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Title: A double-blind, prospective, parallel group evaluation of a novel biologic therapy for perennial allergic rhinitis

PROTOCOL

"A double-blind, prospective, parallel group evaluation of a novel biologic therapy for perennial allergic rhinitis"

Short Title

Novel biologic therapy for allergic rhinitis

Sponsor:	Relez Therapeutics, LLC of Maryland		
Study Number:	PMA 001		
IND Number:	Not applicable	**EudraCT Number:**	Not Applicable
Compound:	FDA approved antigens in propriatory preparation		
Date:	August 7, 2018 Version 6.9.1		

1.0 ADMINISTRATIVE INFORMATION

Contacts

Contact Type/Role	USA Contact
Serious adverse event and pregnancy reporting	Jody R. Tversky, MD Johns Hopkins University School of Medicine, Baltimore, MD 1-410-550-5949
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	Jody R. Tversky, MD Johns Hopkins University School of Medicine, Baltimore, MD 1-410-550-5949

1.1 Approval

REPRESENTATIVES OF JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINES

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

The signatures of the responsible Johns Hopkins University School of Medicine Co-ordinating Investigator and the study Principal and Co-Principal Investigators can be found on this signature page.

Jody R. Tversky, M.D. Principal Investigator Assistant Professor of Medicine Division of Allergy & Clinical Immunology Johns Hopkins University School of Medicine	Date	Antoine E. Azar, MD Co-Principal Investigator Assistant Professor of Medicine Division of Allergy & Clinical Immunology Johns Hopkins University School of Medicine	Date

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 9.2 of this protocol.
- Terms outlined in the Clinical Study Site Agreement.
- Appendix B – Responsibilities of the Investigator.

Signature of Investigator Date

Signature of Co-Investigator Date

Investigator Name (print or type)

Co-Investigator Name (print or type)

Johns Hopkins Bayview Medical Center, Baltimore, MD, USA

Location of Facility

USA

Country

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STUDY SUMMARY

Name of Sponsor: **Relez Therapeutics, LLC**	**Compound:** FDA approved antigens in propriatory preparation	
Title of Protocol: "A double-blind, prospective, parallel group evaluation of a novel novel biologic therapy for perennial allergic rhinitis"	**IND No.:** Not Applicable	**EudraCT No.:** Not Applicable
Study Number: PMA 001	**Phase:** 2 Proof of Concept	

1.2 Abstract and Study Design:

This is a randomized, parallel-group, double-blind, phase 2, single center, proof–of-concept study which will evaluate the effect of a propriatory mixed preparation of FDA approved allergens (PMA) used as a sub-cutaneously administered immunotherapy for the management of allergic rhinitis (perennial and seasonal). Participating study subjects will be required to manifest the signs and symptoms of allergic rhinitis and test positive to at least six allergens using a multi aeroallergen screen at the time of study recruitment . All subjects will undergo standard allergen skin prick testing using six Multi-Test® PC skin prick test devices (Lincoln Diagnostics, Decator, IL) or comparable skin testing technique for a total of 48 SPT. Approximately 36 total subjects will be enrolled.

Following a successful screening study visit and two week medication washout period, a 8 week treatment period will be initiated with bi-weekly study visits being undertaken, through to the end of immunotherapy, for assessment of therapeutic response and safety evaluations. Efficacy evaluation will be monitored using validated instruments that assess study subject clinical response, physician global assessment, and medication use. A safety assessment will be undertaken one month following completion of treatment.

At the screening visit (Screening Visit) a potential study subject will be required to fulfill the requirements of the study inclusion and exclusion criteria, will have a clinical evaluation including medical history and physical examination, blood draw and performance of skin testing. The study subject will then abstain from using intranasal steroids and antihistamines for two weeks and then return to the clinic for administration of sub-cutaneous PMA and post-treatment in-clinic safety evaluation. The latter evaluation period will comprise approximately 60 minutes to assess the study subject's response to PMA immunotherapy. Follow up clinic study visits will continue bi-weekly through 8 weeks and at each of these visits the study subject will receive increasing doses of PMA immunotherapy and will be evaluated for safety. Twice weekly clinical evaluation will also be performed. Following the final administration of PMA immunotherapy, a one month follow-up safety and clinical efficacy evaluation will be conducted by telephone or in the clinic. The duration of the study will be approximately 14 weeks.

Primary Objectives:

To evaluate whether there is a difference in the signs and symptoms of moderate to severe allergic rhinitis when treated with a propriatory mixed preparation of FDA approved allergens, administered sub-cutaneously over a 8-week period, versus the response to placebo and standard of care.

Secondary Objectives:

The secondary objectives of this study are to quantify allergy medication use and adverse events. Serum will also be stored to evaluate changes in IgE and IgG subclasses.

Subject Population: Adult male and female subjects aged 18-65 with moderate to severe allergic rhinitis.	
Number of Subjects: Approximately 36 total study subjects will be recruited Subjects will be equally divided between active treatment and placebo administration.	**Number of Sites:** Single site
Dose Level(s): All subjects will be started on the same dilution of PMA	**Route of Administration:** PMA – sub-cutaneous Placebo – sub-cutaneous
Duration of Treatment: 8 weeks	**Period of Evaluation:** 14 weeks

Main Criteria for Inclusion:

1. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures.
3. The subject is a male or a non-pregnant, non-lactating female between the ages of 18 and 65.
4. The subject is actively manifesting symptoms and signs of moderate to severe allergic PAR with or without SAR component defined as score of at least 28 on the RQLQ and 6 on the TNSS scale. Scores will be determined on the first and second visit (after the 14 day medication washout period). Both scores exceeding their threshold on either day will qualify.
5. Skin test strongly positive (wheal at least 5mm diameter and 2mm greater than negative control) to at least 6 of 48 allergy skin prick tests including at least one species of dust mite.

1.3 Exclusion Criteria

Any subject who meets any of the following criteria will not qualify for entry into the study:

1. The subject has received any investigational compound within 30 days prior to screening.
2. The subject has received allergen immunotherapy or SLIT in a previous clinical study or as a therapeutic agent within the past two years.
3. The subject has a history or clinical manifestations of significant medical conditions (cardiovascular, hepatic, infectious or renal disease, etc.) which in the opinion of the

investigator renders them unacceptable study subjects.

4. The subject has a history of drug abuse (defined as any chronic illicit drug use) or a history of alcohol abuse within 5 years prior to the screening visit.
5. The subject is required to take excluded medications listed in Section 6.3.
6. If female, the subject is pregnant or lactating or intending to become pregnant before, during, or within 1 month after participating in this study; or intending to donate ova during such time period.
7. Subjects found to have on physical exam significant nasal polyps, septal deviation or infectious sinusitis.
8. The subject has a history of allergic rhinitis but is not currently manifesting active signs and symptoms of the disorder.
9. Subject has a history of cancer, other than squamous cell or basal cell carcinoma of the skin that has not been in full remission for at least 5 years prior to Screening. (A history of treated CIN I, II, or CIN III [cervical intraepithelial neoplasia] is allowed.)

Main Criteria for Evaluation and Analyses:

Primary efficacy endpoint

The primary efficacy endpoint for this study is the quantitative comparison of the study subject clinical response of active PMA immunotherapy compared to the placebo treatment. The total combined symptom and medication score (DCS) will be used as a validated assessment.

Secondary efficacy endpoints

The secondary efficacy endpoints for this study are mini-Rhinitis Quality of Life Questionaire (RQLQ) and safety assessment. Serum will also be stored to evaluate changes in IgE and IgG subclasses.

Safety Analysis

Safety outcomes will be assessed by adverse event reporting in active and placebo treated study subjects.

Overall safety and tolerability will be assessed by evaluating the incidence of treatment emergent adverse events (TEAE), vital signs, and other safety variables. Treatment-emergent AEs will be defined as any AEs, regardless of relationship to study drug, which occurs on or after the first double blind dose date and up to 30 days after the last dose date of the double-blind study drug.

Treatment-emergent adverse events (treatment at time of event) will be summarized using the Medical Dictionary for Regulatory Agencies (MedDRA) coding dictionary.

Statistical Considerations:

Efficacy Analyses

The intent-to-treat approach will be used. Baseline characteristics (those collected prior to randomization) will be described using mean and standard deviation for continuous variables and medians and ranges for discrete variables.

The primary efficacy variable is the change in symptoms at the end of the periods of PMA or placebo study drug administration. The p-value, least square (LS) treatment means, difference between the LS treatment means, and 95% confidence intervals for the treatment differences will be presented.

The secondary efficacy variables are rescue medication requirement and adverse events. These changes will be analyzed similarly to that of the primary efficacy variable.

