PROTOCOL Nº: MM09-SIT-063

EU CT Nº: 2023-508547-51-00

Version: 4.0 Date: 2026/04/20

INMUNOTEK S.L.

Madrid, Spain

Medical Department

TITLE: Prospective, randomised, double-blind, placebo-controlled multicenter clinical trial of efficacy and safety with *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* mannan-conjugated allergoids in patients with rhinitis/rhinoconjunctivitis, allergic to *Dermatophagoides pteronyssinus* and/or *Dermatophagoides farinae*

Product:	EP-088_MM09
Indication:	Aetiological treatment of moderate-to-severe allergic rhinitis/rhinoconjunctivitis with or without mild-to-moderate controlled allergic asthma
Country:	Spain and Portugal
Route of administration:	Subcutaneous
[redacted]	[redacted]
No. of subjects:	250
[redacted]	[redacted]

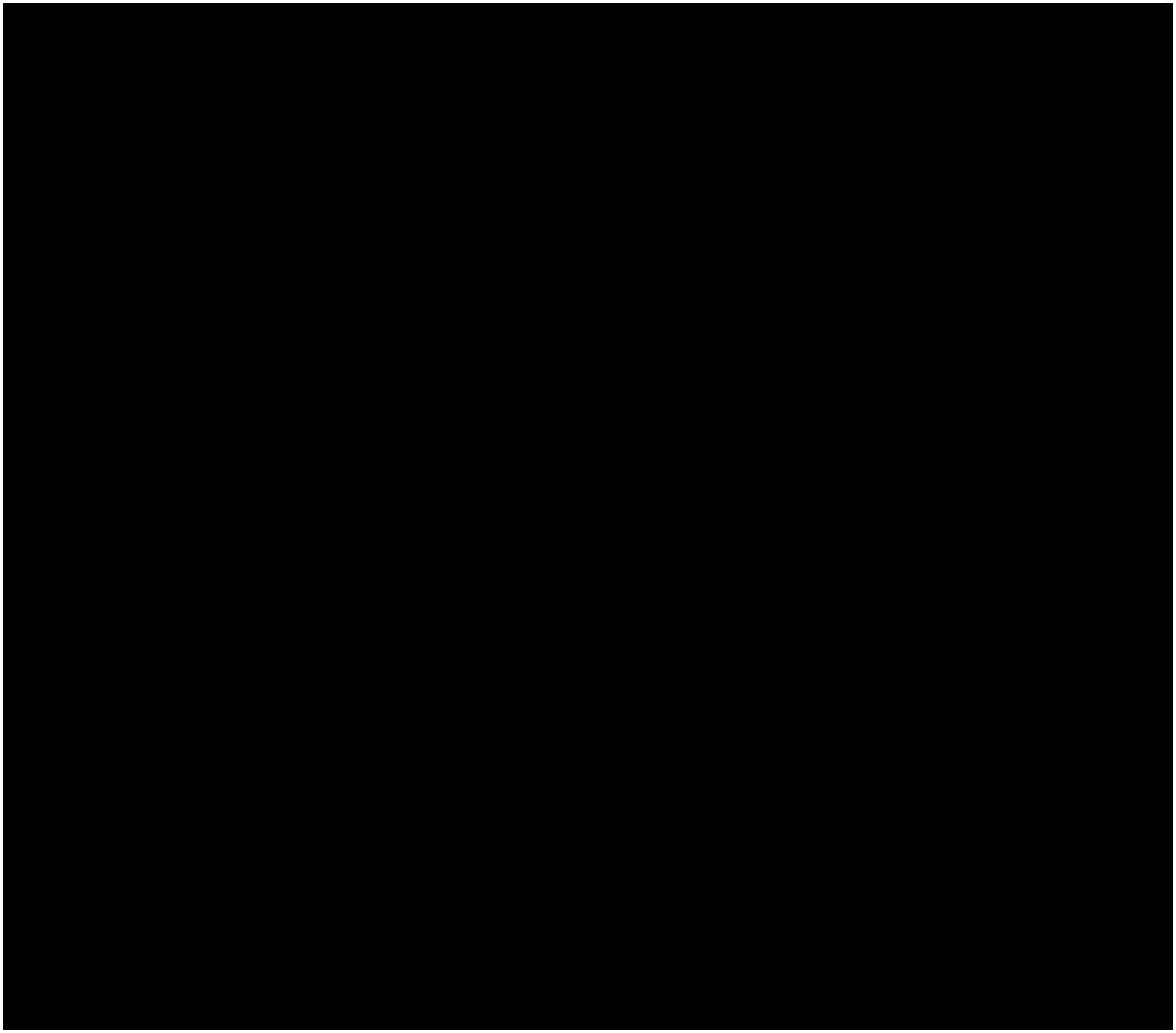
This trial will be conducted in accordance with the Protocol, the Declaration of Helsinki, Good Clinical Practice and applicable Spanish and European regulations.

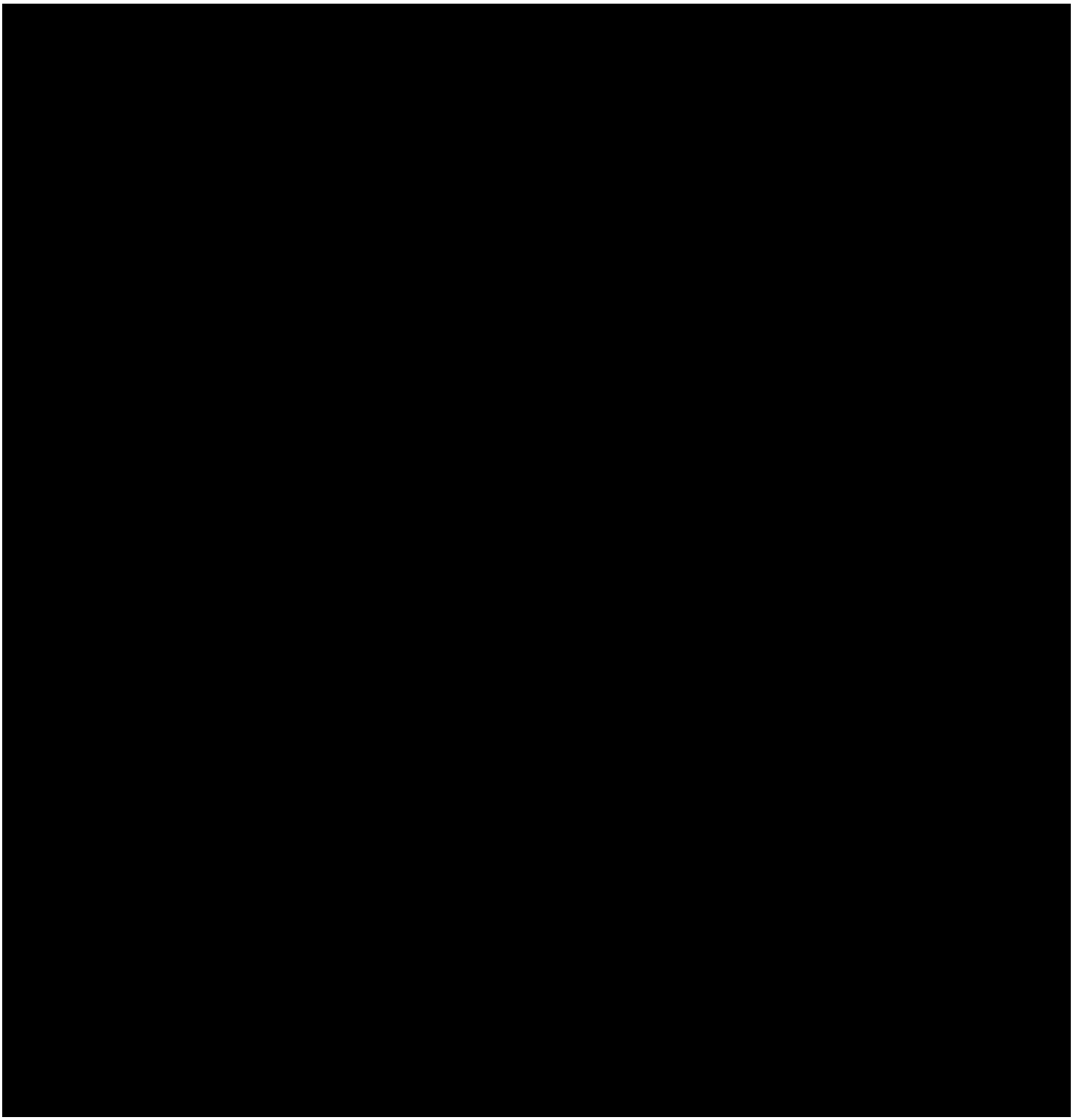
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SIGNATURE SHEET OF COORDINATING INVESTIGATOR AND SPONSOR

The coordinating investigator and the trial sponsor:

"Prospective, randomised, double-blind, placebo-controlled multicenter clinical trial of efficacy and safety with Dermatophagoides pteronyssinus and Dermatophagoides farinae mannan-conjugated allergoids in patients with rhinitis/rhinoconjunctivitis, allergic to Dermatophagoides pteronyssinus and/or Dermatophagoides farinae"





INDEX OF ABBREVIATIONS

ABV	Additional Baseline Visit
ACE	Angiotensin-converting enzyme
ACSMS	Asthma Combined Symptom and Medication Score
AE	Adverse Event
AIT	Allergen-specific immunotherapy
AMS	Asthma Medication Score
AQLQ	Asthma Quality of Life Questionnaire
AR	Adverse Reaction
ARCSMS	Asthma and Rhinitis/Rhinoconjunctivitis Combined Symptom and Medication Score
ARIA	Allergic Rhinitis and its Impact on Asthma
ARMS	Asthma and Rhinitis/Rhinoconjunctivitis Medication Score
ARSS	Asthma and Rhinitis/Rhinoconjunctivitis Symptom Score
ASCA	Anti-*Saccharomyces cerevisiae* antibodies
ASS	Asthma Symptom Score
BV	Screening/baseline visit
CHMP	Committee for Medicinal Products for Human Use
CRO	Contract Research Organization
CSMS	Combined symptom and medication score
dMS	Total daily medication score
DSMB	Data Safety Monitoring Board
EAACI	European Academy of Allergy and Clinical Immunology
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
FDA	US Food and Drug Administration
FEV_1	Forced Expiratory Volume in the first second
FV	Final visit
GCP	Good Clinical Practice
GEMA	Spanish Guidelines for the Management of Asthma
GINA	Global Initiative for Asthma
GMP	Good Manufacturing Practice
GRAS	Generally Regarded as Safe
H1A	H1 antihistamines

HEP	Histamine Equivalent Prick
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ICS	Inhaled Corticosteroids
IEC	Independent Ethics Committee
IgE	Immunoglobulin E
IgG4	Immunoglobulin G4
IM	Intramuscular
im-ITT	Immunological analysis ITT
IMP	Investigational Medicinal Product
INS	Intranasal corticosteroids
IRB	Independent Review Board
ITT	Intention To Treat
IUD	Intrauterine Device
IUS	Intrauterine hormone-releasing system
IWRS	Interactive Web Response Systems
LABA	Long-acting $Beta_2$ Agonists
LOCF	Last Observation Carried Forward
LTRA	Leukotriene receptor antagonists
MAR	Missing at Random
MART	Maintenance and Reliever Therapy
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
mITT	Modified ITT
MMRM	Mixed Models for Repeated Measures
MPL	MonoPhosphopryl Lipid A
mTU	Therapeutic Unit of mannan
N/A	Not Applicable
OCS	Oral Corticosteroids
OIT	Oral immunotherapy
PEF	Peak Expiratory Flow
PP	Per protocol
RCSMS	Rhinitis/Rhinoconjunctivitis Combined Symptom and Medication Score

RMS	Rhinitis/Rhinoconjunctivitis Medication Score
RQLQ	Rhinoconjunctivitis Quality of Life Questionnaire
RSS	Rhinitis/Rhinoconjunctivitis Symptom Score
SABA	Short-acting β2 agonists
SABA	Short-acting $beta_2$ agonists
SAE	Serious Adverse Event
SAF	Safety population
SAP	Statistical Analysis Plan
SS	Score severity
SUSAR	Suspected Unexpected Serious Adverse Reaction
TLR4	Toll Like Receptor 4
TSLP	Thymic stromal lymphopoietin
TU	Therapeutic Unit
VAS	Visual Analogue Scale
WAO	World Allergy Organization

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2 PROTOCOL SUMMARY

Sponsor	Inmunotek, S.L. Punto Mobi, 5 – 28805 Alcalá de Henares- Madrid
Study title	Prospective, randomised, double-blind, placebo-controlled multicenter clinical trial of efficacy and safety with *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* mannan-conjugated allergoids in patients with rhinitis/rhinoconjunctivitis, allergic to *Dermatophagoides pteronyssinus* and/or *Dermatophagoides farinae*
Protocol N°	MM09-SIT-063
EU CT N°	2023-508547-51-00
Indication	Aetiological treatment of moderate-to-severe allergic rhinitis/rhinoconjunctivitis with or without mild-to-moderate controlled allergic asthma
Clinical phase	III
Primary objective	[redacted]
Design	Prospective, randomized, double-blind, placebo-controlled, multicenter, efficacy, and safety clinical trial
Population size	250 subjects
Study population	[redacted]

Inclusion criteria	1. Subjects who have signed and dated Informed Consent Form (ICF). 2. Female or male aged 12 to 65 years, both included. 3. Subjects with confirmed clinical history of inhalation allergy with moderate-severe persistent rhinitis/ rhinoconjunctivitis according to the ARIA classification[(1)] of at least 1 year duration (treated with anti-allergic medication) with or without mild-moderate intermittent or persistent controlled asthma according to the definition of GINA 2023[(2)] caused by *D. pteronyssinus* and/or *D. farinae*. The asthma diagnosis will be valid up to 12 months prior to signing the informed consent. 4. Subjects with positive skin prick test to a standardized allergen extract of *D. pteronyssinus* and/or *D. farinae*. The wheal major diameter must be ≥ 5 mm and greater than or equal to the wheal major diameter of the positive control (histamine). The results will be valid up to 12 months prior to the signature of the informed consent. 5. Subjects with specific IgE against a complete extract of *D. pteronyssinus* and/or *D. farinae* or any of the molecular components of allergenic sources with a value ≥ 3.5 kU/L. The results will be valid up to 12 months prior to the signature of the informed consent. [redacted]

	[redacted] 7. Subjects with negative skin prick test for moulds. 8. Women of childbearing age (i.e., following menarche and until postmenopause, defined as no menses for 12 months without an alternative medical cause, or non-subject to permanent sterilisation methods, such as hysterectomy, bilateral salpingectomy, and bilateral oophorectomy) must confirm menarche and have a urine pregnancy test negative result before enrolling the study. 9. Women of childbearing age must commit to using a highly effective contraception method during the trial and up to 1 months after the end of the investigational medicinal product. Such methods include combined (estrogen and progestogen containing) hormonal, contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable), intrauterine device (IUD), intrauterine hormone-releasing system (IUS), male condom, diaphragm used with spermicide,

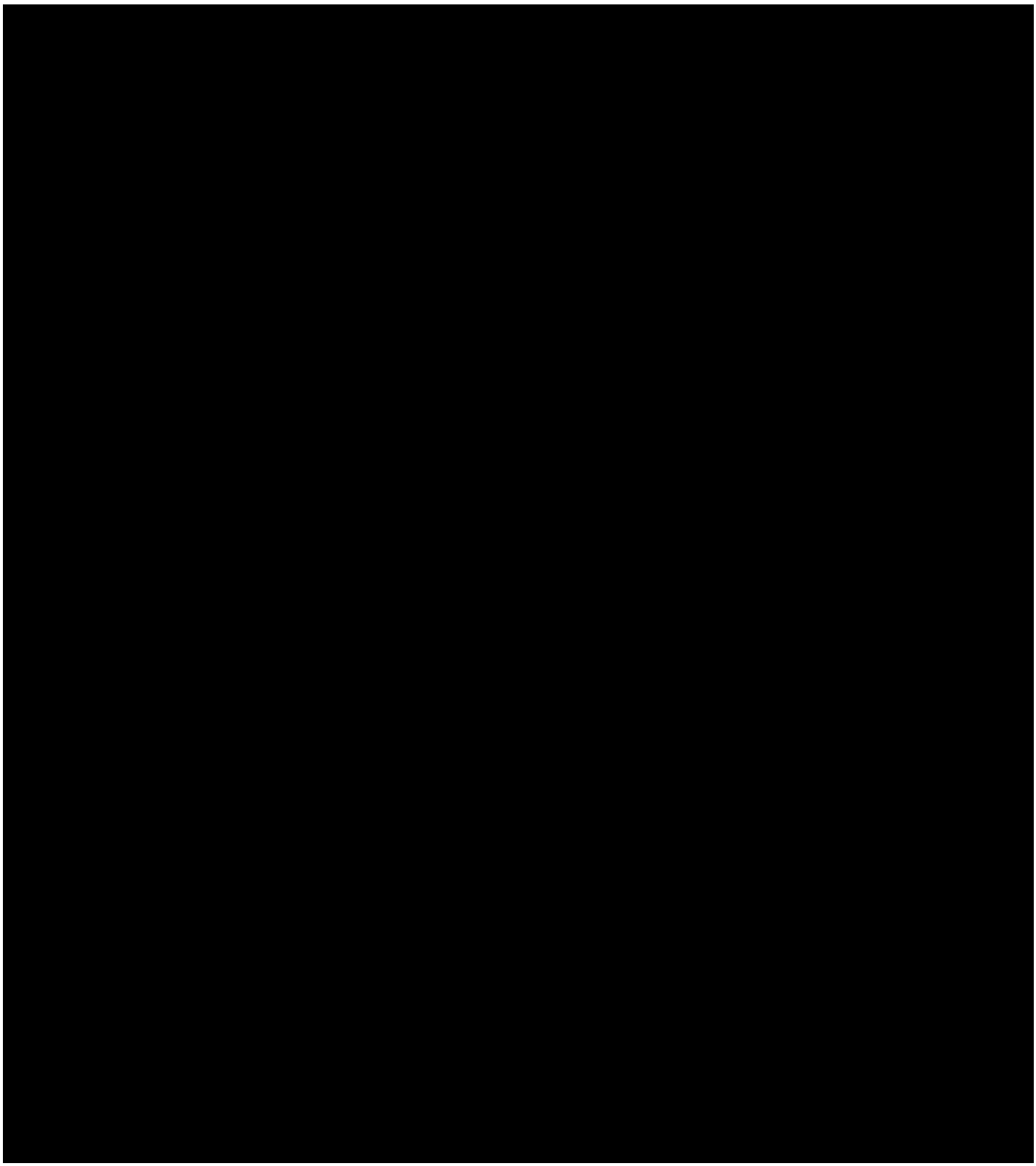
	bilateral tubal occlusion, vasectomised partner, or sexual abstinence. 10. Subjects capable of complying with dosage regimen. 11. Subjects must record symptoms and medication consumption in an electronic diary via smartphone (preferably) or in a paper diary. **To be confirmed at visit 1 (V1)** Only subjects who meet the following criteria will be eligible for randomization: 12. Subjects with a rhinitis/rhinoconjunctivitis combined symptom and medication score (RCSMS) ≥ 2 out of 6, recorded for at least 10 days, corresponding to moderate-to-severe allergic rhinitis/rhinoconjunctivitis (See Section 6.2).
Exclusion criteria	1. Subjects sensitised (positive prick test) to one or more pollens where the time interval between baseline visit (BV) and additional baseline visit (ABV) is more than 7 months. 2. Subjects who have received previous immunotherapy to allergens under study (*D. pteronyssinus* and *D. farinae*) during the last 5 years or currently receiving immunotherapy with any other allergen. 3. Subjects who have undergone any desensitisation process (e.g., oral immunotherapy [OIT], milk, or egg) except those in the maintenance phase since at least 12 months. 4. Those cases in which allergen-specific immunotherapy (AIT) would be a contraindication according to the criteria of European Allergy and Clinical Immunology Immunotherapy Subcommittee.[3] 5. Subjects with uncontrolled asthma, according to GINA 2023[2],asthma with poor symptom control (frequent symptoms or reliever use, activity limited by asthma, night waking due to asthma) and/or frequent exacerbations (≥2/year) requiring oral corticosteroids (OCS), or serious exacerbations (≥1/year) requiring hospitalization.

