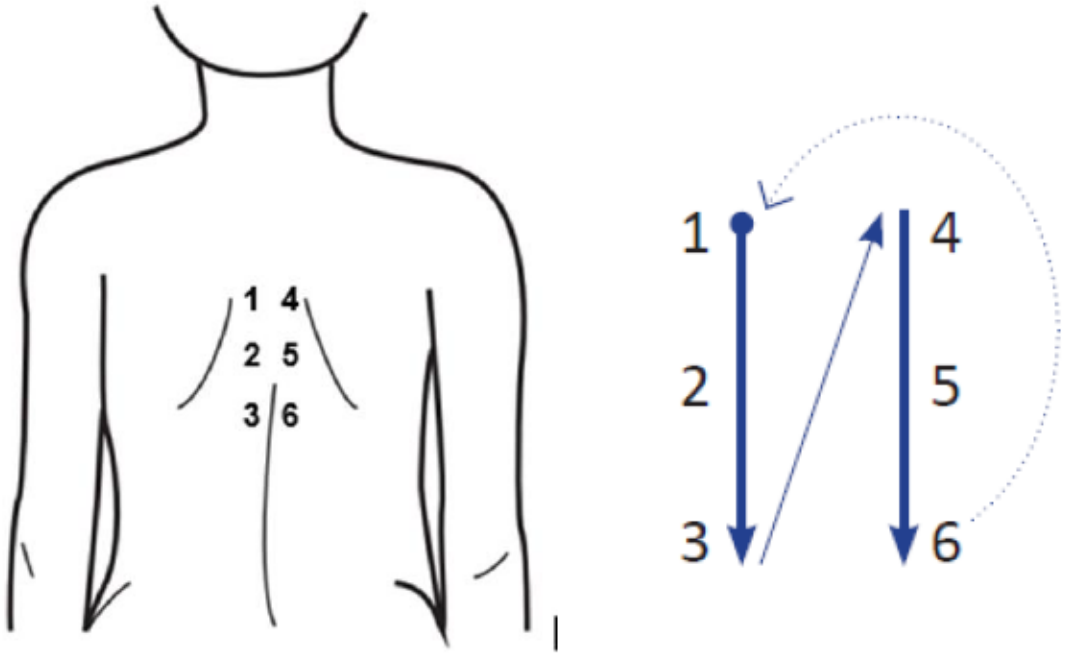
5.2 Administration

In the part A, subjects were to be randomized to receive either active DBV712 containing 100 µg or 250 µg of peanut proteins or placebo, in a 2:2:1 ratio *versus* placebo. The recruitment was to be be suspended after the randomization of 50 subjects. Safety data was to be collected after a 3-month treatment period and evaluated by a DSMB to confirm if the two doses of DBV712 are safe in children 1 to 3 years of age. If the safety profile of DBV712 was confirmed in children 1 to 3 years of age, recruitment was to resume in part B. The new enrolled subjects are to receive either the selected DBV712 dose or placebo to reach the sample size required for the efficacy evaluation. As from protocol v6.0, the selected dose for part B based on DSMB recommendation is 250 µg (see Section 3.1).

During the 12-month blinded treatment period, except for the first 4 weeks (see below), the Viaskin® patch will be applied on the skin for 24 hours (± 4 hours of allowance) every day and renewed on a daily basis, 1 new patch per day.

The location of patch application is the inter-scapular area of the back of the subjects. There will be 6 zones for applying the patch, 3 on each side of the spine (see Figure 2). The first Viaskin® patch will be applied on zone 1, the second on zone 2 (after removal of the first patch), and so forth, until all 6 zones have been used. After zone 6, dosing restarts with zone 1 and continues sequentially, as described.

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



To ensure an enhanced local tolerance at the initiation of Viaskin® patch treatment, the duration of application of the Viaskin® patch will be progressively increased as follows:

- During the first week (from Day 1 through Day 7), the patches will be applied for 2 hours (± 30 minutes) every day;
- During the second week (from Day 8 through Day 14), the patches will be applied for 4 hours (± 30 minutes) every day;
- During the third week (from Day 15 through Day 21), the patches will be applied for 8 hours (± 1 hour) every day;
- During the fourth week (from Day 21 through Day 28), the patches will be applied for 12 hours (± 2 hours) every day;
- From the fifth week onwards (Day 29), the patches will be applied for the entire 24 hours (± 4 hours) every day.

Some subjects may have a higher skin reactivity at the initiation of the treatment, leading to uncomfortable sensations or intense pruritus. These local reactions usually decrease over time as far as the treatment continues. However, some subjects may have difficulties in bearing these uncomfortable sensations or intense pruritus. In these subjects, it is recommended to remove the patch as soon as the subject starts complaining, to clean and to wash the skin area and if necessary use topical corticosteroids. The next patch will be applied the following day on the next skin zone as scheduled. The duration of patch application could usually be increased with time, up to the final targeted 24 hours of patch application; therefore, **the treatment initiation period could be longer than the 4 weeks proposed above,** until tolerance to Viaskin® patch treatment is achieved per the Investigator's assessment.

If possible, the parents or guardians should take advantage of the child bath/shower time to change the patch. The previous Viaskin® patch should be removed just before the bath/shower, and the new Viaskin® patch should be applied a few minutes after the bath/shower and after drying the skin carefully. Application of the Viaskin® patch at a similar time for each daily application (morning or evening) is recommended. If the child does not bathe or shower daily or at the same time daily, it is recommended that the zone where the patch will be applied be cleaned with a moist disposable napkin or tissue and dried prior to application.

In case the Viaskin® patch comes off, it should be immediately discarded and the skin cleaned with a moist disposable napkin or tissue. A Viaskin® patch must not be re-applied.

A new patch can be applied the same day to replace the previous patch that came off only if that patch came off within 2 hours after being applied (only once). Consequently, **no new patch should be applied the same day if the previous patch came off more than 2 hours after being applied.** In that case, a new patch will be applied once 24 hours have passed since the initial patch (the one that came off) was applied. After the Viaskin® patch comes off, or after removing a Viaskin® patch to apply a new one, it is recommended that the subjects' parents/guardians wipe the zone with a moist disposable napkin or a moist disposable tissue and then washes her/his hands to prevent accidental manual transmission of peanut protein.

The first application of the Viaskin® patch will be done in a hospital setting at the study site, with the appropriate emergency treatment (epinephrine) and resuscitation equipment readily available. After the first application of the Viaskin® patch at the study site, all subjects will be observed for at least **3 hours** to check and grade any reactions under or around the patch before being discharged. In case of systemic reaction or severe application site reaction following the first patch application, the next patch application should be postponed until the reaction resolves and should be performed at the study site. Similarly, subjects will be observed for at least 3 hours before being discharged.

On Day 4, Day 22, Month 2 specific phone contacts will be made to the parents/guardians to assess the safety of patch applications on the back during the increase wearing time period (4 first weeks). If required, the subjects may come to the site sooner than planned to be seen and evaluated by the Investigator.

Of note, the recommended duration of daily DBV712 patch application is 24 hours of application per day. However, any daily duration of DBV712 patch application of 24 hours ± 4 hours will be allowed.

5.2.1 Adjustment of Viaskin® Patch Application in Case of Local or Systemic Reactions

When subjects are unable to apply the DBV712 patch for the recommended durations as described above because of local intense or severe reactions, under or adjacent to the patch site, the patch should be removed immediately, the site of application wiped with a moist disposable tissue and a topical corticosteroid medication might be topically applied to treat the reaction. The parents/guardians should take a photo of the back of the subject to document how intense and extended the local reactions are. In the specific case of local intense or severe reactions, it is mandatory that the next Viaskin® patch is applied only the next day on the next zone; no other Viaskin® patch must be applied the same day. In case

of re-appearance of the local intense or severe reactions after application of the next patch the following day, the same process is repeated every day.

The daily duration of Viaskin® patch application should be adjusted/reduced as necessary, and subjects may need more than the 4 weeks previously described before they can apply and tolerate the Viaskin® patch for the full 24 hours daily.

In case of any suspected systemic reactions related to patch application (including cutaneous reactions distant from the sites of patch application), the Viaskin® patch should be removed immediately. A treatment can be given to treat the systemic or local reactions: topical corticosteroids, antihistamines, additional oral corticosteroids or similar anti-allergic drugs, as deemed necessary by the Investigator. **The next patch will only be applied the following day.**

The subject's parents/guardians will be instructed to contact the Investigator in case of systemic or intense or severe local reactions lasting for more than 1 day or any unexpected reactions during the treatment period, in particular in case of appearance of vesicles under the Viaskin® patch or close to the Viaskin® patch site application. It is then recommended that the parents/guardian take a photo of the back of the subject to document these intense or severe reactions.

Appearance of any vesicles (grade 4) or ulcerative skin lesions or any other significant skin lesion seen under the patch while the patch is still applied on the skin or upon removal of the patch which could potentially lead to skin barrier disruption at sites of Viaskin® patch applications will be cautiously managed and follow-up.

Children's parents or guardians will be instructed to take a photograph in case of appearance of any vesicles or ulcerative skin lesions. In these rare specific cases, subjects should transiently discontinue patch application and return to the site for evaluation and treatment of the wounded area, as well as for the next patch application and adequate evaluation and treatment of the wounded zone.

Upon re-application of the new patch, the subject should remain at the site for 1 hour before being discharged. The site must contact the subject's parents/guardians by phone the day after this visit to ensure that no additional local blisters or vesicles developed and to confirm that the treatment can continue normally. The zone with vesicles or severe lesions should not be used for patch application until it has completely healed.

5.2.2 Safety Precaution Information

A leaflet with safety precautions for using the Viaskin® patch and instructions to follow in case of any safety issue will be given to each parent's subject. This safety leaflet will specify at least the following information:

1. Instructions and procedures to apply the patch safely and correctly in the back of the subject;
2. Necessity to call the investigative site staff in case of intense or severe local reactions lasting for more than 1 day or any unexpected reactions during the treatment period, in particular any appearance of vesicles/blisters under the patch or close to the area of patch application and a recommendation to take photos of the site of application to document such a situation;

3. Necessity to call the investigation site staff in case of occurrence of chicken pox or measles. At the same time, interruption of patch application until recovery;
4. In case of active eczema extending on the back of the child: stop applying the patch until recovery from the active eczema on the back;
5. Anaphylaxis Emergency Action Plan in case of a suspected anaphylactic reaction and how to administer the epinephrine auto-injector to rapidly treat the reaction;
6. Subject stopping rules (subject are consequently withdrawn):
   a. Severe anaphylaxis (stage 3 anaphylaxis, see APPENDIX 4) related to Viaskin® patch application (either peanut or placebo patch);
   b. More than 2 intramuscular epinephrine injections for an AE related to Viaskin® patch application (either peanut or placebo patch), and not occurring during the DBPCFC nor related to an accidental food allergen consumption.

5.3 Packaging, Labeling and Storage

The IMP, Viaskin® patch (active and placebo), is manufactured until primary packaging stage (patch in pouch) by CCI. Each pouch will be labeled and packaged by CCI in accordance with Good Manufacturing Practices and applicable local regulatory requirements. The labeled treatment boxes will be dispensed to subjects at each visit, with enough quantity of Viaskin® patches to cover the period between 2 consecutive visits.

The labeled and packaged IMP must be stored in accordance with the Sponsor's instructions (below 25°C [77°F] and should not be frozen). Shipments from depots to clinical sites will be performed at refrigerated temperature between 2°C to 8°C [36°F to 46 F] with a temperature monitoring device.

Upon receipt of a shipment request via IWRS, the IMP will be shipped to the clinical site. The site pharmacist or any other staff member designated for this task will receive and store the IMP until the time of dispensing. Until dispensed by the Investigator to the subjects, the IMP will be stored in a securely locked area, accessible to authorized personnel only. At the end of the study, or at times designated by the Sponsor, and after complete accountability, the site pharmacist or the designated person will be responsible for preparing the return of the used (partially) and unused IMP to the IMP distributor. Destruction of IMP on-site is not allowed.

5.4 Blinding and Breaking the Blind

The study will be performed in a double-blind manner. Active and placebo DBV712 patches will be supplied in identical pouches and will be similar in physical appearance, thereby enabling double-blind conditions.

The treatment codes will be integrated to the IWRS. Investigators have the possibility to unblind a treatment via the IWRS in some specific cases (as detailed below). Further instructions for emergency code break will be provided in a separate IWRS User Guide.

The study blind should not be broken except in a medical emergency (where knowledge of the IMP received would affect the treatment of the emergency) or due to a regulatory requirement (for example for Suspected Unexpected Serious Adverse Reactions

[SUSAR]). The blind will only be broken at the discretion of the Investigator. All unblinding events will be recorded and reported by the IWRS to the Medical Monitor and the Sponsor. In case of IWRS failure, a backup system is operated 24 hours every day of the year enabling unblinding of treatment by calling the IWRS hot line (Please refer to IWRS User Guide).

If the blind is broken, the date, time, and reason must be recorded in the subject's source documents, in the electronic Case Report Form (e-CRF) and any associated AE must be reported.

If a subject (parents/guardians), is unblinded, this must be listed as major protocol deviation and the concerned subject(s) will be withdrawn from the study.

Serious unexpected suspected adverse reactions, which are subject to expedited reporting, will be unblinded before submission to the Regulatory Authorities.

The overall randomization code will be broken only for data analyses of study Part A or Part B, as follows:

- Part A data will be unblinded when the last subject from Part A will have completed the study, and
- Part B data will be unblinded when the last subject from Part B will have completed the study.

Unblinding will be performed when all final clinical data have been entered into the database and all data queries have been resolved, the e-CRF has been signed and locked, and the assignment of subjects to the analysis populations has been completed.

5.5 Drug Accountability

The Investigator is responsible for maintaining accurate IMP accountability records throughout the study. Each site will have to complete a site IMP accountability log and an individual IMP accountability log for each subject. These records should include the amounts and dates that IMP supplies were received on-site, dispensed to the subject, returned by the subject, and returned to IMP distributor (or destroyed on-site, if applicable).

Each dispensing of IMP will be performed via IWRS.

5.6 Compliance

It is the Investigators' responsibility to ensure that subjects' parents/guardians are correctly instructed on how to store and administer the IMP. Records of IMP used and intervals between visits will be kept during the study. Drug accountability will be monitored by CRO site monitor during site monitoring visits and at the completion of the study. Subjects' parents/guardians will be asked to return their unused IMP (boxes and patches) when they come back for their study visits. All unused IMP (boxes and patches) should be returned to the IMP distributor. The IMP should be dispensed by the Investigator, or by a qualified individual under the Investigator's supervision. An up-to-date drug accountability record must be maintained (see Section 5.5).

At each visit, prior to dispensing the IMP, previously dispensed IMP will be retrieved by the Investigator and compliance assessed. Compliance at each visit is to be calculated

taking into account the total number of patches applied since the last visit *versus* the number of days in that period of time. Subjects exhibiting poor compliance (below 80%) at any specific time point during the treatment period should be counseled on the importance of good compliance to the study dosing regimen.

Subjects who are persistently non-compliant will be withdrawn from the study (see Section 4.3).

5.7 Prior and Concomitant Medication

Any medication taken by the subject other than the IMP, including herbal and other non-traditional remedies, is considered as concomitant medication. Any medication used in the last 6 months or being administered at the time of screening is considered as prior medication.

At screening, children parents or guardians will be asked what medications the child has been taking during the last 6 months. At each subsequent study visit, children parents or guardians will be asked what concomitant medications the child is currently taking. All concomitant and prior medications must be recorded in the e-CRF.

The following information must be recorded in the e-CRF for each prior and concomitant medication: generic name, route of administration, start date, stop date, dosage, total daily dose, and indication. Any changes in the dosage or regimen of a concomitant medication must be recorded in the e-CRF.

Of note, prior or concomitant medication prescribed to a subject but not actually taken or administered should not be reported in the e-CRF, such as the epinephrine auto-injector prescribed for use in case of anaphylaxis but never injected intramuscularly.

5.7.1 Permitted Concomitant Medication

Application of a topical corticosteroid to treat any local condition (eczematous lesions, pruritus, edema, etc.) is permitted.

For local reactions to the Viaskin® patch, a topical medication (ointment, gel, cream) with 0.5% to 1% hydrocortisone or equivalent will be distributed to each randomized subject at discharge on Day 1. In case the 1% hydrocortisone topical medication is not sufficient to treat the local reaction, a topical medication containing a more potent corticosteroid can be prescribed and locally applied in accordance to the local approved indication of each product for the subject age class.

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

Oral antihistamines or oral corticosteroids must be washed out for the minimum period of time prior to the skin prick testing or to the food challenges (see Section 5.7.2 for detail on wash-out periods).

Intramuscularly injectable epinephrine (auto-injector EpiPen® or any other trade name available at the right dosage in the different countries) will be distributed to each parent or

guardian at discharge on Day 1 to be used in case of symptoms of anaphylaxis. The Investigator will explain to the parents/guardians when and how to inject the epinephrine according to the Anaphylaxis Emergency Action Plan. The intramuscularly injectable epinephrine will be replaced if used or if it expires. Any use of injectable epinephrine should be recorded as a concomitant medication.

All other treatments prescribed by the Investigator or any other physician to treat any conditions are also permitted. Medications that are not noted in the Section 5.7.2 are also permitted.

5.7.2 Prohibited Prior and Concomitant Medication

Prohibited prior and concomitant medications as outlined in the exclusion criteria (Section 4.2) are the following:

- Moderate daily dose of inhaled corticosteroid or higher (i.e. ≥2 times "low dose"; see APPENDIX 8), treatment with a combination therapy of inhaled corticosteroid with a long-acting inhaled β2-agonist, or with a combination therapy of inhaled corticosteroid and leukotriene receptor antagonist are prohibited. Daily low dose of inhaled corticosteroid, and short course of inhaled corticosteroid indicated for treating either intermittent asthma or bronchitis are permitted,
- Corticosteroids prior to Visit 1:
  - Two or more systemic corticosteroid courses within 3 months prior to Visit 1 for any indication,
  - 1 systemic corticosteroid course within 4 weeks prior to Visit 1 for treating a diagnosed asthma,
  - Any systemic long-acting corticosteroids within 2 weeks prior to Visit 1 for any indication,
  - Any systemic short-acting/intermediate-acting corticosteroids for more than 3 days within 2 weeks prior to Visit 1 for any indication.
- β-blocking agents, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, calcium channel blockers or tricyclic antidepressant therapy, during the screening period or during study participation,
- Anti-tumor necrosis factor drugs or anti-IgE drugs (such as omalizumab) or any biologic immunomodulatory therapy are prohibited if taken within 1 year prior to Visit 1, during screening period or during study participation,
- Cyclosporine or other immunosuppressive agents are prohibited if used within 1 year prior to Visit 1, during the screening period or during the study participation. Topical calcineurin inhibitors are permitted,
- Any prior or concomitant immunotherapy administered to any food (for example EPIT or OIT or SLIT or specific oral tolerance induction). A prior prematurely discontinued OIT (i.e., subject treated less than 1 month) which ended at least 3 months before Visit 1 is permitted,
- Any aeroallergen immunotherapy administered during study participation.

Before the first day of DBPCFC:

The minimal washout period for short and long acting antihistamines (refer to APPENDIX 3) and long-acting β2-agonists (36 hours prior to the DBPCFC) will have to be respected. Regarding systemic corticosteroids, the following minimal wash-out period will be applied:

- Subjects should not have received any course of systemic short-acting/intermediate-acting corticosteroids of more than 3 days within 2 weeks of the DBPCFC, or any course of systemic long-acting corticosteroids within 2 weeks of the DBPCFC. In this case, the DBPCFC should be delayed to allow for 2 weeks of corticosteroid wash-out.
- In case the subject has received a systemic corticosteroid for asthma before the DBPCFC, the food challenge should be delayed to allow for 4 weeks of wash-out.
- If a subject has a reaction during the first day of the DBPCFC that requires treatment with systemic corticosteroids, the subject has to wait at least 3 days before performing the second day of the DBPCFC.

6 VARIABLES AND METHODS OF ASSESSMENT

The efficacy, safety and exploratory endpoints are listed in Section 3.3. The Schedule of Procedures is provided in page 15.

6.1 Efficacy Variables

6.1.1 Response to Treatment – DBPCFC to Peanut

The DBPCFC to peanut will be performed at study entry and post-treatment at Month 12 in order to assess the primary efficacy endpoint (difference between percentage of treatment responders in the selected active DBV712 group [250 µg] compared to the placebo group), as well as the secondary and other efficacy endpoints (see Section 3.3.1).

The DBPCFC is the gold standard to diagnose and assess food allergy. The challenges will be conducted over 2 days; the child will be gradually fed increasing amounts of standardized blinded oral formulas containing either peanut proteins during one of the two days of the challenge, or without any peanut proteins during the other day of the challenge, or vice versa. Challenges must take place under direct medical supervision in a hospital/clinic setting with resuscitation equipment and emergency medications and trained staff immediately available. An intravenous (IV) line can be established prior to the challenge when judged necessary by the Investigator. In that case, a local anesthetic cream could be used prior to establishing the IV line. If a site prefers to have the subjects come to the hospital the day before the conduct of the DBPCFC, to get them ready for the following day, this is allowed and will not be considered an SAE.

If the subject has a concomitant disease such as a rhinitis, bronchitis, gastrointestinal infection, or acute asthma flare-up, which temporarily contra-indicates the performance of the DBPCFC, the test will be postponed until at least 7 days after recovery.

Subjects should wash out any antihistamines for the minimum period of time specified in the table in APPENDIX 3 prior to performing the DBPCFC.

Subjects will not be allowed to use long-acting β2-agonists within 36 hours prior to the DBPCFC. Subjects should not have received any course of systemic short-acting/intermediate-acting corticosteroids of more than 3 days within 2 weeks of the DBPCFC, or any course of systemic long-acting corticosteroids within 2 weeks of the DBPCFC. In these cases, the DBPCFC should be delayed to allow for 2 weeks of wash-out (in case the subject has received a systemic long-acting corticosteroid for asthma before the DBPCFC, the food challenge should be delayed to allow for 4 weeks of wash-out). If a subject has a reaction during the first day of the DBPCFC that requires treatment with systemic corticosteroids on the first day, the subject has to wait at least 3 days before performing the second day of the DBPCFC.

The subject may have a light breakfast and may drink water at home at least 2 hours before starting the DBPCFC at the site. During the conduct of the challenge, drinking a sip of water to help swallow the formulas is allowed, but eating is not allowed. Apple sauce will be given to the subjects during the challenge after each dose from the third dose (10 mg) onwards to improve the acceptability of the food challenge formulas and prevent undue discomfort due to hunger, considering the prolonged fasting required by the procedure in these young children. If apple sauce is not given to the subjects at screening, it should not be given during the DBPCFC at Month 12. A defined apple sauce formulation will be used by all the centers and the amount of apple sauce administered will be standardized and limited so that it does not interfere with the subject's willingness to ingest the food challenge formula. After the last dose of the challenge formula is administered, the medical staff should wait at least 1 hour before feeding the subject with any other food and/or water. This first feeding should be light.
A detailed and study-specific Manual of Procedures for the conduct of the DBPCFC will be provided to the Investigators, the site staff and the unblinded study-trained person responsible for reconstituting the food challenge formulas. Of note, the amounts of apple sauce to be administered are specified in the Manual of Procedures. When needed, updated versions will be made available. An outline of the procedures is specified below.

6.1.1.1 Preparation of Peanut protein and Placebo Formulas

Standardized formulas, centrally produced by CCI [redacted], and packed and released by CCI [redacted], will be distributed to all participating centers for the DBPCFC. One of the formulas will be peanut protein-free (placebo) and the other one will contain peanut proteins. An unblinded person identified at each site by the investigator, specifically trained to reconstitute the formulas in the study and not involved in the challenge itself will be responsible for the preparation, adequate labeling and blinding of the pots containing the prepared/hydrated formulas. The blinded pots will then be handed to the medical team to perform the challenge.

6.1.1.2 Time Interval and Doses

The order of the formulas to be consumed during the first and the second day of the DBPCFC will be pre-determined at random. The unblinded study-trained person will prepare the formula using a specific randomization list provided to her/him for this purpose. Other members of the site staff (for example the Investigator, study coordinators, and study nurses), the subject/parents/guardians will remain blinded to the order of

consumption until the end of the second day of the DBPCFC. Up to 7 days (1 week) between the 2 days of the DBPCFC will be permitted. The 2 days of the DBPCFC may be 2 consecutive days, but not the same day.

The challenge will consist in giving doses of peanut protein or placebo in gradually increasing doses at 20-minute intervals (refer to section 6.1.1.3 for more details).

The starting dose is 1 mg of peanut protein for the entry/screening DBPCFC as well as the post-treatment DBPCFC; the maximum dose is 300 mg of peanut protein for the entry/screening DBPCFC and 2,000 mg for the post-treatment DBPCFC.

The peanut protein dose increments for the entry/screening DBPCFC are:

1 mg, 3 mg, 10 mg, 30 mg, 100 mg and 300 mg.