The percentage of subjects stopping PMA or placebo administration due to intolerance or lack of efficacy will be summarized by treatment group, and the groups will be compared using Fisher's exact test.

Sample Size Justification:

The study sample size is based upon the results of prior immunotherapy investigations undertaken by the Investigators of this study and their colleagues in the Division of Allergy & Clinical Immunology, Johns Hopkins University School of Medicine. Efficacy for immunotherapy was estimated to be 80% for treatmet group and 30% for placebo. Using an error rate (α) of 0.05 and 80% Power we calculate a total sample size needed of 28 subjects. To account for drop off we will recruit up to 36 subjects.

2.0 STUDY REFERENCE INFORMATION

2.1 Endpoints

2.1.1 Primary Endpoints

The primary endpoint is to quantify and compare the clinical difference in signs and symptoms and medication usage that may be apparent when subjects with active perennial allergic rhinitis (PAR) with or without seasonal symptoms (SAR) are treated in a double-blind, prospective, controlled eight weeks study with a PMA versus placebo.

2.1.2 Secondary Endpoint

The secondary endpoints include the global RQLQ index and adverse events profile (AE). Serum will also be stored for measurement of immunoglobulins at a later date.

2.2 Primary Investigator

The sponsor has selected a Signatory Primary Investigator from the investigators who participate in this study. Selection criteria for this investigator included significant knowledge of the study protocol, the study medication, their expertise in the therapeutic area and the conduct of clinical research as well as study participation. The Signatory Coordinating Investigator will be required to review and sign the clinical study report and by doing so agrees that it accurately describes the results of the study.

2.3 List of Abbreviations

AE	adverse event
AR	allergic rhinitis
BMI	body mass index
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CysLTs	cysteinyl leukotreines
DCS	Daily combined score
DNA	deoxyribonucleic acid
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
ICH	International Conference on Harmonisation
ICS	Inhaled corticosteroids
IgE	Immunoglobulin E
IL	interleukin
INR	international normalized ratio
IRB	institutional review board
LFT	liver function tests
LTRA	leukotriene receptor antagonists
MedDRA	Medical Dictionary for Regulatory Activities
PMA	propriatory mixture of allergens
PAR	perennial allergic rhinitis
PNU	Protein Nitrogen Units
PTE	pretreatment event
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SAR	seasonal allergic rhinitis

SOP	standard operating procedure
TEAE	treatment emergent adverse event
TNSS	Total nasal symptom score
ULN	upper limit of normal
WHO	World Health Organization

3.0 INTRODUCTION

3.1 Background

Allergic rhinitis and asthma

Allergic rhinitis (AR) is one of the most common chronic disorders, with reported prevalence ranging from 3% to 19% (1). It is a heterogeneous disorder that includes seasonal AR (SAR) symptoms ('hay fever') and, perennial AR (PAR). The comprehensive review of Kay and colleagues reports that SAR is found in approximately 10% of the general population and PAR in 10% to 20%. (2).

Clinical symptoms of AR include runny nose, itching, sneezing and nasal congestion. More than 80% of persons with allergic asthma have AR and AR is a risk factor for the development of asthma. Hence, there is a significant comorbidity between asthma and AR which is not surprising since there is an uninterrupted air passage from the nose to the alveolar ducts of the lungs. The clearest connection between AR and asthma is based on a shared immunologic response to an identified foreign substance. The term often used for the response is 'allergy', and the foreign substance is an allergen. Kay (2) notes that when Clemens von Pirquet originally introduced the term allergy in 1906, he had applied it to the reactivity found in both protective immunity and hypersensitivity. However, allergy is now identified with the type 1 hypersensitivity disorder of the immune system associated with immunoglobulin E (IgE).

Triggers for episodes of allergic rhinitis

The triggers for AR are aeroallergens associated with, airborne pollens, dust mites, animal dander, molds that induce IgE production. The inflammatory response is similar for both AR and asthma; they share a similar respiratory epithelial structure of ciliated pseudostratified columnar epithelium with goblet cells (6). The pathophysiology of local mediator release, systemic immune response and eosinophil recruitment are alike. During the early-phase response, symptoms in patients with AR typically consist of sneezing, rhinorrhea and conjunctivitis; patients with asthma experience wheezing, coughing and shortness of breath, in addition to objectively demonstrable changes in lung function. There is a similar pattern and time course of early- and late-phase responses in AR and asthma. Approximately 1 hour after allergen provocation, patients with AR experience a peak in symptoms, while patients with asthma experience a steep decline in lung function, measured by forced expiratory volume in 1 second (FEV_1). During the late-phase response, nasal congestion is sustained in patients with AR, while a prolonged fall in lung function is again observed in patients with asthma. Within 12 h to 24 h, both types of reactions may resolve.

Sub-cutaneous allergen immunotherapy

Allergen immunotherapy by injection (desensitization or hyposensitisation) consists of an induction course of injections of increasing doses of the allergen extract, usually given weekly or bi-weekly. The maintenance phase of maximum dosage injections usually lasts between three to 5 years (7). Injections can consist of single or mixed allergen extracts. As reported in a recent Cochrane Review, specific allergen immunotherapy (SIT) for hay fever is widely considered to be effective where grass pollen, ragweed, and birch pollen are causal agents, and there is evidence that its efficacy may continue for many years beyond the treatment period (8). The review concludes that specific allergen injection immunotherapy is a safe and efficacious treatment in reducing symptom severity and the requirement for anti-allergic medication in AR. In view of the occasional occurrence of systemic side effects following injections, it is customary that injection immunotherapy is performed in the immediate presence of a physician and administered by personnel that are fully trained and who are experienced in the early recognition and treatment of such reactions.

3.2 Rationale for the Proposed Study

The proposed study represents a novel and heretofore unpublished method of sub-cutaneous immunotherapy for the management of the spectrum of PAR with or without SAR. The immunologic concept and therapeutic management techniques to be studied in this investigation evolved during the past three decades in the clinical practice observations of some 20,000 patients as undertaken by the "inventor" of the treatment paradigm, William J. Freeman, MD, a Johns Hopkins University School of Medicine graduate and Diplomate of The American Board of Otolaryngology.

The intrinsic difference of the Freeman technique, compared to currently used methodologies of sub-cutaneous immunotherapy for AR, is that a wide-spectrum propriatory mixture of 60 different FDA approved allergens (referenced above as PMA), refined over multiple years of clinical testing and observation, is used for the immunotherapy. In part due to the significantly lower dose of each active allergen, this form of immunotherapy has demonstrated an excellent clinical safety profile and not one single anaphylactoid response has been noted with the use of this propriatory mixture in decades of use and development.

Current sub-cutaneous immunotherapy for the management of AR typically consist of the use of a limited number of relevant antigens (grass pollen, tree pollen, ragweed pollen, dust mites,etc.). Hence, the propriatory antigen mixture that will be used in this investigation that uses more than 60 relevant allergens represents a new immunologic concept that has not been subjected to a controlled, parallel group, prospective and double-blind study.

All the antigens used in the PMA are currently FDA approved for immunotherapy purposes. These consist of both standardized and non-standardized forms of allergen. For the standardized allergen extracts, manufacturers compare the allergen extract to a U.S. reference standard for potency, maintained by the FDA Center for Biologics Evaluation and Research. The precise selection of

antigens, the quantitative amount of the latter in the propriatory mixture and the preparation of three allergenic solutions of "vaccine" for immunotherapy are propriatory intellectual property.

4.0 STUDY OBJECTIVES AND ENDPOINTS

4.1.1 Primary Objective

The primary efficacy endpoint for this study is the quantitative comparison of the study subject clinical response of active PMA immunotherapy compared to the placebo treatment. The Total Nasal Symptoms Score (TNSS) will be used to generate daily symptom scores. The total combined daily symptom and medication score (DCS) will be used as the primary validated assessment.

4.1.2 Secondary Objective

The secondary efficacy endpoints for this study are mini-Rhinitis Quality of Life Questionaire (RQLQ) and safety assessment. Serum will also be stored to evaluate changes in IgE and IgG subclasses.

5.0 STUDY DESIGN AND METHODS

5.1 Study Design

This is a phase 2 proof of concept study. It is being undertaken to characterize and quantify the clinical difference in signs and symptoms that may evolve when subjects with active SAR/PAR are administered a sub-cutaneous form of immunotherapy in a double-blind, prospective, controlled six weeks study wherein a PMA is compared with saline placebo.

Randomization to active PMA versus placebo treatment is on a 1 to 1 ratio. A double-blind study design is used to minimize outcome bias. Randomization measures to minimize bias at study entry include computerized random assigment of treatment versus placebo vials.