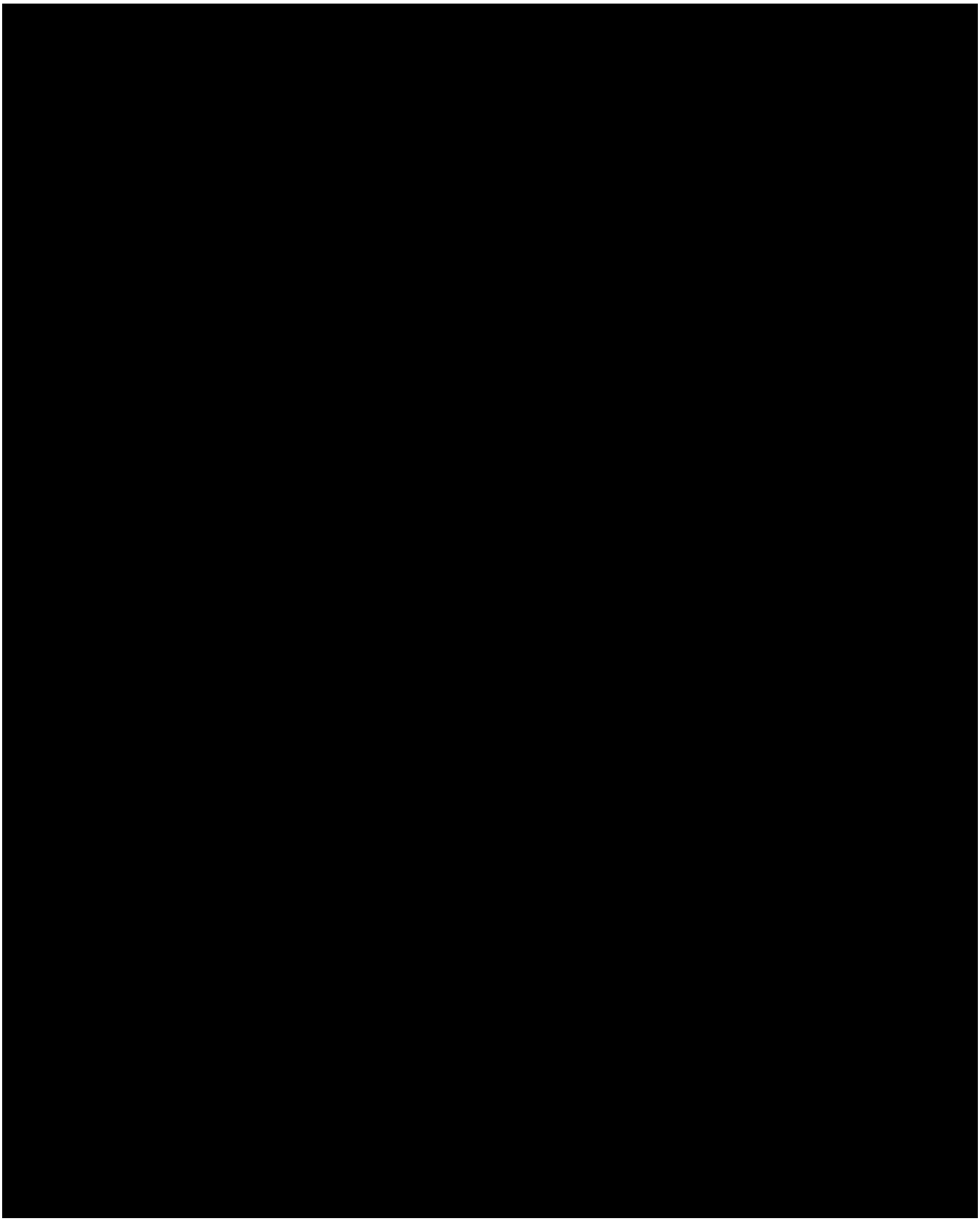
	6. Asthmatic subjects with forced expiratory volume in the first second (FEV_1) <80% despite pharmacological treatment. The result shall be valid up to 12 months prior to signing of informed consent (See Section 9.2). 7. Subjects with severe asthma, according to GINA 2023[(2)], on Step 4 or 5 treatment, who had poor symptom control and had good adherence and inhaler technique. 8. Subjects on treatment with β-blockers, except those administered topically, or angiotensin-converting enzyme (ACE) inhibitors. 9. Subjects on treatment with immunosuppressive (not including corticosteroids), except those administered topically, or biological drug. 10. Subjects requiring regular treatment with systemic corticosteroids (oral or injectable) for the treatment of rhinitis/rhinoconjunctivitis and asthma. The regular use of topical, cutaneous, or inhaled corticosteroids for the treatment of the pathologies mentioned above and atopic dermatitis is permitted. 11. Unstable subjects who have suffered a respiratory tract infection and/or asthma exacerbation within 4 weeks prior to the screening/baseline visit. 12. Subjects who have suffered chronic urticaria, severe anaphylaxis, or family history of angioedema within 2 years prior to the screening/baseline visit. 13. Subjects having any contraindication for the use of adrenaline (e.g., hyperthyroidism, heart disease, or hypertension) according to the investigator's criteria. 14. Subjects with other severe disease not related asthma or rhinitis/rhinoconjunctivitis that could interfere in the study treatment or the follow-up (e.g., epilepsy or nephropathy) according to investigator's criteria. 15. Subjects with uncontrolled autoimmune diseases (e.g., thyroiditis or lupus), tumoral diseases, or immunodeficiencies.

	16. Subjects that could not comply with the study protocol, according to investigator's criteria, or have a serious mental illness. 17. Subjects with known allergy to any of the components of the investigational medicinal products (IMPs) other than study allergens. 18. Subjects with lower respiratory tract diseases, different from asthma, as emphysema, bronchiectasis, or chronic obstructive pulmonary disease. 19. Use of drugs that could interfere with skin prick test reactions (e.g., antihistamines) within the deadlines set out in the protocol (See Section 9.2). 20. Subjects having any nasal condition (e.g., nasal polyp or non-allergic rhinitis) that could affect an appropriate evaluation of the efficacy and/or safety, according to investigator's criteria. 21. Subjects who required regular treatment with antihistamines and/or corticosteroids (systemic – oral or injectable-, topical, cutaneous, or inhaled) for other purposes than alleviating symptoms of allergic rhinitis, except temporal use (≤ 15 days) for diseases including common colds. 22. Breastfeeding or pregnant women. 23. Subjects who are immediate family members of the investigator. 24. Concurrent participation in other clinical trials or previous participation within 30 days prior to the screening/baseline visit. 25. Subjects with history of serious systemic reactions, including food, Hymenoptera venom, drugs, etc. 26. Subjects with controlled or uncontrolled cancer.
Investigational Medicinal Product (IMP)	[redacted]

Study period per participant	[redacted]
Total study period	[redacted]
Primary endpoint	[redacted]
Secondary endpoints	[redacted]

3 GENERAL INFORMATION







4 INTRODUCTION

4.1 Background and rationale

Allergic diseases are one of most prevalent disorders worldwide.[4] Among allergic diseases, such as rhinoconjunctivitis and bronchial asthma, are both chronic inflammatory diseases with increasing prevalence that affect the quality of life of the patients and have a significant economic impact.[5, 6] House dust mites, *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*, are the source of the most important indoor allergens worldwide related to allergic rhinitis, asthma, and atopic dermatitis.[7-10]

Allergic rhinitis is a symptomatic disorder of the mucous membranes lining the nose following allergen exposure in a sensitized individual.[11] It is characterized by symptoms of nasal congestion, sneezing, and mucous discharge. It is a global health problem, affecting 10-40% of the population around the world.[12]

Traditionally, allergic rhinitis has been classified according to the period of exposure to the allergen [13] into:

- Seasonal allergic rhinitis (symptoms typically appear during a particular season when allergens are abundant in the atmosphere, such as pollens and some fungi).
- Perennial allergic rhinitis: the allergens responsible are present in the environment all year round and are generally indoor allergens, such as dust mites, animal dander, fungi, cockroaches, etc.
- Occupational rhinitis: the allergen is present in the work environment.

The current classification of allergic rhinitis is contained in the 2010 revision of the published ARIA consensus. [1] Depending on the symptoms, it is classified as follows:

- Intermittent allergic rhinitis: Symptoms occur less than 4 days a week or for less than 4 weeks.
- Persistent allergic rhinitis: symptoms occur more than 4 days a week or for more than 4 weeks.

Depending on the severity of the symptoms and the impact on the patients' quality of life, it is classified into:

- Mild allergic rhinitis: patients have normal sleep, no disturbance in daily activity, no disturbance in sport or leisure time, normal school or work and no bothersome symptoms.

- Moderate-severe allergic rhinitis: patients have disturbed sleep, disturbed daily activity, disturbed sport and leisure time, disturbed school or work and bothersome symptoms.

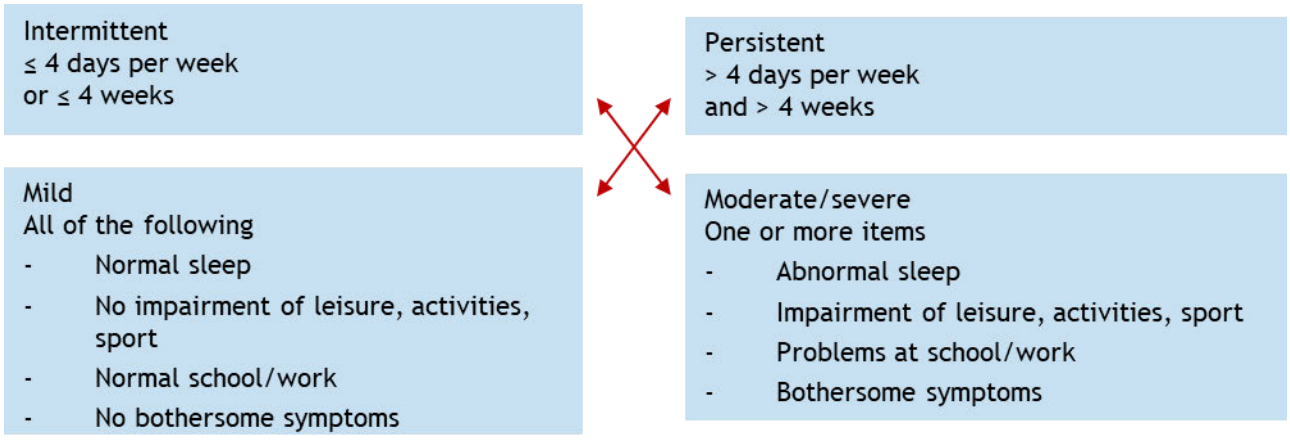


Figure 1: Classification of allergic rhinitis according to ARIA guidelines.

Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms, such as wheeze, shortness of breath, chest tightness and cough, that vary over time in intensity, together with variable expiratory airflow limitation.[14] According to the World Health Organization, the number of patients having asthma is 300 million and with the rising trends it is expected to increase to 400 million, by 2025.[15]

The prevalence of asthma is <2% in subjects without rhinitis while it varies from 10% to 40% in patients with rhinitis. Furthermore, most patients with asthma experience rhinitis, which is a factor in the risk for asthma.[15]

According to the Global Initiative for Asthma (GINA) 2023[2], the management for adults and adolescents to control symptoms and minimize future risks is summarized in the following figure which shows the options for ongoing treatment as two treatment “tracks”, with the key difference being the medication that is used for symptom relief. The “Track 1” is the preferred treatment, and the “Track 2” is the alternative treatment.

In Track 1, the reliever is as-needed low-dose inhaled corticosteroids (ICS)-formoterol, and in Track 2, the reliever is as-needed short-acting beta$_2$ agonists (SABA) or as-needed ICS-SABA.

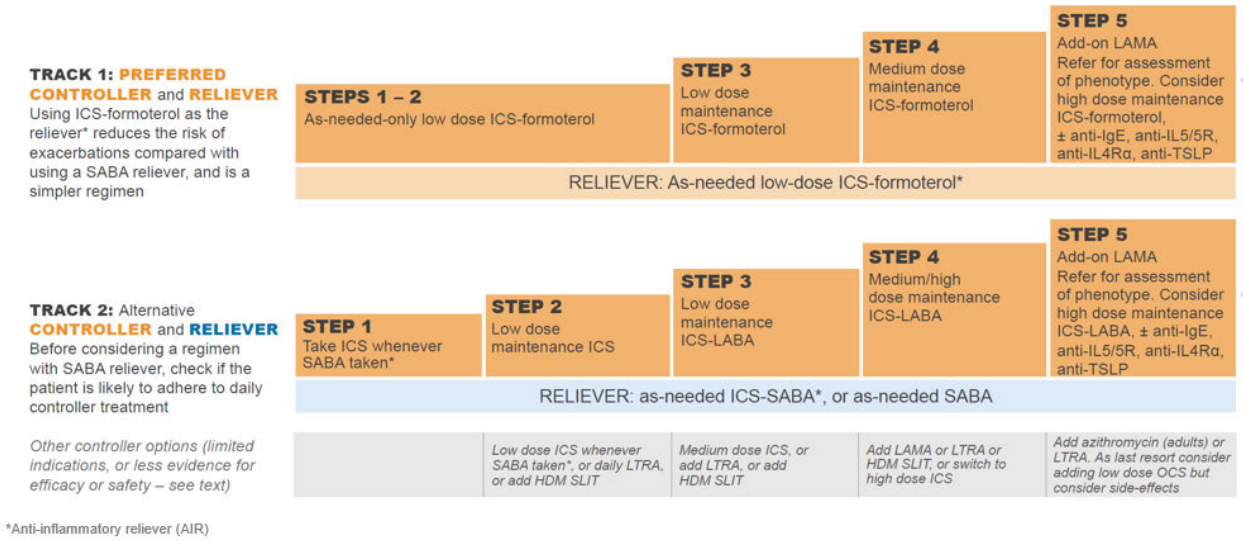


Figure 2: GINA 2023 treatment steps for adults and adolescents.

The five asthma treatment steps are as follows:

Step 1:

- Track 1: Low dose ICS-formoterol in a single inhaler taken as needed for symptom relief.
- Track 2: Low dose ICS taken whenever SABA is taken, in combination or separate inhalers for symptom relief.

Step 2:

- Track 1: Low dose ICS-formoterol in a single inhaler taken as needed for symptom relief.
- Track 2: Low dose maintenance ICS plus as-needed SABA or combination ICS-SABA for symptom relief.

Step 3:

- Track 1: Low dose maintenance ICS-formoterol and reliever therapy (MART*).
- Track 2: Low dose maintenance ICS-LABA plus as-needed SABA or combination ICS-SABA for symptom relief.

Step 4:

- Track 1: Medium dose maintenance ICS-formoterol and reliever therapy (MART*).
- Track 2: Medium or high dose maintenance ICS-LABA plus as-needed SABA or combination ICS-SABA for symptom relief.

Step 5:

- Track 1: Refer for expert assessment, phenotyping, and add-on therapy. Consider high dose maintenance ICS-formoterol (MART*), +/- anti-IgE, anti-IL5/5R, anti-IL4R, anti-TSLP.
- Track 2: Refer for expert assessment, phenotyping, and add-on therapy. Consider high dose maintenance ICS-LABA, +/- anti-IgE, anti-IL5/5R, anti-IL4R, anti-TSLP.

*MART (Maintenance And Reliever Therapy) is a treatment regimen in which the patient uses an ICS-formoterol inhaler every day (maintenance dose), and also uses the same medication as needed for relief of asthma symptoms (reliever doses).

The following table shows the low, medium, and high daily metered doses of inhaled corticosteroids (alone or with LABA):

Table 1: Low, medium, and high daily metered doses of inhaled corticosteroids (ICS).

Adults and adolescents (12 years and older)			
Inhaled corticosteroid (alone or in combination with LABA)	**Total daily ICS dose (mcg) – see notes above**		
	Low	**Medium**	**High**
Beclometasone dipropionate (pMDI, standard particle, HFA)	200–500	>500–1000	>1000
Beclometasone dipropionate (DPI or pMDI, extrafine particle, HFA)	100–200	>200–400	>400
Budesonide (DPI, or pMDI, standard particle, HFA)	200–400	>400–800	>800
Ciclesonide (pMDI, extrafine particle, HFA)	80–160	>160–320	>320
Fluticasone furoate (DPI)	100		200
Fluticasone propionate (DPI)	100–250	>250–500	>500
Fluticasone propionate (pMDI, standard particle, HFA)	100–250	>250–500	>500
Mometasone furoate (DPI)	Depends on DPI device – see product information		
Mometasone furoate (pMDI, standard particle, HFA)	200–400		>400

Currently, there are different classifications for asthma. The classification of asthma severity, recommended and included in most asthma guidelines is that severity should be assessed retrospectively from the level of treatment required to control the patient´s symptoms and exacerbations. Hence:

- Mild asthma is defined as asthma that is well controlled with low intensity treatment, i.e., as needed ICS-formoterol, or with low dose ICS plus as-needed SABA.

- Moderate asthma is defined as asthma that is well controlled with Step 3 or Step 4 treatment e.g., with low or medium dose ICS-LABA in either treatment track.

- Severe asthma is defined as asthma that remains uncontrolled despite optimized treatment with high dose ICS-LABA, or that requires high dose ICS-LABA to prevent it from becoming uncontrolled.

Some guidelines[16, 17], retain a second, older, classification of asthma severity based on symptom and SABA frequency, night waking, lung function and exacerbations before controller treatment is started.[18, 19]

Severity is classified according to the maintenance treatment needs required to achieve control of symptoms and exacerbations.[19] It is traditionally divided into four categories: intermittent, mild persistent, moderate persistent and severe persistent.[20-22]

In addition, asthma symptoms such as wheeze, chest tightness, shortness of breath and cough typically vary in frequency and intensity and contribute to the burden of asthma for the patient. Poor symptom control is also strongly associated with an increased risk of asthma exacerbations. Therefore, assessment of asthma should include the assessment of asthma control (both symptoms control and future risk of adverse outcomes). GINA assessment of asthma control in adults, adolescents and children is described in the following figure:

A. Asthma symptom control

In the past 4 weeks, has the patient had:		Well controlled	Partly controlled	Uncontrolled
• Daytime asthma symptoms more than twice/week?	Yes☐ No☐	None of these	1–2 of these	3–4 of these
• Any night waking due to asthma?	Yes☐ No☐			
• SABA* reliever for symptoms more than twice/week?	Yes☐ No☐			
• Any activity limitation due to asthma?	Yes☐ No☐			

Figure 3: GINA assessment of asthma control in adults, adolescents, and children.

In the World Health Organisation's Opinion article on allergen vaccines, it is stated that "immunotherapy is the only treatment that can alter the natural course of allergic diseases and that can also prevent the development of asthma in patients with allergic rhinitis".[23] Also, allergen-specific immunotherapy (AIT) can prevent new sensitizations to unrelated allergens.[24] It is currently the only treatment available to the allergist to modify the partial or definitive immune response to an allergic process.[25]

AIT has been used in the treatment of allergic disease since it was introduced by Noon in 1911.[26] It consists of the administration, usually subcutaneously but also sublingually, of progressively increasing doses of the allergenic material to which the patient is sensitised, in order to reduce the intensity of the clinical symptoms associated with a new exposure to the causal allergen.[27] Specifically, AIT improves the quality of life, increases the threshold dose eliciting an immediate response using specific challenges[1] and reduces symptoms and/or the need for asthma and rhinoconjunctivitis medication. Thus, international guidelines recommend AIT in patients with allergic rhinitis, with or without concomitant asthma.

In recent years, there have been attempts to improve the safety of allergen immunotherapy to avoid undesirable side effects. These include the use of chemically modified allergens (known as allergoids) and alternative routes of immunotherapy.

Principally, allergoids are obtained by the polymerization of native allergen extracts with aldehydes, including formaldehyde[28, 29] or glutaraldehyde[30, 31]. The polymerisation process does not affect the surface antigenic determinants, retaining sufficient immunogenicity to produce significant clinical effects and an IgG response.[32] Also, the polymerisation of the extracts makes it possible to carry out a type of rush pattern, where the maintenance dose is reached on the first day of treatment, as shown in numerous publications. [33-35]

Other modifications of allergenic extracts, which are being used in current clinical practice, include:

- Extracts polymerised with glutaraldehyde, adsorbed onto tyrosine together with MonoPhosphopryl Lipid A (MPL), a Toll Like Receptor 4 (TLR4) agonist.[36, 37]
- Extracts polymerised with glutaraldehyde together with mannan, a mannose receptor agonist present in dendritic cells.[38-40]

The efficacy of subcutaneous immunotherapy has been documented in numerous double-blind, placebo-controlled trials.[41-44] Mite subcutaneous immunotherapy has been evaluated for several years in clinical trials that have shown promising results on efficacy and safety.[9, 10, 35, 45-61]

Related to tolerance to subcutaneous immunotherapy, it is usually good and the risk of adverse reactions has now been greatly reduced, usually manifesting as local reactions at the injection site, with swelling or redness at the injection site.[62] Occasionally, generalised reactions such as urticaria, angioedema, rhinoconjunctivitis, asthma and, very sporadically, more severe adverse reactions such as anaphylactic shock, may occur. Warning signs for these severe adverse reactions are a sensation of warmth above and below the tongue and pharynx, itching of the skin and the appearance of warmth on the palms of the hands and soles of the feet.

On the other hand, the work of Shamji et al,[63] presents a review conducted by the immunotherapy interest group of the European Academy of Allergy and Clinical Immunology (EAACI) on the main biomarkers used in immunotherapy to measure its effectiveness or that could serve as a prognostic marker of its effectiveness. To do this, they analysed the main clinical trials of the last 20 years carried out in patients receiving immunotherapy versus a control group. Based on the evidence from the clinical trials reviewed, the authors suggested as a potential biomarker of clinical response, the levels obtained by calculating the ratio between specific IgE/Total IgE. The same study also collected data from different trials related to the increase in the amount of IgG4 in blood serum after treatment with immunotherapy, as an indicator of exposure to the allergen. Although there is no information

on a quantitative relationship between IgG4 levels and clinical efficacy, low IgG4 levels are a negative predictive marker and non-induction of IgG4 could indicate poor compliance. Taking these criteria into account, IgG4 levels were considered markers of compliance.

4.2 Name and description of the investigational medicinal product

[redacted]

4.3 Summary of findings from non-clinical studies of potential clinical significance and clinical trials conducted that are relevant to the current trial.

[redacted]

[redacted]

[redacted]

4.4 Summary of potential risks and known benefits, if any, to human subjects

Immunotherapy is the only treatment that can alter the natural course of allergic diseases and that can also prevent the development of asthma in patients with allergic rhinitis.[23] The efficacy of subcutaneous immunotherapy has been documented in numerous double-blind, placebo-controlled trials.[42, 73]

Tolerance to subcutaneous immunotherapy is very good and the risk of adverse reactions, which usually occur at the injection site, with swelling or redness of the area, has now been greatly reduced.[73] Occasionally, anaphylactic shock may occur after administration of the allergen and usually before the onset of a local reaction.

[redacted]

Overall, the risk-benefit assessment is considered positive.

4.5 Description and justification of the route of administration, dose, and duration of the treatment

[redacted]

4.6 Justification of placebo use

According to point 4.3.4 of EMA guideline CHMP/EWP/18504/2006[72], confirmatory trials on specific immunotherapy should be performed using a randomised placebo controlled double-blinded design.

For this reason, a placebo arm was added as a control in this Phase III clinical trial.

4.7 Statement that the trial will be conducted in accordance with the protocol, the Standards of Good Clinical Practice, and relevant regulatory requirements.

This trial will be conducted in accordance with the Protocol, the Declaration of Helsinki, Good Clinical Practice (GCP), and the applicable legal regulations.