The entry/screening DBPCFC challenge is capped at 300 mg as the maximum dose, regardless of whether a reaction occurred or not.

The peanut protein dose increments for the post-treatment DBPCFC are:

1 mg, 3 mg, 10 mg, 30 mg, 100 mg, 300 mg, 1,000 mg and 2,000 mg.

6.1.1.3 Entry/screening DBPCFC

Subjects who have not had an IgE-mediated reaction leading to stopping the DBPCFC at ≤300 mg peanut protein will be considered not sensitive enough and thus ineligible for this study. Hence, the entry/screening DBPCFC is stopped after the 300 mg dose of placebo or peanut has been dispensed on both days; even if there have been no reactions meeting the challenge stopping criteria.

Subjects will receive one formula (placebo or peanut) on the first day and the other formula (peanut or placebo) on the second day. All subjects will undergo both days of the DBPCFC.

If the subject reacted severely or seriously during the first day of the challenge (i.e. need for intubation, hypotension persisting after epinephrine administration, and/or the need for ≥3 doses of epinephrine), the nature of the administered formula will be highly suspected to be the peanut-containing formula. In this rare case and only **in this case only,** the second day of the DBPCFC cannot be performed. The blind on the formula will be opened at the end of the first day to confirm that the subject actually received the peanut formula.

At the end of the second day of challenge, the sequence of the two formulas will be unblinded and revealed to the medical staff by the unblinded person responsible for reconstituting the formulas and the results of the challenge will be established following the decision-making algorithm below:

1. The subject had IgE-mediated symptoms meeting the challenge stopping criteria to the placebo formula at any dose of the challenge. She/he cannot be randomized in the study;
2. The subject had no IgE-mediated symptoms meeting the challenge stopping criteria during the 2 days of the DBPCFC, neither to the placebo nor to the peanut formulas, even at the 300 mg dose of peanut protein. She/he cannot be randomized in the study;
3. The subject had no symptom meeting the challenge stopping criteria when receiving placebo but had symptoms meeting these criteria at one of the doses of the peanut formula consumed between 1 mg and 300 mg inclusive.

The following should be considered to stop the challenge and to dermine the ED:

• **Objective symptoms and/or** • **Moderate abdominal pain with decreased activity associated with other objective symptoms according to APPENDIX 5 and/or** • **Severe and/or persistent abdominal pain with significant change in behavior** (other subjective symptoms will be graded but will not count in the stopping rules of the challenge)	+	**Treatment required** (choice of type of treatment left to the decision of the Investigator)	=	**Stop the challenge**

The Oral Food Challenge Symptom Score Sheet described in APPENDIX 5 will be used to score the severity of each pre-specified objective and subjective symptoms. This scoring is classified under the 5 categories:

I Skin (Pruritus, Urticaria, Angioedema, Erythematous Rash)
II Upper respiratory/Occular (Sneezing/Itching, Nasal Congestion, Rhinorrhea, Laryngeal, Conjunctivitis)
III Lower Respiratory (Wheezing)
IV Gastrointestinal (Subjective Complaints, Objective Complaints)
V Cardiovascular/Neurologic (hypotension/collapse/unconsciousness).

More specifically, the food challenge must be stopped if the following occurs and requires treatment:

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

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

*"Laryngeal" refers to laryngeal oedema symptoms, and must be differenciated from other causes of cough such as transient pharyngeal irritation or lower respiratory symptom (e.g., cough due to bronchospasm). Causes of cough other than laryngeal oedma symptoms will be documented as "other symptom" in the eCRF, and specified in the free textbox. Transient laryngeal irritation will not be considered as an objective OFC symptom and will not be considered in the stopping rules.

**For emesis/vomiting, the symptoms may result from two different situations: vomiting/spitting-up during the feeding, resulting from subjective intolerance to the food formula or vomiting/emesis resulting from a gastrointestinal allergic reaction to the peanut allergen, usually delayed from the feeding. Only the second situation will be considered as an objective OFC symptom and will be considered for the stopping rules.

***Cardiovascular symptoms: hypotension or cardiovascular failure directly related to the systemic allergic reaction. They have to be differenciated from similar symptoms related to another cause, such as a dizziness induced by vomiting.

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

≥ 1-point rise for at least 1 following symptom (i.e. mild, moderate or severe)		**≥ 2-point rise for at least 1 following symptom (i.e. moderate or severe)**
○ Urticaria ○ Angioedema ○ Rash	**AND**	○ Sneezing/Itching ○ Nasal Congestion ○ Rhinorrhea ○ Conjunctivitis ○ Abdominal complaints
OR		
≥ 2-point rise (i.e. moderate or severe)	**AND**	**≥ 2-point rise for at least 1 following symptom (i.e. moderate or severe)**
○ Pruritus		○ Sneezing/Itching ○ Nasal Congestion ○ Rhinorrhea ○ Conjunctivitis ○ Abdominal complaints
OR		
≥ 2-point rise (i.e. moderate or severe)	**AND**	**≥ 2-point rise for at least 1 following symptom (i.e. moderate or severe)**
○ Abdominal complaints		○ Sneezing/Itching ○ Nasal Congestion ○ Rhinorrhea ○ Conjunctivitis ○ Pruritus

For each peanut protein dose step, the consumption must be carried out as fast as possible, not exceeding 30 minutes between the start and end of dose ingestion.

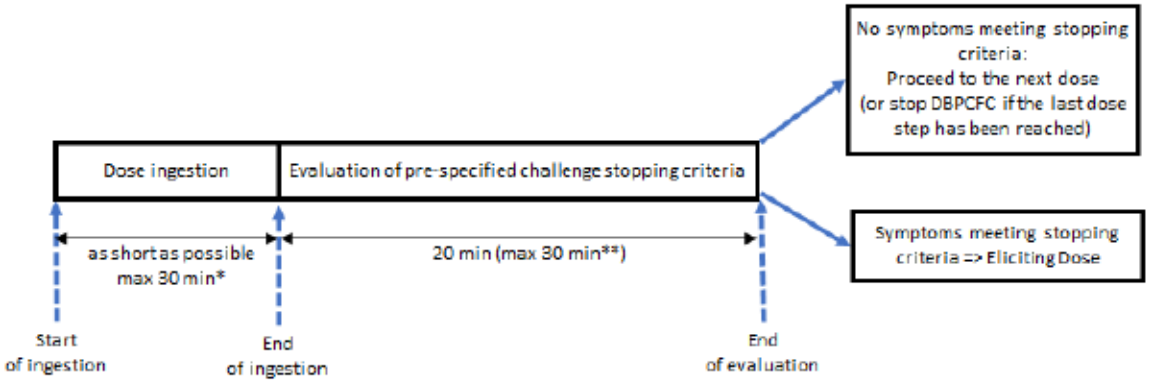
The evaluation of prespecified challenge stopping criteria must be carried out imperatively within a 20-minutes period after the dose has been completely ingested (i.e., 20-minute period starting from the end of dose ingestion):

- If no symptoms meeting the stopping criteria are observed within this 20-minute period, the Investigator must proceed immediately to the administration of the next ascending dose (or stop the DBPCFC if the last dose step has been reached);
- If there is a doubt on a possible development of symptoms meeting stopping criteria at the end of the 20-minute period, the Investigator may excercise his/her clinical judgement and extend the evaluation period to an additional 10 minutes (not exceeding 30-minute evaluation period overall, starting from the end of dose ingestion). If the emerging symptoms have not met the stopping criteria at the end of the additional evaluation period, the Investigator must proceed to the administration of the next ascending dose (or stop the DBPCFC if the last dose step has been reached). However, the administration of the next dose may be

administered more slowly, not exceeding 30 minutes between the start and end of dose ingestion.

- The repetition of a same dose step will not be allowed during DBPCFC. If there are no symptoms meeting the stopping criteria after a maximum of 30-minute evaluation, the Investigator must proceed to the next ascending dose, or must stop the Food Challenge if the last dose step has been reached.

The procedure is schematized below:



* A slower administration (not exceeding 30 minutes) may be possible if emerging symptoms (not meeting stopping criteria) occurred at the end of the evaluation period of the previous dose.
** In case of emerging symptoms at the end of the 20-minute period, evaluation can be extended to an additional 10 minutes (not exceeding 30 minutes overall).

Further details are provided in the study-specific Manual of Procedures for the DBPCFC that will be provided to the sites.

The dose that triggers symptoms meeting the stopping rules will be considered as the ED.

As a safety precaution, the symptoms signaling the end of the DBPCFC will be treated. The choice of type of medication to be used will be left to the Investigator's judgment.

The Investigator and medical staff will use their own clinical judgment for the most effective treatment considering the subject's age, the type of allergic reactions and their severity. Also refer to the recommendations made by Sampson et al. for treating anaphylaxis (39).

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

Should epinephrine need to be administered, it should be injected intramuscularly in the anterolateral thigh using auto-injectors commercially available in each specific site/country or using weight-appropriate doses of epinephrine in a standard syringe. Weight-appropriate doses of epinephrine in a standard syringe should be used in children who weigh less than 15 kg. Intravenous epinephrine should NOT be considered at the investigative sites to treat the reactions.

Subjects will be kept under observation for an additional 3 hours after the ingestion of the last dose of the challenge formula. Based on the Investigator's judgment, the observation period could be extended beyond the first 3 hours to ensure that all symptoms have subsided before the subject is discharged. For instance, an overnight stay may be considered necessary by the Investigator if the symptoms have not completely resolved

within the 3 hours or if the symptoms have been severe or serious and require longer observation periods.

Complete information for all reactions will be reported first in source documents then in the e-CRF, along with FC doses given, symptoms observed and their highest grades, time of appearance of the symptoms and Investigator's assessment of the ED.

6.1.1.4 Post-treatment DBPCFC to Peanut at Month 12

The DBPCFC at Month 12 is conducted following exactly the same procedures as for the entry/screening DBPCFC (refer to the Manual of Procedures for the conduct of the DBPCFC). However, it is not stopped at the 300 mg dose but will be continued up to the last dose of 2,000 mg peanut protein or until reactions leading to stopping the DBPCFC occur.

The patch should be removed before performing the DBPCFC and a new patch should be applied at the end of the DBPCFC (i.e. at the end of the 3-hour observation period).

The same instructions provided above to stop the challenge at the entry challenge will be followed to stop the post-treatment challenge.

If the subject was not fed apple sauce at the entry/screening DBPCFC, then apple sauce should not be administered with this food challenge either.

Food Challenges to other food allergens (besides peanut) may be conducted during the study if medically justified, and only if performed in the context of a diagnosis or for confirming a desensitization. Whether the subject's medical condition is still compatible with their participation in the study should be assessed by the Investigator and the Sponsor's medical monitor, before the food challenge is performed. If not compatible, the Sponsor may decide to discontinue the subject from the study. Importantly, the initiation of immunotherapy to any food allergen remains prohibited during the participation in the study (See Section 5.7.2). The patch should not be applied on the day of a food challenge and until all procedures are completed.

6.2 Safety Variables

6.2.1 Adverse Events

Coding of AEs will be performed as described in Section 9.7.

6.2.1.1 Collection of Adverse Events

It is the responsibility of the Investigator to collect all AEs (both serious and non-serious) derived by spontaneous, unsolicited reports of subjects, by observation and by routine open questionings, for example "How have you felt since I last saw you?". Adverse events will also have to be recorded by the parents/guardians in the subject diaries (see Section 6.2.5).

The occurrence of the following AEs/symptoms will be specifically solicited:

- Pre-specified symptoms of local reactions at application site (itching, redness, swelling), by means of the subject diaries (during the first 6 months for part A, and during the whole treatment duration for part B; See also Section 6.2.5 regarding the rules of AEs reporting of these pre-specified local symptoms).

- Specific application site reactions and systemic events of a potential allergic nature (regardless of causal relationship with the IMP) will also be solicited at each study visit and phone contact for part B only (see Table 1).

Table 1: List of Solicited Adverse Events (Applicable for Part B Only)

Application site reactions	Systemic events of a potential allergic nature
• Pruritus • Erythema • Oedema • Urticaria • Hyperpigmentation • Eczema • Excoriation (erosion) • Ulceration • Blister (vesicles) • Grade 4 patch site reactions (erythema with vesicles) • Pain under the patch	• Asthma aggraviation/exacerbation • Hives • Eyelid oedema • Allergic contact conjunctivitis • Lip swelling • Angioedema

6.2.1.2 Definitions

An AE is any untoward medical occurrence that occurs in a subject or clinical investigation subject administered a pharmaceutical product, and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product.

All AEs, including intercurrent illnesses, occurring during the study will be documented in the e-CRF. Concomitant illnesses, which existed before entry into the study, will not be considered AEs unless they worsen during the treatment period. All AEs, regardless of the source of identification (for example physical examination, laboratory assessment, electrocardiogram [ECG], reported by subject), must be documented.

Pre-existing conditions will be recorded in the e-CRF on the Medical History or appropriate page.

Adverse events due to DBPCFC will also be recorded in the e-CRF but will be analyzed separately.

6.2.1.3 Assessment of Adverse Events

Each AE will be assessed by the Investigator with regard to the following categories.

6.2.1.3.1 Seriousness

An SAE is defined as any untoward medical occurrence that at any dose:

- Results in death;
- Is life-threatening; This means that the subject is at risk of death at the time of the event; it does not mean that the event hypothetically might have caused death if it were more severe

Note: Whereas a systemic anaphylactic reaction is generally considered potentially life-threatening, not all anaphylaxis put the subjects at immediate risk of death, if for example appropriate treatments lead to symptoms reduction or disappearance. As per the Anaphylaxis Staging System (APPENDIX 4), an anaphylaxis assessed as mild or moderate should not be classified as life-threatening.

- Requires hospitalization (at least overnight stay or inpatient hospital admission) or prolongation of existing hospitalization;

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

1. Evaluation or treatment of a pre-existing (before informed consent signature) and non-exacerbating condition:
    a. The condition existed prior to the subject's entry into the study and has been recorded in the subject's disease/medical history and the e-CRF *AND*
    b. The condition has not worsened in severity or frequency during the subject's exposure to the IMP *AND*
    c. The condition has not required a change in treatment management during the subject's exposure to the IMP;
2. Hospitalization the day prior to or after the day of DBPCFC for practical reasons and without fulfilling any other seriousness criterion.

- Results in persistent or significant disability or incapacity (an AE is incapacitating or disabling if it results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions).;
- Is a congenital anomaly or birth defect;
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but that may jeopardize the subject or require intervention to prevent one of the above outcomes. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.
    - An anaphylactic reaction classified as severe using the Anaphylaxis Staging System in APPENDIX 4 (i.e., anaphylactic reaction with cyanosis or SpO2 ≤92%, hypotension with >20% drop in blood pressure, confusion, collapse, loss of consciousness) or requiring 3 or more epinephrine intakes should be reported at least with the seriousness criterion "important medical event";

- In the context of the DBPCFC, in addition to the severe anaphylaxis, the occurrence of:
  - Bronchospasm/audible wheezing with use of accessory muscles,
  - Severe angioedema
  - Admission in Intensive Care Unit and/or requirement of oxygen therapy
  - Intake of 3 or more doses of epinephrine

  should be considered as meeting the seriousness criterion of "important medical event"

Medical and scientific judgment should be exercised in deciding whether a case is serious and whether expedited reporting is appropriate.

6.2.1.3.2 Severity

The severity of each AE must be assessed by the Investigator using 1 of the following categories, and recorded in the e-CRF:

- Mild: The AE was transient and easily tolerated by the subject;
- Moderate: The AE caused discomfort and interference with the subject's general condition;
- Severe: The AE caused considerable interference with the subject's general condition and may have been incapacitating.

Anaphylaxis (including those reported as part of Medical History) will be graded in accordance to the Anaphylaxis Staging System (APPENDIX 4).

6.2.1.3.3 Causality

The Investigator will assess the causality/relationship between the IMP and the AE and record that assessment in the source documents and in the e-CRF.

The most likely cause of an AE/SAE (for example disease under treatment, concomitant disease, concomitant medication, other) will be indicated in the e-CRF with details of the concomitant disease or medication or other cause.

The causal relationship of the AE to IMP will be described in terms of:

- Related: the AE:
  - Follows a clear temporal sequence from application of the IMP.
  - Has no other possible explanations, such as the subject's clinical state, environmental or toxic factors or other therapies administered to the subject.
  - Disappears or decreases on cessation or reduction in dose of the IMP.
  - Follows a clear pattern of response to the IMP.
  - Reappears or worsens upon rechallenge.

- Probable: the AE:
  - Follows a reasonable temporal sequence from application of the IMP.
  - Could not be reasonably explained by the subject's clinical state, environmental or toxic factors or other therapies administrated to the subject.
  - Disappears or decreases on cessation or reduction in dose of the IMP.
  - Follows a known pattern of response to the IMP.
  - Reappears or worsens upon rechallenge.
- Possible: the AE:
  - Follows a reasonable temporal sequence from application of the IMP.
  - Could be reasonably explained by the subject's clinical state, environmental or toxic factors or other therapies administrated to the subject.
  - Follows a known pattern of response to the IMP.
- Unlikely: the AE
  - Does not follow a reasonable temporal sequence from application of the IMP.
  - Could be reasonably explained by the subject's clinical state, environmental or toxic factors or other therapies administrated to the subject.
  - Does not follow a known pattern of response to the IMP.
  - Does not reappear or worsen upon rechallenge.
- Not related:
  - The AE does not meet the above criteria.
  - There is sufficient information that the etiology of the AE is not related to the IMP.

All SAEs assessed as related, probably related, and possibly related will be considered as related for expedited reporting (see Section 6.2.1.5).

The study conduct relatedness for SAEs will also be assessed and documented.

6.2.1.3.4 Local Skin Reactions

The incidence, duration and maximum severity of skin reactions induced by the IMP will be reported by the subject' parents/guardians in the diary. Photos of these local reactions should be taken at home by the parents/guardians. Additionally, the Investigator or delegated trained staff, including but not limited study nurses and physician assistants, will assess the severity of local skin reactions induced by the IMP at each site visit during the physical examination and photos should be taken during the site visits by the medical staff to document these local skin reactions (see Sections 6.2.4 and 6.2.6).

In addition, any occurrence of specific application site reaction will also be solicited at each study visit and phone contact among a pre-specified list of symptoms (see Section 6.2.1.1).

6.2.1.3.5 Adverse Events of Special Interest

Adverse Events of Special Interest (AESI) to the Sponsor are defined as follows:

Local AESI: Any reaction at patch application site which could potentially lead to a skin barrier disruption, such as but not limited to, blister, vesicle, ulcerative skin lesion, bleeding or any Grade 4 patch site reaction.

Skin reactions will be examined at the time points specified in the Schedule of Procedures (page 15) according to grading in Table 3 (Section 6.2.6). Subject's parents/guardians will be instructed to take a photograph in case of appearance of any vesicles or ulcerative skin lesions. In these rare specific cases, subjects should transiently discontinue patch application and return to the site for evaluation and treatment of the wounded area, as well as for the next patch application and adequate evaluation and treatment of the wounded zone.

Upon re-application of the new patch, the subject should remain at the site for 1 hour before being discharged. The site must contact the subject's parents/guardians by phone the day after this visit to ensure that no additional local blisters or vesicles developed and to confirm that the treatment can continue normally. The zone with vesicles or severe lesions should not be used for patch application until it has completely healed.

Local AESI should NOT be reported on the specific AESI form of the eCRF. This specific AESI form is only to be used for systemic AESI (see below).

Systemic AESI: Any acute systemic immediate allergic reactions (rapid onset) after exposure to a known or suspected allergen regardless of the causal relationship to the IMP, and occurring outside the DBPCFCs:

1. Anaphylactic reaction:
    - Any AE diagnosed by physician as an anaphylactic reaction, regardless of the severity and causal relationship to the IMP.
    - Anaphylactic reaction defined as the occurrence of the following allergic symptoms:
        - Major acute allergic reaction (associated or not with other symptoms): acute hypotension (>20% drop in blood pressure) or associated cardiovascular symptoms (hypotonia, confusion, loss of consciousness, collapse, syncope, incontinence);
        - 2 or more concomitant acute allergic symptoms from at least 2 different organ systems such as, but not limited to:
            - Upper airway or respiratory symptoms (dyspnea, wheeze-bronchospasm, stridor, hypoxemia, decreased SaO_2)
            - Acute and persistent gastro-intestinal symptoms (abdominal pain, cramps, vomiting)
            - Acute skin or mucosal tissue symptoms (angioedema, urticaria, pruritus, flush, swollen lips-tongue-uvula)
            - Acute cardiovascular symptoms (hypotonia, reduced blood pressure)
2. Any systemic hypersensitivity reaction leading to epinephrine intake

Any AE fulfilling the above definition must be ticked as an AESI in the AE form of the eCRF. In addition, these AESI must be documented and reported on a specific systemic AESI form by the Investigator on an ongoing basis (guidance and precisions will be given

in the eCRF Completion Guidelines). These specific systemic AESI forms must be completed and sent by the investigator within 24 hours of the site becoming aware of the event.

Potential anaphylactic reactions will be identified by dedicated Standardized MedDRA Queries (SMQ) algorithms. Cases retrieved by the algorithm will then be confirmed by medical review.

6.2.1.3.6 Symptoms during to the Double-blind, Placebo-Controlled Food Challenge

The severity of the objective and subjective symptoms elicited during the entry and post-treatment DBPCFC will be assessed by the Investigator. These objective and subjective symptoms assessed by the Investigator will not be reported as single independent AE in the AE pages of the e-CRF. Complete information for all these symptoms will be reported in the DBPCFC pages of the e-CRF, along with all peanut protein doses given, the symptoms observed, the time of appearance of the symptoms and their specific grades, the time of grade change of each symptom, the doses of epinephrine given, the doses of corticosteroids and antihistamines given and the Investigator's assessment of the peanut ED as well as the peanut cumulative dose. If, as per the Investigator's judgment, the combination of all these symptoms resulted in an anaphylaxis requiring a prolonged (minimally overnight) hospitalization, then this will be considered an SAE. Any such SAE with its specific verbatim (e.g. 'during food challenge' or 'due to food challenge') must be reported in the AE pages of the e-CRF.

6.2.1.4 Recording Adverse Events

Adverse event reporting will start at the signature of the informed consent form (ICF) and end after the 2-week follow-up period (Visit 12: End of Study Visit).

During the screening period (that is, from the time of ICF signature through Day-1), only SAEs will be recorded in the e-CRF; and AEs that do not meet any seriousness criteria will only be documented in the subject's source documents.

Adverse events occurring after the end of the study should be reported to the Sponsor by the Investigator if the Investigator considers that there is a causal relationship with the IMP.

Adverse events still ongoing at the time of the End of Study Visit will be followed up for an additional 30 days, or until they resolve or stabilize, whichever comes first.

All AEs occurring on or after the day of the first dose of IMP, regardless of the relationship to the IMP, will be recorded in the e-CRF.

All AE reports in the e-CRF should contain the following information of the event: date and time of onset, date and time of resolution, severity, treatment required, relationship to IMP, action taken with the IMP, outcome, and whether the event is classified as serious or not.

6.2.1.5 Reporting Serious Adverse Events and AESI of allergic systemic reaction

- All SAEs must be reported within 24 hours of the site becoming aware of the event by filling in the SAE pages in the e-CRF. In case of technical issues with the e-CRF, the reporting can be done by sending a completed SAE Report Form to the DBV Global Safety and Pharmacovigilance team at the email address indicated on

the SAE Report : CCI [redacted] This mailbox is monitored for any incoming SAE report.

The minimum information required for an initial report is:

- Name of person sending the report (that is name and address of Investigator);
- Subject identification (screening number, NOT the subject's name);
- Protocol number;
- Description of the SAE including a comprehensive verbatim term;
- Causality assessment.

However, as far as possible all points in the SAE pages in the e-CRF (or on the SAE Report Form, in case of technical issues with the e-CRF) should be covered in the initial report. If an SAE occurs during the DBPCFC, the verbatim of the SAE must specify "during the DBPCFC" or "due to the DBPCFC" both on the SAE Report Form and in the SAE pages of the e-CRF.

- Treatment emergent systemic AESIs defined in the e-CRF Completion Guidelines provided to the Investigator and regardless of their causal relationship to the IMP must also be reported within 24 hours of the site becoming aware of the event, by filling the systemic AESI specific report form in the e-CRF. In case a systemic allergic reaction is associated with a seriousness criteria, an SAE report form must be completed instead.

Sponsor will either directly or through contracted service providers submit expedited and periodic reports to both Competent Authorities and Ethics Committees as per regulations and procedures in force, taking into account local specific requirements.

SAEs that are both related (according to the sponsor and/or the investigator) to investigational medicinal product and unexpected (according to sponsor and based on the investigational product Reference Safety Information in use) will usually be assessed as reportable by the Sponsor to Competent Authorities.