Subjects who are receiving nasal steroids for their SAR/PAR at screening may continue in the screening process if they agree to discontinue their therapy and comence a 14 day wash-out period of their medication prior to receiving active/placebo immunotherapy. Potential study subjects who, at screening, are not on active treatment for their SAR/PAR and asthma may enter directly into the investigation provided they fulfil entry and exclusion criteria and screening testing requirements.

The population to be studied consists of male and female adults aged 18 years to 65 years who are actively manifesting SAR/PAR have a score of at least 28 on the mini-RQLQ and 6 on the TNSS scale.

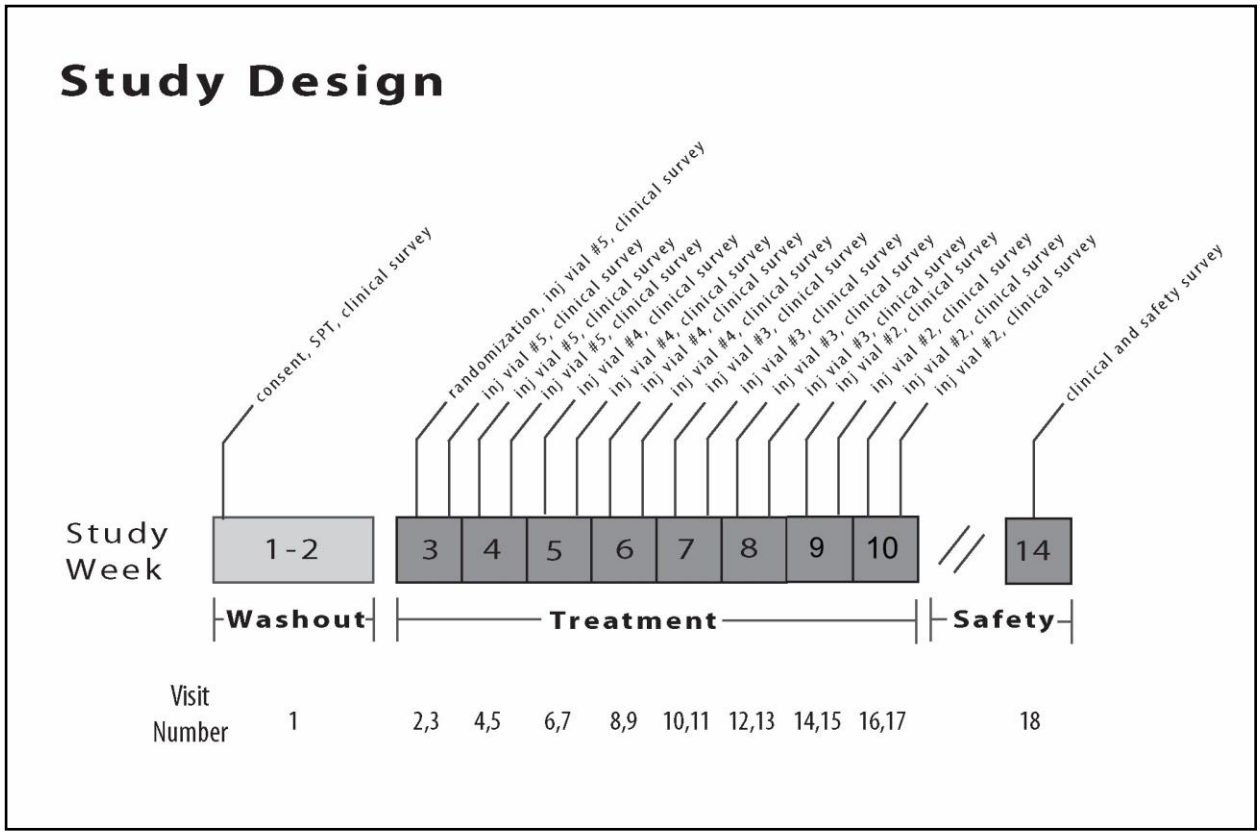
The active treatment phase of the study will be for six weeks with a safety followup assessment at 30 days post-treatment. No interim analysis is planned.

The study immunotherapy that will be evaluated in this study is a new innovative propriatory mixture of FDA approved allergens which has been clinically developed and evaluated, during the past three decades, in some 20,000 patients by the inventor of the mixture (see 3.2). In clinical evaluation this patented antigen mixture has provided clinical symptomatic relief to patients with SAR/PAR in as brief a period as three administrations of immunotherapy injections and has an observed overall success rate of approximately 80 to 90 percent of such treated subjects.

In this study approximately 36 study subjects will be equally randomized to active PMA or placebo. The duration of active PMA or placebo treatment will be 8 weeks with clinic visits twice-weekly during this period and a post-treatment safety follow up assessment at one month following the final administration of immunotherapy. All doses of immunotherapy will be administered in the study site clinic by the investigators or their designees.

A schematic of the study design is included as Figure 5.a. A schedule of assessments is listed in Appendix A.

Figure 5.a Schematic of Study Design



5.2 Justification for Study Design, Dose, and Endpoints

The question to be answered scientifically by this investigation is whether or not a new innovative, patented mixture of FDA approved antigens provides unequivocal superior clinical benefit in the symptomatic relief of individuals manifesting active SAR/PAR. Since extensive prior experience of managing patients with these medical conditions has demonstrated remarkable benefit from the immunotherapy technique within 3 to 6 weeks, the selection of study subjects and the overall study design can be scientifically justified.

The dose of immunotherapy, which will be administered sub-cutaneously bi-weekly for 8 weeks, will be the same for all subjects and will begin with vial number #5 which will be prepared by serial five fold dilutions from the most concentrated vial (#1).

The study sample size is based upon the results of prior immunotherapy investigations undertaken by the Investigators of this study and their colleagues in the Division of Allergy & Clinical Immunology, Johns Hopkins University School of Medicine. Efficacy for immunotherapy was

estimated to be 80% for treatmet group and 30% for placebo. Using an error rate (α) of 0.05 and 80% Power we calculate a total sample size needed of 28 subjects. To account for drop off we will recruit up to 36 subjects.

5.3 Premature Termination or Suspension of Study or Investigational Site

This study may be terminated at any time by the investigators or the sponsor for safety reasons or for just cause.

5.3.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless one or more of the following criteria are satisfied that require temporary suspension or early termination of the study.

- New information or other evaluation regarding the safety or efficacy of the study medication that indicates a change in the known risk/benefit profile for the immunotherapy, such that the risk or benefit is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.

5.3.2 Criteria for Premature Termination or Suspension of the Investigational Site

The study site may be terminated prematurely or suspended if the site is found in significant violation of GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

5.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of the Investigational Site

In the event that the sponsor, the institutional review board or regulatory authority elects to terminate or suspend the study or the participation of the investigational site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by the investigational site during the course of termination or study suspension.

6.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including test results, need to be confirmed prior to the administration of first dose of immunotherapy.

6.1 Inclusion Criteria

1. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject signs and dates a written, informed consent form prior to the initiation of any study procedures.
3. The subject is a male or a non-pregnant, non-lactating female between the ages of 18 and 65.
4. The study subject is currently experiencing active symptoms and signs of moderate to severe PAR with or without SAR component defined as score of at least 28 on the RQLQ and 6 on the TNSS scale. Scores will be determined on the first and second visit (after the 14 day medication washout period). Both scores exceeding their threshold on either day will qualify.
5. Skin test strongly positive (wheal at least 5mm diameter and 2mm greater than negative control) to at least 6 of 48 allergy skin prick tests including at least one species of dust mite.

6.2 Exclusion Criteria

Any subject who meets any of the following criteria will not qualify for entry into the study:

1. The subject has received any investigational compound within 30 days prior to screening.
2. The subject has received multi antigen immunotherapy or SLIT in a previous clinical study or as a therapeutic agent within the past two years.
3. The subject has a history or clinical manifestations of significant medical conditions (cardiovascular, hepatic, infectious or renal disease, etc.) which in the opinion of the investigator renders them unacceptable study subjects.
4. The subject has a history of drug abuse (defined as any chronic illicit drug use) or a history of alcohol abuse within 5 years prior to the screening visit.
5. The subject is required to take excluded medications listed in Section 6.3.
6. If female, the subject is pregnant or lactating or intending to become pregnant before, during, or within 1 month after participating in this study; or intending to donate ova during such time period.
7. Subjects found to have on physical exam significant nasal polyps, septal deviation or infectious sinusitis.

6.3 Excluded Medications

- Immunotherapy that is not part of the investigation
- $Beta_2$ agonists and angiotensin converting enzyme (ACE) inhibitors
- Other medications that may interfere with the test, analysis, or interpretation of results.
- Omalizumab and other anti-asthma biologics, or immune suppression treatment within 6 months of participating in the investigation, including oral corticosteroids within the month.
- Subjects must be instructed not to take any medications including over-the-counter products, without first consulting with the investigator.