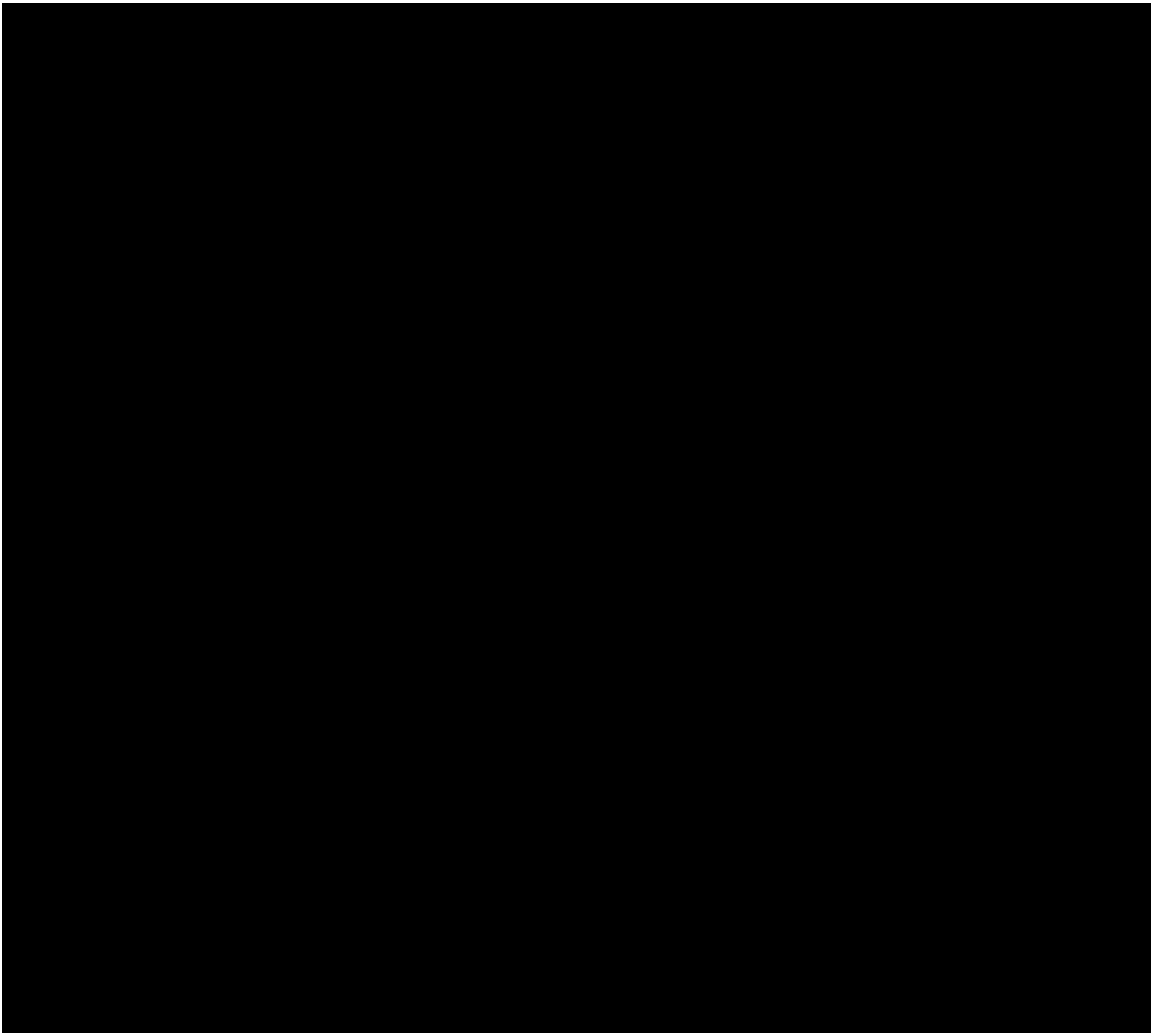
4.8 Study population

[redacted]

4.9 References to literature and data relevant to the trial to provide background information on the trial.

Preclinical and clinical evidence with this product is described in subsection 4.3 of this protocol.

5 AIM AND PURPOSE OF THE TRIAL



6 TRIAL DESIGN

6.1 Description of primary and secondary variables

[redacted]

[redacted]

6.2 Description of trial type/design

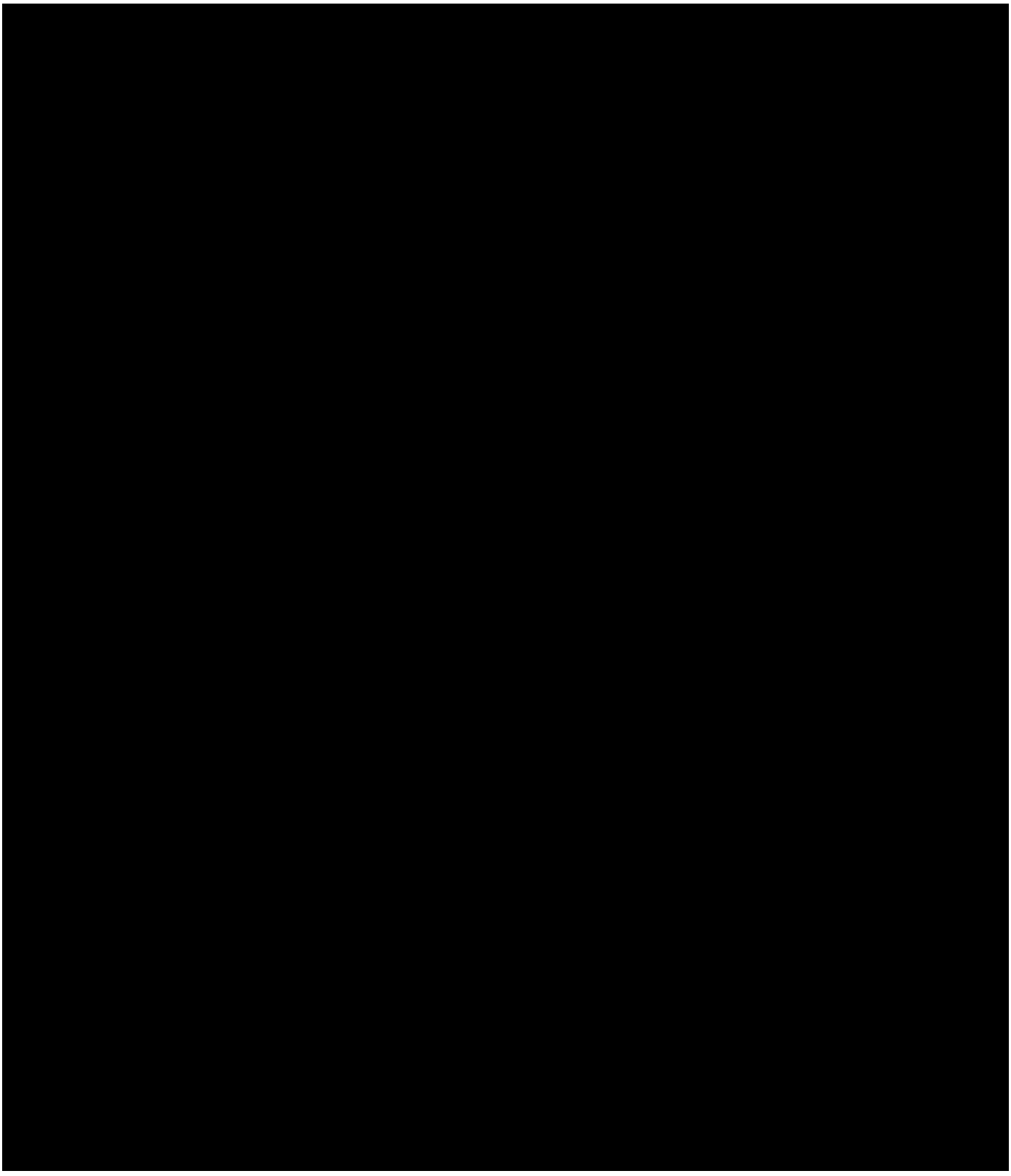
This is a prospective, randomised, double-blind, placebo-controlled, multicenter, efficacy, and safety clinical trial.

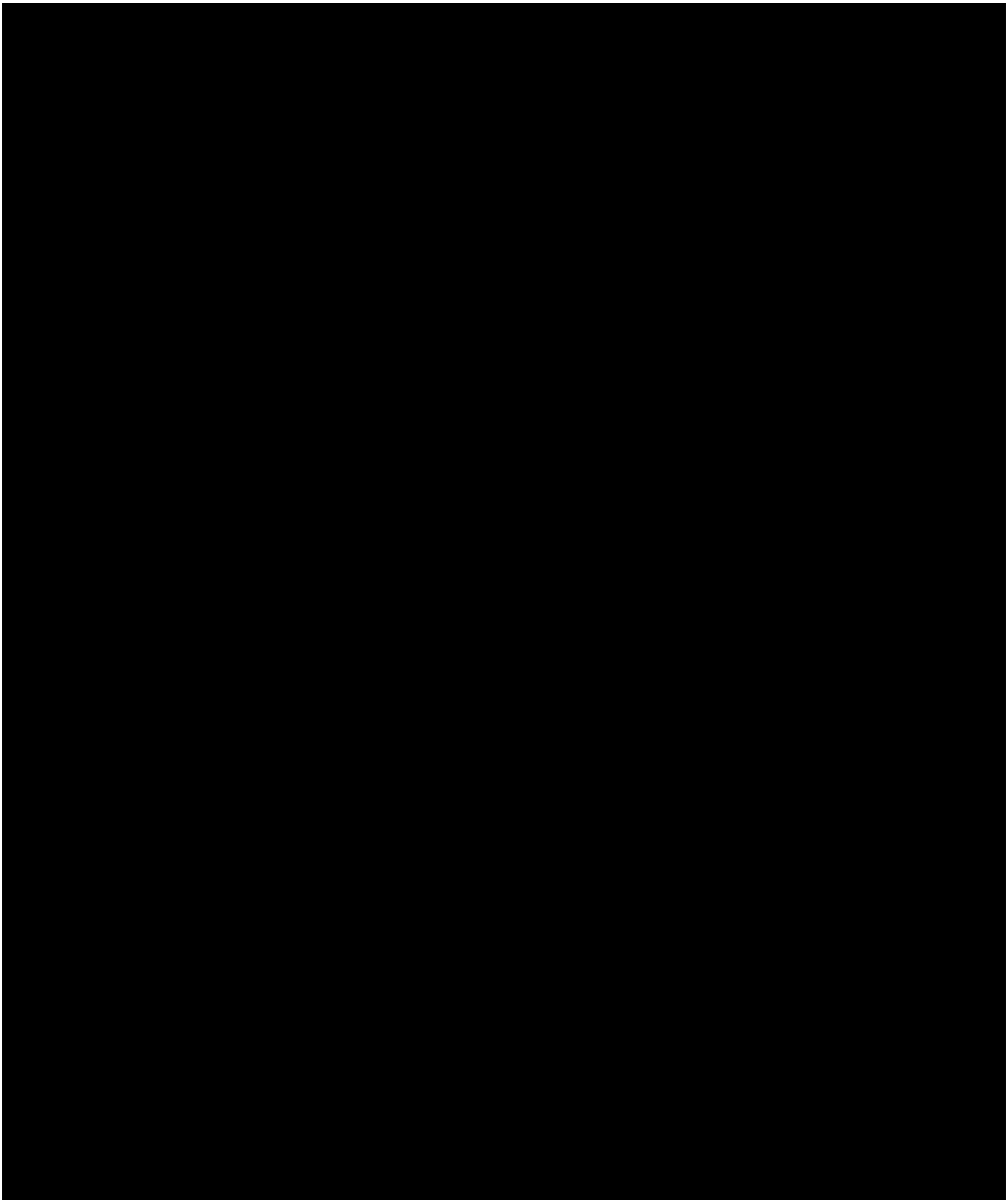
The trial population will comprise 250 subjects aged 12-65 years with moderate-to-severe persistent rhinitis/rhinoconjunctivitis with or without mild-to-moderate intermittent or persistent controlled asthma caused by their hypersensitivity to house dust mites (*D. pteronyssinus* and/or *D. farinae*), amenable to allergen immunotherapy.

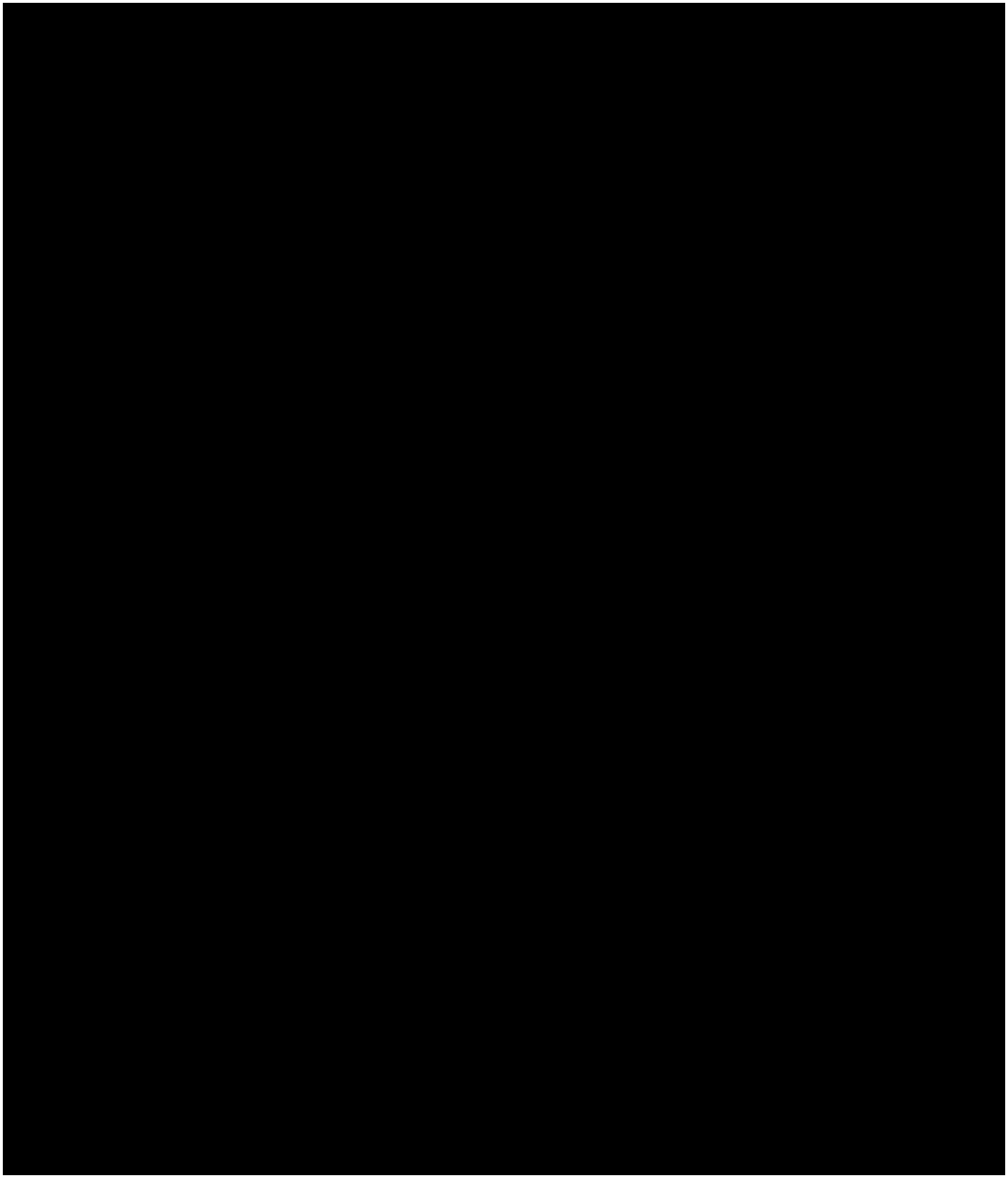
Subjects will be recruited in different sites located in Spain and Portugal.

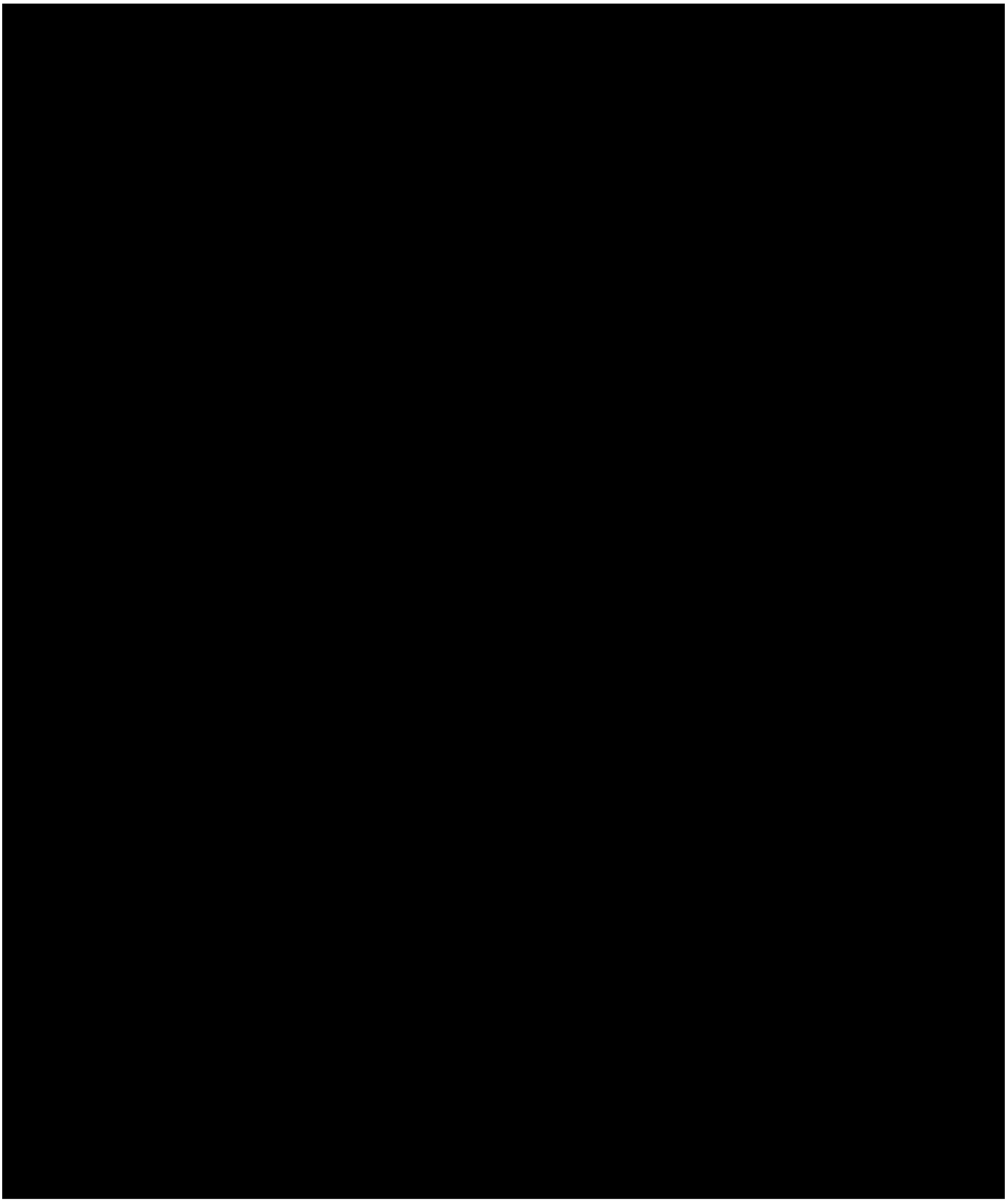
Subjects who accept participation and are eligible for the trial will be included and randomized to receive active IMP or placebo. Neither the subject nor the investigator will be informed of the treatment allocation, both treatments will be same in appearance and route of administration.

[redacted]











7 SELECTION AND WITHDRAWAL OF TRIAL SUBJECTS

7.1 Inclusion criteria of subjects

1. Subjects who have signed and dated Informed Consent Form (ICF).
2. Female or male aged 12 to 65 years, both included.
3. Subjects with confirmed clinical history of inhalation allergy with moderate-severe persistent rhinitis/ rhinoconjunctivitis according to the ARIA classification[(1)] of at least 1 year duration (treated with anti-allergic medication) with or without mild-moderate intermittent or persistent controlled asthma according to the definition of GINA 2023[(2)] caused by *D. pteronyssinus* and/or *D. farinae*. The asthma diagnosis will be valid up to 12 months prior to signing the informed consent.
4. Subjects with positive skin prick test to a standardized allergen extract of *D. pteronyssinus* and/or *D. farinae*. The wheal major diameter must be ≥ 5 mm and greater than or equal to the wheal major diameter of the positive control (histamine). The results will be valid up to 12 months prior to the signature of the informed consent.
5. Subjects with specific IgE against a complete extract of *D. pteronyssinus* and/or *D. farinae* or any of the molecular components of allergenic sources with a value ≥ 3.5 kU/L. The results will be valid up to 12 months prior to the signature of the informed consent.

[redacted]

[redacted]

7. Subjects with negative skin prick test for moulds.
8. Women of childbearing age (i.e., following menarche and until postmenopause, defined as no menses for 12 months without an alternative medical cause, or non-subject to permanent sterilisation methods, such as hysterectomy, bilateral salpingectomy, and bilateral oophorectomy) must confirm menarche and have a urine pregnancy test negative result before enrolling the study.
9. Women of childbearing age must commit to using a highly effective contraception method during the trial and up to 1 months after the end of the investigational medicinal product. Such methods include combined (estrogen and progestogen containing) hormonal, contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable), intrauterine device (IUD), intrauterine hormone-releasing system (IUS), male condom, diaphragm used with spermicide bilateral tubal occlusion, vasectomised partner, or sexual abstinence.
10. Subjects capable of complying with dosage regimen.
11. Subjects must record symptoms and medication consumption in an electronic diary via smartphone (preferably) or in a paper diary.

7.2 Inclusion criteria to be confirmed at visit 1 (V1)

Only subjects who meet the following criteria will be eligible for randomization:

12. Subjects with a rhinitis/rhinoconjunctivitis combined symptom and medication score (RCSMS) ≥ 2 out of 6, recorded for at least 10 days, corresponding to moderate-to-severe allergic rhinitis/rhinoconjunctivitis.