Waiver to expedited reporting:

In case an anaphylactic reaction is experienced during the DBPCFC and assessed as serious by the investigator, this event should be reported within 24 hours of awareness by the investigational site as for other SAEs. Allergic reactions are voluntarily triggered by an "allergen" protein matrix (placebo matrix or "allergen" protein matrix) during the DBPCFC procedures and anaphylaxis are elicited events. These anaphylactic reactions will be considered as expected, if not leading to death (See APPENDIX 9 for Reference Safety Information related to DBPCFC peanut protein matrix). Serious anaphylactic reactions assessed as related to the DBPCFC will not be subject to expedited reporting, unless they lead to death.

6.2.1.6 Follow-up of Adverse Events

All AEs experienced by a subject, irrespective of the suspected causality, will be monitored until the AE has resolved, any abnormal laboratory values have returned to baseline or stabilized at a level acceptable to the Investigator and Medical Monitor, until there is a

satisfactory explanation for the changes observed, until the subject is lost to follow-up, or until the subject has died.

6.2.1.7 Treatment of Overdose of Study Medication

Overdose is defined as **the concomitant application** of 2 Viaskin® patches or more on the skin of the subject, whatever the duration of the concomitance of the multiple patch application.

One patch applied the same day after the previous patch was removed or has fallen off is NOT an overdose.

No specific treatment for overdosing is known. The first action will be to remove any additional patch from the skin, leaving only 1 patch on the skin. Treatment given to a subject in case of overdosing should be symptomatic and supportive.

All overdose cases should be reported in the subject's e-CRF.

Any case of overdose, even if it is not associated with any AE, should be recorded in the AE section of the e-CRF. Any AEs/SAEs associated with the overdose should be reported in the corresponding e-CRF section.

6.2.2 Laboratory Variables

Laboratory assessments will be performed by a central laboratory, as identified in the List of Study Personnel.

Venous blood samples will be taken for hematology and biochemistry testing.

The following laboratory variables will be determined in accordance with the Schedule of Procedures (page 15):

- Hematology: Complete blood count: hemoglobin, hematocrit, platelets, red blood cells, white blood cells with differential cell count;
- Biochemistry: alanine aminotransferase, aspartate aminotransferase, total bilirubin, total protein, blood urea nitrogen, creatinine;

Details of the procedures to be followed for sample collection, storage, and shipment will be documented in the Laboratory Manual.

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

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

The blood volume drawn for all the blood analyses (hematology, biochemistry, immunological markers, epigenetic analyses and BAT) equals to 7.5 mL (8.5 mL in US sites eligible for BAT) for each of the 4 blood samplings taken along the study. The total blood volume for the 12-month duration of the study is 30 mL (34 mL for US sites eligible for BAT). Additional and repeat laboratory safety testing outside the study may be performed at the discretion of the Investigator.

6.2.3 Vital Signs

The following vital signs will be assessed in accordance with the Schedule of Procedures (page 15):

- Blood pressure (systolic and diastolic; mmHg),
- Heart rate (beats per minute),
- Respiration rate (breaths per minute).

Systolic blood pressure and diastolic blood pressure will be measured in sitting position on the same arm after the subject has been resting.

Heart rate will be recorded simultaneously with blood pressure measurements, followed by respiratory rate.

During the study, the measurement of vital signs may be repeated at the discretion of the Investigator for safety reasons. Clinically relevant abnormal findings will be reported as AEs.

Vital signs must be assessed before the DBPCFC. Additional assessments can be repeated during the DBPCFC procedure on both days at any time if judged necessary by the Investigator.

6.2.4 Physical Examinations

Physical examinations will be performed in accordance with the Schedule of Procedures (page 15).

Physical examinations will be performed by a physician or delegated staff properly trained to perform such examination, including but not limited to study nurses and physician assistants, and will include the following:

- General appearance,
- Head, ears, eyes, nose and throat,
- Neck,
- Complete skin examination,
- Cardiovascular system,
- Respiratory system,
- Abdominal system,
- Nervous system,
- Body weight (kg),
- Height (cm).

Body weight will be measured without shoes, jacket, or diaper and per Schedule of Procedures and as frequently as necessary.

Height will be measured without shoes and per Schedule of Procedures and as frequently as necessary for this population of subjects in active growth.

For each body system, an assessment of normal or abnormal will be recorded in the e-CRF at screening and the abnormality will be documented. Besides, the skin aspect will be graded for the sites of patch application (see Section 6.2.6).

Physical examinations must be performed before the DBPCFC. Additional assessments can be repeated during the DBPCFC procedure on both days at any time judged necessary by the Investigator.

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

6.2.5 Subject Diaries

Subject diaries will be provided to each subject's parent/guardian to report specific information between visits as follows: subjects' parents/guardians will be asked to record on a daily basis in the diaries the time of application and removal of each Viaskin® patch, along with the reason for any early removal (should that occur). They will also record the grade of any observed local skin reactions to the Viaskin® patch (grading scale 0 to 3, none, mild, moderate or severe).

Definitions of the grading of each symptom are provided in the diary as presented in Table 2.

Table 2: Grading of Local Skin Reactions by the Parents/Guardians

Grade Local	Itching Local	Redness Local	Swelling
1 = Mild	Itching easily bearable, painless, occasional scratching localized under the Viaskin® patch areas.	Mild redness (pale pink) localized under the Viaskin® patch areas.	Swelling localized under the Viaskin® patch areas.
2 = Moderate	Itching with intermittent scratching, possibly up to 2 minutes each localized under the Viaskin® patch areas.	Redness more intense (brighter pink to red), and/or redness extending beyond the Viaskin® patch areas.	Swelling extending beyond the Viaskin® patch areas.
3 = Severe	Spreading intense itching resulting in continuous scratching unbearable, interfering with daily activities. Requiring treatment.	Very intense redness/rash and/or redness largely extending beyond the Viaskin® patch areas.	Large swelling area extending beyond the Viaskin® patch areas.

These three pre-specified symptoms at patch application sites (itching, redness, swelling) will be graded on a daily basis in the diaries, during the first 6 months for part A subjects, and during the whole treatment duration for part B subjects. Subjects' parents/guardians will also be instructed to record in the diaries any other AEs (including any local skin reactions other than the 3 pre-specified ones at any time of the study, and any pre-specified local skin reactions occurring after the initial 6 months of treatment for part A subjects), and any concomitant medication or treatment taken for any type of AEs.

The site medical staff will review the subject's diary at each subject visit.

- For part A subjects: the 3 pre-specified symptoms solicited during the first 6 months will not be reported by the Investigators in the AE pages of the e-CRF, except if these symptoms are part of another concomitant disease or if these symptoms are leading to the subject's study discontinuation or serious AEs. Any other local skin reactions or any other type of adverse events spontaneously reported in the diaries will be reported by the Investigators in the AE e-CRF form. After month 6, any AE, including the 3 above symptoms, other local skin reactions

or any other type of AE will be reported in the dedicated section of the diaries. These AEs will be reported by the Investigators in the e-CRF.

- For part B subjects: the 3 pre-specified symptoms solicited during the whole treatment duration will be reported by the Investigators as AEs in the e-CRF, regardless of their severity (mild, moderate or severe) or seriousness. The diaries will be also used to supplement additional spontaneously reported events by the parents which will be reviewed and assessed at each visit by the Investigators or delegated trained staff, including but not limited to study nurses and physician assistants.

[redacted]

Subjects' parents/guardians must bring back the diary to the Investigator at each visit, and the Investigator must check the diary for completeness and accuracy. It is the Investigators' responsibility to instruct the subjects' parents/guardians about the use of the diary, and to ensure that it is accurately completed. Any problems with completing the diary will be addressed with the subjects' parents/guardians. All diaries must be returned to the site at completion of the study, or if the subject discontinues.

6.2.6 Skin Reaction and Photography

Local skin reactions under the Viaskin® patch or on any of the previous sites of patch application will be as a whole at each visit according to the recommendations of the European Academy of Allergology and Clinical Immunology (EAACI) and the Global Allergy and Asthma European Network (GA^2LEN) (40), and modified as follows:

Table 3: Skin Reaction Grading System

Skin Reaction	Grade if localized under the patch	Grade if extending beyond the patch
Negative	Grade 0	Grade 0
Only erythema, or erythema and infiltration	Grade 1A	Grade 1B
Erythema and few papules	Grade 2A	Grade 2B
Erythema and many or spreading papules	Grade 3A	Grade 3B
Erythema and vesicles	Grade 4A	Grade 4B

The Viaskin® patch is transparent and the degree of the local reactions under the Viaskin® patch can be easily seen through the patch. Grading of the local skin reactions on the back will start being recorded at Visit 4 right after the Viaskin® patch has been applied and while the subject is kept at site under observation and subsequently when subjects return at site for their visits.

During Visit 4, the first Viaskin® patch will be applied at the study site for 2 hours. The patch will then be removed after 2 hours and all subjects will be observed for 1 additional hour before being discharged. The reactions under or around the patch will be checked and graded: before application, at 30 minutes, 1 hour, 2 hours during patch application and

then 1 hour after the patch removal, before subject discharge. Photographs will be taken at each grading time point.

Appearance of any vesicles (grade 4) or ulcerative skin lesions or any other significant skin lesion seen under the patch while the patch is still applied on the skin or upon removal of the patch which could potentially lead to skin barrier disruption at sites of Viaskin® patch applications will be cautiously managed and follow-up.

Children's parents or guardians will be instructed to take a photograph of the patch skin area at home in case of appearance of any vesicles or ulcerative skin lesions. In these rare cases, subjects should transiently discontinue the patch applications and return to the site for evaluation and treatment of the wounded area, as well as for the next patch application and adequate evaluation and treatment of the wounded zone.

Upon re-application of the new patch, the subject should remain at the site for 1 hour before being discharged. The application duration may be temporarily adapted if deemed necessary. The site must contact the subject's parents/guardians by phone the day after this visit to ensure that no additional local blisters or vesicles developed and to confirm that the treatment can continue normally. The zone with vesicles or severe lesions should not be used for patch application until it has completely healed.

Photographic records of the application sites of the Viaskin® patch will be taken and documented as medical records or source documents. The subject's face will not, at any time, be captured in the photograph. Camera or a specific device and photography acquisition guidelines will be provided to the sites, so that photography process can be standardized as much as possible. All the photographs will be downloaded by the site staff onto a dedicated secured server with a restrictive access to the site staff members, the Sponsor members and Sponsor representatives.

Photographic records will be made available to the DSMB members upon request.

The following information will be systematically collected during the visits:

- The ease of removal of the patch (very easy/ easy / difficult / very difficult);
- The grading whether the removal of the patch was painful (very painful / painful / not painful);
- To specify whether the patch removal caused skin injury (yes / no);
- The suspected cause of adhesion issues, if any.

The duration of application of the assessed Viaskin® patch must be noted, and the assessment by the site staff will use the same scoring system as above.

6.3 Demographics and Baseline Characteristics

Demographics and baseline characteristics consist of those variables that are assessed only at screening/baseline.

6.3.1 Patient Demography

Patient demography consists of:

- Age and date of birth at screening Visit 1,
- Race, whenever the collection is allowed by local regulation,
- Sex.

6.3.2 Disease History and Medical History

History and duration of peanut allergy with well-documented IgE-mediated symptoms after ingestion of peanut must be reported in the disease history form in the e-CRF.

The documentation of the complete medical history will include history and duration of any other allergies and current medical conditions, any allergic reactions (other than peanut IgE-mediated symptoms) in the previous 12 months, past or present cardiovascular, respiratory (including asthma), gastrointestinal, renal, hepatic, neurological, endocrine, lymphatic, hematologic, immunologic, dermatological (including atopy), psychiatric, developmental, and genitourinary disorders, drug and surgical history and any other diseases or disorders.

The disease and medical histories will be obtained by interviewing the subject's parents/guardians and/or by inspecting her/his medical records.

For coding of disease/medical history, see Section 9.7.

6.3.3 Prior and Concomitant Medications

Previous and concomitant medications will be documented as described in Section 5.7.

6.4 Exploratory Variables

6.4.1 Immunological Markers

Venous blood samples will be drawn to assess the immunological markers (peanut-specific IgE and IgG4; IgE and IgG4 specific to each of the following peanut protein component: Ara h 1, Ara h 2 and Ara h 3; and total IgE [total IgE: for Part B subjects only]) at the visits specified in the Schedule of Procedures (page 15).

The following immunological markers will also be assessed at specific time points (Visits 1 and 10): IgE specific to cow's milk, egg, house dust mites, and grass pollen.

Analysis of samples will be conducted by a central laboratory and the results at any time point after baseline will be blinded until the data are unblinded at the study end. Further details of the procedures to be followed for sample collection, storage, and shipment will be documented in the Laboratory Manual.

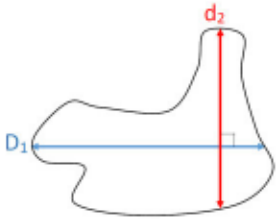
6.4.2 Skin Prick Test

Peanut extract plus negative saline control and positive histamine control will be used for skin prick testing. All materials (SoluPrick® solutions and ancillary materials, CE marked) will be provided free of charge centrally to all sites by the Sponsor, including a detailed procedure for conducting the SPTs.

The subjects should wash out any antihistamines for the minimum period of time (specified in the table in APPENDIX 3) prior to performing the test. Briefly, a skin Duotip II® test is pressed through a small drop of the commercial extract of peanut or positive and negative controls into the epidermis of the volar surface of the forearm.

After 15 minutes the area will be measured by the longest wheal diameter (D1) and the longest perpendicular diameter (d2). The Average wheal diameter = (D1 + d2) / 2.

e.g.



D1: size of the longest diameter in mm

d2: size of the longest perpendicular diameter to D1 in mm

A tracing should be obtained by using a fine ballpoint pen. The tracing will be performed at the demarcation line for the wheal as the skin drops back to flush. Scotch or a clear transport tape should be used to lift the tracing; the tape tracing should be placed on a specific form and filed as part of the subject's source documentation.

6.4.3 Quality of Life Questionnaires

6.4.3.1 Food Allergy Quality of Life Questionnaires / Food Allergy Independent Measure

The FAQLQs are disease-specific health-related quality of life questionnaires for subjects with food allergy. They are considered reliable and valid instruments to measure the impact of food allergy on health-related quality of life (41). The FAIM questionnaires capture the subjects' expectation of something happening because of her/his food allergy (42).

At screening, at Month 12 and at the end of study visit, the subjects' parents/guardians will complete the FAQLQ/FAIM questionnaires (in countries where the translated and validated questionnaires are available and used).

The different versions of the FAQLQ/FAIM questionnaire to be used both at screening and Month 12 for either subjects from Part A or subjects from Part B are provided in APPENDIX 6.

6.4.3.2 Generic Quality of Life Questionnaire: EQ-5D-5L

At screening at at Month 12, the subjects' parents/guardians will complete the EQ-5D-5L questionnaire. The questionnaire will be completed for subjects randomized in Part B only.

The template questionnaire is provided in APPENDIX 10.

6.4.4 Accidental Consumption of Peanuts

Specific reactions triggered by accidental consumption of peanut and the conditions around that consumption will be collected with as much detailed information as possible, in particular with regard to the nature of the food and the quantity consumed. The subjects' parents/guardians will be asked to clarify whether any peanut consumption was accidental or not. The AEs induced by the consumption will be classified and analyzed separately.

As far as possible, a sample of the food having triggered the reactions will be collected and sent for analysis of its peanut content to a specialized laboratory. A specific procedure to organize the collection and the shipment of these samples will be provided to the centers and the subjects' parents/guardians.

6.4.5 Epigenetic analyses

Venous blood samples will be drawn to assess the epigenetic modifications induced by the EPIT treatment with DBV712 on the promoter regions of key genes coding for several allergy-specific proteins. The tests will be managed centrally and the results at any time point after baseline will be blinded until the data are unblinded at the study end. Detailed procedures to be followed for sample collection, storage and shipment will be documented in a specific Manual provided to the sites.

6.4.6 Scoring Atopic Dermatitis

The SCORAD, a scoring index of atopic dermatitis developed by the European Task Force on Atopic Dermatitis (43) will be assessed as specified in the Schedule of Procedures (page 15).

Sections A and B must be assessed and completed by the Investigator or delegated trained staff, while section C is assessed by the subject's parents/guardians. Delegated staff includes but is not limited to study nurses and physician assistants.

The SCORAD is provided in APPENDIX 7.

6.4.7 Basophil Activation Test (United States eligible sites only)

Venous blood samples will be drawn at the visits specified in the Schedule of Procedures (page 15) to assess the activation of basophils after incubation of blood samples with peanut allergen in vitro.

This test will be conducted in all subjects enrolled at eligible sites of the US only. Analyses of samples will be conducted by a central laboratory, and the results at any time point after baseline will be blinded until the data are unblinded at the study end. Further details regarding collection and local processing of samples, samples storage, and samples shipment to the central laboratory will be provided in a dedicated Laboratory Manual.

6.4.8 Other Candidate Exploratory Biomarkers

CCI

[redacted]

7 STUDY CONDUCT

7.1 Schedule of Procedures

The Schedule of Procedures is presented in page 15.

7.2 Procedures by Visit

Visits should occur within the time windows indicated in the Schedule of Procedures (page 15). All times should be recorded using the 24-hour clock (for example 23:20, not 11:20 pm).

7.2.1 Visit 1, Screening (Day -42/D-3)

The first screening Visit (Visit 1) will take place within 42 days prior to the start of the treatment period. Therefore, the duration of the screening period could be less than 42 days.

The following assessments will be performed at this visit:

- Written informed consent, including specific consent for participation in the optional biorepository;
- Check inclusion/exclusion criteria, except for those criteria that depend on the results of the peanut-specific IgE assessment and on the outcome of the entry/screening DBPCFC;
- Disease/Medical history (see Section 6.3.2);
- Parental (father and/or mother) medical history of atopy (any allergies, asthma conditions, eczema/atopic dermatitis);
- Demographics (see Section 6.3.1);
- Physical examination (including a complete skin examination; see Section 6.2.4);
- Vital signs (see Section 6.2.3);
- SCORAD (see Section 6.4.6);
- SPT (see Section 6.4.2);
- Immunological markers (see Section 6.4.1);
- Laboratory tests (see Section 6.2.2); if applicable, subjects with abnormal laboratory assessments due to a concomitant transient disease (flu, viral illness, etc.) can repeat their laboratory assessments or be rescheduled for laboratory assessment at the discretion of the Investigator;
- FAQLQ/FAIM (see Section 6.4.3.1);
- EQ-5D-5L (part B only) (see Section 6.4.3.2);
- Collect blood sample for epigenetic analyses (see Section 6.4.5);
- US eligible sites only: collect blood sample for BAT (see Section 6.4.7);
- AEs recording (including volunteered or solicited AEs and AESI);
- Concomitant medications (see Section 5.7);
- Dispense subject participation card;
- Schedule Visit 2.

7.2.2 Visit 2, Screening (through Day -2)

Visit 2 corresponds to the first day of the entry/screening DBPCFC. This visit can take place any time through Day -2, as soon as the peanut-specific IgE results for the subject are obtained by the site from the central laboratory. If the subject fulfills all inclusion criteria including the peanut-specific IgE value (>0.7 kU/L), then Visit 2 may proceed.

The following assessments will be performed at this visit:

- Physical examination (including a complete skin examination; to take place before DBPCFC; see Section 6.2.4);
- Vital signs (to take place before DBPCFC; see Section 6.2.3);
- Entry/screening DBPCFC (first day) (see Section 6.1.1.3)
- AEs recording (including volunteered or solicited AEs, AESIs and recording of AEs/allergies in response to the DBPCFC);
- Concomitant medications (including any medications given to treat allergic symptoms; see Section 5.7);
- Schedule Visit 3.

Physical examinations and assessment of vital signs can be repeated during the DBPCFC as deemed necessary by the Investigator.

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

7.2.3 Visit 3, Screening (within 1 week of Visit 2 and through Day -1)

Visit 3 corresponds to the second day of the entry/screening DBPCFC. It takes place within a week following Visit 2 (the first day of the entry/screening DBPCFC). Visit 3 could take place 1 day prior to Visit 4.

The following assessments will be performed at this visit:

- Physical examination (including a complete skin examination; to take place before DBPCFC; see Section 6.2.4);
- Vital signs (to take place before DBPCFC; see Section 6.2.3);
- Entry/screening DBPCFC (second day) (see Section 6.1.1.3)
- AEs recording (including volunteered or solicited AEs, AESIs and recording of AEs/allergies in response to the DBPCFC);
- Concomitant medications (including any medications given to treat allergic symptoms; see Section 5.7);
- Schedule Visit 4.

Physical examinations and assessment of vital signs can be repeated during the DBPCFC as deemed necessary by the Investigator.

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

7.2.4 Visit 4 (Day 1), First Day of Treatment

All screening assessments must be completed and subject eligibility must be checked before entry into the double-blind treatment period. In some specific cases, a subject may need to be re-screened to be able to enter the double-blind treatment period. These situations will be discussed with the Sponsor's medical monitor on a case-by-case basis.

After the screening period is completed, dates of all study visits will be scheduled relative to the date of Visit 4. Visit 4 will take place at a maximum of 42 days after Visit 1 and might occur even closer to Visit 1 provided that Visit 2 and Visit 3 have been performed in between. Ideally, it will take place 1 day after Visit 3 and it may take place up to several weeks after Visit 3, respecting the maximum interval of 42 days after Visit 1. Visit 4 may take place the same day as Visit 3 for those Investigators willing to combine the 2 visits, under the condition that all procedures of both visits and their specific durations are respected.

The following assessments will be performed at this visit:

- Physical examination (including a complete skin examination; see Section 6.2.4);
- Vital signs (see Section 6.2.3);
- Confirm eligibility of subject and perform randomization;
- AEs recording (including volunteered or solicited AEs and AESI);
- Concomitant medications (see Section 5.7);
- Dispense first box of IMP (instruct subjects 'parents/guardians on the proper application, timing and storage);
- Apply the first Viaskin® patch to the subject for a total duration of 2 hours. Stick the peal-off part of the pouch label in the appropriate section of the subject diary. After 2 hours the patch will be removed and the subject will be observed for 1 additional hour before being discharged.
- Check skin reaction under or around the patch without removing it and grade severity (see Table 3, Section 6.2.6) at the following time points:
    - before application
    - 30 minutes
    - 1 hour
    - 2 hours during patch application
    - and then 1 hour after the patch removal, before subject discharge
- Without removing the patch, take a photograph of the site of application of the Viaskin® patch at the same time point than the skin reaction grading. These photographs will be loaded onto the study-specific server (described in section 6.2.6) and kept it in the subject's medical records or source documents;
- Patch adhesion Investigator's assessment: Investigator assesses the adhesion of the patch to the skin as well as the occlusion of the patch chamber right after first application and after 2 hours prior to discharge;
- Dispense subject diary and instruct parents/guardians on the use (see Section 6.2.5);

- Dispense the camera and the card with its lanyard or the device to the parents/guardians and instruct them when and how to use it;
- Dispense the subject safety leaflet;
- Dispense the kit and instructions for the accidental peanut consumption food sampling.
- Dispense an auto-injector of epinephrine and explain in detail the anaphylaxis emergency action plan to the parents/guardians before discharge;
- Dispense 1% hydrocortisone ointment;
- Schedule the Day 4 phone contact and Visit 5.

The subject should be discharged 3 hours after the Viaskin® first patch application.

7.2.5 Phone Contacts (Day 4±2 days and Day 22±2 days), Treatment Period

At Day 4 after the patch should have been applied 2 hours daily for 3 days, and at Day 22 (Week 3 of treatment), the patch should have started to be applied 12 hours daily, specific phone contacts will be made to the parents/guardians to assess the safety of patch applications on the back. During the phone contacts, the site staff could ask to be provided with photos of the back of the subject to assess the local skin reactions. If required, the subjects may be seen earlier by the Investigator.

The following assessments will be performed during the phone contact:

- AEs recording (including volunteered or solicited AEs and AESI);
- Concomitant medications (see Section 5.7);
- Check for any accidental peanut consumption (see Section 6.4.4);
- Check with the parents/guardians to ensure that the diary has been completed accurately and that the parents/guardians is/are comfortable with using the diary;
- Remind of Visit 5 and Visit 6, respectively.

7.2.6 Visit 5 (Day 8±3 days), Visit 6 (Month 1±3 days) and Visit 9 (Month 9±7 days), Treatment Period

The following assessments will be performed at these visits:

- Physical examination (including a complete skin examination; see Section 6.2.4);
- Vital signs (see Section 6.2.3);
- AEs recording (including volunteered or solicited AEs and AESI);
- Concomitant medications (see Section 5.7);
- Check for any accidental peanut consumption (see Section 6.4.4);
- Check that the subject diary has been completed accurately and ensure that the parents/guardians is/are comfortable with using the diary;
- Dispense subject diary (re-instruct parents/guardians on the use, if necessary; see Section 6.2.5);
- Collect the treatment box dispensed at the previous visit, check the unused medication and assess medication compliance;

- Dispense a new box of IMP (re-instruct parents/guardians on the proper application, timing and storage, if necessary);
- Patch adhesion Investigator's assessment: with the patch still applied, the Investigator assesses the adherence of the patch to the skin as well as the occlusion of the patch chamber. This assessment will only be made if the subject is wearing the patch at the time of the visit. Any issues reported by the subjects' parents/guardians related to the patches application or removal will also be reported;
- Check skin reactions under or around the patch (if the patch is still worn by the subject at the time of the visit but without removing it) and all other zones of application and grade severity of the skin reactions (see Table 3, Section 6.2.6);
- Take a photograph of the sites of application of the Viaskin® patch, load it onto the study server (described in section 6.2.6) and keep it in the subject's medical records or source documents; download the photographs taken by the parents' subject from the camera memory card or the device, if any photos were taken since the previous visit and review them;
- Review the use of the auto-injector of epinephrine and the anaphylaxis emergency action plan;
- Schedule next phone contact and Visit 6, Visit 7, and Visit 9 respectively.