Note that prior use of medications commonly used to treat allergic rhinitis such as nasal steroids, antihistamines, opthalmologic antihistamines, cromolyn, azelastine, decongestants and other OTC allergy medications are not excluded. However, these medication will be stopped during the 14 day washout period. Patients are encouraged to abstain from using these medications for the duration of the study. If symptoms are not adequately controlled the rescue medications will be added in a stepwise fashion as outlined in section 12.1.3.

6.4 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study medication should be recorded in the CRF using the following categories. For screen failure subjects, refer to Section 8.1.11.

1. Pretreatment event (PTE) or adverse event (AE). The subject has experienced a PTE or AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the PTE or AE.
2. Significant protocol deviation. The discovery postrandomization or after the first dose of study immunotherapy that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
3. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented.
4. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the

CRF. All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded.

5. Study termination. The sponsor, IRB, or regulatory agency terminates the study.
6. Pregnancy. The subject is found to be pregnant.

   Note: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 8.1.10.

7. The investigator has determined that continued participation would pose an unacceptable risk to the subject.

   Note: After the 30 minute wait period, subjects that develop local swelling at the site of the injection greater than 50mm diameter will have their next dose decreased by one step. Subjects having a Grade 1-2 systemic reaction will have their next injection decreased by two steps. Systemic reaction Grade 3 or more will require withdrawal from the study. Systemic reactions are defined by the World Allergy Organization anaphylaxis grading system (13).

7.0 CLINICAL TRIAL MATERIAL MANAGEMENT

This section contains information regarding all medication and materials provided directly by the sponsor, and/or sourced by other means, that are required by the study protocol, including important sections describing the management of clinical trial material.

7.1 Drugs / Substances / Devices

Study immunotherapy solutions (noted above as PMA), composed of FDA approved allergens, will be supplied by the sponsor. PMA is prepared from a selection of FDA approved allergens and allergen mixtures listed in **Appendix E FDA Approved Allergens to be Used for Treatment**. Allergens used for skin prick testing are listed in **Appendix G Allergens used for skin prick testing**.

7.1.1 Dosage Form, Preparation and Labeling

The dosage (dilution) of PMA will be the same for all subjects and will begin with vial number #5 which will be prepared by serial five fold dilutions from the most concentrated vial (#1).

One PMA active treatment set will be prepared by compounding three separate concentrated vials (#1) each containing approximately 30 antigen mixtures (no more than about 75 total antigens each) and labeled mix A, B and C. No more than 0.9 ml of each manufacturer supplied stock material will be placed in a 100ml vial and brought to volume with diluent. Each of the #1 vials (A, B and C) will then be serially diluted 5 fold, several times approximately as follows:

	Mix A (Pollens)	**Mix B (Indoor)**	**Mix C (Molds)**	**Exact Preparation**
Vial #1	1:1	1:1	1:1	Described above
Vial #2	1:5	1:5	1:5	20ml Vial #1 + 85ml diluent
Vial #3	1:25	1:25	1:25	4ml Vial #1 + 85ml diluent
Vial #4	1:125	1:125	1:125	4ml Vial #2 + 85ml diluent
Vial #5	1:625	1:625	1:625	4ml Vial #3 + 85ml diluent

7.1.2 Vials #1-2 will have an expiration date of six months and dilutions #3-5 may be used for up to three months.

7.1.3 One placebo set will also be prepared in a similar manner using sterile saline and an equivalent amount of glycerin/phenol. Because up to 20% of patients receiving active treatment may notice local swelling and itch, histamine will be added to the stock placebo vials (vial 1) at a concentration of 50ug/ml (0.05mg/ml). Thus vial #2 will have a final concentration of 0.01mg/ml histamine. This is expected to elicit a mild itch in about 20% of control subjects based on experience.

Folic acid will also be added to the placebo vials to yield a slightly yellow color similar to the active treatment vials. Stock placebo (#1 vials) will contain 1mg/ml folic acid by adding 20ml of 5mg/ml folic acid to 80ml diluent. This will be further diluted 5 fold to yield (#2 vial) for a final concentration of 0.2mg/ml folic acid and so on.

The labeling of study PMA and placebo solutions will be undertaken by the compounding pharmacy of this investigation and undertaken in conjunction with the sponsor so that a double-blind study technique can be employed during the investigation. Each active and placebo vial set will be labeled randomly either set I or II. The set, mix letter, dilution, and use by date will also be included as shown by the example below. Only the pharmacy and sponsor will hold the treatment set randomization code. Recruited subjects will alternate between sets I and II.

Figure 7.a

Labeling

Set II Dilution #3 **Mix A** Relez Therapeutics Use by (3.1.17)	Set II Dilution #3 **Mix B** Relez Therapeutics Use by (3.1.17)	Set II Dilution #3 **Mix C** Relez Therapeutics Use by (3.1.17)

7.1.3.2 Investigational immunotherapy

The investigational immunotherapy used in this study protocol will be prepared by the Johns Hopkins University School of Medicine Division of Allergy and Clinical Immunology Laboratory (DACI) a national reference laboratory facility according to institutional policy and in accordance with USP 797 compounding standards. The allergens that will be used to constitute the study immunotherapy solutions will be directly shipped by nationally licensed corporate suppliers such as Greerlabs, Lenoir NC 28645-0800 and Allergy Laboratories, Oklahoma, City. All allergens used in the compounding of study immunotherapy solutions will be FDA approved materials.

Sterile saline, used for the production of the study placebo solution will be supplied by the vendor compounding pharmacy. A comparable amount of glycerin and phenol as well as histamine will be added to the placebo vials to mimic any local irritant reactions that may occur in the active treatment vials.

7.1.3.3 Storage

Investigational immunotherapy solutions and placebo saline solutions will be refrigerated at 4 degrees celcius and stored in an appropriate, limited-access, secure place until it is used for the investigation or returned to the sponsor or designee for destruction. Storage will comply with the conditions specified on the label, and remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained every working day.

7.1.4 Immunotherapy Dose and Regimen

Recruited subjects alternate to be assigned either treatment set I or II (representing either placebo or active PMA treatment in a binded fashion). The assigned treatment set will remain for the duration of the study for each subject. On the day of an injection, 0.3ml from each of the appropriate vial set mix (A-C) will be combined in a sterile 5 ml bottle. Using a new sterile syringe, 0.15-0.60ml of the PMA solution or placebo will be removed for injection purposes according to the injection schedule (Appendix I). A sterile 27G ½ inch syringe will be used for administration. Immunotherapy will be adminitered bi-weekly in the study clinic for a total of eight consecutive weeks. Appendix I lists the precise immunotherapy injection schedule.

All patients are required to remain in the clinic under close observation by the study nurse for a period of 30 minutes following their injection. A physician is required to be present in the clinic at all times. In addition, one of the investigators must be present on campus and available by cell phone during scheduled treatment sessions. Emergency medications such as albuterol, oxygen, diphenhydramine, and at least two epi-pens will be readily available in the treament area.

It is important to note that the maximum concentration of each individual allergen is quite low compared to more traditional immunotherapy regimens. The maximum PNU/ml (Protien Nitrogen Units) in vial #1 will be no more than about 180 PNU/ml per allergen (eg 0.9ml of 20,000 PNU/ml stock material into 100ml solution). In most cases the actual concentration of each stock allegen is much lower than 20,0000 PNU/ml since the material may be provided as a mixture of several allergens. We would estimate therefore that subjects would receive no more than about 7.2 PNU of antigen contained in the highest injection (0.2ml Vial #2). Typically, allergens are administered via immunotherapy in a range of about 2000 PNU. Thus the dosage of each allergen is less than 0.36% of a typical dose administered in our clinics. The lower overall dosing scheme provided in this study would therefore be considered to be extremely safe with minimal adverse events.

7.1.5 Overdose

An overdose is defined as a known deliberate or accidental administration of investigational immunotherapy to a study subject, at a dose above that which is assigned to that individual subject according to the study protocol.

All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the CRF, in order to capture this important safety information consistently in the database. Cases of overdose without manifested signs or symptoms are not considered AEs. AEs associated with an overdose will be documented on an AE CRF according to Section 9.0, Pretreatment Events and Adverse Events.

Serious adverse events (SAEs) associated with overdose should be reported according to the procedure outlined in Section 9.2.2, Collection and Reporting of SAEs.

In the event of immunotherapy overdose, the subject should be treated symptomatically.

7.2 Investigational drug Assignment and Dispensing Procedures

A study subject randomization schedule will be developed by the study vendor compounding pharmacy or designee. In addition, stratification of study subject entry into the investigation will be determined by the study site investigators correlated with the study subject's clinical entry diagnostic criteria (see 6.1).