7.3 Exclusion criteria of subjects

1. Subjects sensitised (positive prick test) to one or more pollens where the time interval between baseline visit (BV) and additional baseline visit (ABV) is more than 7 months.
2. Subjects who have received previous immunotherapy to allergens under study (*D. pteronyssinus* and *D. farinae*) during the last 5 years or currently receiving immunotherapy with any other allergen.
3. Subjects who have undergone any desensitisation process (e.g., oral immunotherapy [OIT], milk, or egg) except those in the maintenance phase since at least 12 months.

4. Those cases in which allergen-specific immunotherapy (AIT) would be a contraindication according to the criteria of European Allergy and Clinical Immunology Immunotherapy Subcommittee.[3]
5. Subjects with uncontrolled asthma, according to GINA 2023[2],asthma with poor symptom control (frequent symptoms or reliever use, activity limited by asthma, night waking due to asthma) and/or frequent exacerbations (≥2/year) requiring oral corticosteroids (OCS), or serious exacerbations (≥1/year) requiring hospitalization.
6. Asthmatic subjects with forced expiratory volume in the first second (FEV_1) <80% despite pharmacological treatment. The result shall be valid up to 12 months prior to signing of informed consent (See Section 9.2).
7. Subjects with severe asthma, according to GINA 2023[2], on Step 4 or 5 treatment, who had poor symptom control and had good adherence and inhaler technique.
8. Subjects on treatment with β-blockers, except those administered topically, or angiotensin-converting enzyme (ACE) inhibitors.
9. Subjects on treatment with immunosuppressive (not including corticosteroids), except those administered topically, or biological drug.
10. Subjects requiring regular treatment with systemic corticosteroids (oral or injectable) for the treatment of rhinitis/rhinoconjunctivitis and asthma. The regular use of topical, cutaneous, or inhaled corticosteroids for the treatment of the pathologies mentioned above and atopic dermatitis is permitted.
11. Unstable subjects who have suffered a respiratory tract infection and/or asthma exacerbation within 4 weeks prior to the screening/baseline visit.
12. Subjects who have suffered chronic urticaria, severe anaphylaxis, or family history of angioedema within 2 years prior to the screening/baseline visit.
13. Subjects having any contraindication for the use of adrenaline (e.g., hyperthyroidism, heart disease, or hypertension) according to the investigator's criteria.
14. Subjects with other severe disease not related asthma or rhinitis/rhinoconjunctivitis that could interfere in the study treatment or the follow-up (e.g., epilepsy or nephropathy) according to investigator's criteria.
15. Subjects with uncontrolled autoimmune diseases (e.g., thyroiditis or lupus), tumoral diseases, or immunodeficiencies.
16. Subjects that could not comply with the study protocol, according to investigator's criteria, or have a serious mental illness.

17. Subjects with known allergy to any of the components of the investigational medicinal products (IMPs) other than study allergens.
18. Subjects with lower respiratory tract diseases, different from asthma, as emphysema, bronchiectasis, or chronic obstructive pulmonary disease.
19. Use of drugs that could interfere with skin prick test reactions (e.g., antihistamines) within the deadlines set out in the protocol (See Section 9.2).
20. Subjects having any nasal condition (e.g., nasal polyp or non-allergic rhinitis) that could affect an appropriate evaluation of the efficacy and/or safety, according to investigator's criteria.
21. Subjects who required regular treatment with antihistamines and/or corticosteroids (systemic – oral or injectable-, topical, cutaneous, or inhaled) for other purposes than alleviating symptoms of allergic rhinitis, except temporal use (≤ 15 days) for diseases including common colds.
22. Breastfeeding or pregnant women.
23. Subjects who are immediate family members of the investigator.
24. Concurrent participation in other clinical trials or previous participation within 30 days prior to the screening/baseline visit.
25. Subjects with history of serious systemic reactions, including food, Hymenoptera venom, drugs, etc.
26. Subjects with controlled or uncontrolled cancer.

7.4 Criteria and procedures for withdrawal of subjects

7.4.1 *When and how to withdraw subjects from the trial/investigational product*

Any subject who has signed the informed consent form will be considered to be included in the trial. The informed consent shall indicate to subjects that they have the right to withdraw from the trial at any time without any explanation and without any detriment to themselves.

Any subject who withdraws from the trial or drops out before having received the IMP, even if he/she has signed the informed consent form, will be considered as a **"screening failure".**

With regard to **voluntary drop-outs**, the investigator will collect data to determine the causes, which will fall into one of the following categories:

- Any adverse event for which the investigator would not have considered it necessary to abandon the trial.

- Coexisting condition for which the investigator would not have considered it necessary to abandon the trial.
- Withdrawal of consent.
- Other (give details).

With regard to the **criteria of subject's withdrawal** from the trial, the following cases have been established:

- Major deviation protocol.
- Less than 10 days of registration of the Subject's Diary at baseline visit (BV) or additional baseline visit (ABV) (See inclusion criteria 12).
- Treatment with non-allowed medication, as defined in this protocol.
- Screening failure: failure to meet all the inclusion and none of the exclusion criteria at the time of enrollment.
- Loss to follow-up (See section 7.4.5).
- If, according to the investigator's criteria, subject's continuation in the trial would be detrimental to the subject's well-being.
- If the medication intake (antihistamines, systemic -oral or injectable, topical, cutaneous, or inhaled corticosteroids) for pathologies other than rhinitis/rhinoconjunctivitis and asthma (i.e., urticaria, inflammatory process, common colds …) is ≥ 15 days.
- Unbearable adverse event, according to the investigator's criteria.
- If the period of treatment interruption due to rhinitis/rhinoconjunctivitis symptoms and/or asthma exacerbations is longer than 8 weeks (including days of window period).
- If the period of treatment interruption due to any adverse event is longer than 5 weeks (including days of window period).
- Pregnancy.
- Comply the stopping rules. These rules are specific criteria for participants discontinuation during the treatment phase. These are listed below.
  - <u>Stopping rules related to immediate reactions (that occur within 30 minutes after the injections)</u>
    - If a participant experiences a local reaction (wheal diameter > 10 cm) following the injection of 0.2 mL at visit 1 or following the injection of 0.2 mL at visit 2 to visit 11 as part of an already split dose.

- If a participant experiences a systemic reaction grade III-V following the injection of 0.2 mL at visit 1 or following the injection of 0.2 mL at visit 2 to visit 11 as part of an already split dose.
- If a participant experiences a systemic reaction grade III-V following the injection of 0.3 mL at visit 1 or following the injection of 0.3 mL (second injection of an already split dose) at visit 2 to visit 11.
- If a participant experiences a systemic reaction grade III-V following the injection of 0.5 mL at visit 2 to visit 11.

➢ <u>Stopping rules related to delayed reactions (that occur after 30 minutes after the injections)</u>

- If a participant experiences a local reaction (wheal diameter >20 cm during the follow up at home) following any of the injections at visit 1.
- If a participant experiences a systemic reaction grade III-V at home following any of the injections at visit 1.
- If a participant experiences a systemic reaction grade III-V at home following of the injection of 0.5 mL at visit 2 to visit 11.
- If a participant experiences a systemic reaction grade III-V at home following any split dose at visit 2 to visit 11.

➢ <u>Other stopping rules</u>

- Lack of treatment adherence: the subject is considered as non-adherent to treatment if there is a delay of more than 80 days in administration (including the 5-day window period).

The date and cause of subject's withdrawal from the trial shall be recorded in the electronic case report form (eCRF) and in the subject's medical record. If more than one withdrawal cause has been recorded by the investigator, the main cause shall be indicated.

All cases of withdrawal due to an adverse event shall be reported immediately to Inmunotek S.L., as trial sponsor.

7.4.2 *<u>Data to be collected from withdrawn subjects</u>*

All subjects who discontinue the trial, regardless of the reason, shall be included in the statistical assessment of the results. The total number of withdrawals, the different causes, and the time they occur in relation to the trial period shall be reported in detail.

If the withdrawn subject agrees, the investigator will schedule and perform all procedures described in the final visit (FV) in an early termination visit, approximately one month after the visit where the subject was withdrawn. The subject must have completed the visit 6 (V6) in order to perform the blood collection at the early termination visit.

The early termination visit can be conducted by telephone, provided that the subject has discontinued the study before V6.

The investigator must make some attempts (at least 2) to schedule the early termination visit. All attempts must be thoroughly documented (e.g., date/time of telephones calls) in the source documents.

From subjects considered as screening failures, the date of informed consent signature, compliance with inclusion criteria, demographics, reason for screening failure, and adverse events (if any) will be recorded.

7.4.3 *Subject replacement*

Subjects who are considered to be screening failure will be counted as subjects included in the trial since they have signed the informed consent form and obtained a subject number, but they will not be evaluable because they are not part of the study population (N=250) . For this reason, they will not be replaced.

However, participants who are considered a screening failure due to not complying with inclusion criterion 6c, could be re-included provided that:

- When considered a screening failure, the participant complied with all the selection criteria (inclusion and exclusion) except for inclusion criterion 6c.
- The participant has not been randomised.
- The investigator has re-evaluated the patient's current health status to ensure that all selection criteria are met, including inclusion criteria 6c.
- The sponsor approves the participant's re-inclusion in writing, after reviewing the anonymised participant's re-evaluation provided by the site.
- The participant must voluntarily agree to rejoin the trial without any coercion.
- The participant signs a new ICF.

A new participant ID number will be assigned to the re-included participant. The new ID will be used throughout the whole study, and the old participant's ID number will be associated with the new one only for traceability. In addition, data collected in BV could be used in the new participant ID upon sponsor and investigator approval to avoid unnecessary activities such as additional blood sampling or prick testing. However, the completion of the questionnaires (AQLQ and RQLQ) and VAS and the Subject's Diary will be carried out again.

7.4.4 *Follow-up of withdrawals*

In case of voluntary discontinuation, no follow-up will be carried out.

All cases of discontinuation caused by an adverse event will be reported immediately to Inmunotek S.L., as the trial sponsor. Inmunotek S.L. will perform the follow-up according to the legal regulations in force.

7.4.5 *Loss to follow-up*

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to withdraw consent, the investigator should show "due diligence" by contacting the subject or family. The investigator must make at least 2 contact attempts (not on the same day) and get no response to consider a subject as lost to follow-up.

The steps taken to contact the subject (e.g., dates of telephone calls) should be recorded in the source documents.

A subject should not be considered lost to follow-up until due diligence has been completed. Subjects lost to follow up should be recorded as such in the eCRF.

7.5 Trial termination

The trial termination date will be the last visit or procedure of the last subject. A subject shall be considered to have completed the trial when he/she has completed the visits until the final visit (FV) as defined in the study flow-chart or has completed the early termination visit, provided that the subject agrees to perform it.

In case of withdrawal from the trial or termination of the trial, the subject should be treated according to standard clinical practice.

All participants who complete the study, regardless of whether they have received active treatment or placebo treatment, if they wish, receive the study vaccine free of charge, provided that clinical benefit from this vaccine has been demonstrated during the study. The end of the trial, for the purpose of reporting to Independent Review Board (IRB)/ Independent Ethics Committee (IEC) and Regulatory Authorities will occur when database lock is performed.

The sponsor reserves the right to end the trial at any time. Reasons include, but are not limited to:

- Safety aspects.
- The investigator does not comply with the protocol, GCP, and/or any contract between the investigator and the sponsor laboratory.
- Inadequate subject recruitment by the researcher.

If the sponsor decides to end the trial prematurely, all subjects will be discontinued from the trial and the investigator will provide subjects with the necessary medical support. If the trial ends prematurely for other reasons, a plan for treatment of the subjects will be established.

If the percentage of losses initially considered is exceeded, it will be studied appropriately at the analysis stage.

If the study ends prematurely, all unused materials should be returned to the sponsor. The principal investigator will keep the investigator's file and a copy of the data collected. If no subjects are recruited, all materials will be returned to the sponsor.

8 TREATMENT OF SUBJECTS

8.1 Treatment of subjects

[redacted]

8.2 Supply, storage, packaging and labelling of the research product

The Technical Director of Inmunotek S.L. guarantees the manufacturing and adequate quality of the IMPs, according to "Detailed Commission guidelines on Good Manufacturing Practice for investigational products for human use, pursuant to the second subparagraph or Article 63 (1) of Regulation (EU) No 536/2014".

Inmunotek S.L. will keep the manufacturing and batch control protocols, of the products manufactured for the clinical trial in the trial master file and must keep samples of each batch up to twelve months after the expiration date.

The IMP will be supplied by Inmunotek S.L. to the hospital's Pharmacy Department. The latter will acknowledge receipt of the delivered treatments in writing and will be responsible for their custody, storage under specified conditions and dispensing. All supplies of IMP will be kept in a refrigerated room (between +2°C and +8°C). Access to the IMP shall be limited to the principal investigator and authorised members by the principal investigator.

The IMP will be supplied in a box containing 3 vials of 2.5 mL each, with a crimp cap and a rubber stopper, covered with an aluminium seal.

The IMP will be labelled in accordance with Annex VI of Regulation (EU) No 536/2014.

- Labels for the secondary packaging (box) will include the following information:
  a) Name, address, and telephone number of the sponsor.
  b) Pharmaceutical form, route of administration, number of units.
  c) Batch No. or code used to identify the contents and the packaging operation.
  d) Reference code used to identify the trial.
  e) Kit number.
  f) Trial subject identification or subject number.

g) Instructions for use.

h) "Use for clinical trials only".

i) Storage conditions.

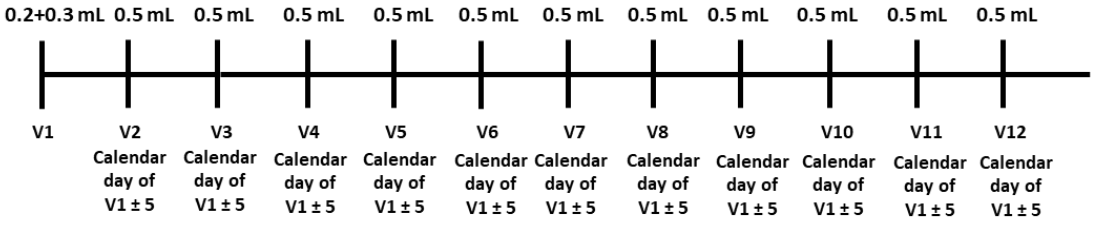
j) Expiration date, in month/year format (MM/YYYY).

k) "Keep out of the reach of children", unless the product is intended for hospital use only.

- Labels on the primary packaging (vials) shall include the following information:
  - ~ Name of the sponsor.
  - ~ Pharmaceutical form, route of administration, number of units.
  - ~ Batch No. or code used to identify the contents and the packaging operation.
  - ~ Expiration date, in month/year format (MM/YYYY).
  - ~ Reference code used to identify the trial.
  - ~ Kit number.

8.3 Dosage, method of administration and treatment periods

[redacted]



[redacted]



8.3.2 *Administration*

The IMP is supplied in vials containing 2.5 mL. Vials with a crimp cap and a rubber stopper, covered with an aluminium seal. The IMP will be administered by qualified health care personnel, using a 1 mL insulin syringe, graduated in tenths of mL. Needles should be subcutaneous, approximately 5 or 6 tenths of a mm, 1 cm long.

The instructions for administration are as follows:

- Check the vial and the corresponding dose of administration beforehand.
- Gently shake the vial before drawing the dose to be administered.
- Slowly inject the full dose subcutaneously, avoiding intravenous or muscular misadministration, in the mid-dorsal region of the upper arm, 5 to 10 cm above the elbow, alternating arms at each administration.
- Avoid massaging or applying heat to the injected area avoid exercise, sunbathing or bathing in hot water within 3 hours after the administration.

After the application of each dose, the subject will remain in the centre for at least 30 minutes to identify any immediate reactions.

8.3.3 *Treatment period*

The full treatment period for each patient will be 12 months.

8.4 Dosage modification criteria

As usual in immunotherapy, dosage may need to be adjusted, depending on the response of the individual participant.

8.4.1 *In case of adverse events, rhinitis/rhinoconjunctivitis symptoms and/or asthma exacerbations*

The investigator may discontinue the IMP if deemed necessary due to the subject's physical condition.

Temporary stopping criteria for adverse events, rhinitis/rhinoconjunctivitis symptoms and/or asthma exacerbations:

- If the interruption of treatment is less than 2 weeks (including days of window period), the study treatment regimen will not be modified.
- If the interruption of treatment is longer than 2 weeks (including days of window period), the study treatment regimen will be modified. At the following visit, the volume to be injected will be split into two doses consisting of 0.2 mL and 0.3 mL. The 0.2 mL are injected into one arm, followed by a 30-minute observation phase. Then the 0.3 mL are injected into the other arm, followed by a 30-minute observation phase.

Permanent stopping criteria:

- For any adverse event: In case the interruption period is longer than 80 days (including days of window period).
- For rhinitis/rhinoconjunctivitis symptoms and/or asthma exacerbations: In case the interruption period is longer than 8 weeks (including days of window period).

8.4.2 *In case of adverse reactions*

In case of local or systemic reactions, a dose split may be necessary: At the following visit, the volume to be injected will be split into two doses consisting of 0.2 mL and 0.3 mL. The 0.2 mL are injected into one arm, followed by a 30-minute observation phase. Then the 0.3 mL are injected into the other arm, followed by a 30-minute observation phase.

If both injections of a dose split are well tolerated, the volume of the injection can be increased to 0.5 mL at the next visit.

8.4.2.1 *Dose split in case of immediate reactions*

A dose-split of the investigational product has to be performed at the following visit:

- If a participant experiences a local reaction (wheal diameter >10 cm) following the injection of 0.3 mL at visit 1 or 0.5 mL at visit 2 to visit 11.
- If a participant experiences a local reaction (wheal diameter >10 cm following the injection of 0.3 mL (second injection of a dose split) at visit 2 to visit 11.
- If a participant experiences a systemic reaction grade II following the injection of 0.2 mL at visit 1 or following the injection of 0.2 mL at visit 2 to visit 11 as part of an already split dose.
- If a participant experiences a systemic reaction grade II following the injection of 0.3 mL at visit 1 or following the injection of 0.3 mL (second injection of an already split dose) at visit 2 to visit 11.
- If a participant experiences a systemic reaction grade II following the injection of 0.5 mL at visit 2 to visit 11.

8.4.2.2 *Dose split in case of delayed reactions:*

A dose-split of the investigational product has to be performed at the following visit:

- If a participant experiences a delayed local reaction (wheal diameter >20 cm) following the injection of 0.5 mL at visits 2 to visit 11.
- If a participant experiences a delayed local reaction (wheal diameter >20 cm) following any split dose at visit 2 to visit 11.
- If a participant experiences a systemic reaction grade II at home following any of the injections at visit 1.
- If a participant experiences a systemic reaction grade II at home following of the injection of 0.5 mL at visit 2 to visit 11.
- If a participant experiences a systemic reaction grade II at home following any split dose at visit 2 to visit 11.

8.5 Counting procedures for the investigational medicinal product

The IMP will be sent to the hospital's Pharmacy Department, after Inmunotek S.L. has obtained the approval of the Ethics Committee, and the authorisation from the competent Regulatory Authority and the contract with the study site is signed.

The IMP must be dispensed or administered in accordance with the procedures described in this trial protocol. In compliance with all applicable regulatory requirements, only those individuals included in the trial and randomized are allowed to receive the IMP.

The IMP should be stored in a safe place, between +2 and +8ºC until it is administered to the trial subjects.

The principal investigator or his/her designee will be responsible for counting the IMP, reconciliation, and record records, which will be provided by Inmunotek S.L. This person will

document the amount of IMP received from Inmunotek S.L. and the quantity administered to the trial subjects.

At the end of the trial, the monitor and principal investigator will take inventory of the remaining IMP, which will be returned to Inmunotek S.L., as trial sponsor.

The IMP will be destroyed according to Inmunotek's internal procedures.

8.6 Medication

Concomitant treatment will be all products that the subject may take for other pathologies not related to the pathologies of the study.

Study pathology-related medication will be all medication taken by the subject for the treatment of rhinitis/rhinoconjunctivitis and asthma-related symptoms (rescue or on-demand medication and control or maintenance medication).

At screening/baseline visit (BV), the following medication should be recorded in the eCRF:

~ Symptomatic treatment for allergy (rhinitis/rhinoconjunctivitis and/or asthma): medication taken at the time of study inclusion, as well as medication that might be needed during the study.

~ Treatment for concomitant pathologies: medication taken at the time of study inclusion.

During the study, subjects will register medications taken for allergy (rhinitis/rhinoconjunctivitis and/or asthma), both rescue or on-demand and control or maintenance, in the Subject's Diary , the investigator will confirm these data with the subject and register any change in medication should be recorded in the eCRF.

The medication recorded in the eCRF for the study pathologies must match with the medication registered in the Subject's Diary for each subject.

All other medications (such as antibiotics, mucolytics, anti-inflammatory drugs, supplements, probiotics, etc.) are considered concomitant treatments and should be recorded by the physician in the eCRF.

The administration of a concomitant medication during the trial will be justified by an adverse event, by the subject's medical history, or by prophylaxis.

Treatment identification, its dose, route of administration, dosage regimen, the start and end dates (or "continued" if not yet completed), and the indication will be recorded in the eCRF.

If during the trial, participants take any medication that could alter the course of rhinitis/rhinoconjunctivitis and/or asthma (systemic – oral or injectable, topical, cutaneous, or inhaled corticosteroids, antihistamines) for pathologies other than those of the study (urticaria, common colds ...) for 15 days or more, the subject must be withdrawn of the study.

8.6.1 *Non-allowed drugs*

Subjects under treatment with β-blockers (e.g., propanolol, atenolol, etc.) or **angiotensin-converting enzyme (ACE) inhibitor** or **biologic** medications will not be included, and its use is strictly **prohibited** during the trial. In addition, subjects on regular treatment with systemic corticosteroids (oral or injectable) for the studies pathologies (rhinitis/rhinoconjunctivitis and asthma) will also not be included.

Due to the β-blockers and immunosuppressive are considered as relative contraindication for subcutaneous immunotherapy[3], the **β-blockers (e.g., eye drops) and immunosuppressive (e.g., tacrolimus) administered topically will be allowed**.