7.2.7 Phone Contacts (Month 2±3 days, Month 4.5 ±7 days and Month 7.5±7 days), Treatment Period

The parents/guardians of the subject will be called to assess the subject's condition since the last Visit.

The following assessments will be performed during the phone contact:

- AEs recording (including volunteered or solicited AEs and AESI);
- Concomitant medications (see Section 5.7);
- Check for any accidental or peanut consumption (see Section 6.4.4);
- Check with the parents/guardians to ensure that the diary has been completed accurately;
- Remind of Visit 7, the possibility of Visit 7bis, Visit 8 and Visit 9 respectively.

7.2.8 Visit 7 (Month 3±7 days), Visit 7bis (between Month 3 and 12 – depending on the inclusion duration) and Visit 8 (Month 6±7 days), Treatment Period

For Part A, the Visit 7 after 3 months of treatment was to be the last visit before the planned interim safety analysis for the doses selection. This interim analysis was to be performed once the last subjects of Part A will have had their Visit 7. The first randomized subject should have not yet reached the 12-month treatment, depending on the actual recruitment duration of the first 50 subjects of the Part A.

Visit 7bis (Only for part A subjects):

Depending on the DSMB recommendation (see Section 3.1), subjects included in the Part A may need to receive a new treatment box. In these situations, the treatment was to be blindly assigned by the IWRS during Visit 7bis, ensuring the study blind. The dose of the

DBV712 groups was either to be kept unchanged (i.e., no Visit 7bis needed), reduced or increased. The placebo group will continue with Viaskin® placebo treatment.

After the interim safety analysis, both doses of DBV712 were shown to be safe, and no dose switching is required (see Section 3.1). As a consequence, Visit 7bis will be not applicable.

Visit 7 and Visit 8:

Both visits are made of the same assessments:

The following assessments will be performed at these visits:

- Physical examination (including a complete skin examination; see Section 6.2.4);
- Vital signs (see Section 6.2.3);
- SCORAD (see Section 6.4.6);
- SPT (see Section 6.4.2);
- Immunological markers (see Section 6.4.1);
- Laboratory tests (see Section 6.2.2);
- Collect blood samples for epigenetic analyses (see Section 6.4.5);
- US eligible sites only: collect blood sample for BAT (see Section 6.4.7);
- AEs recording (including volunteered or solicited AEs and AESI);
- Concomitant medications (see Section 5.7);
- Check for any accidental peanut consumption (see Section 6.4.4);
- Check that the subject diary has been completed accurately and ensure that the parents/guardians are comfortable with using the diary;
- Dispense subject diary (re-instruct parents/guardians on the use, if necessary; see Section 6.2.5);
- Collect the treatment box dispensed at the previous visit, check the unused medication and assess medication compliance;
- Dispense a new box of IMP (re-instruct parents/guardians on the proper application, timing and storage, if necessary);
- Patch adhesion Investigator's assessment: made with the patch still applied, the Investigator assesses the adherence of the patch to the skin as well as the occlusion of the patch chamber. Any issues reported by the subjects' parents/guardians related to the patches application or removal will also be reported;
- Check skin reactions under or around the current patch (do not remove patch) and all other zones of application and grade severity of the skin reactions (see Table 3, Section 6.2.6);
- Take a photograph of the sites of application of the Viaskin® patch, load it onto the study server (described in Section 6.2.6) and keep it in the subject's medical records or source documents; download the photographs taken by the parents' subjectfrom the camera memory card or the device, if any photos were taken since the previous visit and review them;

- Review the use of the auto-injector of epinephrine and the anaphylaxis emergency action plan;
- Schedule next phone contact and Visit.

7.2.9 Visit 10 (Month 12±7 days), Treatment Period

Visit 10 corresponds to the first day of the post-treatment DBPCFC.

The following assessments will be performed at this visit:

- Physical examination (including a complete skin examination; to take place before DBPCFC; see Section 6.2.4);
- Vital signs (to take place before DBPCFC; see Section 6.2.3);
- SCORAD (see Section 6.4.6);
- SPT (see Section 6.4.2);
- Immunological markers (see Section 6.4.1);
- Laboratory tests (see Section 6.2.2);
- FAQLQ/FAIM (see Section 6.4.3.1);
- EQ-5D-5L (part B only) (see Section 6.4.3.2);
- Collect blood sample for epigenetic analyses (see Section 6.4.5);
- US eligible sites only: collect blood sample for BAT (see Section 6.4.7);
- Post-treatment DBPCFC (first day) (see Section 6.1.1.4); the patch should be removed before performing the DBPCFC and a new patch should be applied at the end of the DBPCFC (i.e. at the end of the 3-hour observation period);
- AEs recording (including volunteered or solicited AEs, AESIs and recording of AEs/allergies in response to the DBPCFC);
- Concomitant medications (including any medications given to treat allergic symptoms) (see Section 5.7);
- Check for any accidental peanut consumption (see Section 6.4.4);
- Check that the subject diary has been completed accurately;
- Dispense subject diary (re-instruct parents/guardians on the use, if necessary; see Section 6.2.5);
- Collect the treatment box dispensed at the previous visit, check the unused medication and assess medication compliance;
- Dispense the treatment box to the subject's parents/guardians for application until the 2nd day of the challenge (re-instruct parents/guardians on the proper application, timing and storage, if necessary);
- Patch adhesion Investigator's assessment: made with the patch still applied, the Investigator assesses the adherence of the patch to the skin as well as the occlusion of the patch chamber. Any issues reported by the subjects' parents/guardians related to the patches application or removal will also be reported;

- Check skin reactions under or around the current patch (without removing it) and all other zones of application and grade severity of the skin reactions (see Table 3, Section 6.2.6);
- Take a photograph of the sites of application of the Viaskin® patch, load it onto the study server (described in Section 6.2.6) and keep it in the subject's medical records or source documents; download the photographs taken by the parents' subject from the camera memory card or the device, if any photos were taken since the previous visit and review them;
- Review the use of the auto-injector of epinephrine and the anaphylaxis emergency action plan;
- Schedule Visit 11.

Physical examinations and assessment of vital signs can be repeated during the DBPCFC as deemed necessary by the Investigator.

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

7.2.10 Visit 11 (≤1 week after Visit 10), End of Treatment Period

Visit 11 corresponds to the end of the 12-month treatment period. Patch application ends at this visit. The patch worn by the subject when she/he arrives to this visit is removed and there will be no further patches applied beyond Visit 11.

For the subjects who will accept to participate in the extension study, the Visit 12 will be cancelled. The inclusion in the study extension will occur at the end of the Visit 11.

Visit 11 corresponds to the second day of the post-treatment DBPCFC after 12 months of treatment. It takes place within a week following the first day of the post-treatment DBPCFC.

The following assessments will be performed at this visit:

- Physical examination (including a complete skin examination; to take place before DBPCFC; see Section 6.2.4);
- Vital signs (to take place before DBPCFC; see Section 6.2.3);
- Post-treatment DBPCFC (second day) (see Section 6.1.1); the patch should be removed before performing the DBPCFC;
- AEs recording (including volunteered or solicited AEs, AESIs and recording of AEs/allergies in response to the DBPCFC);
- Concomitant medications (including any medications given to treat allergic symptoms) (see Section 5.7);
- Check for any accidental peanut consumption (see Section 6.4.4);
- Collect and check that the subject diary has been completed accurately. The diary will not be given back to the subject;
- Collect the treatment box dispensed at the Visit 10 (Month 12 visit), check the unused medication and assess medication compliance;

- Patch adhesion Investigator's assessment: made with the patch still applied, the Investigator assesses the adherence of the patch to the skin as well as the occlusion of the patch chamber. Any issues reported by the subjects' parents/guardians related to the patches application or removal will also be reported;
- Check skin reactions under or around the current patch (without removing it) and all other zones of application and grade severity of the skin reactions (see Table 3, Section 6.2.6);
- Take a photograph of the sites of application of the Viaskin® patch, load it onto the study server (described in section 6.2.6) and keep it in the subject's medical records or source documents; download the photographs taken by the parents' subject from the camera memory card or the device, if any photos were taken since the previous visit and review them;
- Schedule Visit 12.

Physical examinations and assessment of vital signs can be repeated during the DBPCFC as deemed necessary by the Investigator.

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

7.2.11 Visit 12 (4 weeks after Visit 11), End of Study Period

The following assessments will be performed at this visit:

- Physical examination (including a complete skin examination; see Section 6.2.4);
- Vital signs (see Section 6.2.3);
- FAQLQ/FAIM (see Section 6.4.3.1);
- EQ-5D-5L (part B only) (see Section 6.4.3.2);
- AEs recording (including volunteered or solicited AEs and AESI);
- Check for any accidental peanut consumption (see Section 6.4.4);
- Concomitant medications (see Section 5.7);

This visit will not be performed by the subjects who will be included in the extension follow-up study.

7.2.12 Early Termination Visit

Subjects who discontinue early from the study should have, if possible, an Early Termination Visit. This visit should take place as soon as possible after the subject stops applying the IMP).

The following assessments will be performed at these visits:

- Physical examination (including a complete skin examination; see Section 6.2.4);
- Vital signs (see Section 6.2.3);
- SPT (see Section 6.4.2);
- Immunological markers (see Section 6.4.1);
- Laboratory tests (Section 6.2.2);

- US eligible sites only: collect blood sample for BAT (see Section 6.4.7);
- AEs recording (including volunteered or solicited AEs and AESI);
- Concomitant medications (see Section 5.7);
- Check for any accidental peanut consumption (see Section 6.4.4);
- Check subject diary;
- Check unused medication and assess medication compliance;
- Patch adhesion Investigator's assessment: made with the patch still applied, the Investigator assesses the adherence of the patch to the skin as well as the occlusion of the patch chamber. This assessment will only be made if the subject is wearing the patch at the time of the visit. Any issues reported by the subjects' parents/guardians related to the patches application or removal will also be reported;
- Check skin reactions and grade severity (see Table 3, Section 6.2.6);
- Take a photograph of the sites of application of the Viaskin® patch, load it onto the study server (described in Section 6.2.6) and keep it in the subject's medical records or source documents; download the photographs taken by the parents' subject from the camera memory card or the device, if any photos were taken since the previous visit and review them.

7.2.13 Unscheduled Visit

Subjects may come to the site for visits outside of the scheduled visits in case of AEs, Viaskin® patch adhesion problems, etc.

The following assessments will be performed at these visits, at the discretion of the Investigator:

- Physical examination (including a complete skin examination; see Section 6.2.4);
- Vital signs (see Section 6.2.3);
- Laboratory tests (Section 6.2.2);
- AEs recording (including volunteered or solicited AEs and AESI);
- Concomitant medications (see Section 5.7);
- Check for any accidental peanut consumption (see Section 6.4.4);
- Check subject diary;
- If necessary dispense a new box of IMP (re-instruct parents/guardians on the proper application, timing and storage);
- Check unused medication and assess medication compliance;
- Patch adhesion Investigator's assessment: made with the patch still applied, the Investigator assesses the adherence of the patch to the skin as well as the occlusion of the patch chamber. Any issues reported by the subjects' parents/guardians related to the patches application or removal will also be reported;
- Check skin reactions under or around the current patch (without removing it) and all other zones of application and grade severity of the skin reactions (see Table 3, Section 6.2.6);

- Take a photograph of the sites of application of the Viaskin® patch, load it onto the study server (described in Section 6.2.6) and keep it in the subject's medical records or source documents; download the photographs taken by the parents' subject from the camera memory card or the device, if any photos were taken since the previous visit and review them.

8 STATISTICAL METHODS

The statistical considerations summarized in this section outline the plan for data analysis of this study.

A separate detailed Statistical Analysis Plan (SAP) providing detailed methods for the analyses outlined below will be prepared before first subject inclusion and finalized before unblinding.

Any deviations from the planned analyses will be described and justified in the final integrated study report.

8.1 Study Subjects

8.1.1 Analysis Populations

All analysis populations will be identified and finalized in the SAP. Data from Part A is planned to be assessed separately from Part B, prior to the completion of Part B. However, data from Part A will be assessed with Part B as a single pooled supportive analysis, described in this document.

8.1.1.1 Safety Population

The Safety population will be comprised of all subjects who are randomized and have received at least 1 dose of IMP in Part B. This population will be used to assess comparative safety information. In case the wrong IMP is dispensed, the subject will be analyzed according to the IMP received for the longest period of time.

8.1.1.2 Intent-to-treat Population

The Intent-to-treat (ITT) population will be comprised of all subjects who are randomized in Part B. Subjects will be analyzed according to the treatment they have been randomized to.

8.1.1.3 Per-protocol Population

The Per-Protocol (PP) population will include all subjects from the ITT population who do not have major deviations from the protocol that may affect the primary efficacy endpoint (for instance, subjects who have not performed adequately the post-treatment DBPCFC at Month 12, subjects with a global treatment compliance below 80%, etc.). The deviations to consider will be listed more exhaustively during the blinded data review meeting The PP population will be used to present robustness analyses of the primary and secondary efficacy evaluations.

8.1.1.4 Part A Population

The Part A population will be comprised of all subjects who are randomized in Part A. Subjects will be analyzed according to the treatment they have been randomized to. This population will be used for descriptive efficacy and safety analyses, as detailed in the SAP.

8.1.2 Disposition of Subjects

Subject disposition will be summarized for the ITT population. The number and percentage of subjects randomized, subjects in each study population (Safety, ITT, PP), and subjects who completed the study, who discontinued the study, and the primary reason for discontinuation from the double-blind period will be tabulated by treatment group and overall.

An enrollment summary will be presented overall and by site, showing the first date of consent, and the last study visit exit date among enrolled subjects, duration (in days) which is calculated as last study visit exit date – first date of consent +1, number of subjects enrolled, randomized and completed. The number and percentage of subjects enrolled in total and by site will be summarized for each treatment group and overall.

8.1.3 Protocol Deviations

Deviations from the protocol including violations of inclusion/exclusion criteria will be assessed as "minor" or "major" prior to unblinding. Major deviations from the protocol that impact the primary efficacy evaluation will lead to the exclusion of a subject from the PP population.

8.2 General Considerations

8.2.1 Statistical Methods

The statistical analyses for the entire study as further outlined in the SAP will be included in the Clinical Study Report (CSR) for this protocol. The SAP will give a detailed description of the summaries and analyses (primary and secondary) that will be performed and clearly describe when these analyses will take place. The SAP will be prepared after the final protocol and finalized well ahead of the database lock to ensure the integrity of the statistical analysis and study conclusions.

All pre-defined statistical analyses will be performed after the database is released for unblinding. Statistical analyses will be performed using SAS® Version 9.3 or higher (SAS Institute, Cary, NC, USA).

Categorical variables will be summarized using number of observations and percentages. The denominator for percentages will be the number of subjects in the population with data available unless otherwise stated. Continuous variables will be summarized using descriptive statistics (number of observations [n], mean, standard deviation, minimum, first quartile [Q1], median, third quartile [Q3], and maximum).

8.2.2 Analysis and Data Conventions

8.2.2.1 Definition of Baseline

The baseline assessment will be the latest, valid pre-dose assessment available.

8.2.2.2 Visit Windows

Assessments outside of protocol allowable time windows will be taken into account in the analysis according to the visit in which the data are entered.

8.2.2.3 Unscheduled Assessments

Extra assessments (laboratory data or vital signs associated with non-protocol clinical visits or obtained in the course of investigating or managing AEs) will be included in listings, but not summaries. If more than 1 laboratory value is available for a given visit, the first valid observation will be used in summaries and all observations will be presented in listings. It is noted that invalid laboratory data may not be used (from hemolyzed samples, mishandled samples, quantity not sufficient, or other conditions that would render the values invalid).

8.2.2.4 Missing Data Conventions

Every attempt must be made by the Investigator to provide complete data. The handling of missing data will be detailed in the SAP.

8.2.2.5 Pooling of Centers

Considering the expected small number of subjects to be randomized by center, the center effect will not be investigated. Nevertheless, the region (Australia/Europe/North America) effect will be explored for the primary efficacy endpoint in the ITT population.

8.3 Demographics, Disease and Medical Histories, Baseline Characteristics, and Concomitant Medications

Descriptive statistics will be produced for continuous demographic and baseline characteristics (including age, height, weight, body mass index, peanut-specific IgE and peanut-specific IgG4) for each treatment group and overall. The number and percent of subjects in each group of the categorical demographic and baseline characteristics (including age, race, medical history, and SPT) will be tabulated by treatment group and overall.

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

Medical history will be reported by SOC and PT and coded using the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Disease history will also be described, including

- age at time of diagnosis,
- time from diagnosis to study enrolment,
- physician category who made the diagnosis,
- main reason having led to the diagnosis (reaction after ingestion, parental/sibling history of atopy, other risk factors)
- diagnosis criteria (SPT, IgE, positive food challenge, peanut allergic reaction)
- Most recent results of peanut allergy diagnostic tests performed,

- Description of allergic reactions (number of reactions per subject, number of reaction in the previous year…).

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

8.4 Treatment Compliance and Exposure

Treatment compliance (see Section 5.6), extent of exposure (days), and total dose of peanut protein received during the study (mg) will be summarized for each treatment group by means of descriptive statistics (details will be provided in the SAP).

8.5 Efficacy Analyses

8.5.1 Primary Efficacy Analysis

The primary efficacy endpoint is the difference between the percentage of treatment responders in the selected active DBV712 group (250 µg) compared to the placebo group after 12 months of EPIT treatment.

A subject is defined as a treatment responder if:

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

  OR

- The initial ED was ≤10 mg peanut protein and the ED is ≥300 mg peanut protein at the post-treatment DBPCFC at Month 12.

8.5.1.1 Statistical Methods

The primary efficacy analysis will be performed on the ITT population, using missing=failure imputation method (which means that subjects with missing DBPCFC peanut ED value at Month 12 will be considered as non-responders).

The primary measure of treatment effect will be the difference in response rates between active and placebo treatment groups. The primary analysis will apply a Wald test at a 2-sided 5% significance level to evaluate a null hypothesis of no difference, and 2-sided 95% Newcombe confidence interval (CI) for the difference in response rates will be calculated. The pre-specified threshold for the primary analysis will be defined by a ≥15% lower CI bound, and this condition will determine whether the primary objective has been successfully met.

8.5.1.2 Supportive Analysis

A supportive analysis will be performed in subjects randomized in parts A and B. This analysis will apply the same statistical method as for the primary analysis.

8.5.1.3 Subgroup Analyses

Response rates by treatment groups and treatment effect will be provided on the following subgroups:

- Screening ED subgroup (Screening ED > 10 mg, Screening ED ≤ 10 mg)
- Region (North America, Europe, Australia)
- Gender (Male/Female)

- Race (White/Black or African American/Asian/Other)
- Subjects with / without history of asthma
- Subjects with / without history of food allergy other than peanut
- Subjects with / without history of atopic dermatitis or eczema.

Analysis will be performed only on subgroups containing at least 15 subjects included.

8.5.2 Secondary Efficacy Analyses

The change from baseline to Month 12 in peanut protein CRD and in peanut protein ED will be summarized descriptively by treatment group for the ITT population using Baseline Observation Carried Forward imputation method, as well as for the PP population.

In addition, the peanut protein CRD and the ED in each treatment group at Month 12 will be compared in the selected active DBV712 group (250 µg) *versus* the placebo group.

8.5.3 Pre-defined Hierarchical Order for the Analysis of Efficacy Endpoints

In order to handle multiple comparisons *versus* placebo, the overall type-I error will be controlled at a level of 5% (2-sided) by the use of a hierarchical inferential approach. The primary analysis in the overall population must be positive according to the success criterion (pre-specified threshold described in Section 8.5.1.1). The first secondary efficacy analysis (difference in CRD) must meet its success criterion before drawing an inferential conclusion about the next secondary comparison (difference in peanut protein ED). The pre-defined hierarchical order and success criteria are summarized in Table 4.

Table 4: Pre-defined Hierarchical Order for Analysis of Efficacy Endpoints — ITT population

Order	Efficacy endpoints (at Month 12)	Success criterion	Hierarchical Testing threshold
1	Percentages of treatment responders	95% CI lower bound ≥15%	-
2	Change in peanut protein ED from baseline	-	p ≤0.05
3	Change in peanut protein CRD from baseline	-	p ≤0.05

Abbreviations: CI = Confidence interval; CRD = Cumulative reactive dose; ED = Eliciting dose; ITT = Intent-to-treat.

8.5.4 Other Efficacy Analyses

The percentage of subjects reaching a cumulative dose ≥1,444 mg peanut protein at Month 12, the percentage of subjects reaching a cumulative dose ≥3,444 mg peanut protein at Month 12, and the percentage of subjects unresponsive (i.e, showing no symptoms leading to stop the DBPCFC) to the highest dose (2,000 mg peanut protein) at Month 12 will be summarized descriptively by treatment group for the ITT population using missing=failure imputation method, as well as for the PP population.

No further adjustments will be made for the other efficacy endpoints for which p-values will be provided for descriptive purpose only. The following efficacy analyses will be performed using observed data (no imputation will be done).

- Peanut-specific IgE and IgG4 analysis over time: peanut-specific IgE and IgG4 levels at baseline and changes from baseline to Months 3, 6 and 12 will be summarized descriptively by treatment group on the ITT population, using observed data.

The mean change from Baseline of the peanut-specific IgE and IgG4 will be compared.

- Skin Prick Test analysis: The mean change from baseline at Months 3, 6 and 12 in mean wheal diameter will be evaluated for each treatment group on the ITT population using observed data.
- A quality of life score from the FAQLQ/FAIM Parent Form will be summarized at Month 12 and compared to baseline for both treatment groups for the overall ITT population, using observed data. FAQLQ-Parental Form (FAQLQ-PF) questionnaires will also be summarized by main domains of quality of life using specific scores:
    - Emotional impact,
    - Food-related anxiety,
    - Social and Dietary limitations.

  The relationship between FAQLQ-PF scores and treatment response will also be studied.

8.6 Safety Analyses

Safety endpoints will be evaluated for the Safety population (all subjects who received at least 1 dose of IMP).

For all safety analyses, data will be summarized for active DBV712 group *versus* placebo group.

8.6.1 Adverse Events

Treatment-emergent AEs will be defined as any AEs, regardless of relationship to IMP, which occur during or after the initial Viaskin® patch application or any event already present that worsens in either severity or relationship to IMP following exposure to Viaskin® patches.

All AEs will be reported by SOC and PT and coded using the latest available version of the MedDRA dictionary.

An overall summary of TEAEs will be provided showing the number and percentage of subjects in each treatment group with any TEAEs, any potentially drug-related TEAEs, any DBV712-induced local TEAE, any severe DBV712-induced local TEAE, any severe TEAEs, any severe potentially IMP-related TEAEs, any serious TEAEs, any potentially IMP-related serious TEAEs, any TEAEs leading to discontinuation, any TEAEs leading to epinephrine intake and any TEAEs leading to death. The number of events will also be presented.

The number of events as well as the number and percentage of subjects who experienced at least one event will be summarized by SOC, PT and treatment group. The incidence of the following events will be summarized:

- TEAEs (distinguished from symptoms/reactions elicited during the DBPCFCs): incidence, maximum severity and duration;
- Local skin tolerance at sites of Viaskin® patch application as assessed by the subjects (incidence, duration and severity) (see Section 8.6.5);

- Local skin tolerance at sites of Viaskin® patch application as assessed by the Investigator (severity) (see Section 8.6.6);
- SAEs, serious TEAEs and serious potentially IMP-related TEAEs;
- Potentially IMP-related TEAEs;
- TEAEs leading to study treatment discontinuation and TEAEs leading to epinephrine intake;
- Local AESIs and systemic AESIs (see Section 6.2.1.3.5) .

Additionally, the proportions of patches during the one-year exposure period that led to mild, moderate or severe TEAE considered related to IMP will be summarized.

All AEs will be listed. SAE and TEAE leading to an epinephrine intake will also be listed separately.

The reactions appearing during a DBPCFC (as they are expressly provoked) will be differentiated from those AEs occurring outside of the DBPCFC. Objective and subjective symptoms/reactions elicited during the DBPCFCs in the different treatment groups (see Section 6.1.1 for full details) will be summarized separately.