Subjects will be assigned to receive their treatment according to the randomization schedule provided to the study site by the vendor compounding pharmacy. The immunotherapy ID Number will be entered onto the study subject's CRF. All study immunotherapy will be administered to the study subjects while they are in the study site clinic.

Investigational immunotherapy blind maintenance will be undertaken by the vendor compounding pharmacy. During regularly scheduled monitoring visits, a study monitor from the sponsor or a designee will perform an inventory of blinded investigational immunotherapy solutions. All

unassigned treatment immunotherapy solutions will be reconciled and returned to the sponsor or a designee before study closure.

7.3 Unblinding Procedure

The investigational drug blind shall not be broken by the investigator unless information concerning the investigational immunotherapy is necessary for the medical treatment of the subject. In the event of a medical emergency, if possible, the medical monitor should be contacted before the investigational immunotherapy blind is broken to discuss the need for unblinding.

For unblinding a subject, the investigational immunotherapy blind can be obtained by contacting the vendor compounding pharmacist. The sponsor must be notified as soon as possible if the investigational immunotherapy blind is broken. The date, time, and reason the blind is broken must be recorded in the study subject's source documents and the same information must be recorded on the subject's CRF. Investigational immunotherapy must be stopped immediately and the subject must be withdrawn from the study.

7.4 Accountability and Destruction of Sponsor-Supplied Drugs

Immunotherapy supplies will be counted and reconciled at the site before being returned to the sponsor or designee.

The investigator or designee must ensure that the sponsor-supplied immunotherapy solutions are used in accordance with the protocol and administered only to subjects enrolled in the study. To document appropriate use of sponsor-supplied immunotherapy solutions, the investigator or designee must maintain records of all sponsor-supplied study solutions supplied to the study site, site inventory, administration to each subject, and return to the sponsor or designee.

Upon receipt of sponsor-supplied drug, the investigator or designee must verify the contents of the shipments against the packing list. The investigator should ensure that the quantity is correct, and the solutions are in good condition. If quantity and conditions are acceptable, investigator or designee should acknowledge the receipt of the shipment from the vendor compounding pharmacy by signing the packing list and confirming by fax or e-mail while maintaining aq record of the confirmation. The packing list should be filed in the investigator's essential document file.

The investigator or designee must maintain 100% accountability for all sponsor-supplied immunotherapy solutions during their entire participation in the study. Proper immunotherapy solutions accountability includes, but is not limited to:

- Continuously monitoring expiration dates if provided by the vendor compounding pharmacy
- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for the solutions administered to an individual study subject.

- Verifying that all immunotherapy solution containers used are documented accurately on the log.

Prior to site closure or at appropriate intervals, a representative from the sponsor or its designee will perform sponsor-supplied immunotherapy solutions accountability and reconciliation before sponsor-supplied solutions are returned to the vendor compounding pharmacy. The investigator or designee will retain a copy of the documentation regarding sponsor-supplied study solutions accountability, return, and/or destruction, and originals will be sent to the sponsor or designee.

The investigator will be notified of any expiry date of sponsor-supplied study solutions during the study conduct. On expiry date notification from the vendor compounding pharmacy, the site must complete all instructions outlined in the notification, including segregation of expired sponsor-supplied study solutions for return to the vendor compounding pharmacy for destruction.

8.0 STUDY PLAN

8.1 Study Procedures

The following sections describe the study procedures and data to be collected. For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. The Schedule of Study Procedures is located in Appendix A.

8.1.1 Informed Consent Procedure

Informed consent must be obtained prior to the subject entering into the study and before any protocol-directed procedures are performed.

A unique subject identification number (subject number) will be assigned to each study subject at the time that the study subject signs the informed consent. This subject number will be used throughout the study.

8.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include date of birth, sex, ethnicity, race as described by the subject, and smoking status of the subject at Screening.

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the diagnose of SAR/PAR (i.e., diseases under study) that stopped at or prior to signing of informed consent. Ongoing conditions are considered concurrent medical conditions (see Section 8.1.8).

8.1.3 Physical Examination Procedure

A baseline physical examination (defined as the assessment prior to first dose of investigational immunotherapy) will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; (11) other. All subsequent physical examinations should assess clinically significant changes from the assessment prior to first immunotherapy examination.

8.1.4 Weight, Height

A subject should have weight and height measured while wearing indoor clothing and with shoes off.

8.1.5 Vital Sign Procedure

Vital signs will include body temperature, respiratory rate, blood pressure (resting more than 5 minutes), pulse (bpm), and peaked flow (PFR).

When vital signs are scheduled at the same time as blood draws, the blood draw will take priority and vital signs will be obtained within 0.5 hour before or after the scheduled blood draw.

8.1.6 Primary Efficacy Measurement

The primary efficacy measurement is based upon validated efficacy instruments. Details of the efficacy assessments are described in Appendix F

8.1.7 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study immunotherapy. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by the study sponsor. At each study visit, subjects will be asked whether they have taken any medication other than the study medication (used from signing of informed consent through the end of the study), and all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the CRF.

8.1.8 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. The investigators will decide upon the significance or non-significance of an ongoing clinical condition or laboratory abnormality.

8.1.9 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures. Blood will be drawn at the start of the study and at the completion. The maximum volume of blood at any single visit is less than 10.0 mL, and the approximate total volume of blood for the study is less that 20 mL. Serum collected at the screening visit will be stored for later analysis. Blood will be redrawn at the final visit (week 14) so that pre and post immunoglobulin levels can be measured including specifc IgE, and IgG4 and possibly IgG3.

The Johns Hopkins Bayview Medical Center laboratory will perform laboratory tests as indicated above. The investigator or designee is responsible for transcribing or attaching laboratory results to the CRF. The investigator will maintain a copy of the laboratory accreditation and the reference ranges for the laboratory used.

8.1.10 Pregnancy

If any subject is found to be pregnant during the study she should be withdrawn and immunotherapy should be immediately discontinued. If the pregnancy occurs during administration of active PMA study immunotherapy the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Section 1.0.

Should the pregnancy occur during or after administration of immunotherapy, identified as being PMA, the investigator must inform the subject of their right to receive treatment information. Subjects randomized to placebo do not need follow-up.

8.1.11 Documentation of Screen Failure

Investigators must account for all subjects who sign an informed consent. If screening factors dictate that the subject is not eligible to continue in the investigation, the investigator should complete the CRF.

The primary reason for screen failure is recorded in the CRF using the following categories:

- PTE/AE.
- Did not meet inclusion criteria or did meet exclusion criteria.
- Significant protocol deviation.
- Lost to follow-up.
- Voluntary withdrawal.
- Study termination.
- Other

Subject numbers assigned to subjects who fail screening should not be reused.

8.1.12 Documentation of Study Randomization

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for randomization into the immunotherapy treatment phase.

8.1.13 Allergen Skin Prick Testing Procedures

All subjects will undergoallergen skin prick allergy testing (SPT) as per standard of care using the Multi-Test PC (Lincoln Diagnostics, Decator, IL) or comparable skin testing device.The results of the skin testing will dictate if subjects qualify for the study. In addition to having clinical symptoms of perennial allergic rhinitis, all subjects test positive to at least 6 of 48 total SPT including at least one dust mite species (D. farinae or D. pteronissinus). A positive skin test will be defined as a minimum wheal diameter of 5mm and at least 2mm greater than the saline control. A list of allergens used for testing is shown in Appendix H.

8.2 Monitoring Subject Treatment Compliance

Study subject compliance will be monitored by the accuracy of their attendance at the study site for their bi-weekly immunotherapy treatments. If a subject is persistently noncompliant with the follow up clinic visits for immunotherapy, it may be appropriate to withdraw the subject from the

study. All subjects should be reinstructed about the essentiality of scheduled clinic follow-up visits for immunotherapy during each of their scheduled clinic visits.

8.3 Schedule of Observations and Procedures

The schedule for all study-related procedures for all evaluations is shown in Appendix A. Assessments should be completed at the designated visit/time point(s).

8.3.1 Screening

Subjects will be screened prior to the 14 day medication washout period. Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 6.0. See Section 8.1.11 for procedures for documenting screening failures.

Procedures to be completed at Screening (Visit 1) include:

- Informed consent.
- Demographics, medical history, and medication history.
- Physical examination.
- Vital signs.
- Weight, height
- Concomitant medications.
- Concurrent medical conditions.
- Allergy skin prick skin testing.

8.3.2 Study Entrance Randomization

Study Randomization will take place on study day 1 (Visit 1). The following procedures will be performed and documented during Study Randomization:

- If the subject has satisfied all of the inclusion criteria and none of the exclusion criteria for randomization and the investigator deems the laboratory screening and skin testing are acceptable for continuance in the investigation, the subject should be randomized using the randomization sequence provided by the sponsor.
- Subjects will receive their first sub-cutaneous administration of immunotherapy with dose vial #5.
- The procedure for documenting Screening failures is provided in Section 8.1.11.