In relation to treatment with other types of **vaccines (e.g., live attenuated, inactivated or toxoid vaccines),** it is reminded that the interval between the administration of these vaccines and the IMP shall be at least 2 weeks.

The physician should register it in the eCRF any not-allowed medication taken by the subject during the study.

8.6.2 *Allowed drugs*

No medication for the treatment of both rhinitis/rhinoconjunctivitis and asthma will be supplied by Inmunotek S.L.

8.6.3 *Allowed medication for rhinitis/rhinoconjunctivitis:*

Based on the work of Pfaar et al,[77] the allowed drugs for these pathologies are:

- Oral or topical (eye or nose) non-sedative H1 antihistamines (H1A).
- Intranasal corticosteroids (INS) with/without H1A.
- *Oral corticosteroids (OCS) with/without (INS) with/without H1A.

**There is no maximum dose limit for oral corticosteroids.*

8.6.4 *Allowed medication for asthma:*

According to the GINA 2023[2] guideline the categories of asthma medications are:

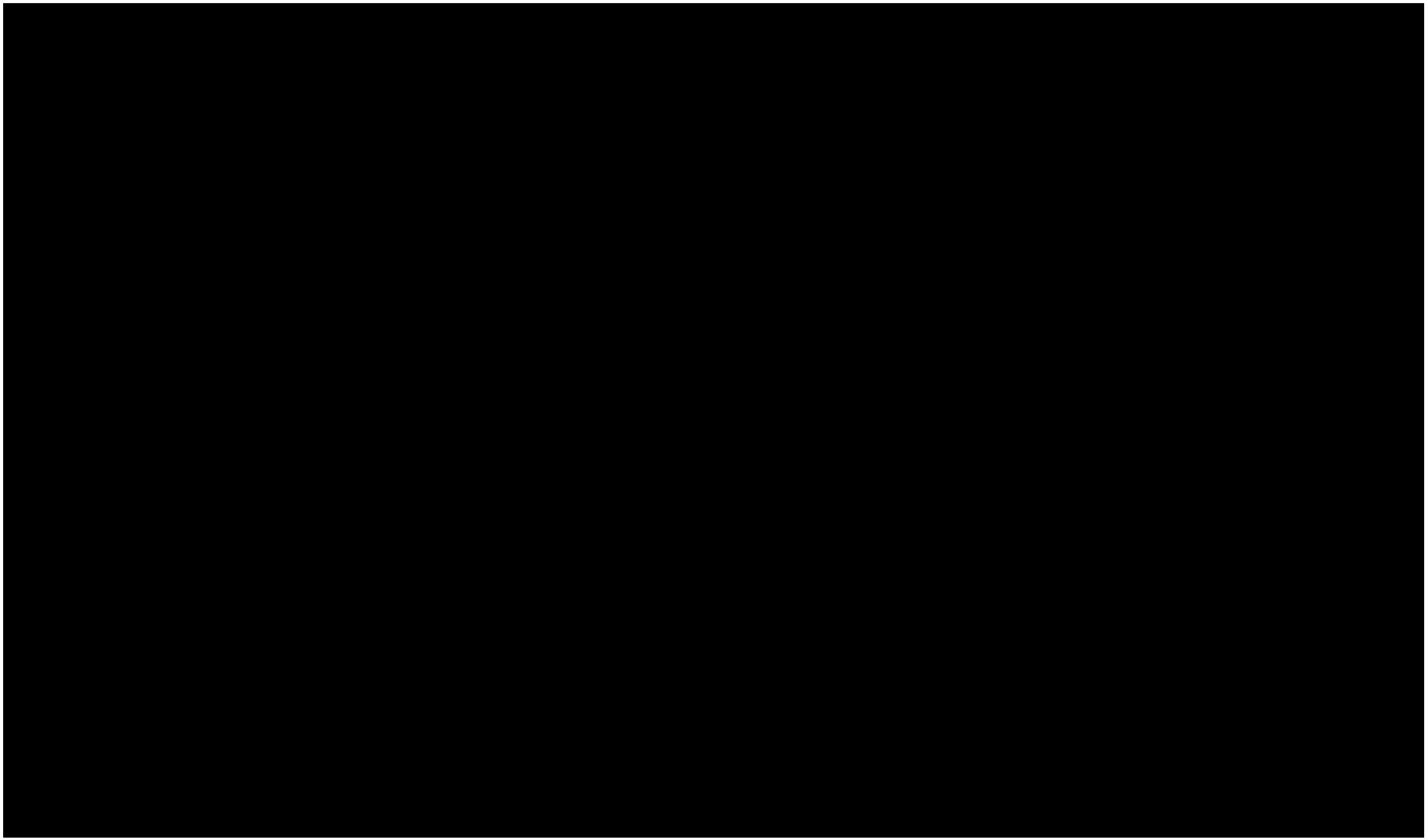
- Controller medications: In Track 1, controller treatment is delivered through an anti-inflammatory reliever, low dose ICS-formoterol, taken when symptoms occur and before exercise or allergen exposure; in steps 3-5, the patient also takes maintenance controller treatment (daily or twice daily ICS-formoterol). This is called maintenance-and-reliever therapy (MART). The dose and regimen of controller medications should be optimized to minimize the risk of medication side-effects, including risks of needing OCS.

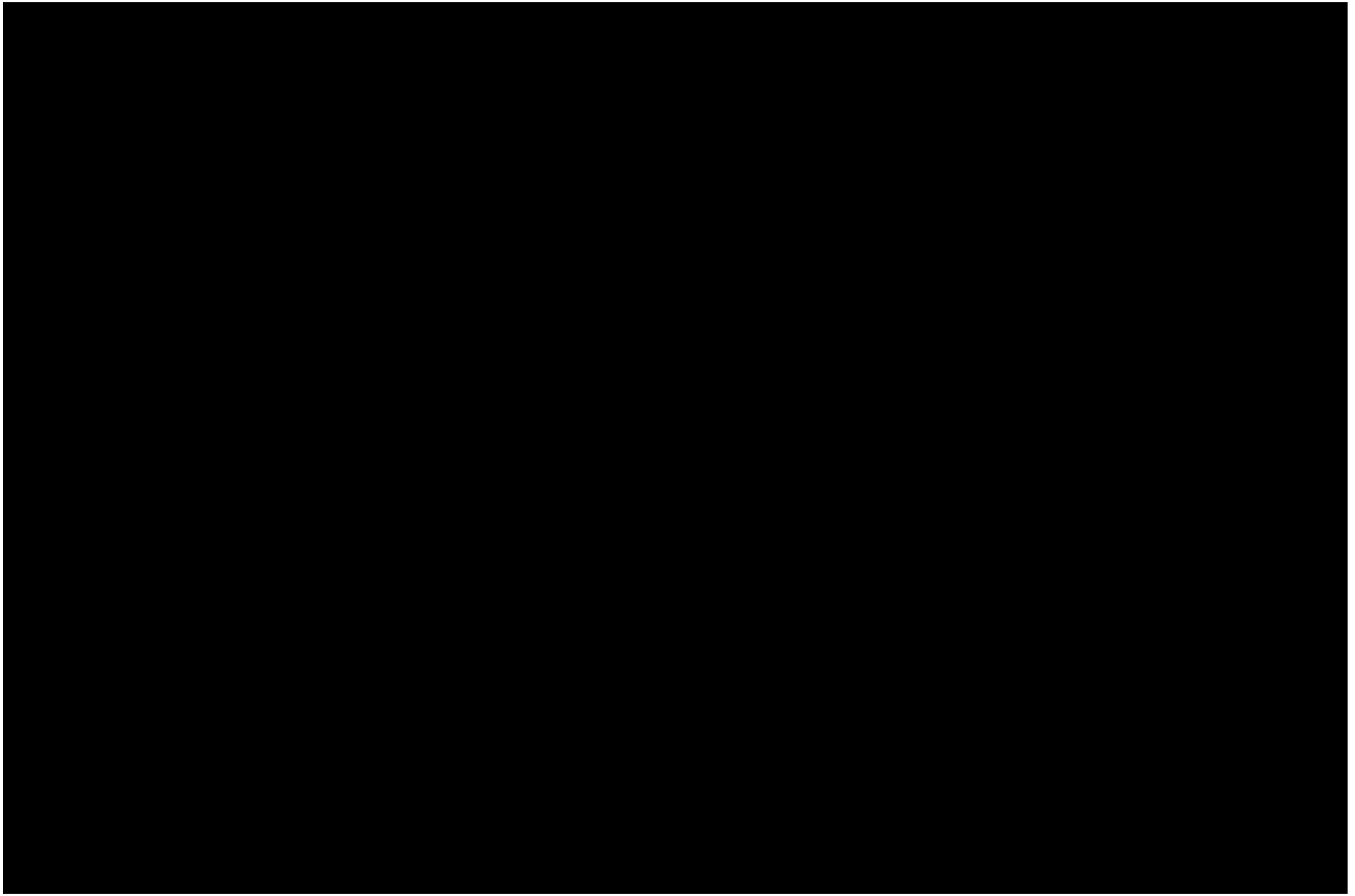
- Reliever medications: these are provided to all patients for as-needed relief of breakthrough symptoms, including during worsening asthma or exacerbations. They are also recommended for short-term prevention of exercise-induced bronchoconstriction. Relievers include the anti-inflammatory relievers ICS-formoterol and ICS-SABA, and SABA alone.
- Add-on therapies including for patients with severe asthma: these may be considered when patients have uncontrolled asthma despite adherence with maximal optimized treatment with high doses controller medications and management of contributory factors.

8.7 Procedures for monitoring subject's adherence to treatment

IMP is administered subcutaneously and will be injected by a qualified health care personnel during the scheduled visits for assessment. A subject will be considered as non-adherent to treatment if there is a delay of more than 80 days in administration (including the 5-day window period).

9 TRIAL PROCEDURES

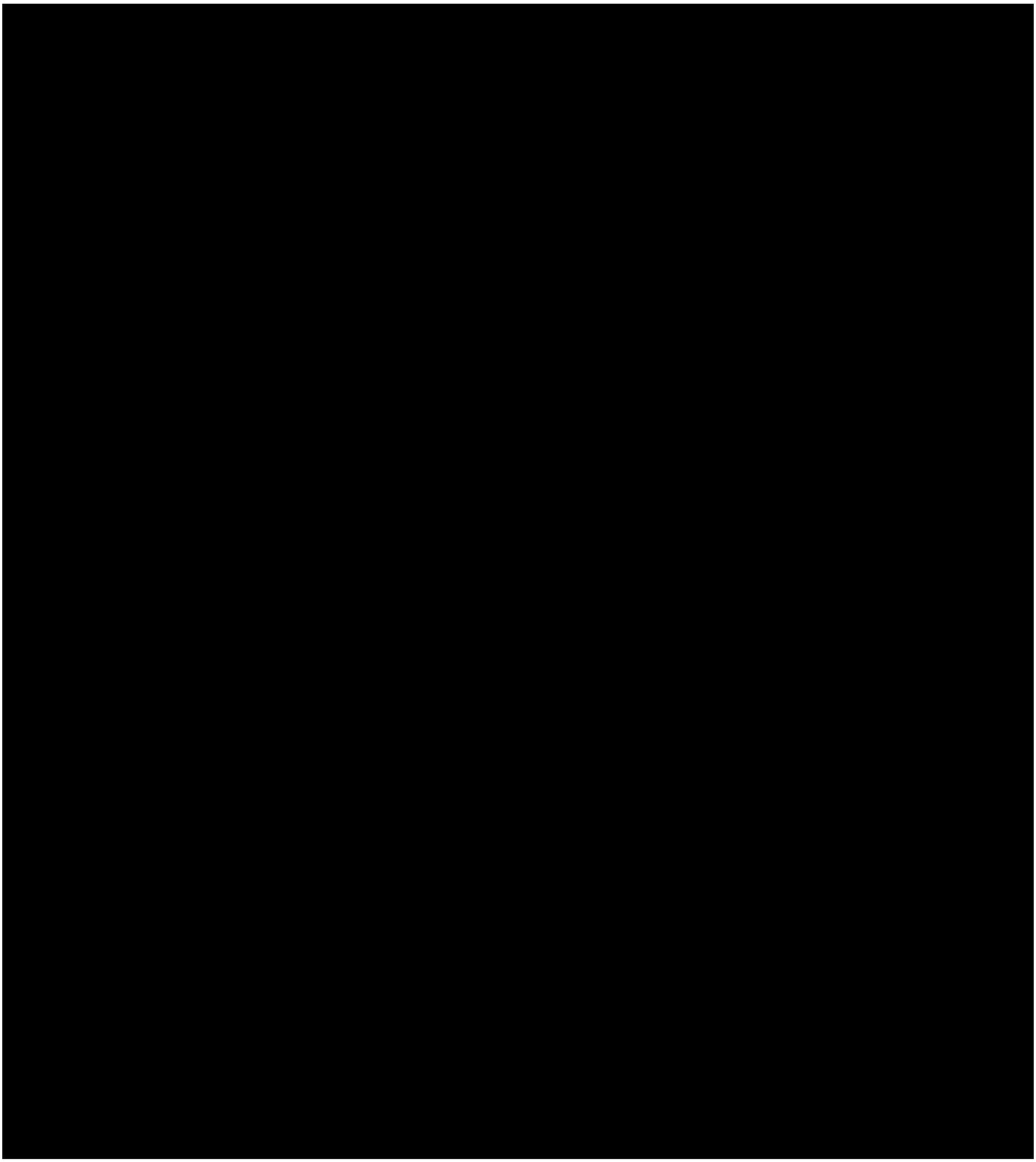


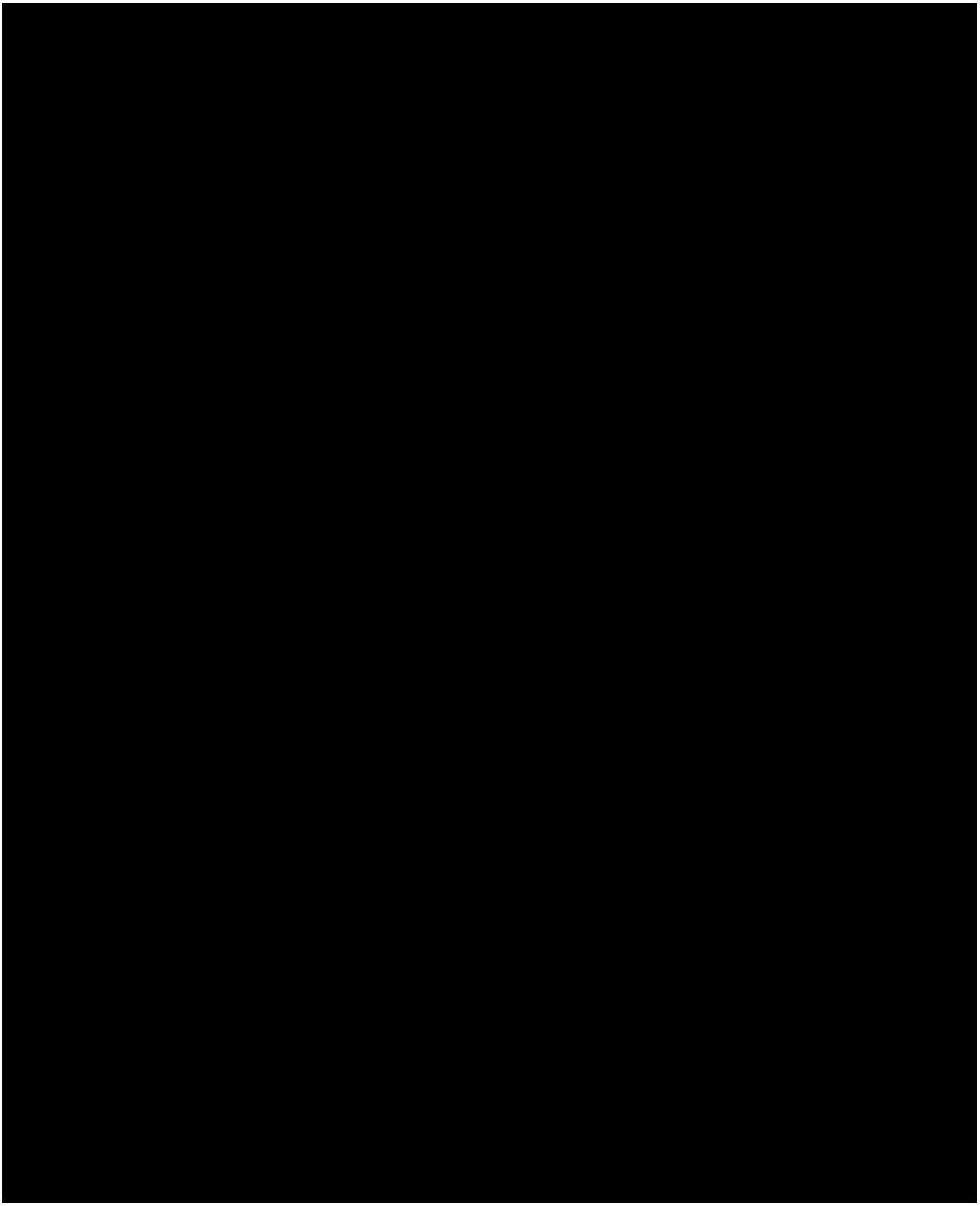


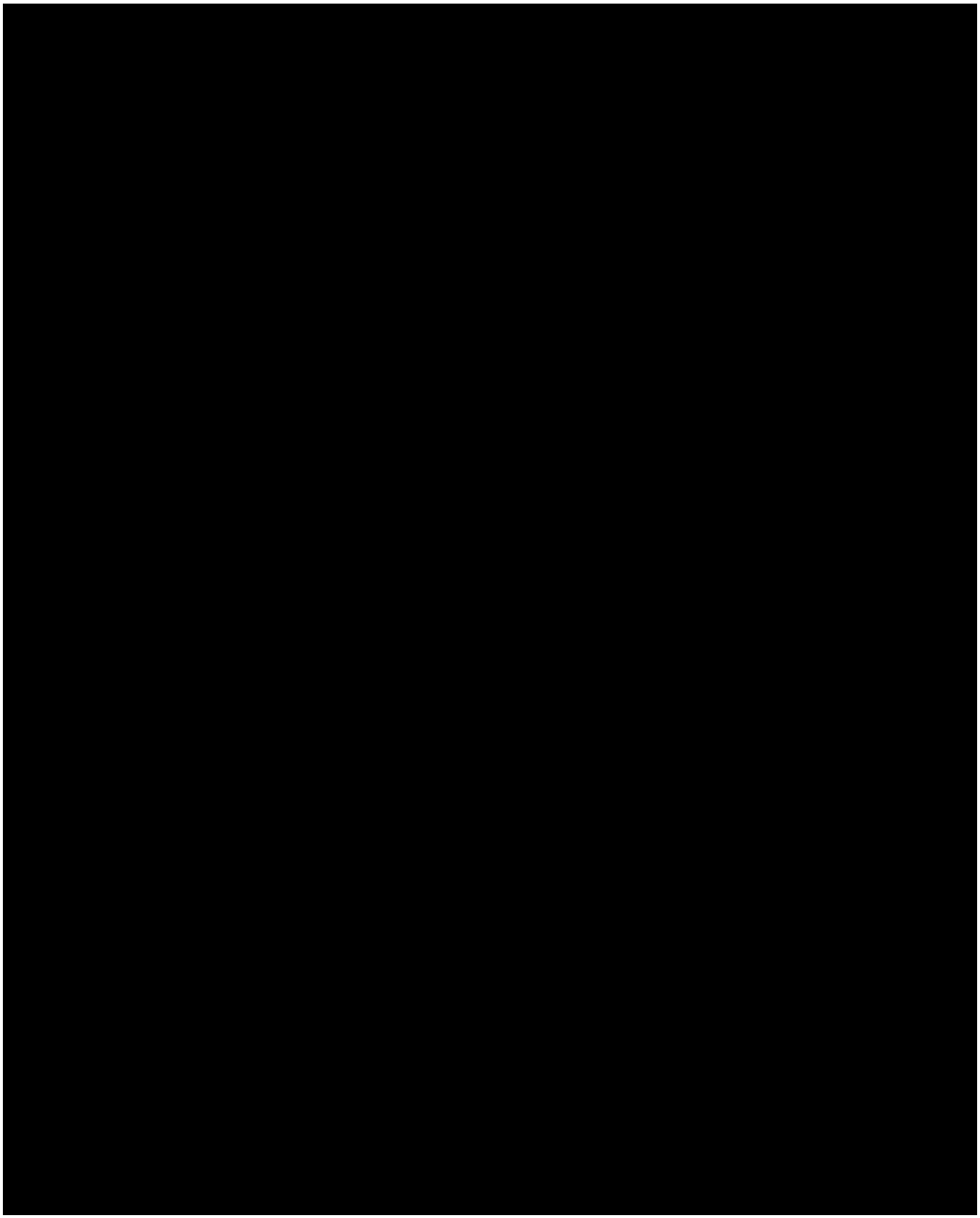
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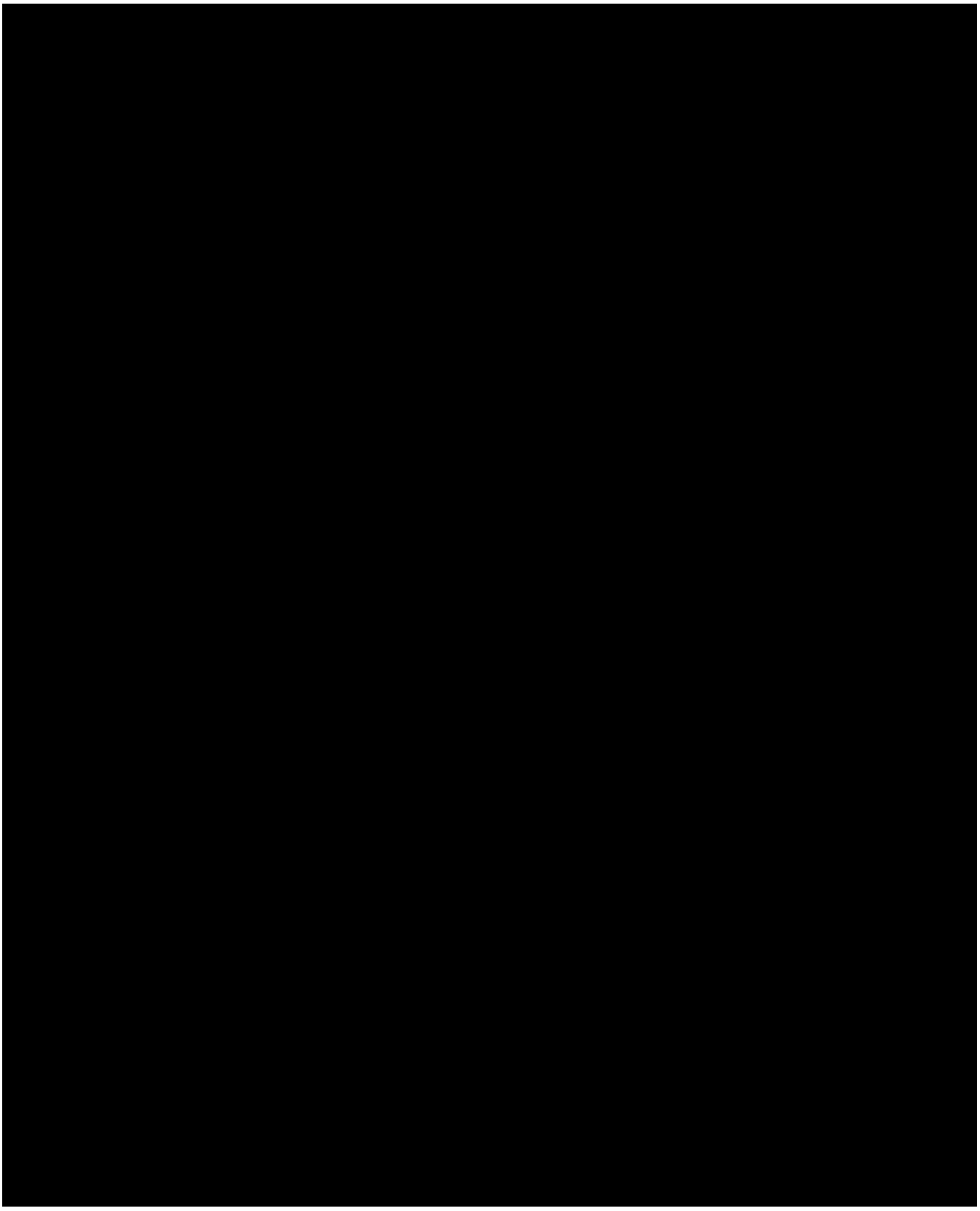