8.6.2 Laboratory Assessments

Descriptive statistics will be calculated for clinical laboratory tests (hematology and biochemistry) performed at Visit 1 (Day -42), Visit 7 (Month 3), Visit 8 (Month 6) and Visit 10 (Month 12). Categorical variables will be summarized by frequency and percentages of subjects in corresponding categories.

Changes in laboratory data from baseline will also be presented.

In addition, summaries of laboratory values categorized based on Common Toxicity Criteria for Adverse Events (CTCAE) grade will also be presented.

Shift tables of test abnormalities will be generated to compare baseline values to the values collected at other time points.

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

8.6.3 Vital Signs

Observed vital sign values and changes from baseline will be descriptively summarized by visit and treatment group. All vital signs data will be listed.

The analysis of vital signs will focus on the incidence of clinically relevant abnormalities. The number of subjects evaluated and the number and percentage of subjects with clinically relevant post-baseline abnormalities at each visit will be presented. The criteria for clinically relevant post-baseline abnormalities are shown in Table 5.

Table 5: Criteria to Assess Clinically Relevant Abnormalities in Vital Signs

Vital Sign Criteria for Abnormalities	Criteria for Abnormalities
Pulse	>165 beats per minute or an increase from pre-dosing of >20 beats per minute, or <85 beats per minute or a decrease from pre-dosing of >20 beats per minute
Systolic blood pressure	>120 mmHg or an increase from pre-dosing of >30 mmHg, or <75 mmHg or a decrease from pre-dosing of >20 mmHg
Diastolic blood pressure	>80 mmHg or an increase from pre-dosing of >25 mmHg, or <45 mmHg or a decrease from pre-dosing of >15 mmHg

8.6.4 Physical Examination

Physical examination data will be summarized by visit and treatment group and listed.

Changes in physical examination data from baseline will be presented. Skin reactions observed during the physical examinations will also be reported and the corresponding data will be tabulated separately (see Section 8.6.6).

8.6.5 Subject Diaries

Subject diary data will be summarized where appropriate and listed.

The number of days of itching, redness and swelling of Grade 1, 2, or 3 will be summarized separately by treatment group and overall (during the first 6 months for part A, and during the whole treatment duration for part B).

The most severe grades of itching, redness and swelling, documented in the diary, will also be summarized. The maximum grade of local reactions reported (itching, redness or swelling) will also be tabulated.

8.6.6 Skin Reactions

Viaskin® patch site examination data will be summarized where appropriate and listed.

Examination of the skin at the site of patch application will be graded by the Investigators or delegated trained staff on a scale of Grade 0 (negative) to Grade 4 (erythema, vesicles). Localization of the skin reaction (under the patch/beyond the patch) will also be collected. These results will be summarized using descriptive statistics and presented by visit and treatment group, regardless of the localization as well as for each type of localization. The worst grade reported will also be tabulated.

8.6.7 Symptomatic Reactions during the DBPCFC

The incidence of objective and subjective symptoms/reactions elicited during the DBPCFCs will be summarized. A severity score based on the grades of symptoms elicited during the DBPCFCs will be described at baseline and at Month 12. The change in the severity score from baseline will also be presented.

8.7 Exploratory Analyses

There will be no adjustments for multiplicity for any of the following exploratory analyses.

The following exploratory analyses will be performed in the Safety Population:

- Analysis of IgE and IgG4 specific to peanut protein components: descriptive analysis will be conducted for IgE and IgG4 specific to peanut protein components using observed data;
- Analysis of total IgE, using the same statistical method as described for IgE and IgG4 specific to peanut protein components;
- Frequency of accidental peanut consumptions, conditions around the accidental consumptions (including the frequency of deliberate consumption to evaluate risk-taking behaviors), estimated quantity consumed at each occurrence, and associated reactions and severity of reactions will be studied on the Safety population;
- Descriptive analyses of epigenetic modifications of some specific genes in both treatment groups using observed data;
- Descriptive analysis will be conducted for each of the other allergen-specific IgE analyzed (cow's milk, egg, house dust mites, grass pollen) and the change from baseline will be tabulated using observed data;
- SCORAD change from baseline at Months 3, 6 and 12 will be presented using observed data;
- Quality of Life analysis using the EQ-5D-5L;
- Analyses of basophil activation: changes from baseline over time will be presented and correlation with DBPCFC outcomes will be explored;
- CCI .

8.9 Interim Analyses

8.9.1 End of Part A – 3-month Safety analysis

A safety analysis was to be conducted when the first 50 subjects randomized in the study have reached 3 months of patch application. These safety data were to be reviewed unblindly by the DSMB for forming their recommendation on the highest safe dose to be selected for the remaining subject inclusions (Part B). After review of the 3-month safety data of the 51 actually randomized subjects in part A, the DSMB had no safety concern and considered both doses as well tolerated with a good safety profile. The 250-µg dose was selected for part B.

For the subjects of the Part A, depending on the DSMB recommendation, the dose of the DBV712 groups was to be kept either unchanged, reduced or increased. Upon DSMB recommendations, all subjects from Part A were to remain in their initially randomized treatment arm (doses unchanged).

8.9.2 Interim analysis of immunological activity

An analysis will be conducted when 50 subjects from Part B will have reached 6 months of active DBV712 treatment with the dose selected from the Part A (250 µg). Immunological parameters (peanut-specific IgE and peanut-specific IgG4), SPT and main safety data will be presented.

A specific futility analysis will be conducted on the peanut-specific IgG4 measurements. The relative change from baseline [calculated as (Month 6 value – baseline value) / Baseline value] of the peanut-specific IgG4 levels in the selected active treatment group (250 µg) will be numerically compared to the change in the placebo group. The median of the active group is expected to be greater than the placebo group median to evidence a treatment activity on the 1-3 year children's immune system.

In the situation where the median relative change from baseline of the peanut-specific IgG4 is equal or lower than the median relative change in the placebo group, the premature stop of the study for lack of evidence of therapeutic benefit will be considered. This unblinded data review will be conducted by the DSMB who will be responsible of issuing the recommendation to the sponsor.

8.9.3 Part A analysis

An analysis will be conducted after the last subject from Part A will have completed the study. The aim is to describe the efficacy and safety data among all subjects enrolled in Part A. All analyses will be detailed in a separate interim SAP.

8.10 Determination of Sample Size

The total number of subjects to randomize in EPITOPE will be approximately 400, as presented in Table 6.

Table 6: Randomized Subjects

Randomized subjects	DBV712 100 µg	DBV712 250 µg	Placebo	Total
Part A	20	20	10	50
Part B	0	233	117	350

In this age population, the estimated screen failure rate could be as high as 60% based on our previous experience in 4 to 11 years old subject population. As a consequence, approximately 1,000 peanut-allergic children 1 to 3 years may need to be screened to get the 400 randomized subjects.

Details for Part A and Part B are presented below.

Part A

During the first safety part of the study (Part A), 50 subjects (10 placebo subjects, 20 subjects at the 100 µg DBV712 dose, 20 subjects at the 250 µg DBV712 dose) will be randomized. The 20 subjects initially randomized at the dose of DBV712 not retained will continue at that dose up to Month 12 if there are no safety concerns regarding this dose.

After the 3-month safety DSMB analysis, 250 µg was selected as the highest safe dose.

Part B

The objective of the EPITOPE study is to assess the efficacy and safety of DBV712 to induce desensitization to peanut in peanut-allergic children 1 to 3 years after a 12-month treatment period of EPIT. This will be evaluated by assessing the percentage of treatment responders in the active DBV712 group selected for Part B (250 µg) compared to the placebo group.

Potential sample size reestimation for Part B

The analysis of Part A should provide a more accurate assessment of whether the sample size for Part B is appropriate or whether it needs to be adjusted. The current sample size calculation was done at a time when no data in 1-3 year-old subjects existed for DBV712. Therefore, the unblinded data from Part A is essential in refining the current sample size calculation for Part B.

Sample size adjustment could be proposed based on a combination of (but not limited to):

- a formal computation of probability of success (45).
- a reeassement of placebo response rate assumption.

If, for instance, the exact observed percentages of responders in Part A are believed to be the "true" rates in the population, then a higher placebo rate could require a greater sample size, as shown in Table 7 below.

Table 7: Examples of Exact Observed Percentages of Responders in Part A

Placebo responder rate	DBV712 250 µg responder rate	Total Sample Size
10%	40%	350
20%	50%	462
30%	60%	519

Regulators and IRBs will be informed if any sample size adjustments are needed.

9 ETHICAL, LEGAL, AND ADMINISTRATIVE ASPECTS

9.1 Informed Consent

The Investigator is responsible for and will obtain a signed ICF from each subject's parents/guardians, before each subject is admitted to the study, in accordance with the ICH-Good Clinical Practice (GCP) Guidelines, the Declaration of Helsinki, and local applicable regulatory requirements.

This consent form must be dated, signed and retained by the Investigator as part of the study records. The Investigator will not undertake any investigation specifically required only for the clinical study until valid consent has been obtained. The terms of the consent and when it was obtained must be documented in the subject's medical records and the e-CRF.

Subjects' parents/guardians will be informed of the nature of the study, its aim, its possible risks constraints, its expected benefits, its duration, and the compensation that they might receive. The protocol will be explained during a meeting prior to study enrollment, and each subject/parents/guardians must be informed that participation in the study is voluntary and that the subject may withdraw from the study at any time. The parents/guardians should read the ICF before signing and dating it and a copy of the signed document should be given to the parents/guardians. No subject can enter the study before informed consent has been obtained from her/his parents/guardians.

If a protocol amendment is required, the ICF may need to be revised to reflect the changes to the protocol. If the consent form is revised, it must be reviewed and approved by the

appropriate IEC/IRB, and signed by the parents/guardians of all subjects subsequently enrolled in the study as well as those currently enrolled in the study.

The Investigator should inform the subject's primary physician about participation in the clinical study wherever required.

9.2 Data Quality Assurance

The Sponsor or Sponsor's designee will conduct a site visit or a site phone contact, in case the investigator and the center are already known from DBV, to verify the qualifications of each Investigator, inspect the site facilities, inform the Investigator of his/her responsibilities and the required procedures for ensuring adequate site selection and proper documentation.

9.3 Database Management and Quality Control

All data generated by the site personnel will be captured electronically at each study center using e-CRFs. Data from external sources (such as laboratory data and exploratory BAT) will be imported into the central database.

Once clinical data are entered and validated in the e-CRF, they are transmitted and recorded by the central server in the central database. Computerized edit-checks will be developed in addition to manual review to detect any discrepancies and to ensure consistency of the data. The appropriate staff at the study site will answer queries sent to the Investigator. The reason for changes, the name of the person who performed the changes, together with the time and date will be automatically record by the Electronic Data Capture (EDC). An electronic audit trail system will be used to track all data changes in the database subsequent to the first data entry

If additional corrections are needed, the responsible monitor or data manager or the Sponsor will raise a query in the EDC application. Appropriate feedback to the study staff or other corrective measures will be undertaken if any missing data, inconsistent data, outlier data and potential protocol deviations are identified during routine remote data review.

Once all source data verification is complete and all queries are closed, the monitor will freeze the e-CRF page.

The specific procedures to be used for data entry and query resolution using the EDC system/e-CRF will be provided to study sites in a training manual. In addition, site personnel will receive training on the EDC system/e-CRF.

9.4 Source Documentation

All source documents from which e-CRF entries are derived should be kept in the subject's medical records.

For all e-CRF entries, for each subject, it must be possible to check these against source documents at the study site, excepted for the data generated for the study and recorded directly in the e-CRF.

As a minimum requirement, the following data must be source data verifiable in the subject's source documentation other than the e-CRF:

- Identification of subject (subject identifier: subject name, sex and date of birth)
- Confirmation of participation in the study (study identification, subject identification number and signed and dated informed consent);
- Diagnosis/indication under investigation;
- Relevant medical history, concomitant illness;
- Visit dates;
- Data related to the adverse events;
- Reason for subject exclusion during the selection or withdrawal from the study;

The Investigator will receive the laboratory reports from the central laboratory. The Investigator must review, sign and date the laboratory reports on the day of evaluation. The signed laboratory reports must be retained by the site as source documentation.

Data that will be entered directly into the e-CRF (those for which there is no prior written or electronic record of data) are considered to be source data. These data will be defined in the monitoring guidelines.

The pre-specified e-CRF entries, depending on the pre-specified source verified data, for each subject should be checked against source documents at the study site by the site monitor. Instances of missing or uninterpretable data will be discussed with the Investigator for resolution.

9.5 Data Collection/ electronic Case Report Form (e-CRF)

The Investigators (and appropriately authorized staff) will be given access to an online web−based EDC/e-CRF system, which is Food and Drug Administration (FDA) 21 CFR Part 11 compliant. This system is specifically designed for the collection of the clinical data in electronic format. Access and rights to the EDC system will be controlled and configured according to each individual's role throughout the study. In general, only the Investigator and authorized staff will be able to enter data and make corrections in the e-CRFs.

The specific procedures to be used for data entry and query resolution using the e-CRF will be provided to study sites in a training manual. In addition, site personnel will be trained on the e-CRF system.

The e-CRF should be promptly completed for each subject form whom an ICF was obtained and should reflect the latest observations on the subject participating in the study. Therefore, the e-CRFs are to be completed as soon as possible during or immediately after the subject's visit or assessment. The Investigator must verify that all data entries in the e-CRF are accurate and correct. If some assessments cannot be done, or if certain information is unavailable, not applicable or unknown, the Investigator should indicate it in the e-CRF.

Computerized data-check programs and manual checks will identify any clinical data discrepancies for resolution. Corresponding queries will be loaded into the system and the site will be informed about new issues to be resolved on-line. All discrepancies will be solved on-line directly by the Investigator or by authorized staff. Off-line edit checks will be done to examine relationships over time and across panels to facilitate quality data.

Information concerning IMP dispensation to the subject will be tracked in the e-CRF. After completion, the Investigator will be required to validate and electronically sign-off the clinical data recorded in each e-CRF.

9.6 Access to Source Data

9.6.1 Routine Monitoring

During the study, a Contract Research Organization (CRO) site monitor will make site visits to review protocol compliance, compare e-CRF entries and individual subject's medical records, assess drug accountability, and ensure that the study is being conducted according to ethical and pertinent regulatory requirements. The e-CRF entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that subject confidentiality is maintained.

Checking of the e-CRF entries for completeness and clarity, and cross-checking with source documents, will be required to monitor the progress of the study. Direct access to source data will be required for the monitoring activities.

9.6.2 Inspections and Auditing Procedures

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

Moreover, Regulatory Authorities of certain countries, IRBs and IECs may wish to carry out such source data checks and/or on-site audit inspections. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and medical confidentiality. The Investigator assures CRO and the Sponsor of the necessary support at all times.

The purpose of an audit is to assess whether ethics, regulatory and quality requirements are fulfilled.

9.7 Data Processing

All data will be entered by site personnel into the e-CRF (as detailed in Section 9.3).

The data-review and data-handling document, to be developed during the initiation phase of the study, will include specifications for computerized edit-checks: consistency and plausibility checks on data and will also include data-handling rules for obvious data errors. Query/correction for unresolved queries will be automatically sent for resolution with the Investigator. The database will be automatically updated after corrections are made by the investigator's staff.

Previous and concomitant medications will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutical Chemical (ATC) classification system. Disease and Medical histories/current medical conditions and AEs will be coded using the MedDRA terminology.

The actual versions of the coding dictionaries will be provided in the CSR.

9.8 Archiving Study Records

All data derived from the study will remain the property of the Sponsor. Records must be retained in accordance with the current ICH Guidelines on GCP. All essential study documents including records of subjects, source documents, e-CRFs and IMP inventory must be kept in a study-specific file.

Trial documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or planned marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the product.

For this study, the Investigator site files records must be retained by the Investigator at least 15 years after the completion of the trial, or longer if required by their national regulation.

Subjects' medical records must be kept for the maximum period permitted by the hospital, institution or private practice.

The Investigator will not discard any relevant records to this study without prior written permission from the Sponsor. The Investigator shall notify the Sponsor in writing of their intent to destroy all such material. The Sponsor shall have 30 days to respond to the Investigator's notice, and the Sponsor shall have a further opportunity to retain such materials at the Sponsor's expense.

The Investigator shall take responsibility for maintaining adequate and accurate hard copy source documents of all observations and data generated during this study. Such documentation is subject to inspection by the Sponsor, its representatives and Regulatory Authorities. If an Investigator moves, withdraws from the study or retires, the responsibility for maintaining the records may be transferred to another person who will accept responsibility. Notice of transfer must be made to and agreed by the Sponsor.

9.9 Good Clinical Practice

The procedures set out in this study protocol are designed to ensure that the Sponsor and Investigator abide by the principles of the ICH-GCP Guidelines, and of the Declaration of Helsinki (APPENDIX 1). The study also will be carried out in keeping with local legal requirements.

9.10 Protocol Approval and Amendment

Before the start of the study, the study protocol and/or other relevant documents will be reviewed and approved by the IEC/IRB/Regulatory Authorities, in accordance with local legal requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first subject is enrolled in the study.

This protocol is to be followed exactly. Any change to the protocol must be handled as a protocol amendment. Any potential amendment must be approved by the Sponsor. A written amendment must be submitted to the appropriate Regulatory Authorities and to the IRB/IECs assuming this responsibility. The Investigator must await IRB/IEC approval of substantial protocol amendments before implementing the changes, except where necessary to eliminate apparent immediate hazard to subjects.

All substantial amendments to the protocol must be approved in writing by both the appropriate Regulatory Authorities and the IRB/IEC, except for administrative amendments, which require notification but not written approval. Once approved, the protocol amendment will be distributed to all recipients of the original protocol, with instructions to append the amendment to the protocol. If, in the judgment of the local IRB/IEC, the Investigator and/or Sponsor, the protocol amendment alters the study design, procedures and/or increases the potential risk to the subject, the currently approved written ICF will require modifications. The modified ICF must also be reviewed and approved by the Sponsor, appropriate Regulatory Authorities, and the IRB/IEC. In such cases, repeat informed consent must be obtained from the enrolled subjects' parents/guardians before participation continues.

9.11 Data and Safety Monitoring Board

A DSMB composed of experts in food allergy and in the methodology of clinical studies will be established in due time for the first data review. This DSMB will be independent of the Sponsor and will review safety data from the study at specified intervals during the study and on an ad hoc basis as deemed necessary by the DSMB Chair person or when conveyed by the Sponsor.

The DSMB members will review blinded data, but may have access to unblinded data as deemed necessary during the closed review meetings. During these review meetings, the DSMB will assess whether the nature, frequency, and severity of the AEs associated with the study treatment warrant any recommendations or corrective actions of the study conduct in the best interest of the subjects.

A specific DSMB meeting will review the safety analysis on the initial 50 first subjects included in the 3 treatment arms of the Part A, DBV712 100 µg and 250 µg and placebo when they will reach 3 months of patch application. These safety data will be reviewed unblindly be the DSMB for forming their recommendation on the dose selection for the study part B.

Another specific DSMB meeting will be conducted on the futility analysis based on peanut-specific IgG4 measurements and the safety data when all the subjects of the Part B will reach 6 months of treatment. These data will be reviewed unblindly by the DSMB for forming their recommendation on the continuation of the study.

The roles, responsibilities, constitution, and operations of the DSMB will be described in the DSMB Charter, which will be reviewed and signed by each member before the first subject is enrolled in the study.

9.12 Duration of the Study

For an individual subject, the maximum duration of study participation will be up to 62 weeks (including up to 6 weeks for screening, 12 months of treatment and up to 4 weeks for follow-up). The planned overall study duration is expected to be approximately of 30 months. The date of the study start will be defined as the date of the first visit of the first subject and the study end will be defined as the last visit of the last subject.

9.13 Premature Termination of the Study

If the Investigator, the Sponsor, or the Medical Monitor becomes aware of conditions or events that suggest a possible hazard to subjects if the study continues, the study may be terminated after appropriate consultation between the relevant parties. The study may also be terminated early at the Sponsor's discretion in the absence of such a finding.

Conditions that may warrant termination include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the subjects enrolled in the study;
- Failure to enroll subjects at an acceptable rate;
- A decision on the part of the Sponsor to suspend or discontinue development of the drug;
- A decision from the Regulatory Authorities to suspend or discontinue the study;
- Lack of evidence of therapeutic benefit according to the interim futility analysis.

In terminating the study, the Sponsor and the Investigator will ensure that adequate consideration is given to the protection of the subjects' interests.

9.14 Confidentiality

All information including the skin photos, obtained during the conduct of the study with respect to the subject's state of health will be regarded as confidential. For disclosure of any such information, an agreement will be obtained in writing. The Investigator must ensure that each subject's anonymity is maintained. On e-CRFs, the other documents and the skin photos transmitted to the Sponsor or its representatives, subjects must not be identified by name. Instead, subjects will only be known by the unique subject screening number allocated to them in order to ensure confidentiality on all study documentation. Subjects will retain this unique number throughout the study. The Investigator will keep a separate log of these codes.

In order to comply with government regulatory guidelines and to ensure subject safety, it may be necessary for the Sponsor and its representatives, the IEC/IRB, or Regulatory Authority to review subjects' medical records as they relate to this study. Only the subject's unique number in the e-CRFs will identify her/him, but their full names may be made known to a Regulatory Authority or other authorized government or health care officials, if necessary, and to personnel designated by the Sponsor.

Documents that are not for submission to the Sponsor (for example consent forms) will be maintained by the Investigator in strict confidence, except to the extent necessary to allow monitoring by the Sponsor and its representatives, and auditing by regulatory authorities. No documents identifying subjects by name will leave the investigative site and subject identity will remain confidential in all publications related to the study.

9.15 Contractual and Financial Details

The Investigator (and/or, as appropriate, the hospital administrative representative) and the Sponsor will sign a clinical study agreement prior to the start of the study, outlining overall Sponsor and Investigator responsibilities in relation to the study. The contract should

describe whether costs for pharmacy, laboratory and other protocol-required services are being paid directly or indirectly.

Financial Disclosure Statements will need to be completed, as requested by FDA CFR 21 part 54.

9.16 Liability and Insurance

The Sponsor will take out reasonable third-party liability insurance coverage in accordance with all local legal requirements. The civil liability of the Investigator, the persons instructed by her/him and the hospital, practice, or institute in which they are employed and the liability of the Sponsor with respect to financial loss due to personal injury and other damage that may arise as a result of the carrying out of this study are governed by the applicable law.

Deviations from the study protocol, especially the prescription of a dose other than that scheduled in the study protocol, other modes of administration, other indications, and longer treatment periods, are not permitted and shall not be covered by the statutory subject insurance scheme.

The Sponsor will arrange for subjects participating in this study to be insured against financial loss due to personal injury caused by the pharmaceutical products being tested or by medical steps taken in the course of the study.

9.17 Publication Policy

By signing the study protocol, the Investigator agrees with the use of results of the study for the purposes of national and international registration, publication and information for medical and pharmaceutical professionals. If necessary, Regulatory Authorities will be notified of the Investigator's name, address, qualifications and extent of involvement.

An Investigator shall not publish any data (poster, abstract, paper, etc.) without having consulted with the Sponsor in advance and having received a written approval for such a publication. Details are provided in a separate document.

9.18 Study Center File Management

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

- IB;
- Current, signed version of the protocol and any previous versions of the protocol;
- Protocol amendments (if applicable);
- Operations Manual (if applicable);
- Current ICF (blank) and any previous versions of the ICF;
- Curricula Vitae of Investigator(s) and sub-investigator(s) and photocopy of their respective license(s) where required by law; Original US FDA Form 1572 (for all studies conducted under US Investigational New Drug [IND] regulations), signed by all Principal Investigators. The names of any sub-investigators must appear on this

form. Investigators must also complete all regulatory documentation as required the ICH GCP and by local or national regulations;

- Documentation of IRB/IEC approval of the protocol, the ICF, any protocol amendments, and any ICF revisions;
- All correspondence between the Investigator, IRB/IEC, and the Sponsor/ CRO relating to study conduct;
- Laboratory Manual and certification(s);
- Monitoring log;
- IMP accountability forms;
- Signature list of all staff completing e-CRFs;
- Signature list of all staff completing drug accountability summaries; and
- Delegation log.

9.19 Clinical Study Report

A final CSR will be prepared according to the ICH E3 guideline on Structure and Contents of CSRs. A final CSR will be prepared regardless of whether the study is completed or prematurely terminated. The Sponsor will provide each Investigator with a copy of the final report or synopsis for retention.