8.3.3 Treatment Phase

Study visits 1 through 12 will be conducted (Figure 6a) in the study clinic and at each of these visits the study subject will have a safety and efficacy assessment and if deemed appropriate by the investigator will receive their next sub-cutaneous administration of study immunotherapy. A 60 minute post treatment in-clinic safety assessment will be conducted.

8.3.4 Final Visit or Early Termination

The Final Visit will be performed on visit 18 or at an Early Termination Visit. The following procedures will be performed and documented:

- Physical examination.
- Vital signs.
- Concomitant medications.
- Concurrent medical conditions.
- Efficacy assessment.
- Safety assessment.
- Blood draw.

For all subjects receiving study medication, the investigator must complete the End of Study CRF page.

8.3.5 Follow-up

Follow-up will begin the first day after the last injection and will continue until for 30 days at which time a final in-clinic visit (visit 18) will be conducted for a safety assessment and blood draw.

8.3.6 Post Study Care

The study immunotherapy will not be available upon completion of the subject's participation in the study. The subject should be returned to the care of a physician and standard therapies as required.

Subject to applicable laws and feasibility, access to the study immunotherapy may be available to individual subjects for whom the investigators deem the treatment to be essential and wherein the subject is at risk of significant morbidity or mortality. The investigator should contact the medical monitor to determine if access is possible.

9.0 PRETREATMENT EVENTS AND ADVERSE EVENTS

9.1 Definitions

9.1.1 PTEs

A PTE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

9.1.2 AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the drug.

9.1.3 Additional Points to Consider for PTEs and AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre existing conditions underlying disease should not be considered PTEs or AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study medication or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.
- PTEs/AEs caused by a study procedure (eg, a bruise after blood draw) should be recorded as a PTE/AE.

Diagnoses vs signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as a PTE(s) or as an AE(s).

Pre-existing conditions:

- Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as PTEs or AEs. Baseline evaluations (eg, laboratory tests, ECG, X-rays etc.) should NOT be recorded as PTEs unless

related to study procedures. However, if the subject experiences a worsening or complication of such a concurrent condition, the worsening or complication should be recorded appropriately as a PTE (worsening or complication occurs before start of study medication) or an AE (worsening or complication occurs after start of study medication). Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of…").

- If a subject has a pre-existing episodic condition (eg, gout, epilepsy) any occurrence of an episode should only be captured as a PTE/AE if the episodes become more frequent, serious or severe in nature, that is, investigators should ensure that the AE term recorded captures the change in the condition from Baseline (eg "worsening of…").

Worsening of PTEs or AEs:

- If the subject experiences a worsening or complication of a PTE after starting administration of the study medication, the worsening or complication should be recorded appropriately as an AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").
- If the subject experiences a worsening or complication of an AE after any change in study medication, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Changes in severity of AEs /Serious PTEs:

- If the subject experiences changes in severity of an AE/serious PTE, the event should be captured once with the maximum severity recorded.

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered PTEs or AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be captured appropriately as a PTE or an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as PTEs or AEs, but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Insufficient clinical response (lack of efficacy):

- Insufficient clinical response, efficacy, or pharmacologic action, should NOT be recorded as an AE. The investigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

Overdose:

- Cases of overdose with the immunotherapy without manifested side effects are NOT considered PTEs or AEs, but instead will be documented on an Overdose page of the CRF. Any manifested side effects will be considered PTEs or AEs and will be recorded on the AE page of the CRF.

9.1.4 SAEs

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

1. Results in DEATH.
2. Is LIFE THREATENING.
    - The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
    - May require intervention to prevent items 1 through 5 above.
    - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
    - Includes any event or synonym described in the Takeda Medically Significant AE List (Table 9.a).

Table 9.a Sponsor's Medically Significant AE List

Term	
Acute respiratory failure/acute respiratory distress syndrome	Hepatic necrosis
Torsade de pointes / ventricular fibrillation / ventricular tachycardia	Acute liver failure
	Anaphylactic shock

Malignant hypertension	Acute renal failure
Convulsive seizure	Pulmonary hypertension
Agranulocytosis	Pulmonary fibrosis
Aplastic anemia	Confirmed or suspected endotoxin shock
Toxic epidermal necrolysis/Stevens-Johnson syndrome	Confirmed or suspected transmission of infectious agent by a medicinal product
	Neuroleptic malignant syndrome / malignant hyperthermia
	Spontaneous abortion / stillbirth and fetal death

PTEs that fulfill 1 or more of the serious criteria above are also to be considered SAEs and should be reported and followed up in the same manner (see Sections 9.2.2 and 9.3).

It is important to note that out of more than 20,000 patients personally treated with the proprietary PMA allergen immunotherapy by Dr. William Freeman over the past 40 years, there HAS NEVER BEEN AN INCIDENT OF ANAPHYLAXIS OR SERIOUS SYSTEMIC REACTION attributed to the treatment. Epinephrine has never been required because of the treatment. Typical but uncommon side effects have included mild-moderate local swelling. These mild reactions occur at a rate of less than 20 percent.

9.1.5 Severity of PTEs and AEs

The different categories of intensity (severity) are characterized as follows:

Mild: The event is transient and easily tolerated by the subject.

Moderate: The event causes the subject discomfort and interrupts the subject's usual activities.

Severe: The event causes considerable interference with the subject's usual activities.

9.1.6 Causality of AEs

The relationship of each AE to study immunotherapy will be assessed using the following categories:

Related: An AE that follows a reasonable temporal sequence from administration of the immunotherapy (including the course after withdrawal of the study immunotherapy), or for which possible involvement of the immunotherapy cannot be ruled out, although factors other than the immunotherapy, such as underlying diseases, complications, concomitant drugs and concurrent treatments, may also be responsible.

Not Related: An AE that does not follow a reasonable temporal sequence from administration of the immunotherapy and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant drugs and concurrent treatments.

9.1.7 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all PTEs and AEs.

The relationship should be assessed as Related if the investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as Not Related.

9.1.8 Start Date

The start date of the AE/PTE is the date that the first signs/symptoms were noted by the subject and/or physician.

9.1.9 Stop Date

The stop date of the AE/PTE is the date at which the subject recovered, the event resolved but with sequelae or the subject died.

9.1.10 Frequency

Episodic AEs/PTE (eg, vomiting) or those which occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

9.1.11 Action Concerning Study Medication

- Stop immunotherapy – the study immunotherapy is stopped due to the particular AE.
- Immunotherapy not changed – the particular AE did not require stopping the study immunotherapy.
- Unknown – only to be used if it has not been possible to determine what action has been taken.
- Not Applicable – the immunotherapy was stopped for a reason other than the particular AE eg, the study has been terminated, the subject died, dosing with the study immunotherapy was already stopped before the onset of the AE.

9.1.12 Outcome

- Recovered/Resolved – Subject returned to first assessment status with respect to the AE/PTE.
- Recovering/Resolving – the intensity is lowered by one or more stages: the diagnosis or signs/symptoms has almost disappeared; the abnormal laboratory value improved, but has not

returned to the normal range or to baseline; the subject died from a cause other than the particular AE/PTE with the condition remaining "recovering/resolving".

- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/ symptoms or laboratory value on the last day of the observed study period has got worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE/PTE state remaining "Not recovered/not resolved".
- Resolved with sequelae – the subject recovered from an acute AE/PTE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis.
- Fatal – the AEs/PTEs which are considered as the cause of death.
- Unknown – the course of the AE/PTE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

9.2 Procedures

9.2.1 Collection and Reporting of AEs

9.2.1.1 PTE and AE Collection Period

Collection of PTEs will commence from the time the subject signs the informed consent to participate in the study and continue until the subject is first administered study immunotherapy (visit 2) or until screen failure. For subjects who discontinue prior to study immunotherapy administration, PTEs are collected until the subject discontinues study participation.

Collection of AEs will commence from the time that the subject is first administered study immunotherapy (visit 2). Routine collection of AEs will continue until visit 14 .

9.2.1.2 PTE and AE Reporting

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing a serious PTE must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or there is a satisfactory explanation for the change. Non-serious PTEs, related or unrelated to the study, need not to be followed-up for the purposes of the protocol.