[redacted]

9.3 Tests and procedures during treatment phase

[redacted]

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9.4 Follow-up at the end of treatment (end of study)

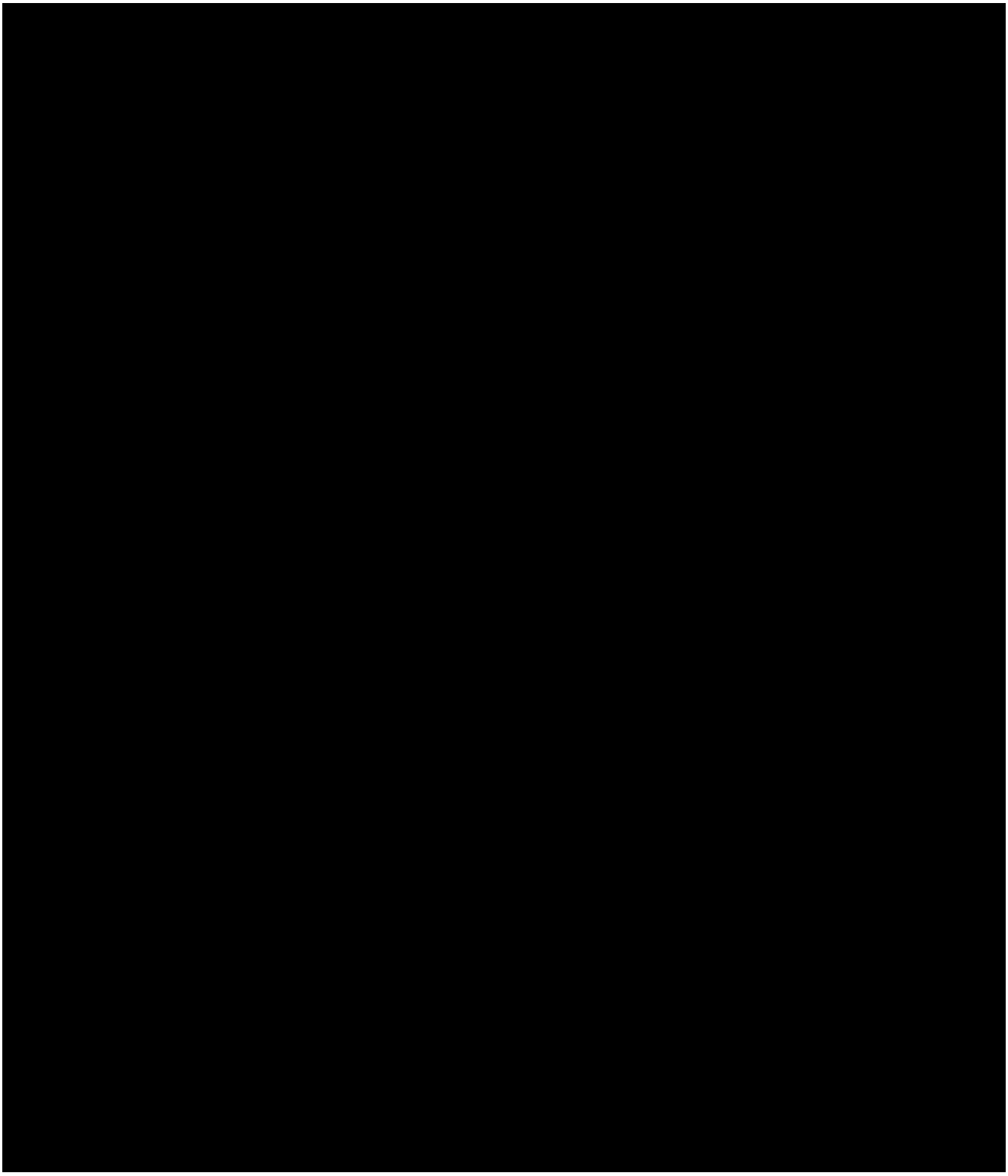
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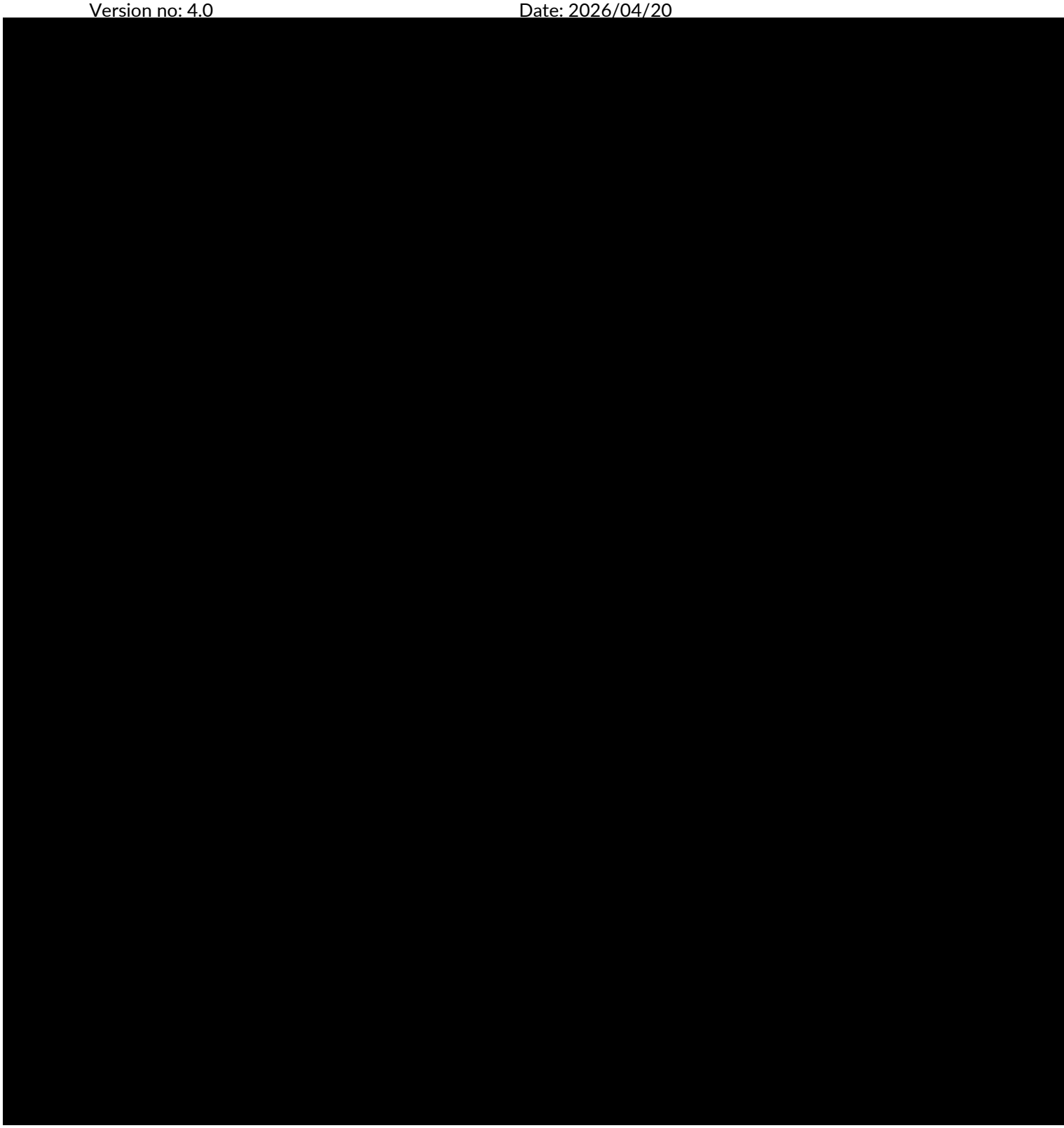
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10 ASSESSMENT OF EFFICACY

10.1 Specification of the efficacy parameters of the primary variable

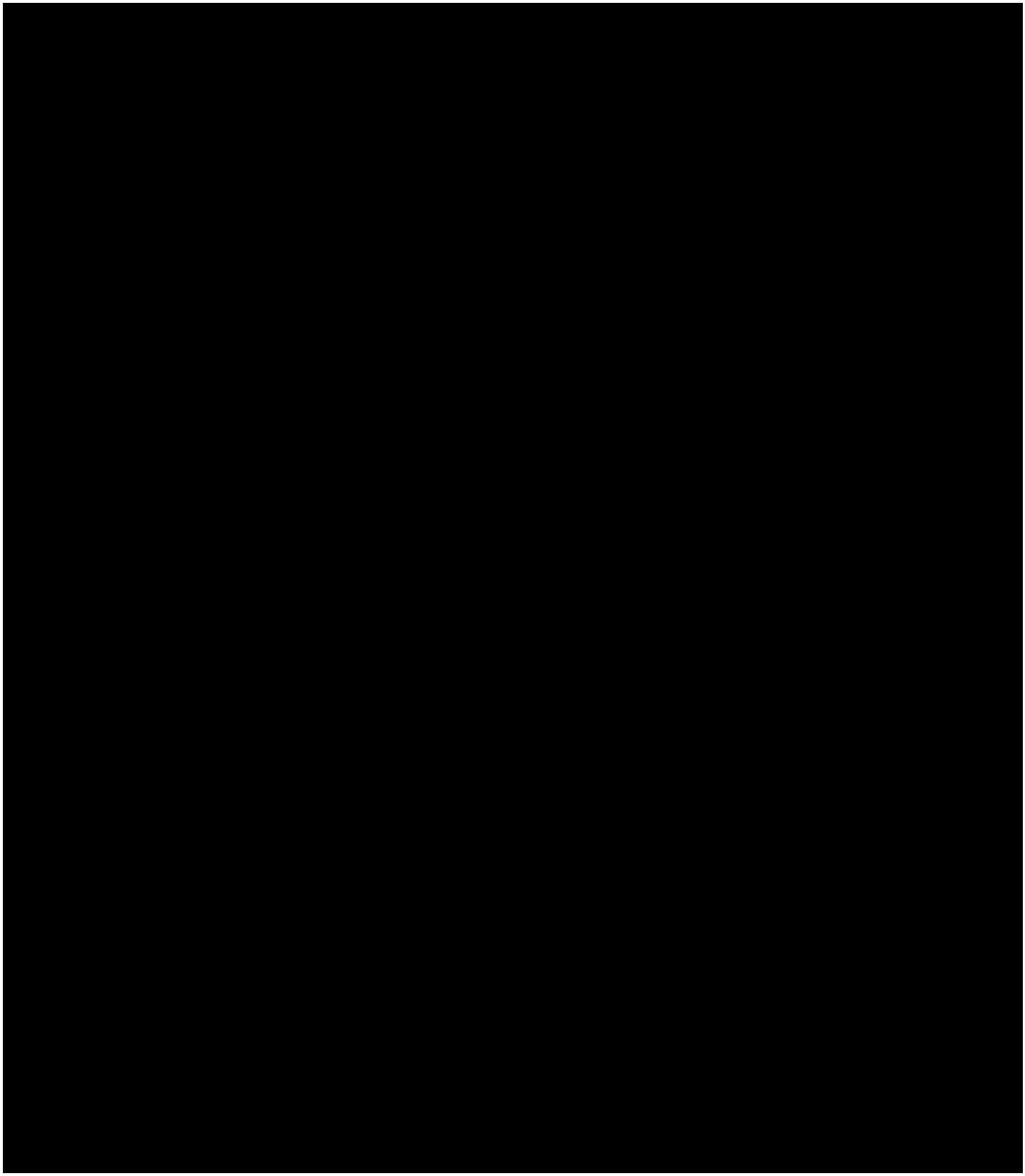
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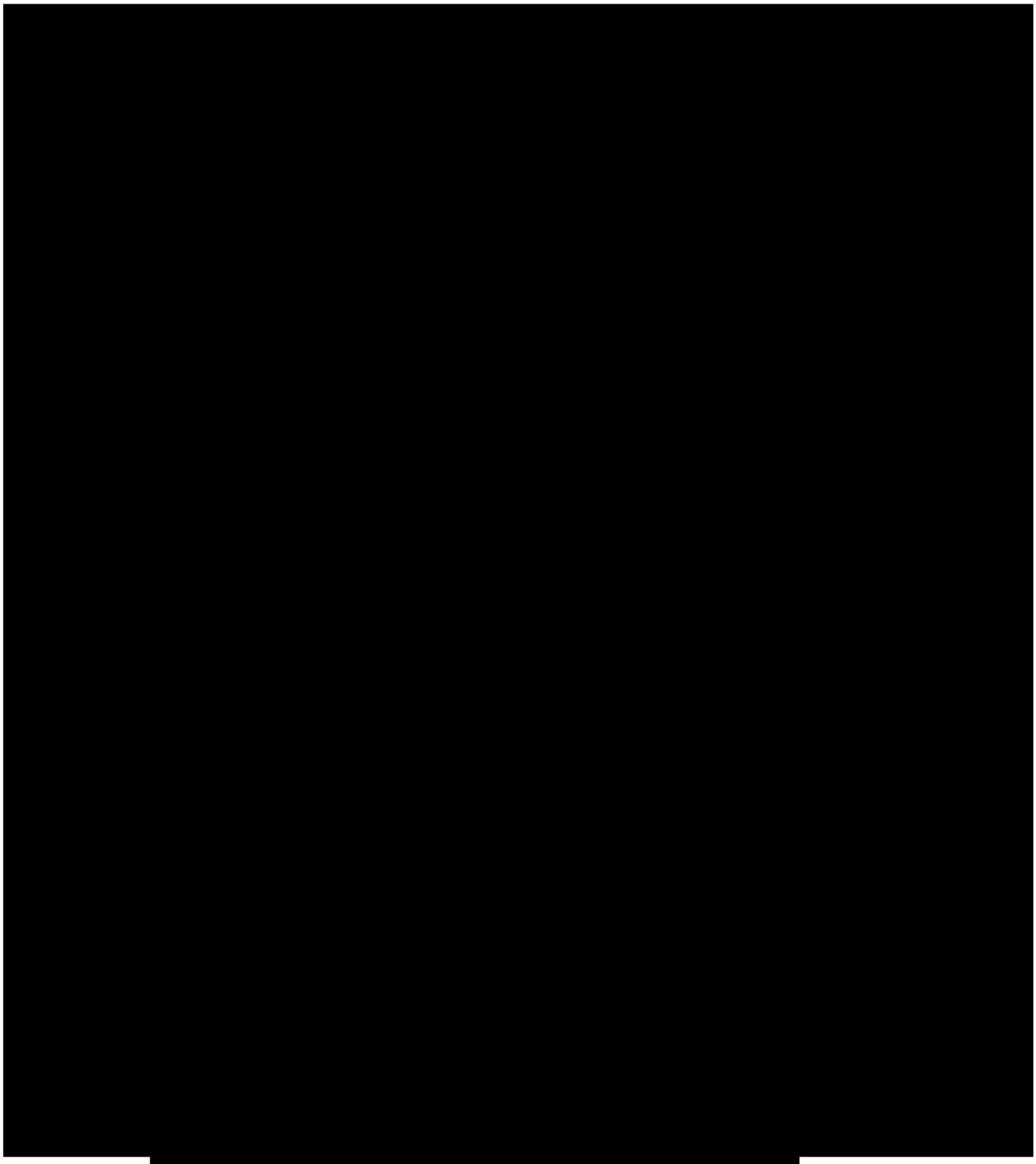