10 Literature Cited

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11 APPENDICES

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APPENDIX 1

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APPENDIX 2

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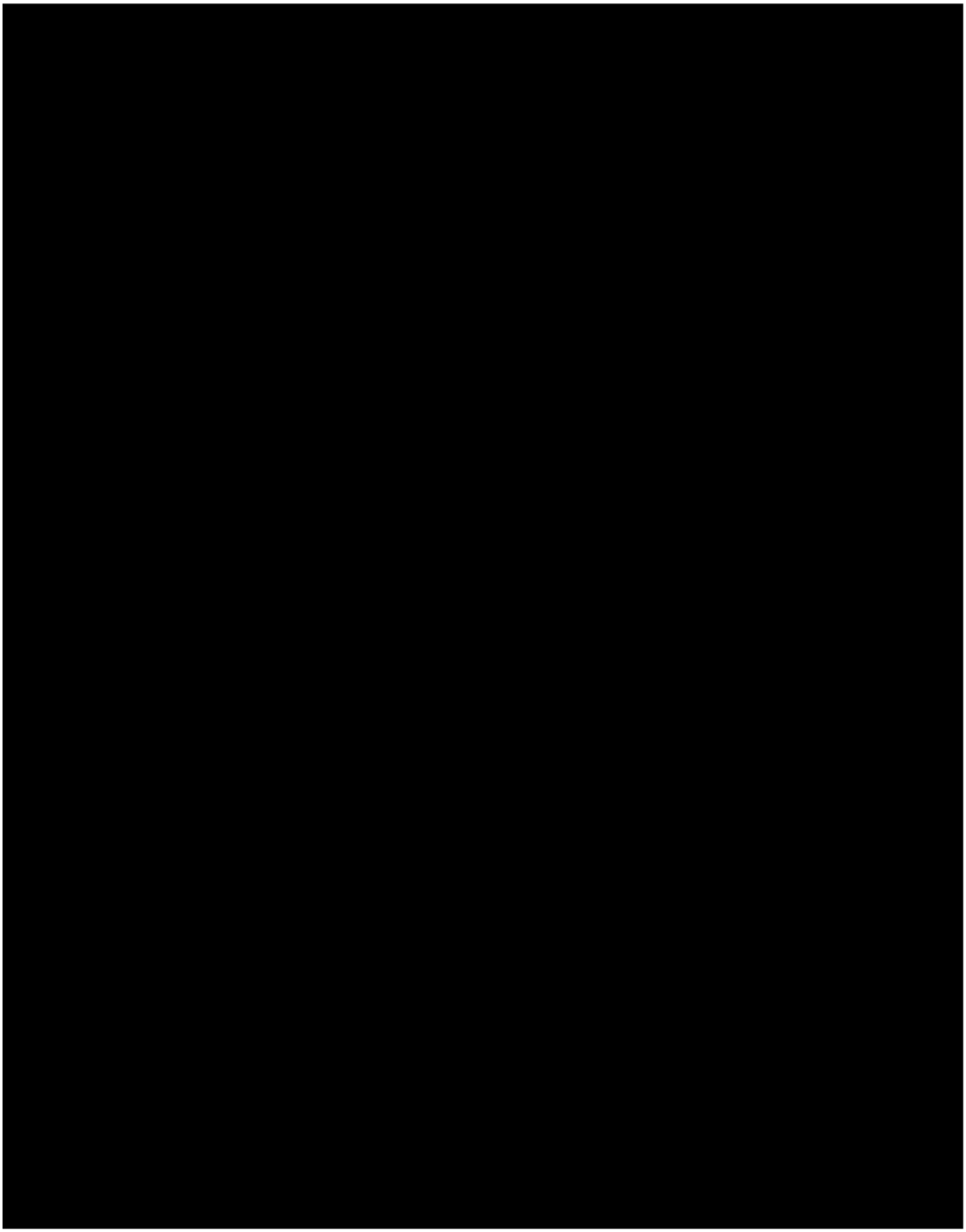
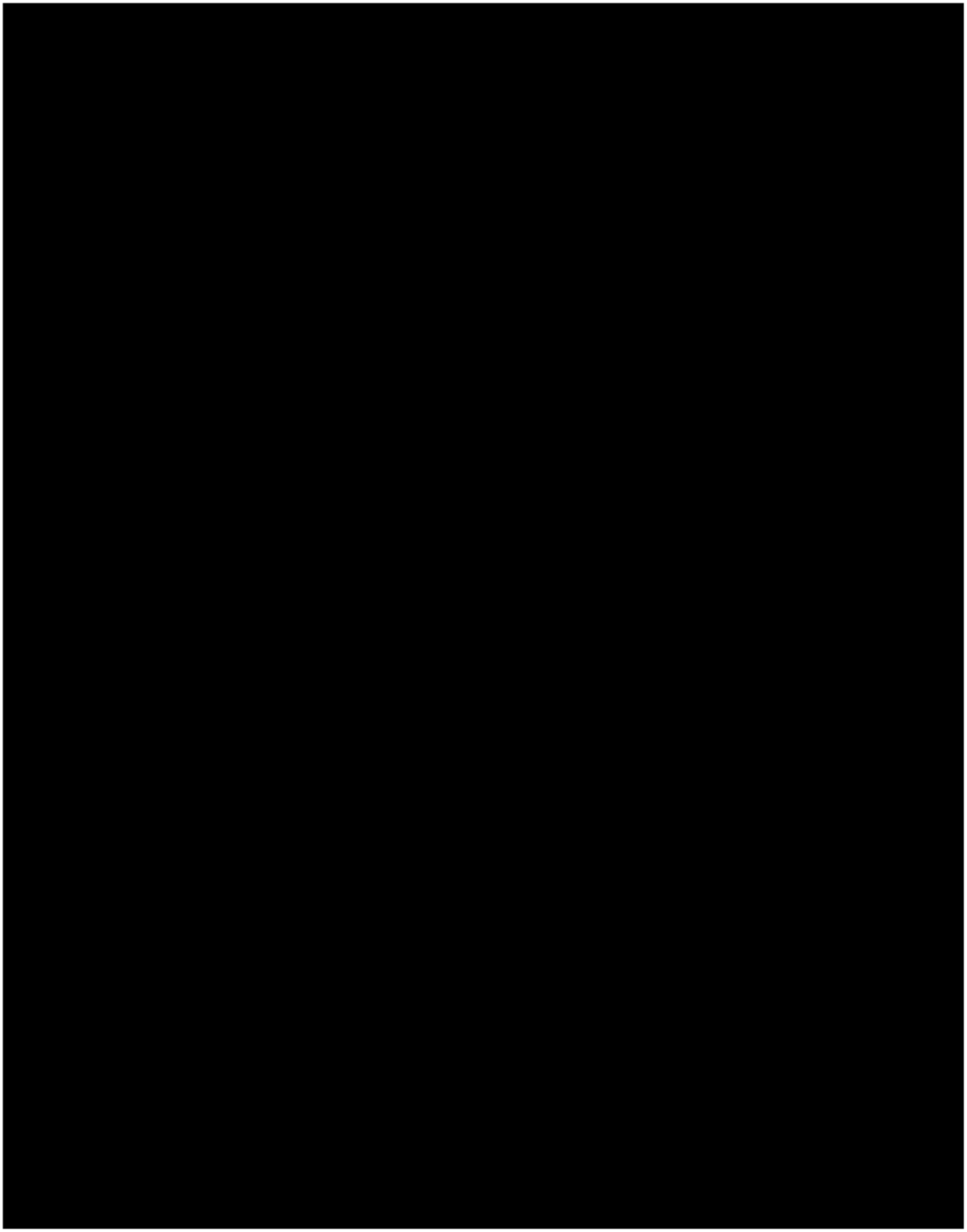
APPENDIX 3

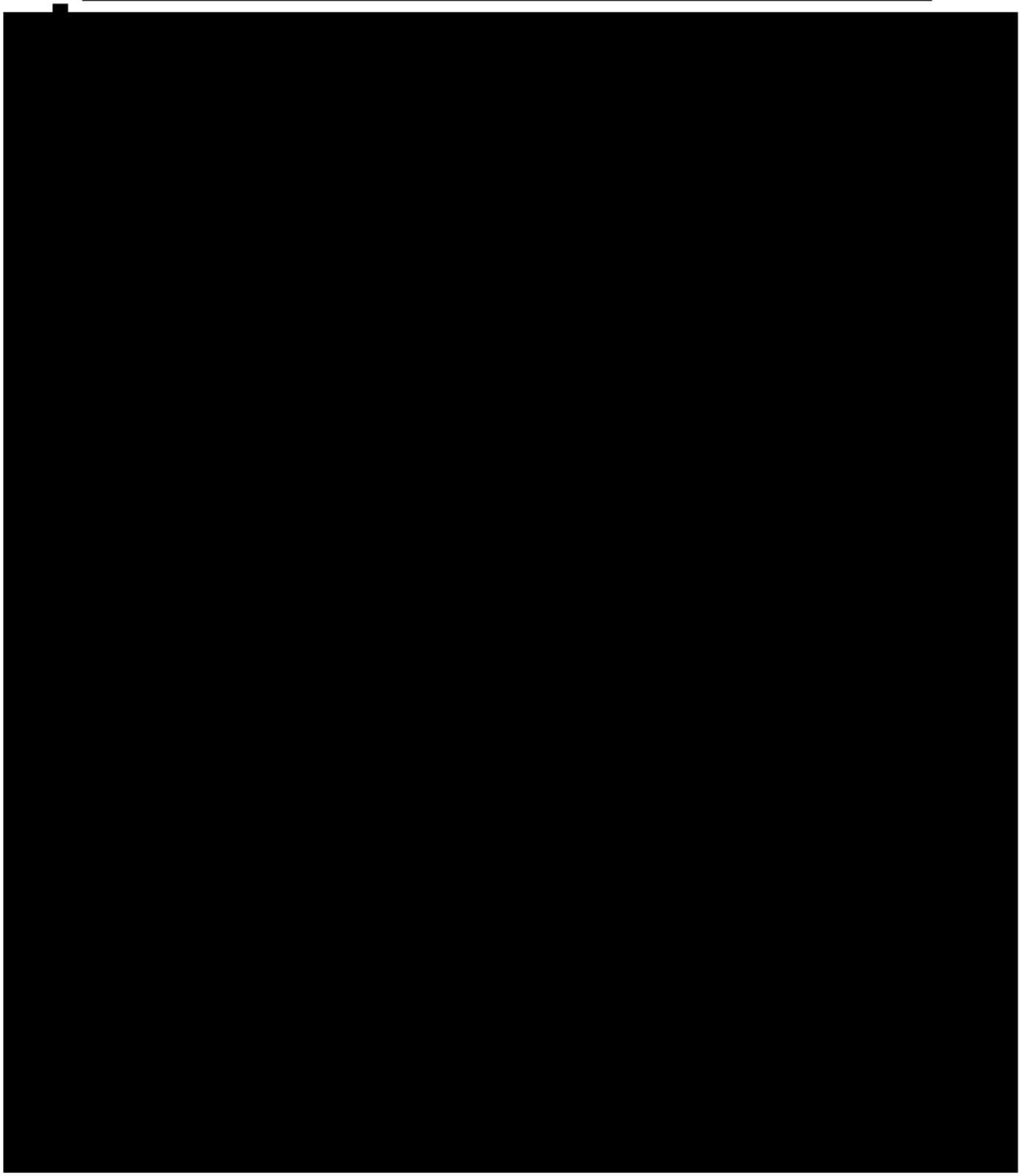


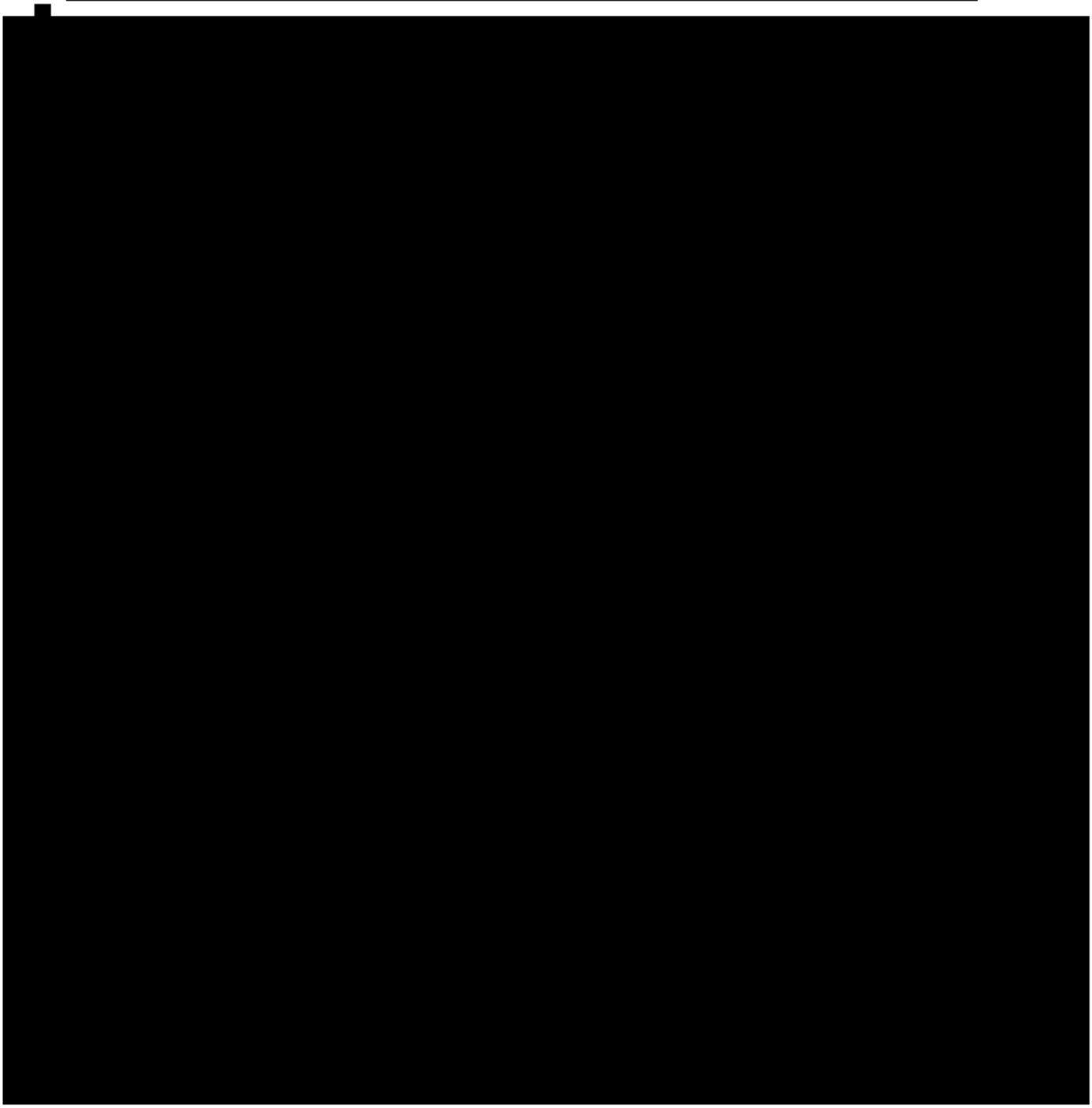
APPENDIX 4

[1]Sampson, Hugh A. (2008) Anaphylaxis and Food Allergy. In : Dean D. Metcalfe, coord.: Food allergy. Adverse reactions to foods and food additives. 4th ed. Malden, Mass: Blackwell Publishing, p. 157-170

APPENDIX 5







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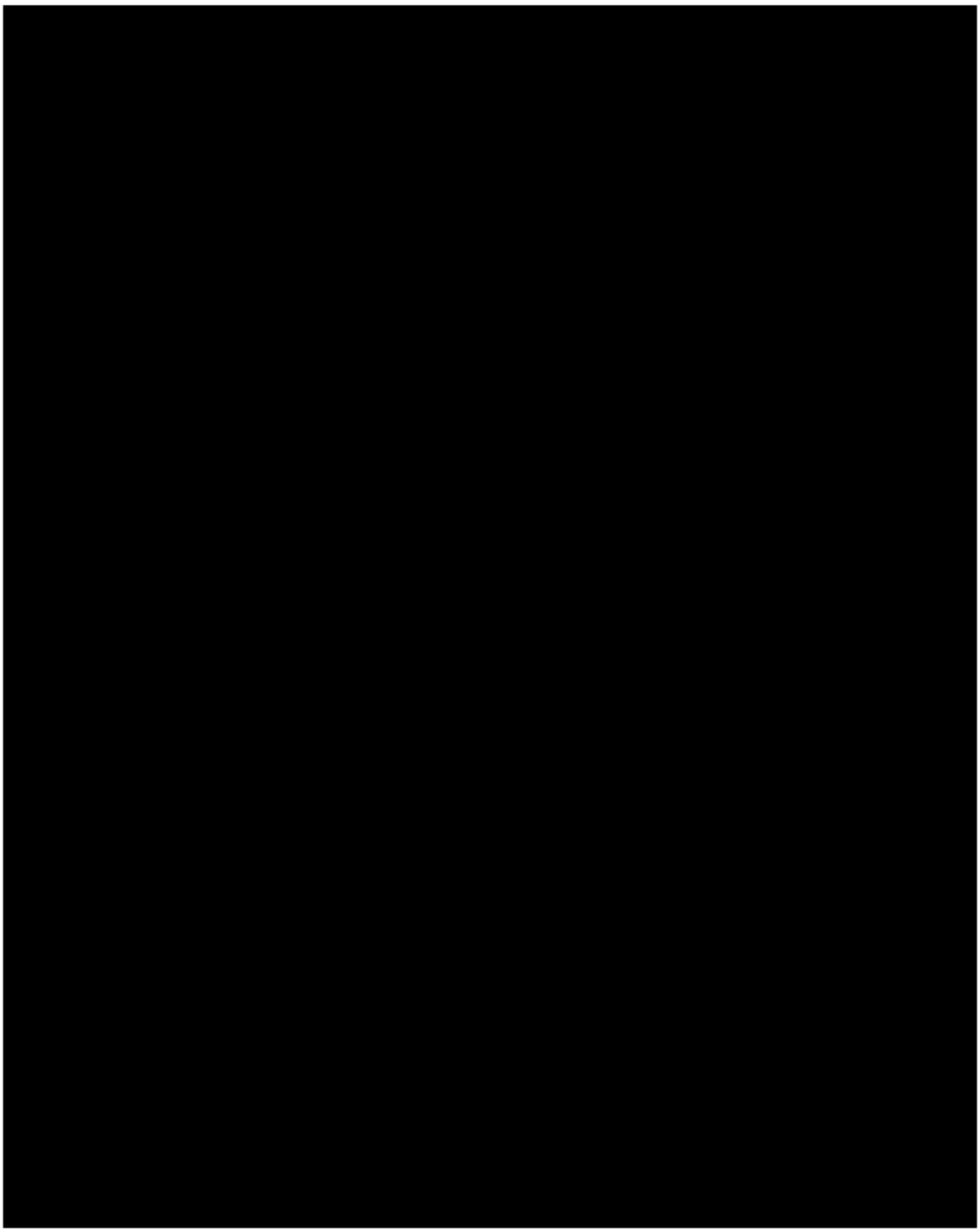

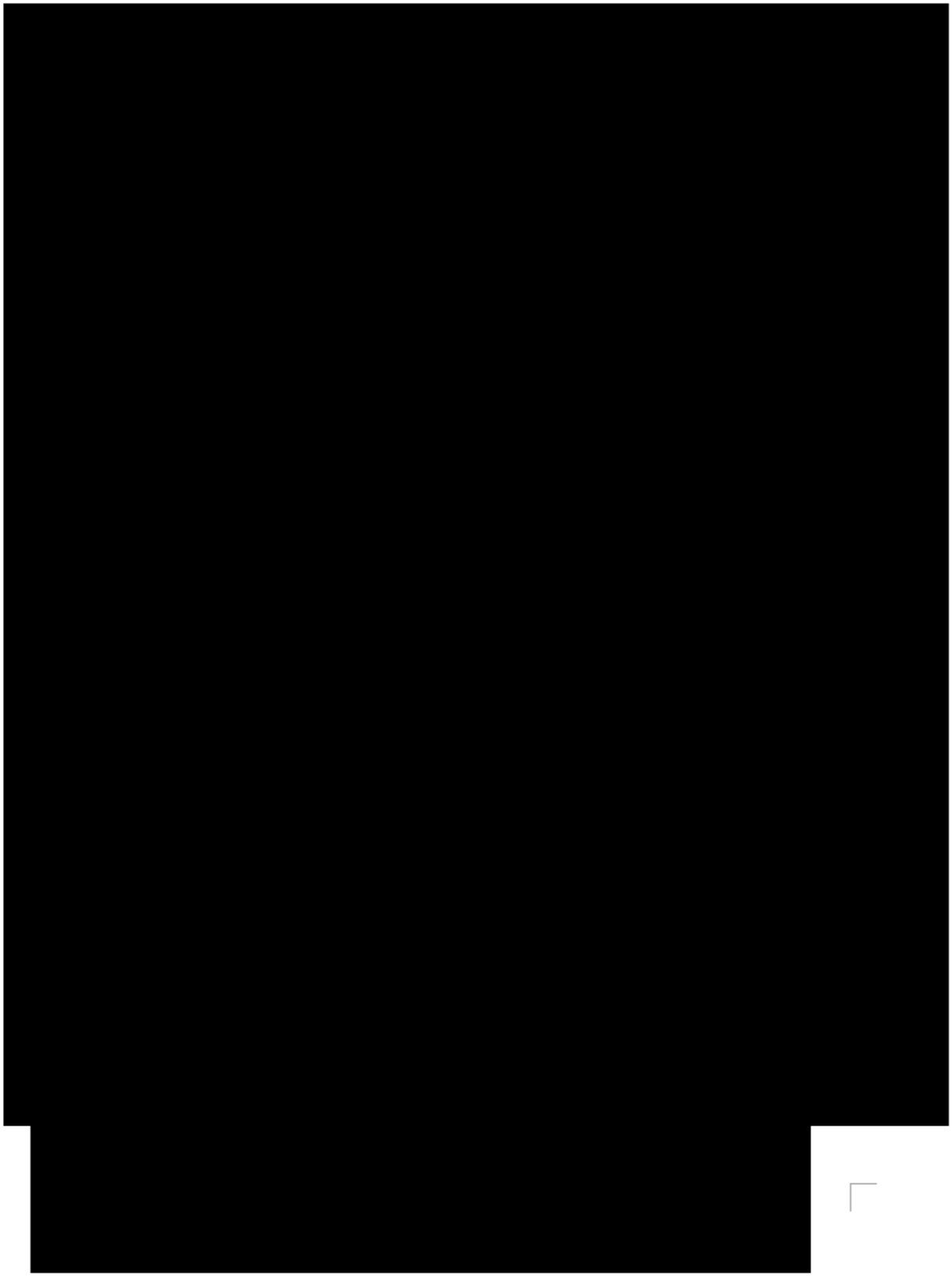

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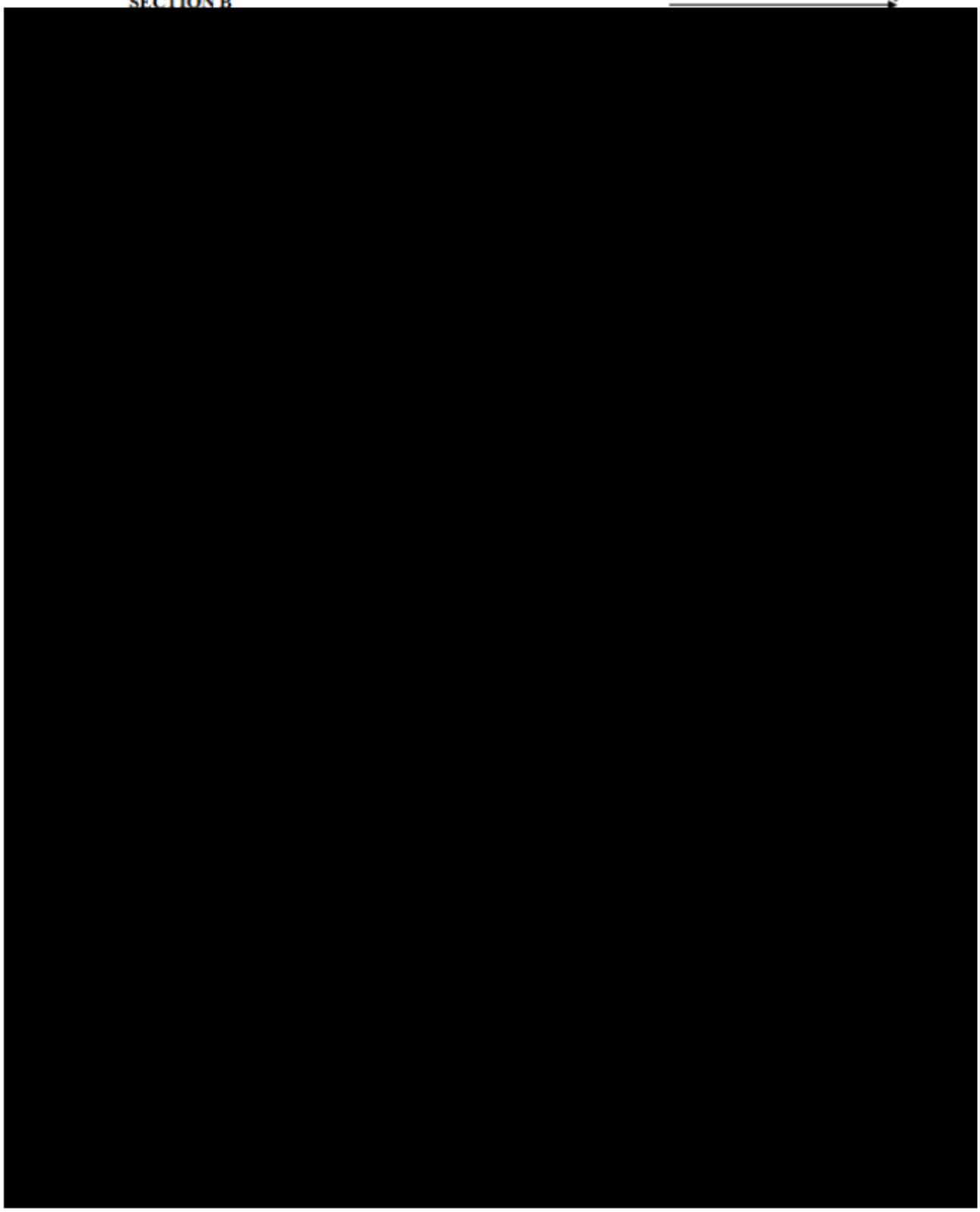