All subjects experiencing AEs, whether considered associated with the use of the study immunotherapy or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until there is a satisfactory explanation

for the changes observed. All PTEs and AEs will be documented in the PTE/AE page of the CRF, whether or not the investigator concludes that the event is related to the immunotherapy. The following information will be documented for each event:

1. Event term.
2. Start and stop date.
3. Severity.
4. Investigator's opinion of the causal relationship between the event and administration of study immunotherapy (related or not related) (not completed for PTEs).
5. Investigator's opinion of the causal relationship to the study immunotherapy, including the details of the suspected immunotherapy administration.
6. Action concerning study immunotherapy (not applicable for PTEs).
7. Outcome of event.
8. Seriousness.

9.2.2 Collection and Reporting of SAEs

When an SAE occurs through the AE collection period it should be reported according to the following procedure:

A sponsor SAE form must be completed, in English, and signed by the investigator immediately or within 24 hours of first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum:

An SAE should be reported to the sponsor (described in the separate contact information list) within 1 business day of first onset or subject's notification of the event. The principal investigator should submit the completed SAE form within 10 calendar days. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious.
- Subject identification number.
- Investigator's name.
- Name of the study immunotherapy.
- Causality assessment.

The SAE form should be transmitted within 24 hours to the attention of the contact listed in Section 1.0.

Any SAE spontaneously reported to the investigator following the AE collection period should be reported to the sponsor if considered related to study participation.

Reporting of Serious PTEs will follow the procedure described for SAEs.

9.3 Follow-up of SAEs

If information not available at the time of the first report becomes available at a later date, the investigator should complete a follow-up SAE form or provide other written documentation and fax it immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

9.3.1 Safety Reporting to the Johns Hopkins IRB and Regulatory Authorities

The study site investigators, in conjunction with the sponsor, will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to the Hopkins IRB. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as expedited report within 3 business days for fatal and life-threatening events and 10 business days for other serious events, unless otherwise required by Hopkins IRB regulations.

10.0 STUDY-SPECIFIC COMMITTEES

No study specific committees are being used for this study.

11.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, PTEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

11.1 CRFs (Paper)

Completed CRFs are required for each subject who signs an informed consent.

The sponsor will supply the investigative site with paper CRFs. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. All paper CRFs must be filled out legibly in black or blue ballpoint ink.

After completion of the entry process, queries may be issued by the sponsor or contracted CRO and will be answered by the site.

Corrections to the CRF are to be made by making a single-line strikeout of the incorrect information and writing in the revisions. All corrections must be initialed and dated.

The principal investigator must review the CRFs for completeness and accuracy and must sign and date the appropriate CRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the CRFs.

After submission of the CRFs to the sponsor, any change of, modification of or addition to the data on CRFs should be made by the investigator with use of change and modification records of CRFs (Data Clarification Form) provided by the sponsor. The principal investigator must review the Data Clarification Form for completeness and accuracy, and must sign and date the form.

After the lock of the clinical study database, any change of, modification of or addition to the data on the CRFs should be made by the investigator with use of a Data Clarification Form provided by the sponsor. The principal investigator must review the data change for completeness and accuracy, and must sign and date.

CRFs will be reviewed for completeness and acceptability at the study site during periodic visits by the study monitor. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the CRFs. The completed CRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

11.2 Record Retention

The investigator agrees to keep the records stipulated in Section 11.1 (clarify correct number) and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, source worksheets, all original

signed and dated informed consent forms, copies of all paper CRFs and query responses and detailed records of the study immunotherapy solutions to enable evaluations or audits from regulatory authorities, the sponsor or its designees. The ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

12.0 STATISTICAL METHODS

12.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to unblinding of subject's treatment assignment. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

A blind data review will be conducted prior to unblinding of subject's treatment assignment. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods.

12.1.1 Analysis Sets

All efficacy and safety analyses will be analyzed using the full analysis set (FAS). The FAS will consist of all subjects who were randomized and received at least one dose of double-blind study immunotherapy. Efficacy analyses will be analyzed according to the treatment received and safety analyses will be analyzed according to the actual treatment received.

Unless otherwise specified, all statistical tests and confidence intervals will be two-sided and conducted at the 0.05 significance level.

12.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographic and baseline characteristics (eg, age, race, gender, height, weight, etc) will be summarized using descriptive statistics for all subjects and by Sequence group if necessary. For categorical variables (eg, race, gender, etc) the number and percent of subjects in specified categories will be presented. Unless otherwise specified, descriptive statistics on continuous variables (eg, age, height, weight) will consist of the number of subjects (N), mean, standard deviation (SD), median, minimum and maximum.

12.1.3 Efficacy Analysis

The intent-to-treat approach will be used. Baseline characteristics will be described using mean and standard deviation for continuous variables and medians and ranges for discrete variables. The primary efficacy variable of comparing PMA versus placebo will be undertaken by quantifying the instrument-asessment scores of each study subject in each of the two therapeutic arms of the investigation. The p-value, least square (LS) treatment means, difference between the LS treatment means, and 95% confidence intervals for the treatment differences will be presented. The success of blinding will be assessed by asking the patient and staff which treatment set they thought they were getting, i.e. active treatment or placebo. The results will be recorded at each study visit.

Total Nasal Symptoms Score (TNSS) and the Mini-RQLQ attached in Appendix F will be used to evaluate clinical efficacy. TNSS along with rescue medication use is recorded at home on a daily

card as shown in Appendix K. Daily scores will only be recorded on weeks 2, 10, and 14. The mini-RQLQ will be recorded in person at screening, during each study visit, and at followup. The correct use of the TNSS survey is to score 0-12 based on symptoms reported that day while the mini-RQLQ is scored 0-84 based on symptoms reported over the past week. Higher scores indicate worse symptoms.

The primary outcome measure is the average daily combined score (DCS) which is calculated by adding the average TNSS + average medication score as well as the mini-RQLQ at weeks 2,10 and 14.

Secondary outcomes will include the adverse events rate and TNSS between both groups using a one-tailed Fischer's exact test and/or unpaired t test.

Other outcomes include baseline characteristics, use of epinephrine, and drop out between both treatment groups I and II using a one-tailed Fischer's exact test and/or unpaired t test. Trend tests for comparison of both groups will be performed such as the Jonckheere-Terptsra trend test. A sum of Mann-Whitney-Wilcoxon tests may also be sensitive and reveal a mild trend. Other trend tests may also be used.

A Kaplan-Meier or similar product limit estimator function will also be used to calculate the effect of treatment over time.

Medications commonly used to treat allergic rhinitis such as nasal steroids, antihistamines, opthalmologic antihistamines, cromolyn, azelastine, decongestants and other OTC allergy medications will be stopped during the 14 day washout period. Patients must abstain from using these medications for the duration of the study, however rescue medications will be offered in a predetermined manner as follows. At each study visit the patient will be asked subjectively if symptoms are adequately controlled. If symptoms are uncontrolled then medications will be added in the following stepwise fashion according to Appendix I. Rescue medications will not be increased after week ten.

Medication use is recorded daily at home during weeks 2, 10, and 14 and at each bi-weekly study visit so that adjustments can be made. Each allergy rescue medication will be assigned a numerical score as per Appendix I. We expect that most subjects will have daily medication scores between 0-6.

12.1.4 Safety Analysis

Overall safety and tolerability will be assessed by evaluating the incidence of TEAE, laboratory tests, vital signs, and other safety variables. Treatment-emergent adverse events will be defined as any AEs, regardless of relationship to study immunotherapy, that occur on or after the first double blind immunotherapy administration date and up to 30 days after the last dose date of the double-blind immunotherapy and will be assigned to the treatment at the time of the event.

Treatment-emergent adverse events will be summarized using the full analysis set. Adverse events will be summarized using the MedDRA coding dictionary. In general, AEs will be tabulated at each of the following levels: overall summary (subject with at least 1 AE), the MedDRA system organ class (SOC) and the MedDRA preferred term (PT). Tabulations at each level of a term will present count (n) and percentage of subjects reporting any event for that term. Subjects reporting more than one occurrence for the term (level) being summarized will be counted only once and assigned to the drug assignment at time of the event.

Laboratory test variables will be summarized by active PMA or placebo assignment and study visit using descriptive statistics. Laboratory data collected from baseline and up to 7 days after a subject's last dose of study immunotherapy will be included in the analysis. Markedly abnormal laboratory values will be determined and listed by study group. The number and percentage of subjects with marked abnormality in each of the laboratory parameters will be presented.

Descriptive statistics will be used to summarize vital signs by treatment group and study visit. Vital sign data collected from baseline and up to a subject's last dose of study immunotherapy will be included in the analysis.

12.2 Interim Analysis and Criteria for Early Termination

No interim analyses are planned.

12.3 Determination of Sample Size

The study sample size is based upon the results of prior immunotherapy investigations undertaken by the Investigators of this study and their colleagues in the Division of Allergy & Clinical Immunology, Johns Hopkins University School of Medicine. Efficacy for immunotherapy was estimated to be 80% for treatmet group and 30% for placebo. Using an error rate (α) of 0.05 and 80% Power we calculate a total sample size needed of 28 subjects. To account for drop off we will recruit up to 36 subjects.