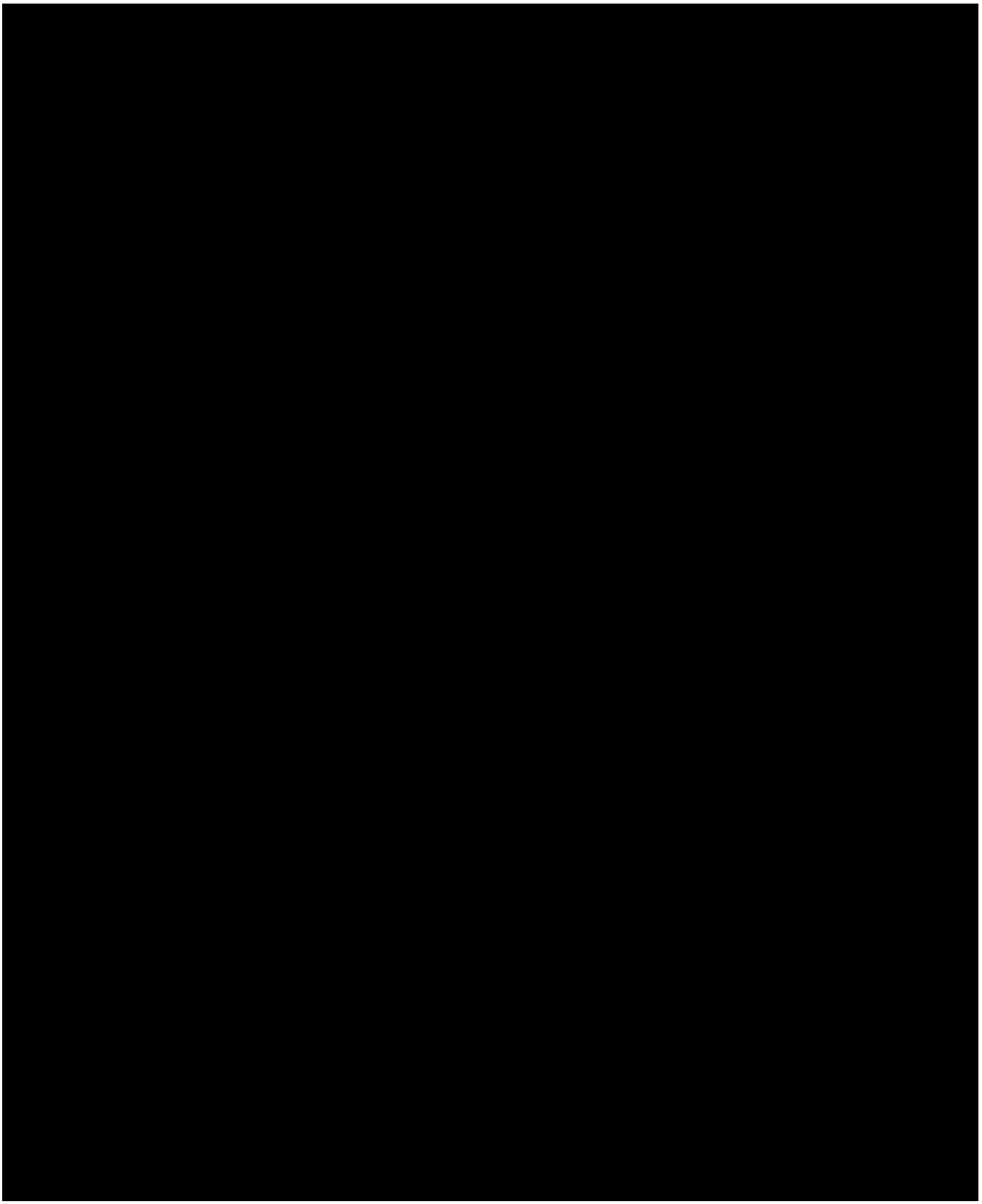


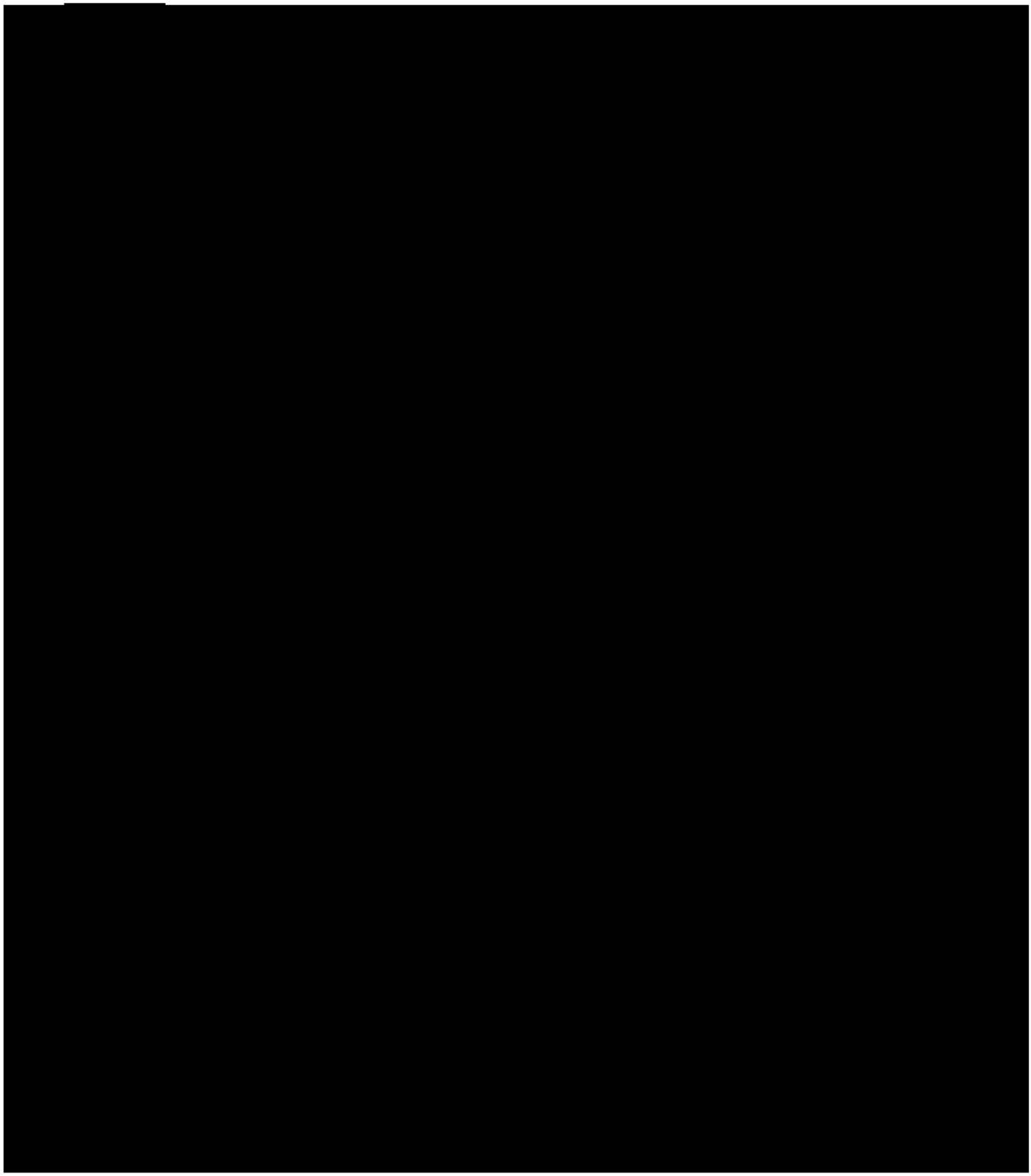
Step	Medication	Score
Step 6	High-dose ICS + LABA + systemic corticosteroids with/without LTRA with/without SABA as needed	3.0
Step 5	High-dose ICS + LABA with/without LTRA with/without SABA as needed	2.5
Step 4	Medium-dose ICS + LABA with/without LTRA with/without SABA as needed	2.0
Step 3	Low-dose ICS + LABA or medium-dose ICS with/without LTRA with/without SABA as needed	1.5
Step 2	Low-dose ICS Alternative: LTRA with/without SABA as needed	1.0
Step 1	SABA as needed	0.5
	Total daily medication score (dMS)	0–3

[redacted]











11 SAFETY ASSESSMENT

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 11.3.

11.1 Specification of safety parameters

After administration of immunotherapy, mild adverse reactions such as pruritus, erythema, local oedema may occur. There is a risk, albeit rare and exceptional, of systemic reactions, sometimes severe (urticaria, asthma, anaphylactic shock, etc.).[88]

The IMP must always be administered under medical supervision and by specialised health personnel, which will allow the correct treatment of a generalised reaction, and therefore, at the site of subcutaneous administration of the immunotherapy, the following must be available:

- Stethoscope and sphygmomanometer.
- Tourniquet, syringes, intramuscular needles.
- Equipment for intravenous administration.
- Equipment for administration of O_2.
- Aqueous adrenaline 1:1000, diphenhydramine injection, anti-H2 antihistamines.
- Intravenous corticosteroids, vasopressors.
- Rarely used: direct laryngoscopy, defibrillator for cardioversion.

After administration of the IMP, the subject will remain for 30 minutes in the centre under observation to monitor possible adverse reactions.

11.1.1 *Definitions and terminology associated with the handling of safety information during testing.*

According to the Good Clinical Practice guidelines and the ICH guideline E2A for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, they are defined as:[89]

- **Adverse event (AE):** any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal

(investigational) product, whether or not related to the medicinal (investigational) product.

- **Adverse reaction (AR):** all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.
- **Serious adverse event (SAE) or serious adverse reaction (SAR):** A serious adverse event or reaction is any untoward medical occurrence that at any dose:

  - ✓ Results in death.
  - ✓ Is life-threatening. The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
  - ✓ Requires inpatient hospitalisation or prolongation of existing hospitalisation. In general, "hospitalisation" means that the subject has been admitted to hospital for at least one night.
  - ✓ Results in permanent or major disability or incapacity, or
  - ✓ Is a congenital anomaly/birth defect.
  - ✓ Clinically significant. The investigator shall apply medical judgement in deciding whether an AE/AR is serious in other situations like major medical events that are not immediately life-threatening or do not result in death or hospitalisation but may endanger the subject or require intervention to prevent one of the other situations listed in the above definition.

  Any suspected transmission of an infectious agent via the IP is also considered a SAE/SAR.

- **Suspected Unexpected Serious Adverse Reaction (SUSAR):** A reaction that, at any dose, requires hospitalisation or prolongation of hospitalisation, results in permanent or significant disability or incapacity, results in congenital anomaly or malformation, is life-threatening or fatal or clinically significant and whose nature or severity is not consistent with the available product information (the investigator's brochure in the case of an IMP not authorised for marketing, or the product label in the case of an authorised medicinal product).

Reports which add significant information on specificity or severity of a known, already documented (described in the IB) serious AR constitute unexpected events.

11.2 Methods and timing for capturing and assessing parameters

The investigator is responsible for ensuring that all adverse events (see Section 11.1.1 for definition) are recorded in the eCRF in the "Adverse event" section and reported to the Sponsor in accordance with instructions provided in section 11.3.

For each adverse event recorded on the Adverse Event CRF, the investigator will make an assessment of seriousness (see Section 11.1.1 for seriousness criteria), severity (see Section 11.2.3), and causality (see Section 11.2.4).

11.2.1 *Adverse event reporting period*

Investigators will seek information on adverse events at each subject contact. All adverse events, whether reported by the subject or noted by study personnel, will be recorded on the Adverse Event eCRF.

During the interval between the time when the subject signs the informed consent form and the commencement of treatment with the IMP, investigators will also be required to gather all AEs and promptly report any SAEs either resulting from an external factor (e.g., an accident) or caused by some kind of initial intervention indicated in the informed consent (e.g., an AE related to initial procedures such as allergen skin testing). See Section 11.3 for instructions for reporting serious adverse events.

After initiation of IMP, all adverse events, and serious adverse events regardless of attribution will be collected until 72 hours following the last administration of study treatment or until study discontinuation/termination. Subject will be asked, among other things, whether any new adverse events have occurred at the final visit (FV).

After this period, investigators should report only SAE that are considered to be related to prior study treatment (see Section 11.3).

11.2.2 *Eliciting adverse event information*

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all subject evaluation timepoints. Examples of non-directive questions include the following:

- "How have you felt since your last clinic visit?"
- "Have you had any new or changed health problems since you were last here?"

All adverse events will be recorded on the Adverse Event eCRF.

11.2.3 *Assessment of severity of adverse events*

The investigator shall perform an assessment of the severity of each adverse event (both severe or non-severe adverse event) reported during the clinical trial whether or not it is related to the IMP. The assessment shall be based on the investigator's clinical judgement.

The severity of each adverse event recorded in the eCRF should be classified into one of the following categories:

- **Mild:** an event that is easily tolerated by the subject and causes minimal discomfort without interfering with daily activities.
- **Moderate**: an event that causes discomfort in a way that interferes with activities of daily living.
- **Severe**: an event that prevents daily activities.

Severity (intensify) describes the degree to which an adverse event influences the patient's daily life, regardless of whether the event is serious (SAE) or not (AE). A severe adverse event should not be confused with a serious adverse event.
The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.
An adverse event reflecting a change in severity grade should be reported on two separates lines with respective severity grade. The Investigator's original description of the adverse event must be the same for the first and repeated adverse event, so that they are coded with the same dictionary term. The outcome date of the first adverse event should be the same as the start date of repeated adverse event, and the outcome of the first adverse event should be ticked for data management purpose, as resolved.

11.2.4 *Assessment of causality of adverse event*

Investigator has the obligation to uses his or her knowledge of the subject, the circumstances surrounding the event and an evaluation of any potential alternative causes to assess the relationship between the IMP and the occurrence of each adverse event. Decisive factors for the assessment include, may not be limited to, temporal relationship between the adverse event and IMP, known adverse reactions, medical history, concomitant medication, course of the underlying disease, alternative aetiology, etc.

Causality shall be qualified using one of the following categories:

- **Related**: There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
- **Unrelated**: There is not a plausible temporal relationship between the onset of the adverse event and administration of the study drug and/or there is evidence that the adverse event has an aetiology other than the study drug (e.g., pre-existing condition, underlying disease, concurrent illness, or concomitant medication).

11.2.5 *Procedure for recording adverse events*

Investigators should use correct medical terminology/concepts when recording adverse events on the adverse event eCRF. Avoid colloquialism and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

Adverse events, broken down by severity and seriousness, will be summarised using the MedDRA dictionary, by treatment group, organ or system and preferred term, showing the number of subjects per treatment group, number and frequency of subjects experiencing the event and the number of events. The same terms must be used in the source documentation and in the eCRF. Any discrepancies between the subject's own word on his/her own record and the corresponding medical terminology should be clarified in the source documentation.

To assess safety, all adverse events occurring during the course of the trial shall be recorded and assessed. These will be thoroughly explored, both at scheduled visits and at any time the subject reports an abnormal occurrence. However, the events described below are excluded from being considered adverse events:

- A flare and a wheal as result of the skin prick test procedure.

- Symptoms related to the pathologies of the study.

- Asthma exacerbation or bronchospasm.

- Hospital admission due to asthma exacerbation.

- Emergency visits due to asthma exacerbation.

Symptoms related to the disease under study will be collected through the Subject's Diary.

Information related to the occurrence of asthmatic exacerbations or bronchospasm will be collected in the eCRF on the page "Asthma exacerbation record".

The information related to hospital admissions and emergency visits due to exacerbations will be collected in the eCRF on the page "Consumption of health resources".

11.2.6 *Classification and management of local adverse reactions*

According to EAACI,[90] local adverse reactions are those occurring at the site of administration:

- ✓ Immediate: when they appear within 30 minutes of administration of the IMP.
- ✓ Late: when they appear 30 minutes after administration of the IMP.

Local reactions are considered if a wheal >5 cm in diameter occurs within 30 minutes of administration (immediate local reactions) or >10 cm if later (delayed local reactions).

11.2.7 *Classification and management of systemic adverse reactions*

According to EAACI,[90] systemic adverse reactions are those that occur in organs distant from the administration site. These reactions usually start within a few minutes after IMP administration (immediate reaction), rarely after 30 minutes (delayed reaction). The severity of these adverse reactions is classified according to the indications proposed by the World Allergy Organization[91] in 2010,[92] which were subsequently updated[93] as shown in Table 4, according to the following grades:

Table 6: Updated WAO Grading system for systemic allergic reactions[93].

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Mild symptom/sign(s) only: NB: Reactions can be further categorized as: • **1t**: transient (<20 mins) • **1s**: single organ system only, ≥20 mins • **1m**: 2+ organ systems, ≥20 mins	Any 1 (or more) of the following moderate symptom/sign(s):	Any 1 (or more) of the following symptom/signs:	Any 1 (or more) of the following symptom/ signs:	Any 1 (or more) of the following symptom/ signs:
Cutaneous *(any one of)*: • Limited (few) or localized hives/urticaria[a] • Skin flushing (few areas of faint erythema) or mild pruritus[a] • Swelling (e.g. lip edema)[a] [a]*excluding localized symptoms at application site*	***Cutaneous*** *(any one of)*: • Systemic urticaria (e.g. numerous or widespread hives) • Generalized (≥50% BSA) erythema • Widespread pruritus with protracted scratching • Significant angioedema (excluding lip swelling and laryngeal edema)	***Lower respiratory*** • Bronchospasm (e.g. wheezing, shortness of breath) which responds to first line treatment • Cough due to laryngeal or lower respiratory involvement	***Respiratory*** • Severe bronchospasm (not improving with 2 doses of IM epinephrine ± other appropriate treatment) • Stridor (with increased work of breathing)	***Respirator*** • Respiratory failure requiring positive pressure ventilation • Respiratory arrest
Or	And/or	And/or	And/or	And/or
Upper respiratory • Nasal symptoms (e.g., sneezing, rhinorrhea, itch, congestion) • Throat-clearing (itchy throat)[a] or throat tightness/discomfort • Cough due to throat irritation or nasal symptoms		***Upper respiratory/laryngeal*** • Throat tightness with vocal hoarseness • Stridor without increased work of breathing • Persisting (≥20 mins) odynophagia (pain on swallowing)	***Cardiovascular*** • Hypotension with associated symptoms of end-organ dysfunction (e.g. hypotonia, dizzy[§], collapse[§], syncope) OR • decrease in systolic blood pressure (sysBP) ≥30% from that person's baseline OR • SysBP <90 mmHg in adults (in children ≤10 years, sysBP <70 mmHg + [2 × age in years]) [§]*excluding vasovagal events (these present with dizziness/fainting which rapidly resolve on lying flat)*	***Cardiovascular*** • Anaphylactic shock i.e. requirement for IV vasopressor infusion to maintain sysBP ≥90 mmHg or MAP ≥65 mmHg in adults and children >10 years (or age-appropriate sysBP in younger children) • Cardiac arrest
Or		And/or		
Gastrointestinal • Nausea • Mild abdominal pain (for example, without a change in activity level)	***Gastrointestinal*** • Persisting (≥20 mins) and non-distractable abdominal pain and/or • Vomiting (not due to gag or taste aversion) and/or diarrhea	***Gastrointestinal AND Cutaneous*** Severe GI symptoms together with cutaneous features which meet WAO 2020 criteria for anaphylaxis (e.g. severe crampy abdominal pain, repetitive vomiting, *especially after exposure to a non-ingested allergen)*		
Or		And/or	And/or	
Other • Conjunctival reddening (not due to eye rubbing), pruritus, or tearing • Metallic taste		**Uterine** cramps ± uterine bleeding	***Neurological*** • *Glasgow Coma Scale < 13*	

Table 4. Grade 2 reactions are not usually considered anaphylaxis according to WAO (World Allergy Organization) 2020 clinical criteria but may respond to treatment with epinephrine. IM, intramuscular, BSA, body surface area; sysBP, systolic blood pressure; MAP, mean arterial pressure. Application-site reactions are considered local reactions, see text for more information on classification of local reactions

Treatment of this type of reaction must be immediate, in order to minimize the potential risks involved, particularly in participants with asthma. In cases of suspected anaphylaxis, intramuscular (IM) adrenaline (epinephrine) will be administered into the anterolateral aspect of the thigh, at a dose of:

- 0.01 mg/kg body weight, up to a maximum of 0.5 mg.
- This is equivalent to 0.01 mL/kg of the 1 mg/mL (1:1000) solution, up to a maximum of 0.5 mL in adults.

- The dose may be repeated every 5–15 minutes if symptoms persist or recur.

According to the WAO 2020 Guideline [94], intramuscular adrenaline should be administered immediately, without delaying its use while awaiting other adjunctive treatments. IM adrenaline is the first-line treatment and should be considered even when symptoms affect only one of the critical systems (respiratory or cardiovascular), as anaphylaxis may progress rapidly. If there is upper airway obstruction, the use of nebulized adrenaline may be considered as an additional measure.

Bronchoconstriction in the context of anaphylaxis
If bronchospasm occurs as part of the systemic reaction (wheezing, dyspnoea, chest tightness), in addition to intramuscular adrenaline, adjunctive medications may be used:

- Inhaled short-acting β2-agonist (SABA)

  o Salbutamol/albuterol via pressurized metered-dose inhaler with spacer or nebulizer.
  o Important: these are an adjunctive treatment for bronchospasm; they do not replace repeated IM adrenaline administration if anaphylaxis continues.
  o Routine use of parenteral β2-agonists or methylxanthines (aminophylline) is not recommended in the treatment of anaphylaxis, given their limited benefit and higher risk of adverse effects compared with the combination of IM adrenaline + appropriate supportive care.

- Systemic corticosteroids (oral or intravenous)

  May be used as add-on treatment, especially if there is an asthmatic component, to reduce symptom duration and the risk of recurrence, however, evidence of benefic in the acute phase is limited and routine use is controversial.

- H1 antihistamines

  o They have a secondary role, mainly useful for pruritus and rash; they should not delay or replace adrenaline administration. The WAO 2020 guidelines suggest that second-generation H1 antihistamines may avoid adverse effects; however, first-generation H1 antihistamines are currently the only ones available for parenteral administration. Rapid intravenous administration of first-generation H1 antihistamines may cause hypotension; therefore, it should be performed with caution.

Predominant cutaneous manifestations (generalized urticaria, pruritus, flushing)

If there is generalized urticaria, pruritus or generalized flushing, but without criteria for anaphylaxis, treatment may include:

• H1 antihistamines orally or parenterally, depending on severity, to relieve pruritus and urticaria.
• Systemic corticosteroids (oral or intravenous) as adjunctive treatment, especially if a more prolonged reaction is anticipated.

In mild cases, the same antihistamine used for rhinitis may be administered orally, with or without a corticosteroid. In moderate–severe cases, administration of a parenteral antihistamine and intravenous corticosteroid may be considered, in accordance with the site's usual clinical practice.

According to WAO 2020, antihistamines and corticosteroids do not treat the respiratory or cardiovascular manifestations of anaphylaxis, and their administration must not delay adrenaline.

Anaphylactic shock, cyanosis, severe dyspnoea or wheezing

In the presence of anaphylactic shock, cyanosis, severe dyspnoea or severe wheezing, the following actions will be taken:

• Administer immediate intramuscular adrenaline, according to the regimen indicated above, repeating the dose every 5–15 minutes if symptoms persist.

• Place the patient in the supine position (or the position of greatest respiratory comfort; recovery position if unconscious). The seated position should be avoided in patients with haemodynamic compromise, as it may precipitate cardiovascular collapse. If the patient is pregnant, she should be placed in the left lateral decubitus position.
• Administer high-flow oxygen, preferably close to 100%, via a non-rebreather mask, in all patients with respiratory or haemodynamic compromise.

• Ensure patent intravenous access and initiate intravenous crystalloid fluids (e.g., 20 mL/kg boluses in cases of hypotension or shock).

• Periodically monitor blood pressure, heart rate, oxygen saturation, respiratory rate, and mental status. The guideline recommends observing the patient for an appropriate period based on severity, as approximately half of biphasic reactions occur within the first 6–12 hours.

• WAO 2020 also indicates that, in patients taking beta-blockers who do not respond adequately to adrenaline, intravenous glucagon may be considered as an adjunctive treatment.

11.2.8 *Diagnosis versus signs and symptoms*

For adverse events, a diagnosis (if known) should be record on the Adverse Event eCRF rather than individual signs and symptoms. However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event could be recorded on the adverse event eCRF. If a diagnosis is subsequently established, all previously reported adverse event based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of eventual diagnosis.

11.2.9 *Recurrent adverse events*

A recurrent adverse event is one that resolved between the subject evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded separately on the eCRF.

11.2.10 *Abnormal laboratory values*

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms.
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation).
- Results in a medical intervention or a change in concomitant therapy.
- Is clinically significant in the investigator's judgment.
- It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.
- If a clinically significant laboratory abnormality is a sign of a disease or syndrome should not be recorded on the Adverse Event eCRF, but in rather clinical history.
- If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating if the test result is above or below the normal range.

11.2.11 *Pre-existing medical conditions*

Pre-existing medical conditions is one that is found as a result of the screening procedures. Such conditions should be recorded on Medical History and eCRF.

A pre-existing medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study.

11.2.12 *Lack of efficacy*

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as events. However, if there is any uncertainty as to whether an event is a result of disease progression, it should be reported as an adverse event.

11.2.13 *Hospitalization or prolonged hospitalization*

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as serious adverse event (the definition of serious adverse event in section 11.1.1), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or serious adverse event:

- Hospitalization planned before entry into the clinical study.
- Hospitalization for elective* treatment of a pre-existing condition.
- Consultation in an emergency ward, on outpatient basis and which do not result in overnight hospitalization (unless fulfilling one of the seriousness criteria).

(*) Elective means a planned hospital admission because of a pre-planned surgery or a pre-existing disease that has not changed in intensity, quality, or frequency (e.g., for diagnostic measures).
These hospitalizations will be collected in different sections of the eCRF depending on whether they are related or not to the study pathologies:

- Not related to the study pathologies: the information will be collected on the page “Other interventions/hospitalizations not related to study pathologies”.
- Related to the study pathologies: the information will be collected on the page “Consumption of heath resources”.

11.2.14 *Adverse events associated with medication errors*

For this study a medication error refers to any unintentional error which may include either an inappropriate route of administration or any deviation from specified doses as defined

in the protocol (e.g., the subject has received either a product overdose or an under dosing). The medication error must be documented on the Adverse Event eCRF.