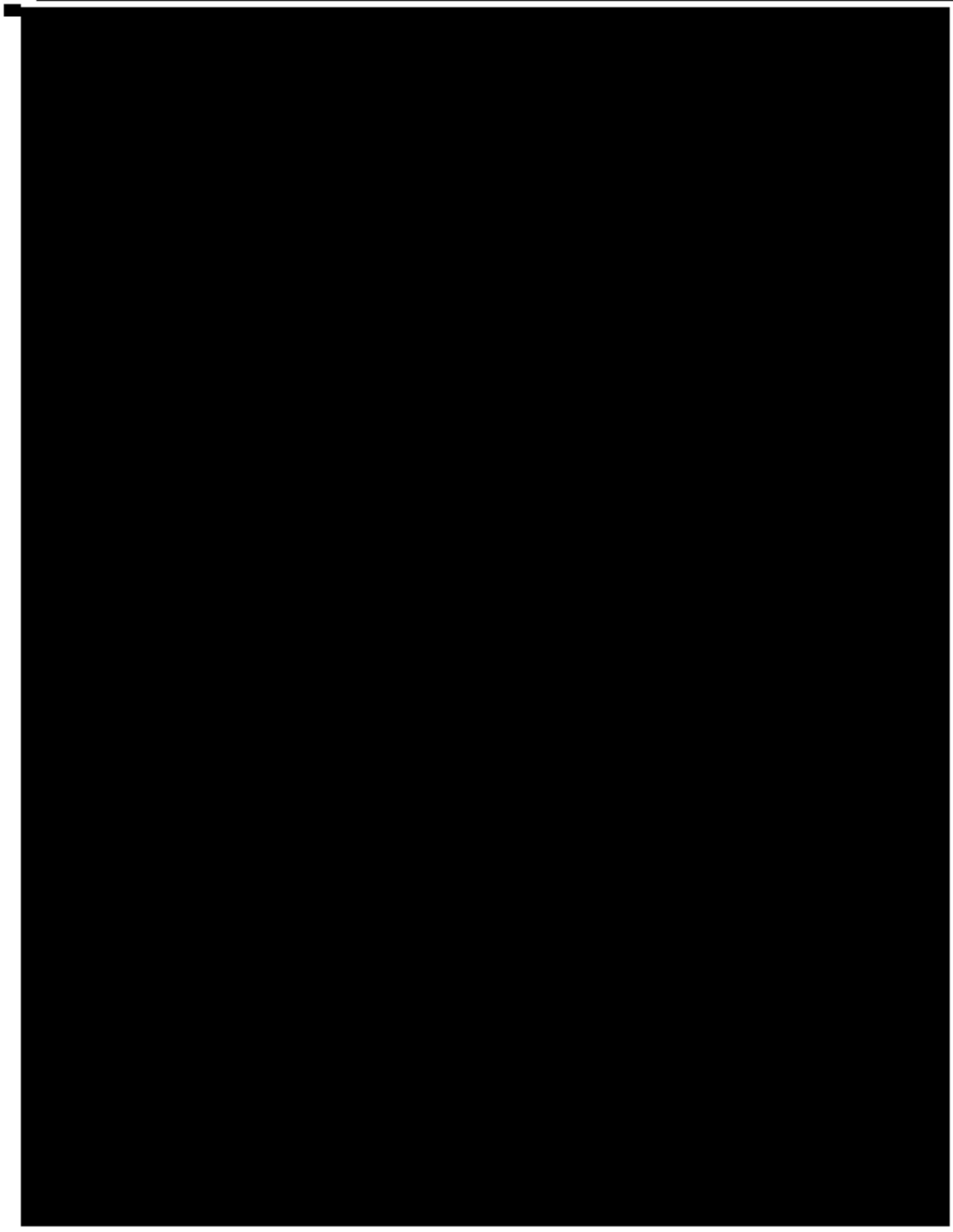

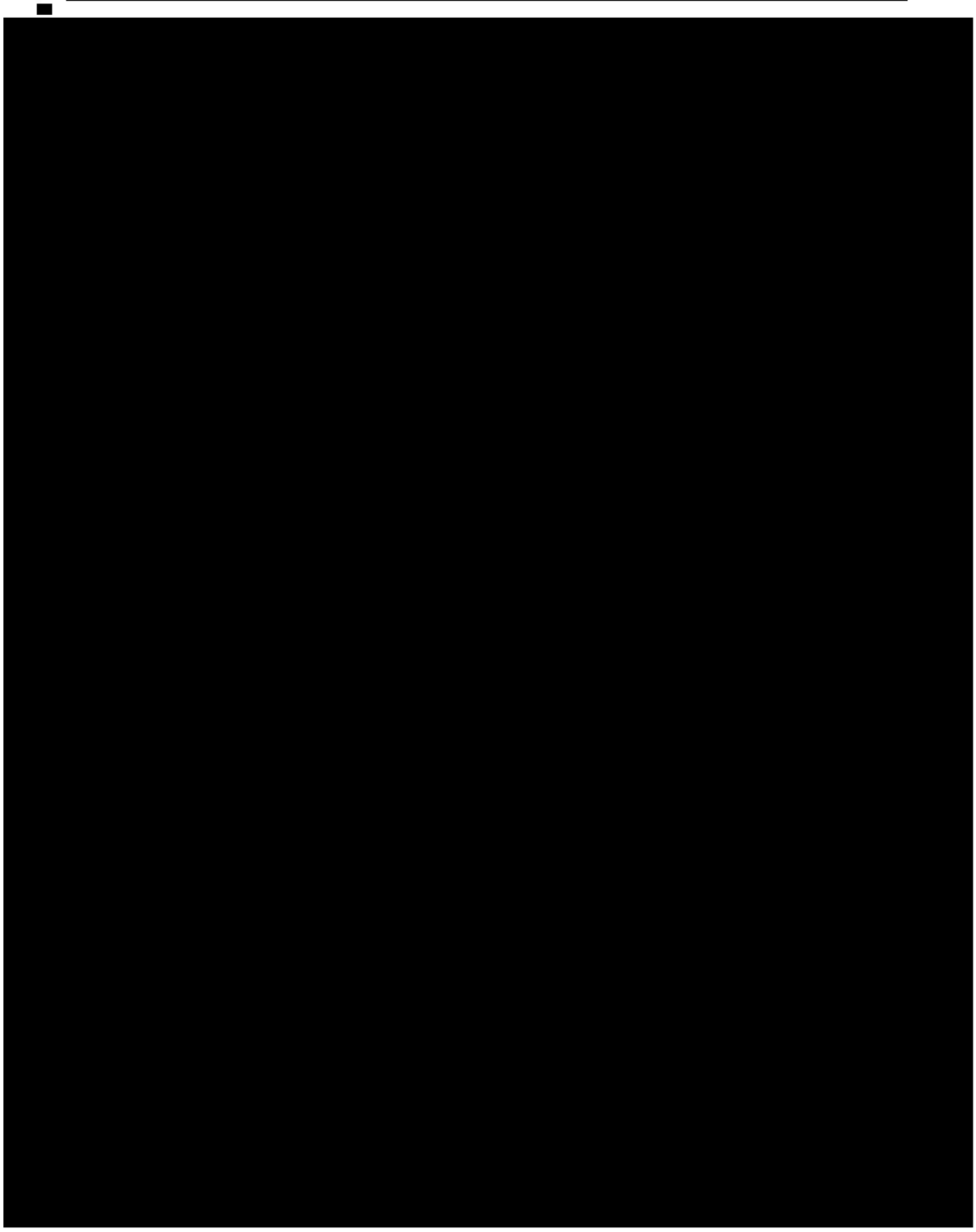

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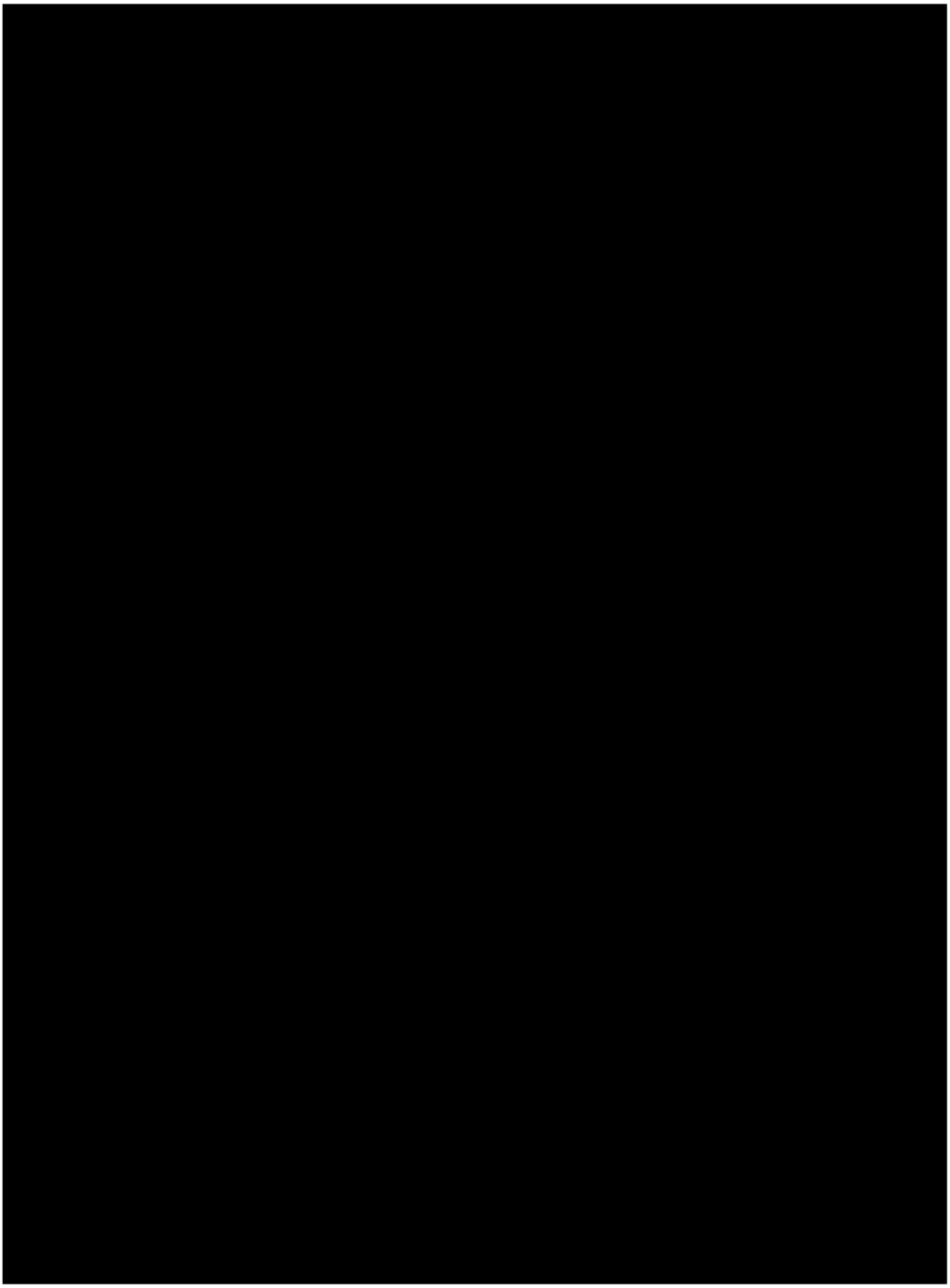

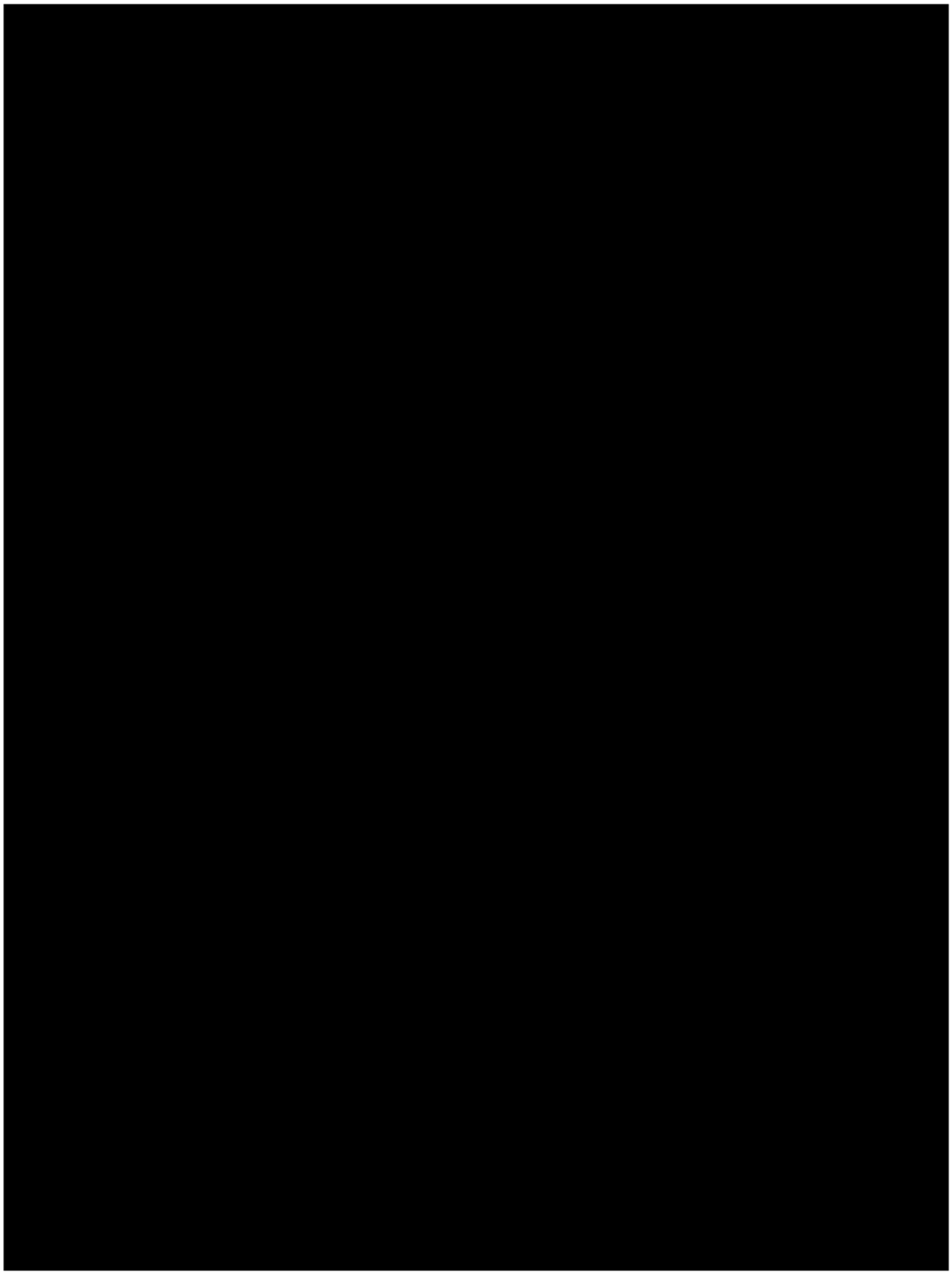

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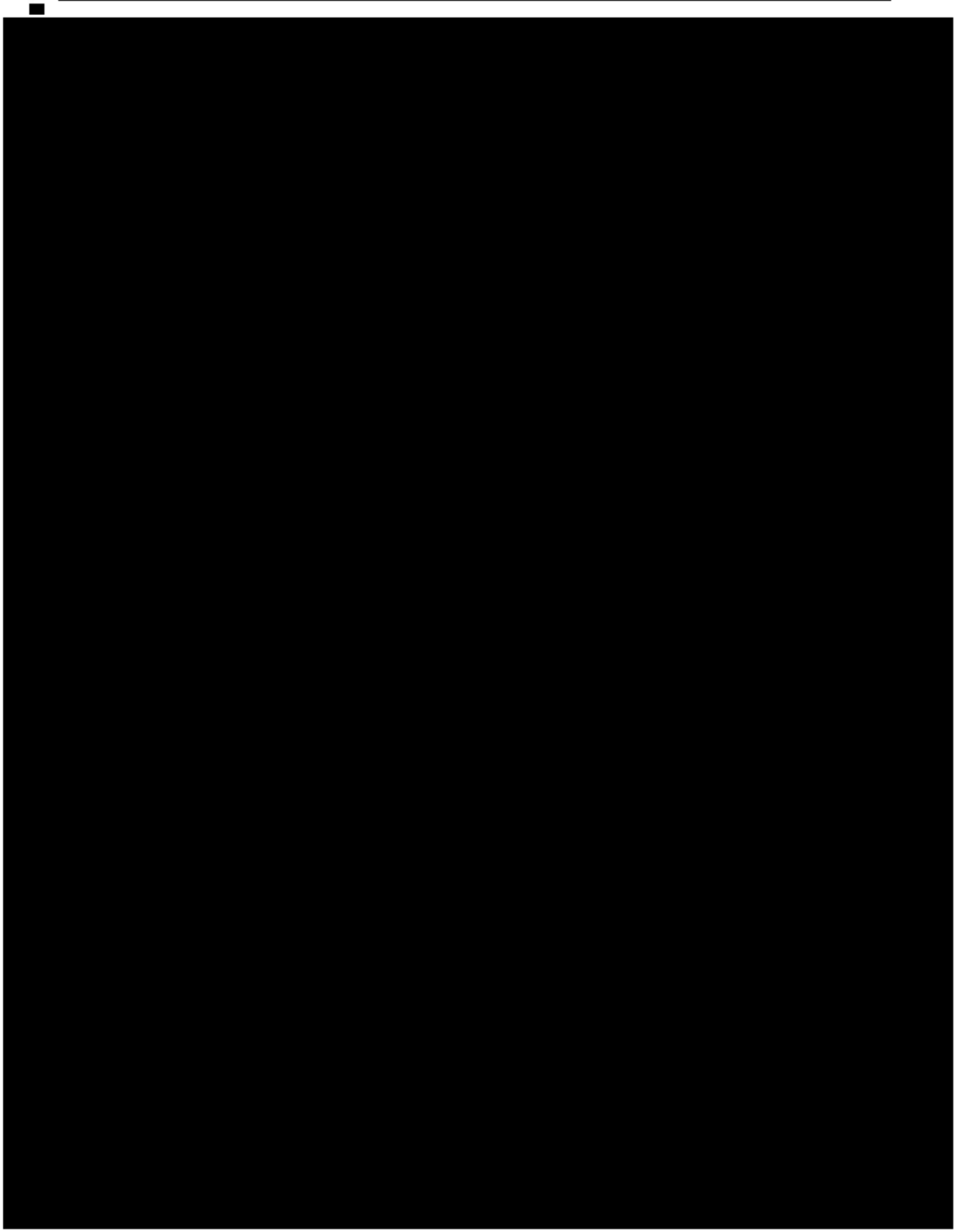