All adverse events associated with a mediation error of study drug should be recorded as Adverse Event eCRF.

No safety data related to overdosing of study drug are available.

11.2.15 *Pregnancy*

Women of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study. Similarly, male subjects must inform the investigator immediately if their partner becomes pregnant.

If a woman becomes pregnant during the study, the trial medication should be discontinued, as noted before on section 7.3.

The women (participant in the study or partner of male participant) who become pregnant shall then be asked for permission to follow up the pregnancy and shall sign a specific informed consent form to this situation.

Then, whether or not the woman has given consent for the pregnancy to be followed up, the investigator should complete the Clinical Trial Pregnancy Report Form included in the eCRF. Pregnancy and suspected pregnancy (including positive pregnancy tests, regardless of age or disease) occurring in a subject enrolled in the trial or up to 30 days after her last dose of IMP should not be recorded as Adverse Event in the eCRF.

If the subject is taking the IMP and becomes pregnant, the IMP should be discontinued immediately, and the subject should be withdrawn from the trial (see section 7.3). Monitoring of the subject should continue until conclusion of the pregnancy. The investigator will request follow-up reports from the subject containing detailed information on the pregnancy, the outcome of the pregnancy, and the status of the new-born until the age of eight weeks.

The investigator will inform the Sponsor without delay using the specific form (Clinical Trial Pregnancy Report Initial-Form A or Clinical Trial Pregnancy Report Outcome-Form B) that is included in the eCRF. Any information that becomes available during the course or outcome of the pregnancy can be submitted as follow-up information on these forms.

Please be advised that any adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during and after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported to the sponsor, within 24 hours via email to [redacted] and by completing the corresponding eCRF section. If the pregnancy outcome is abnormal (including spontaneous or therapeutic abortion), the investigator should record it in the Clinical Trial Pregnancy Report Outcome-

Form B of the eCRF. In addition, if the abnormal outcome meets any of the seriousness criteria, it should be reported to the sponsor within 24 hours via email to f[redacted].

Any neonatal death occurring within 28 days of delivery, regardless of causality, should be reported as an SAE. Likewise, any infant death occurring within the first year (after 28 days of delivery), and if the investigator believes it to be related to exposure to the IMP during pregnancy, should also be reported as a SAE to sponsor, within 24 hours via email to [redacted] and by filling the eCRF sections.

All the information will be collected in the Pregnancy Forms available for the study. The timelines and procedures for the management of this information are included in section 11.3.

11.3 Management of adverse reactions (dose split, stopping rules and treatment)

Ensuring the safety of subcutaneous immunotherapy is essential to minimize risks and protect patient safety. This section outlines how to identify and manage adverse reactions, including when to reduce the dose or discontinue treatment (In more detail in section *7.4.1 and section 8.4*). Specific measures for addressing systemic reactions are also provided.

If the participant experiences an adverse reaction, this section outlines specific actions and dose modifications that investigators must follow, depending on whether the adverse reactions are immediate or delayed.

In case of local or systemic reactions, a dose split may be necessary: At the following visit, the volume to be injected will be split into two doses consisting of 0.2 mL and 0.3 mL. The 0.2 mL will be injected into one arm, followed by a 30-minute observation phase. Then the 0.3 mL will be injected into the other arm, followed by a 30-minute observation phase. If both injections of a dose split are well tolerated, the volume of the injection can be increased to 0.5 mL at the next visit.

i. Dose split in case of immediate reactions:

A dose-split of the investigational product must be performed if a participant experiences:

- A local reaction (wheal diameter > 10 cm) following the injection of 0.3 mL at visit 1 or 0.5 mL at visits 2 to 11, or after the injection of 0.3 mL (second injection of a dose split) at visits 2 to 11.
- A grade II systemic reaction following any injection of 0.2 mL 0.3 mL or 0.5 mL at visits 1 to 11 as part of an already split dose or during the first visit.

ii. Dose split in case of delayed reactions:

A dose-split of the investigational product must be performed If a participant experiences:

- A delayed local reaction (wheal diameter >20 cm) following the injection of 0.5 mL at visits 2 to visit 11 in the first dose or after the injection of 0.2ml+0.3ml at visits 2 to visit 11 in the split dose.
- A systemic reaction grade II at home following any of the injections at visit 1 to visit 11 in both the first dose and the split dose.

The stopping rules related to both immediate and delayed adverse reactions in situations of this nature are described in detail in *Section 7.4.1* of the protocol. Investigators are advised to consult this section for specific guidance on treatment discontinuation criteria.

iii. Treatment of systemic adverse reaction (SAR)

Treatment of severe systemic allergic reactions (anaphylaxis) must be immediate, especially in participants with asthma.

Intramuscular adrenaline (epinephrine) will be administered in the anterolateral aspect of the thigh at a dose of 0.01 mg/kg (maximum 0.5 mg; 1 mg/mL solution [1/1000]). The dose may be repeated if necessary.

If there is bronchospasm (as a manifestation of the systemic reaction), in addition to adrenaline the following may be administered as adjunctive treatment:

- Inhaled short-acting β2 agonists.
- Systemic corticosteroids (oral or parenteral) according to severity.
- Antihistamines for control of accompanying symptoms (pruritus, rash).

Routine use of β2 agonists by the parenteral route or methylxanthines (aminophylline) is not recommended.

If there is generalized urticaria, pruritus or generalized flushing, without criteria for anaphylaxis, antihistamines will be used and, according to severity, oral or parenteral corticosteroids. In mild cases, the same antihistamine used for rhinitis may be administered orally, with or without a corticosteroid; in more severe cases, a parenteral antihistamine may be used in combination with an intravenous corticosteroid.

If there is anaphylactic shock, cyanosis, intense dyspnea or severe wheezing, intramuscular adrenaline will be administered, oxygen to correct hypoxemia (with the flow required to maintain adequate saturation), and a patent intravenous line will be ensured with infusion of intravenous fluids, in addition to close clinical monitoring.

11.4 Reporting requirements from investigator to sponsor

All events that meet the definition of AEs should be collected and recorded from the first trial-related activity (after the subject has signed the informed consent form) until final visit

after the date of the last IMP administration, premature termination, or withdrawal, even if no IMP was taken (See Section 11.2.1).

All adverse events will be actively sought for each visit. Complete, accurate and consistent data on all adverse events, whether observed by the investigator or reported by the subject, should be recorded in the appropriate section of the eCRF and evaluated by the investigator. For each adverse event, the Investigator should specify the following information: the description of adverse event, start date, time to onset between last IMP intake and adverse event occurrence, stop date, duration, action taken with the IMP, treatment for the adverse event, and outcome. The Investigator should evaluate the event in terms of severity, relationship to the IMP, and seriousness.

Serious adverse events (SAE), whether or not considered as related to IMP, and pregnancies require immediate reporting measures to address potential new risks in a clinical study. The investigator must report immediately such events to the Sponsor, within a maximum of 24 hours of occurrence or Investigator's awareness by telephone or email to [redacted]

The investigator should first report it to the sponsor, and then collect it from the trial's eCRF, completing the appropriate SAE form, even if the data are incomplete or if it's obvious that more data will be needed to draw any conclusion, which should be given to the investigator at the start of the trial.

The investigator shall preferably make a diagnosis of AE or SAE based on the presenting signs, symptoms and/or other clinical information (See section 11.2).

Reporting procedures and timelines are the same for any follow-up information.

11.4.1 *Follow-up of subjects after adverse events*

The Investigator should follow each adverse event until the event has resolved to baseline grade or improved, the event is assessed as stable by the investigator, the subject is lost to follow-up, or the subject withdrawn consents.

Additional information (i.e., lab data, hospital report) should be provided to Sponsor or designee in a timely manner to ensure accurate follow-up of each case. SAEs and SARs must be followed up until resolution or until stabilization (until a final outcome can be reported).

The Sponsor or designee may contact the Investigator to obtain further relevant information regarding a SAE or a SAR in order to perform an independent medical assessment of the reported case.

In final Visit (FV), the Investigator will try to follow the adverse event until the outcome of the event is "in recovery" (for chronic conditions) or "recovered", but in case the AE still remains unresolved, it will be recorded as "not recovered".

11.4.2 *Adverse event that occurs after the study*

If the Investigator becomes aware of a SAE that is believed to be related to IMP, the events must be reported directly to the sponsor immediately via email to [redacted] (i.e., with a maximum of 24 hours of occurrence or Investigator's awareness) through use of the SAE/SAR form.

11.5 Sponsor's reporting requirements

The sponsor shall notify all SUSAR on the IMP to the Investigators, the Health Authorities and Ethics Committees, if necessary, according to the regional regulations.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events in relation to the applicable product information, using the reference safety information (RSI) contained within the Investigator's Brochure of EP-088_MM09 (Mannan-conjugated allergoid (polymerized) *Dermatophagoides pteronyssinus/Dermatophagoides farinae* parenteral vaccine).

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by sponsor as needed.

The sponsor of the clinical trial must report all the Suspected unexpected serious adverse reaction (SUSAR) from a clinical trial to Health Authorities, Investigators and to the International Ethics Committee (IEC) within the following timelines.

- In case of SUSARs resulted in death or endangered the life of the participant, as soon as possible, and in any case within seven days after becoming aware of the reaction.
- In case of SUSARs not resulted in death or endangered the life of the participant, no later than 15 days after becoming aware of the reaction.
- In case of SUSARs resulted in death or endangered the life of the participant that were not initially considered as such, as soon as possible, and in any case within seven days after becoming aware of the reaction.
- The SUSAR including all relevant follow-up information must subsequently be reported again with an additional 8 days (this also applies if no new information has been received).

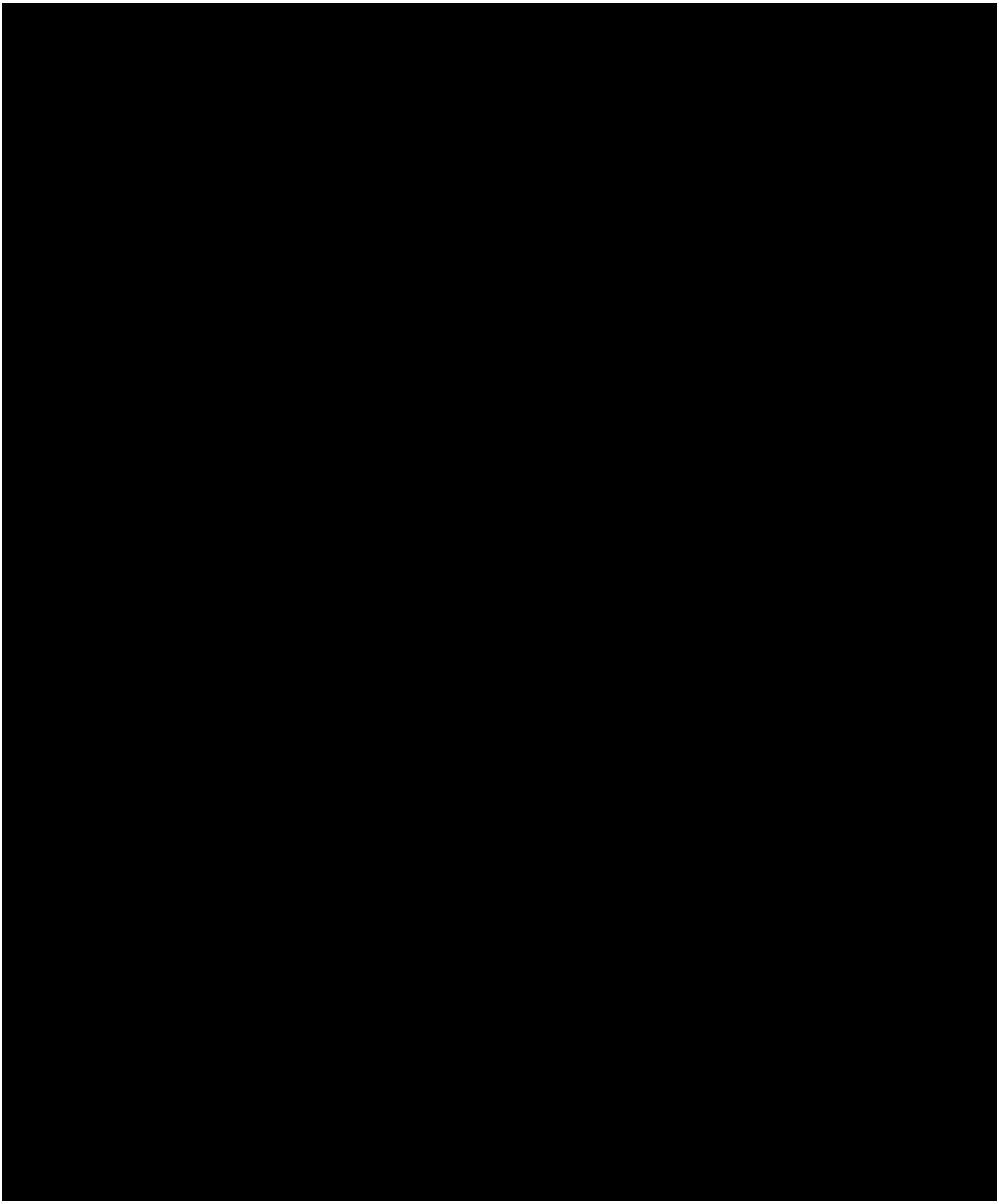
ITK-PHV is responsible for reporting SUSARs within required timelines to the CAs, IEC or to investigator. SUSARs to CAs, IECS and investigators outside EEA will be reported according to local requirements.

11.6 Data Safety Monitoring Board (DSMB)

[redacted]

12 STATISTICS

[redacted]



[redacted]

13 GENERAL ASPECTS OF THE TRIAL

13.1 Direct access to source data/documents

Source documents are all original documents, data, and records (e.g., medical records, clinical and administrative charts, laboratory reports, subject diaries or evaluation questionnaires, drug dispensing records, data recorded by computerised instruments, copies or transcripts certified after verification as exact copies, X-rays, subject files, and records kept in the pharmacy, laboratories and medical-technical departments involved in the clinical trial). Subjects' diaries, quality of life questionnaires, asthma symptom control questionnaire, and visual analogue scales shall also be considered as source documents.

Both the principal investigator and collaborating investigators shall allow the trial monitors to inspect the source documents and eCRFs upon request throughout the trial period.

The researcher shall also provide access to source data/documents in the following cases:

- Inmunotek S.L. wants to perform an audit of the clinical trial.
- The Competent Authorities may wish to conduct an inspection of the clinical trial as part of the process of confirming the validity of the conduct of the trial and the integrity of the data collected.
- The IRB/IEC involved wish to check the progress of the trial.

The principal investigator(s) or collaborating investigator(s) will request in writing the subject's permission to have direct access to the subject's data during the informed consent process. At the time of participation acceptance, the subject also grants permission to examine, analyze, verify, and reproduce any medical records and reports relevant to the evaluation of the trial. Any party (e.g., domestic, and foreign regulatory authorities, trial monitors, and auditors) with direct access will take all reasonable precautions within the limits of applicable legal requirements to maintain the confidentiality of subjects' identities and the sponsor's proprietary information.

13.2 Document archiving

The principal investigator should maintain adequate records to enable the trial to be fully documented. All source documentation and trial records and other trial-related documents should be retained in accordance with Good Clinical Practice (GCP). Trial documents should not be destroyed unless there is prior written agreement between the sponsor's representatives and the principal investigator. If the principal investigator leaves the site or retires, the responsibility for maintaining the records may be transferred to another person, with prior notice and agreement of the sponsor.

The investigator should retain and maintain the essential documents as defined by GCP and local regulations after the trial has been discontinued or terminated. The subjects' medical

records and other original data should be retained for as long as the hospital permits. The sponsor should provide the investigator with a file for this purpose, which should be updated by the investigator as necessary.

The investigator's file shall be made available during monitoring visits, in the case of audit and/or inspection.

Inmunotek S.L. will be responsible of the trial master file including all documentation related to the trial and should retain all such information for the duration of the investigational product's validity. Any changes in data holdings should be documented. In all cases, the documents shall be made available to the Health Authorities upon request.

13.3 Data processing and archiving

The processing of the data collected by the sponsor during the study will be subject to the current legality regarding data protection, following the local Spanish and Portuguese regulations which develop the European Regulation 2016/679 (General Data Protection Regulation). Subjects will be identified in the registers only with the code number. The subject must be guaranteed anonymity and must be informed that all communication will take place between the subject and the researcher, and not with the study sponsor.

Inmunotek S.L. will provide an eCRF which must be completed in full. The omission of data must be justified in all cases.

The investigator will provide a list with the signature and handwritten initials of each collaborator authorised to make data entry or changes in the eCRF. The study site staff will be trained on how to use the eCRF. In case of any modification during the trial, an updated list of authorised persons will be provided.

Data on subjects collected in the eCRF during the trial will be identified only by subject number. The number assignment will be in order of inclusion in the trial, always starting with the lowest number (001) and proceeding sequentially in increasing order, as detailed in section 6.3.1.

If, exceptionally, it is necessary to identify the subject for safety reasons or on the instructions of the Health Authorities, the investigator shall be obliged to keep this information confidential.

All information in the eCRF must be traceable to the original documents stored in the subject's file. Data without an original written or electronic record shall be defined prior to the start of the trial and shall be recorded directly in the CRFs, which shall be documented as original data.

At the monitoring visits, the monitor will review the eCRFs, noting any discrepancies, concerns, or observations in a separate document. The monitor should discuss this list of

discrepancies with the investigator to correct the corresponding data in the CRFs. Corrections should be made by the investigator or authorised site staff. Neither the trial monitor nor any representative of Inmunotek S.L. is authorised to enter data or corrections in the eCRF.

13.4 Quality control and quality assurance

Inmunotek S.L., as trial sponsor, is responsible for implementing and maintaining the quality assurance and quality control systems of the trial, through updated Standard Operating Procedures, and proper monitoring of the clinical trial.

To ensure the quality of the trial, Inmunotek S.L., through the trial monitor, will verify that:

- Source documents and other trial records are accurate, complete, up to date and properly archived.
- Data required in the protocol are accurately recorded in the eCRF and are consistent with the source data.
- Both the principal investigator and collaborating investigators follow the approved protocol and approved modifications, if any.
- Written informed consent was obtained prior to each subject's participation in the trial.
- The investigator and their trial staff perform the trial-specific functions in accordance with the protocol and have not delegated these functions to unauthorised people.
- The researcher recruits only subjects who meet the selection criteria.
- All doses and/or any treatment modifications are well documented for each trial subject.
- AEs are reported in accordance with the protocol.
- Whether all AEs have been communicated appropriately and within the timelines foreseen in the GCP, the protocol, the IRB/IEC, the sponsor, and the relevant legal requirements.
- If the investigator maintains essential documents.
- The investigator has been informed of any deviation from the protocol, Standard Operating Procedures or GCP and current legislation, and the necessary measures have been taken to prevent recurrence of the detected deviations.

13.5 Ethical issues related to the trial

All parties involved in this trial undertake to strictly observe the Standards of Good Clinical Practice (GCP) and ethical considerations required by current Spanish and Portuguese clinical trial regulations, as well as the corresponding recommendations derived from Community Legislation.

13.6 Informed consent/assent

To ensure the rights of subjects, the principal Investigator or collaborating investigators, through the participant information sheet, will explain the objectives and requirements of the trial, the nature of the study product, and its potential side effects, in language understandable to the subject and to the parent(s)/legally authorized representative(s).

Subjects or the parent(s)/legally authorized representative(s) should be informed that their participation in the trial is voluntary and that they are free to withdraw their consent at any time without giving reasons. Withdrawal of consent will mean that no new data will be collected from the subject, and no new information will be included in the trial database, except for data related to the final visit. The subject or the parent(s)/legally authorized representative(s) will be informed of the possibility to withdraw consent at any time during the trial, and to request that all samples be destroyed to prevent future analyses, in accordance with local regulations.

In case of subjects aged 12 to 17, informed consent will be obtained from their parents or legally authorized representatives, and additionally information will be provided to them in a language adapted to their age. Their willingness to participate will be respected and obtained through an assent.

Subjects or parent(s)/legally authorized representative(s) should be informed that both the Health Authorities and people authorised by the sponsor may examine their data, but that personal information will be kept strictly confidential and will not be publicly available. Subjects should be given sufficient time and opportunity to inquire about the details of the trial before deciding to participate in the trial.

All the forms will also be dated and signed by the investigator or the designated person who obtained the informed consent/assent according to local regulations. The subject and parent(s)/legally authorized representative will receive a copy of the corresponding form(s) and the original(s) will be filed in the Investigator's Trial File.

If the informed consent or the assent form is amended during the study, the investigator must use the amended form with the ongoing and the new patients.

Informed consent and assent procedures will be documented in medical history.

All subjects or parent(s)/legally authorized representatives must give written informed consent prior to inclusion in the trial. An eCRF must not be started, nor may any study specific procedure be performed before having obtained his/her or/and parent(s)/legal representative written consent/assent. Informed consent forms will be retained in the trial file by the investigator during the conduct of the trial and thereafter for the time stipulated by applicable law.

If any new information that could influence the subject and/or parent(s)/legal representative decision to remain in the study becomes available, it will be communicated without delay to the subject or/and parent(s)/legal representative.

13.7 Financing and insurance

The source of funding is the sponsor, Inmunotek S.L.

The sponsor has taken out an insurance policy to cover damages that a subject may suffer as a result of participating in the following clinical trial.

13.8 Publication policy

The results or conclusions of this trial shall be reported as a matter of priority in scientific publications with reference to the relevant IRB/IEC. The anonymity of the subjects participating in the trial shall be maintained at all times.

The fully or partially publication or disclosure of the data or conclusions of the clinical trial will be carried out by mutual agreement between the investigators and Inmunotek S.L. In the event that the trial sponsor fails to do so within one year, the investigators will be free to publish the results obtained.

14 ANNEXES

- Annex I. Financial report.
- Annex II. Quality of Life Questionnaire in Asthma (AQLQ).
- Annex III. Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ).
- Annex IV. Asthma Control Questionnaire (GINA 2023).
- Annex V.A Investigator Visual Analogue Scale (VAS).
- Annex V.B Subject Visual Analogue Scale (VAS).

The annexes are in separate documents.

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