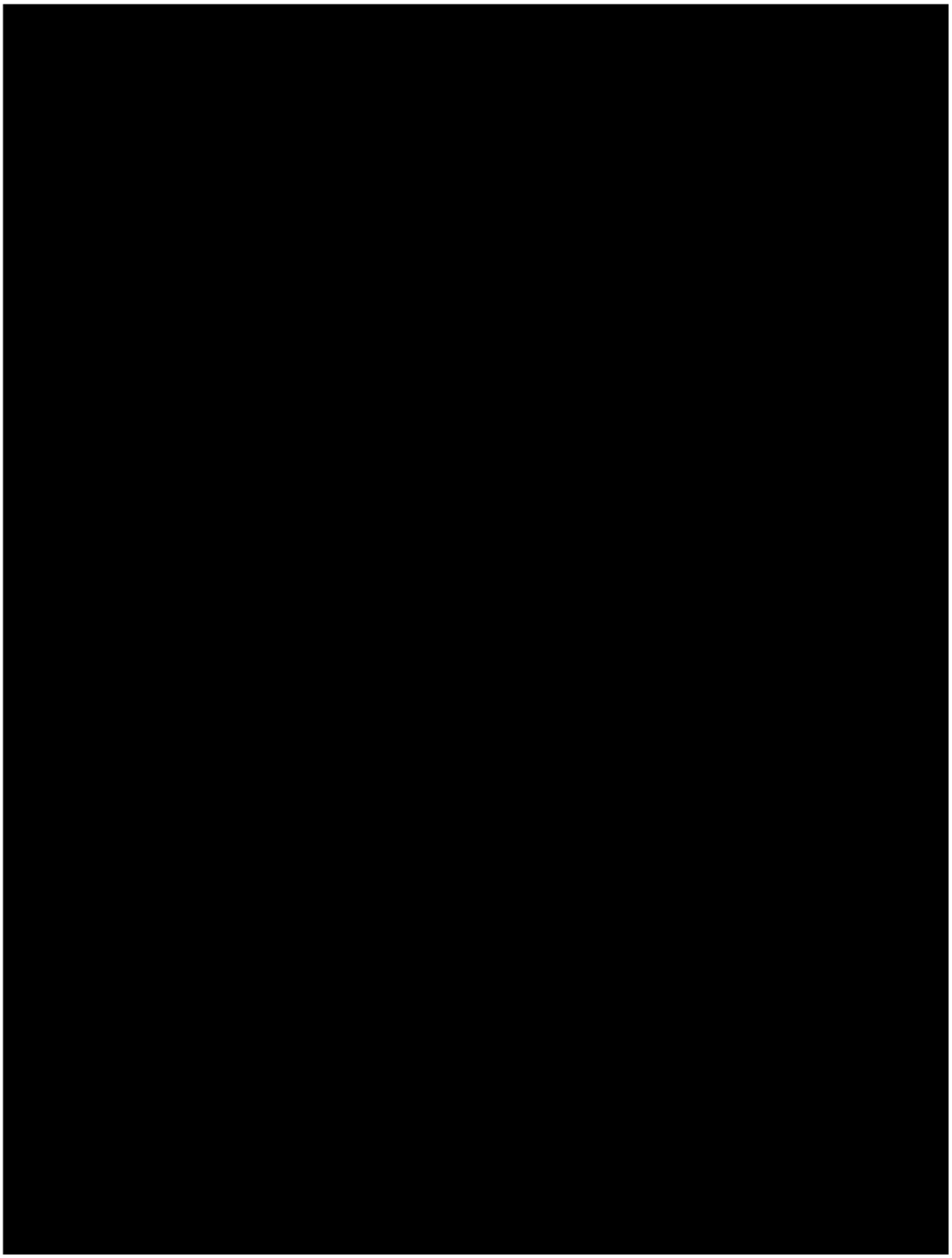

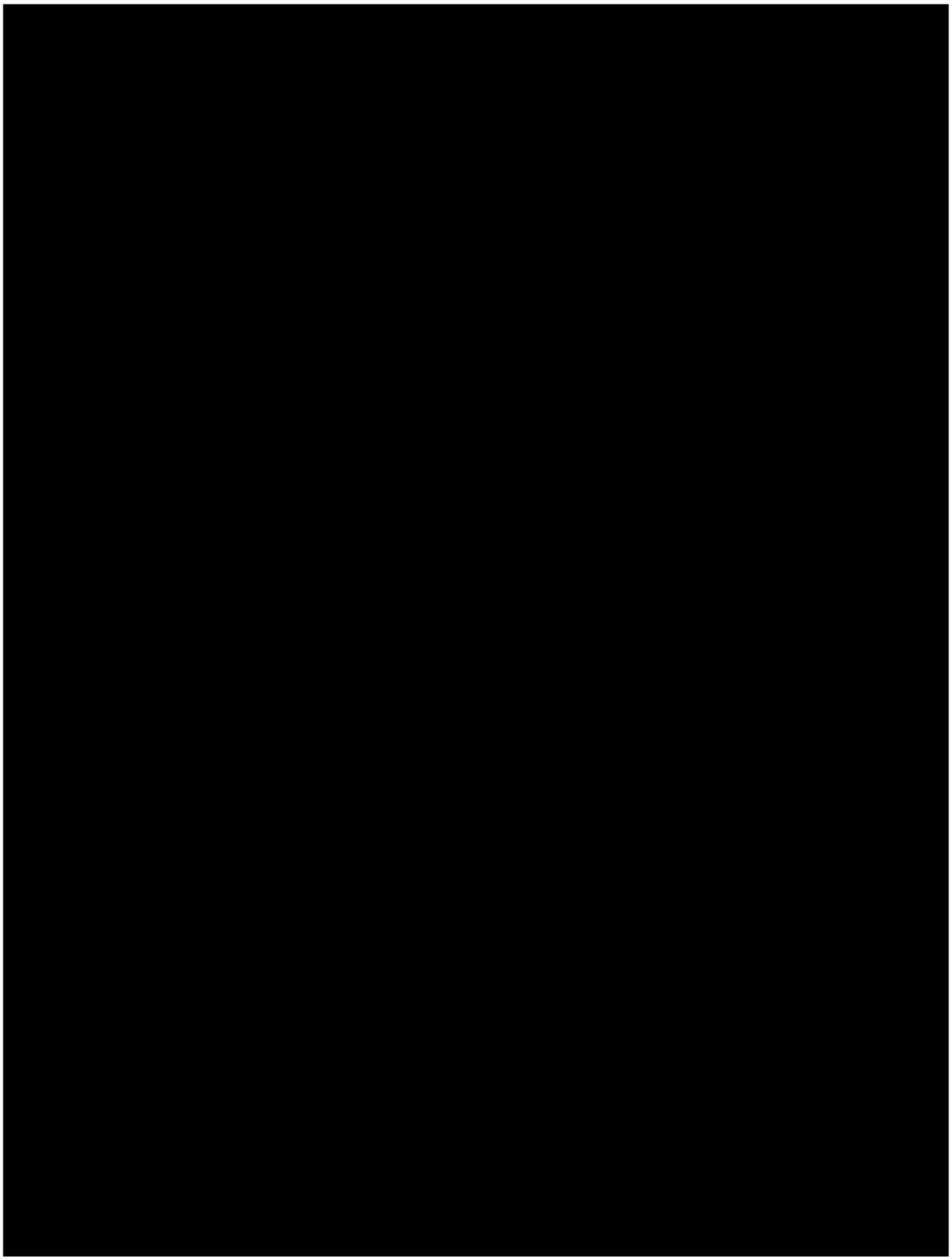

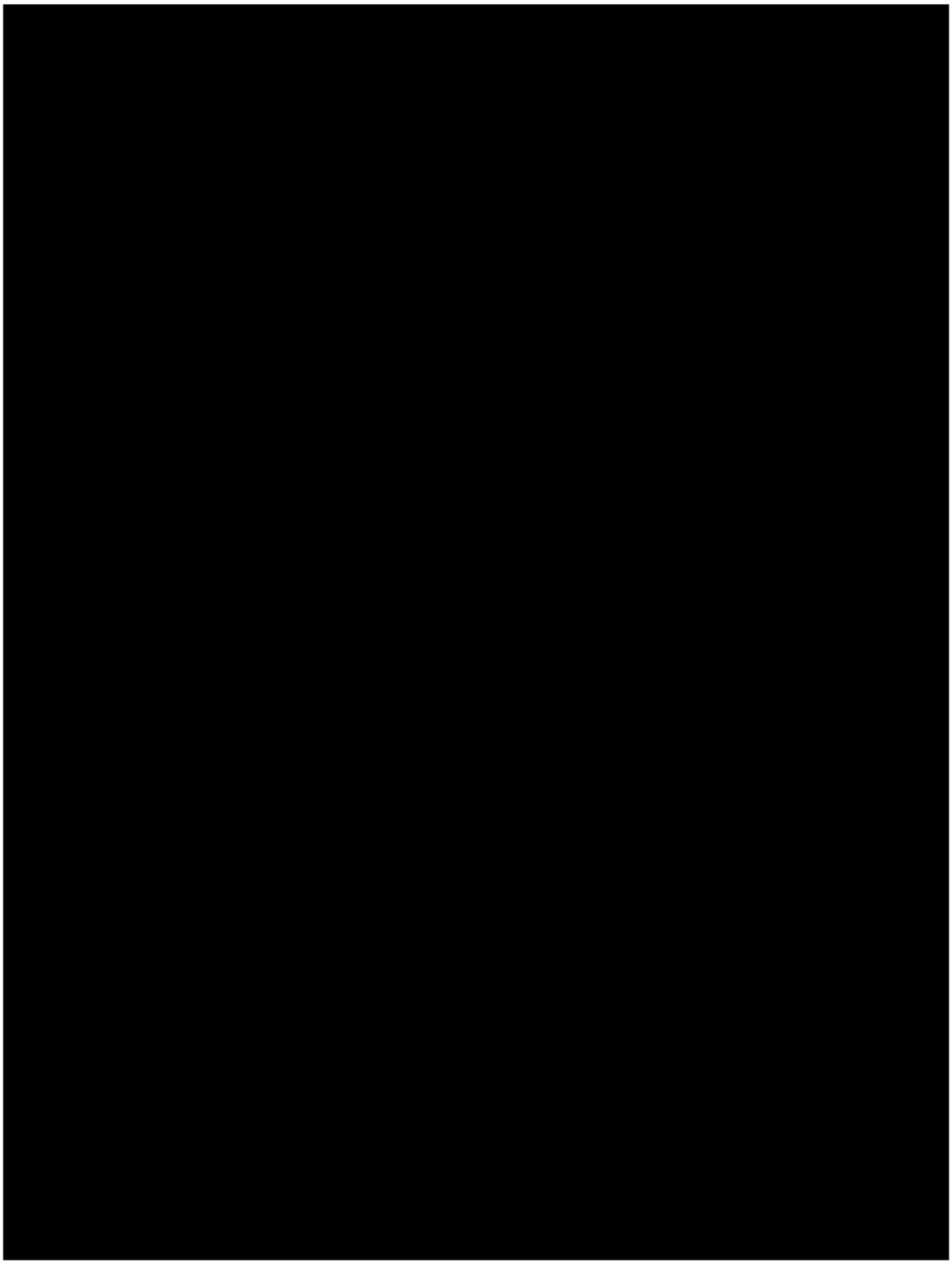

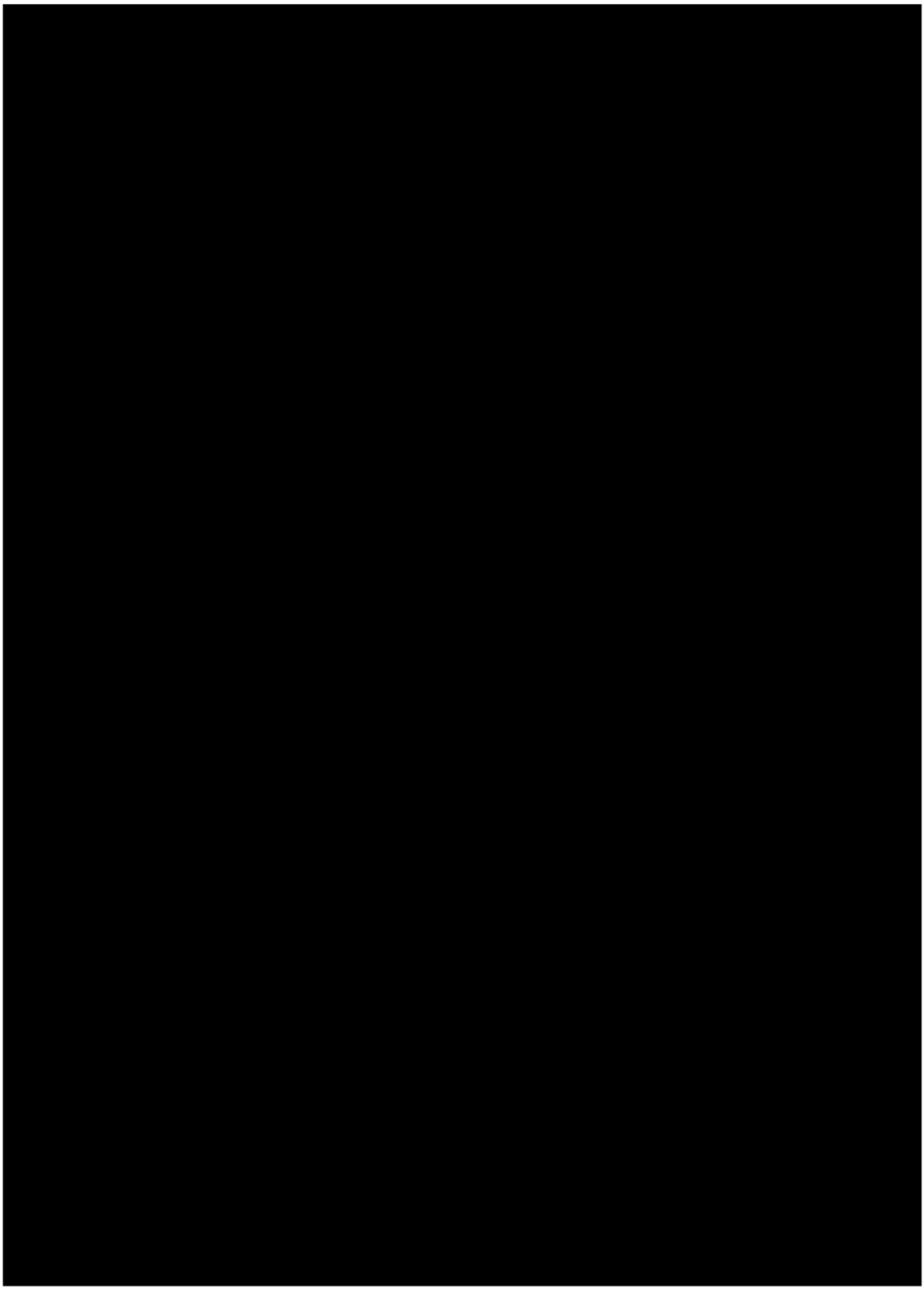

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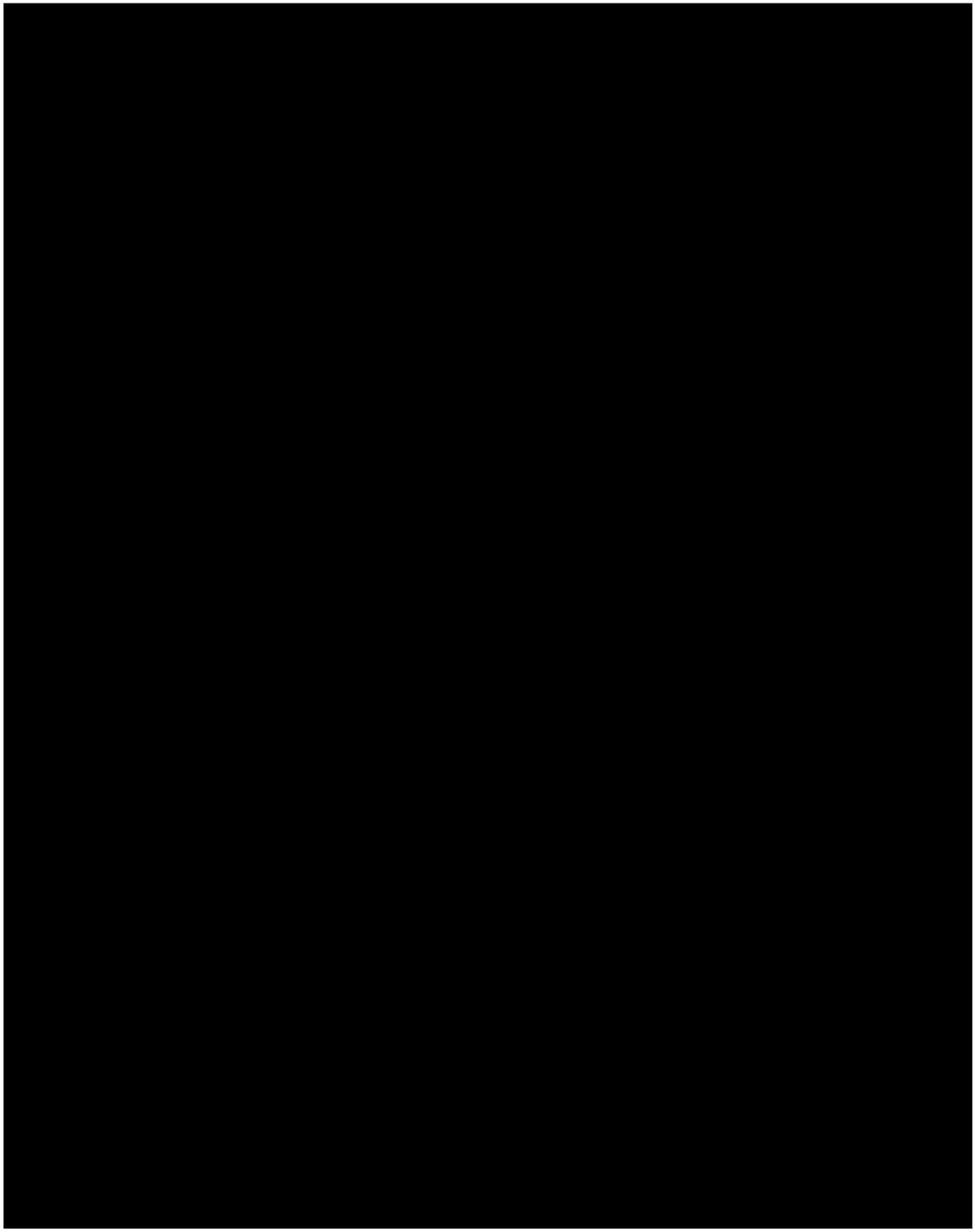

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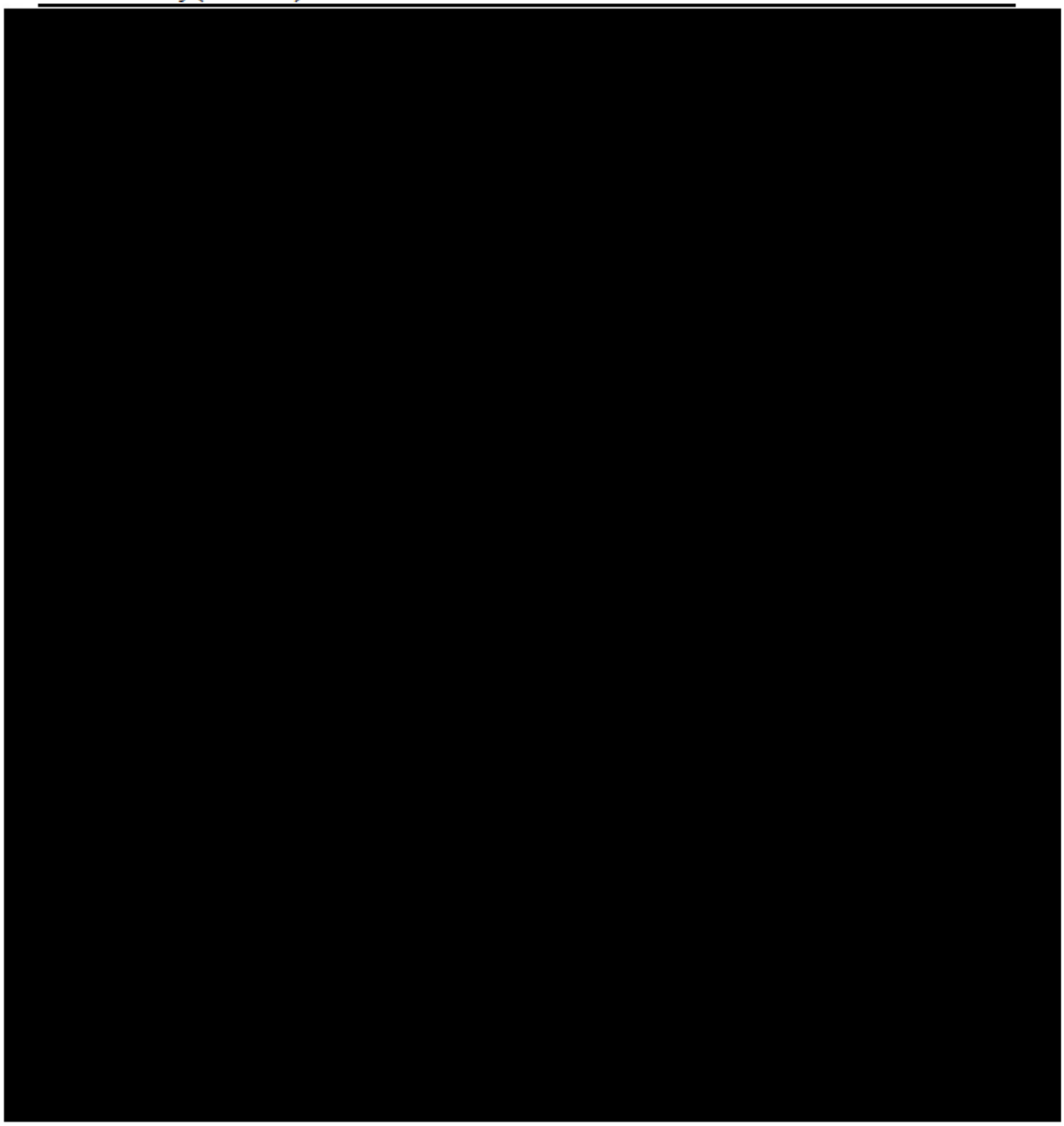

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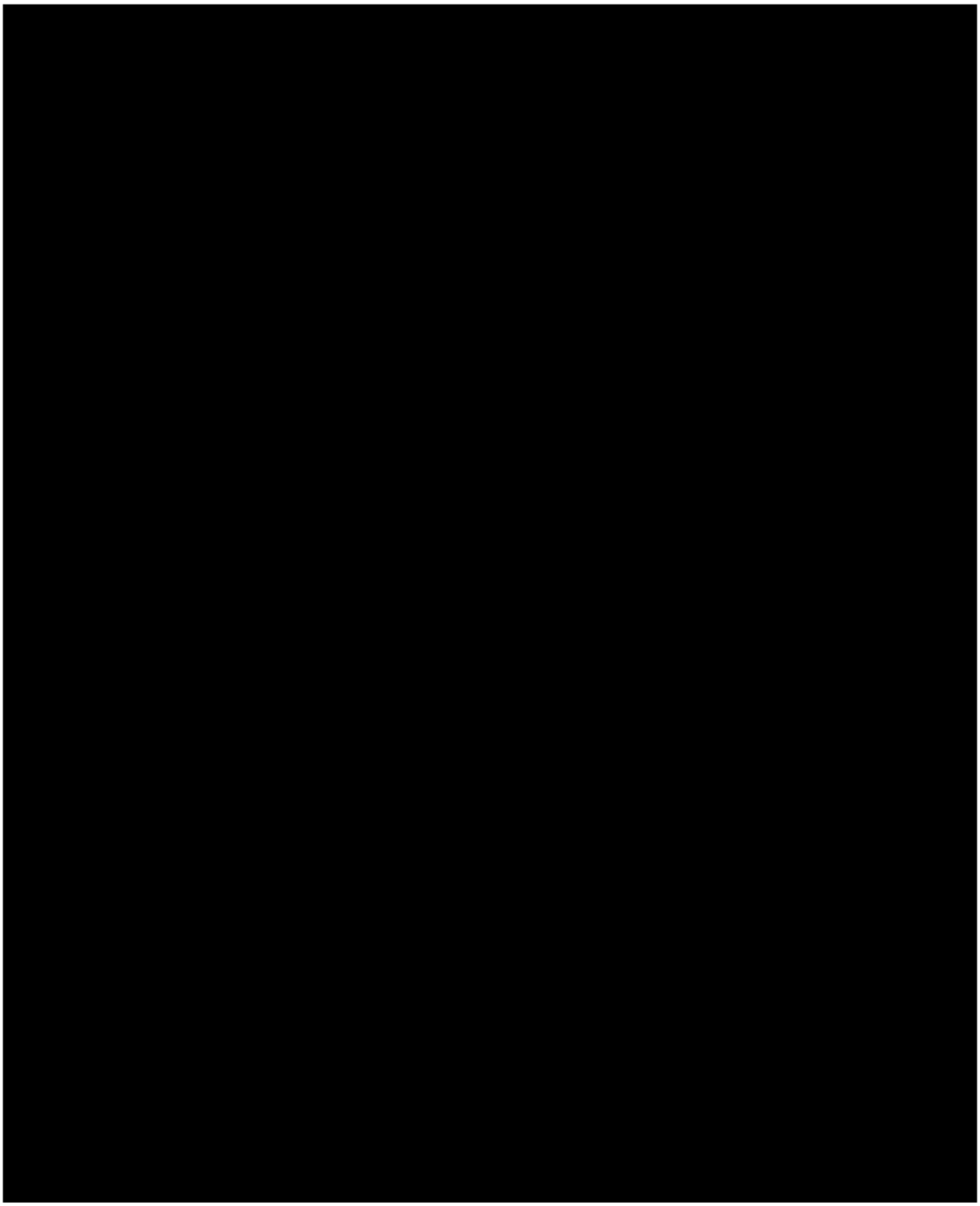

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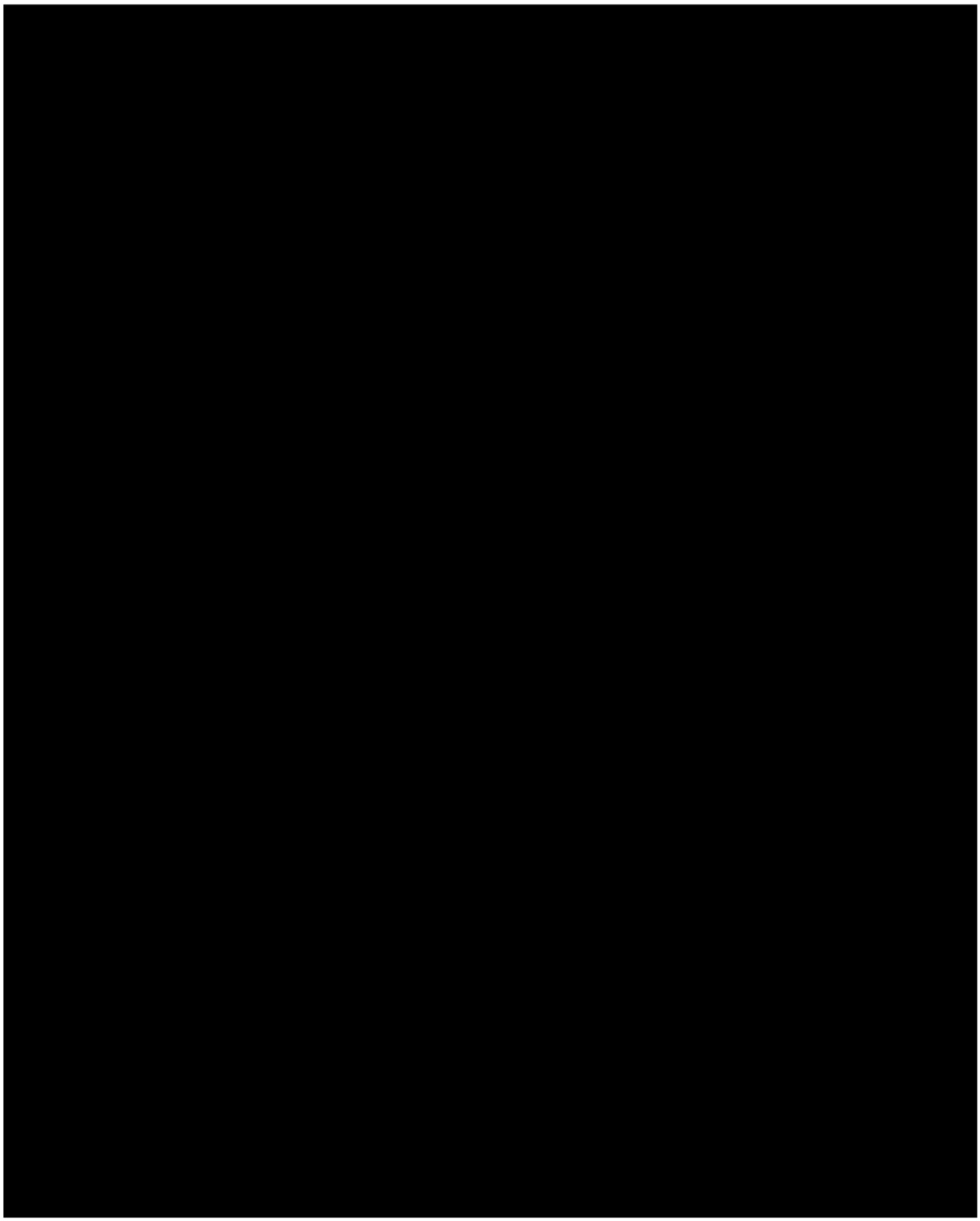

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