13.0 QUALITY CONTROL AND QUALITY ASSURANCE

13.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the CRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor.

All aspects of the study and its documentation will be subject to review by the sponsor or designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study medication, subject medical records, informed consent documentation, and review of CRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

13.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB, as required) to determine the appropriate course of action. There will be no exemptions for a prospectively approved deviation from the inclusion or exclusion criteria.

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment. A Protocol Deviation Form should be completed by the site and signed by the sponsor or designee for any significant deviation from the protocol.

Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the immunotherapy medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including the FDA. If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 13.1.

14.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual study participants. In the study protocol, the ethical principles that have been described that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. The investigators will conduct the study according to applicable Hopkins IRB requirements and align their conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix B. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

14.1 IRB Approval

The Johns Hopkins Hospital IRB must be constituted according to the applicable requirements. The sponsor or designee will require documentation noting the Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The sponsor or designee in conjunction with the study site investigators will supply relevant documents for submission to the Hopkins IRB for the protocol's review and approval. This protocol, a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to the IRB for approval. The IRB's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before shipment of the sponsor-supplied immunotherapy). The IRB approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date. The sponsor will supply immunotherapy solutions once the sponsor has confirmed the adequacy of site regulatory documentation and the sponsor has received permission from the competent authorities (Hopkins contracting office and Hopkins IRB) to begin the trial. Until the site receives the study immunotherapy no protocol activities, including screening may occur.

The study site must adhere to all requirements stipulated by the IRB. This may include notification to the IRB regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by subjects, safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the IRB, and submission of the investigator's final status report to the IRB. All IRB approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB and sponsor.

14.2 Risks

Allergy Skin test The risk of performing allergy skin testing is minimal. Serious reactions are rare. This study uses histamine and allergen for testing, which very rarely can cause serious reactions.

Most individuals experience mild to moderate itching at the site of testing that spontaneously resolves. You may feel some mild discomfort from the skin prick device itself.

Immunotherapy The most common side effect from allergen immunotherapy is slight swelling and discomfort at the site of the injection. This usually resolves in 1-2 days with the use of a cool pack. There is a very small chance of having a serious allergic reaction. If symptoms of a serious allergic reaction occur we would administer epinephrine and possibly other allergy medications such as antihistamines.

Some participants will receive placebo instead of active immunotherapy. These individuals may not see an improvement in their symptoms. All patients will be required to discontinue nasal steroids for two weeks prior to starting treatment. There is a risk that nasal symptoms could worsen when you stop the medication.

Blood Draw The most common side effect of blood draw is discomfort from the needle. This can sometimes lead to bruising of the skin. There is a very small chance of getting an infection from puncturing the skin.

Other risks There always exists the potential for loss of confidentiality; however, there are procedures in place to minimize this. Study information will not be associated with your private demographic information directly but linked via a numerical code only to be accessed by the study designers. However, there still remains the possibility that information about you may become known to people outside of this study.

You may get tired or bored when we are asking you questions or you are completing questionnaires. You do not have to answer any question you do not want to answer. There may be side effects and discomforts that are not yet known.

14.3 Benefits

There is no direct benefit to subjects for being in this study. Taking part in this study, may help others in the future.

Subjects will be paid up to $325 for time and effort ($18 per visit). A parking pass will also be provided for subjects who need this. Total payment will be prorated based on the number of study visits completed and paid in two lump sums made once the study regimen begins and the rest will

be paid at the end of the study. Payment will be made by mailing a check within 1-2 weeks. Checks will be mailed to the address provides at the time of the consent.

14.4 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form describes the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form further explains the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigators in conjunction with the sponsor is responsible for the preparation, content, and IRB approval of the informed consent form. The informed consent form must be approved by both the IRB and the sponsor prior to use.

The informed consent form must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the informed consent form to the study subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the Hopkins IRB. In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with the IRB regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the informed consent form must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and prior to the subject entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the informed consent form at the time of consent and prior to subject entering into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by the Hopkins IRB.

Once signed, the original informed consent form will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. A copies of the signed informed consent form shall be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent form.

14.5 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, FDA) the sponsor's designated auditors, and the Hopkins IRB to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process.

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's CRF).

14.6 Publication, Disclosure, and Clinical Trial Registration Policy

14.6.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for

any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

14.6.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, the sponsor will register this study on ClinicalTrials.gov.

14.6.3 Clinical Trial Results Disclosure

The sponsor will post the results of this investigation on ClinicalTrials.gov.

14.7 Insurance and Compensation for Injury

Refer to the Clinical Study Site Contract and Written Consent Form regarding the policy on subject compensation and treatment for injury.

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Appendix A Schedule of Study Procedures

Study Week:	Screen (Week 1)	Washout (Week 1-2)	Treatment (Week 3-11)	Follow-up safety assessment (Week 14)
Visit Number:	**1**	**N/A**	**2-17**	**18**
Discussion and Recruitment	X			
Informed consent	X			
Inclusion/exclusion criteria	X			
Demographics and medical history	X			
Medication history	X			
Physical examination	X			
Vital signs	X		X	
Weight and height	X			
Concomitant medications	X	X	X	X
Concurrent medical conditions	X			X
Skin Testing	X			
Blood Draw	X			X
Post-immunotherapy safety f/u				X
Administer immunotherapy/safety f/u			X	
Clinical Survey (RQLQ) and TNSS	X		X	X
Site return compliance	X		X	X
PTE assessment	X	X		
AE assessment		X	X	X

Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations.

The investigator agrees to assume the following responsibilities by signing the FDA form 1572 if needed.

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that study related procedures, including study specific (non routine/non standard panel) screening assessments are NOT performed on potential subjects, prior to the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
5. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to CFR Part 56 if needed. ICH, and local regulatory requirements.
6. Ensure that the IRB will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB, and issue a final report within 3 months of study completion.
7. Ensure that requirements for informed consent, as outlined in CFR Part 56 if needed. ICH and local regulations, are met.
8. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB. Each informed consent form should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study.
9. Prepare and maintain adequate case histories of all persons entered into the study, including CRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.

11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied immunotherapy, and return all unused sponsor-supplied study solutions to the sponsor.
12. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix C Elements of the Subject Informed Consent

In seeking informed consent, the following information shall be provided to each subject:

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the subject's participation.
4. A description of the procedures to be followed, including invasive procedures.
5. The identification of any procedures that are experimental.
6. The estimated number of subjects involved in the study.
7. A description of the subject's responsibilities.
8. A description of the conduct of the study.
9. A statement describing the immunotherapy treatment and the probability for random assignment to each treatment.
10. A description of the possible side effects of the treatment that the subject may receive.
11. A description of any reasonably foreseeable risks or discomforts to the subject and, when applicable, to an embryo, fetus, or nursing infant.
12. A description of any benefits to the subject or to others that reasonably may be expected from the research.
13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject and their important potential risks and benefits.
14. A statement describing the extent to which confidentiality of records identifying the subject will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB, and the monitor may inspect the records. By signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
15. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
16. The anticipated prorated payment(s), if any, to the subject for participating in the study.
17. The anticipated expenses, if any, to the subject for participating in the study.
18. An explanation of how to contact the investigators or designees for answers to pertinent questions about the research, subject's rights, and IRB and whom to contact in the event of a research-related injury to the subject.

19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
22. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
23. A written subject authorization (either contained within the informed consent form or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the study. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:
    a) that personal information (including personal health information) may be processed by or transferred to other parties for clinical research and safety reporting purposes, including, without limitation, to the following: (1) the sponsor, (2) business partners assisting the sponsor (3) regulatory agencies and other health authorities; and (4) the Hopkins IRB;
    b) the sponsor will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;
    c) that personal information (including personal health information) may be added to the sponsor's research database for purposes of developing a better understanding of the safety and effectiveness of the study immunotherapy, studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;
    d) that subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and
    e) that the subject's identity will remain confidential in the event that study results are published.
24. Female subjects of childbearing potential (eg, nonsterilized, premenopausal female subjects) who are sexually active must use adequate contraception (as defined in the informed consent) from Screening throughout the duration of the study. Regular pregnancy tests will be

performed throughout the study for all female subjects of childbearing potential. If a subject is found to be pregnant during study, study immunotherapy will be discontinued and the investigator will offer the subject the choice to receive unblinded treatment information.

25. Male subjects must use adequate contraception (as defined in the informed consent) from Screening throughout the duration of the study. If the partner or wife of the subject is found to be pregnant during the study, the investigator will offer the subject the choice to receive unblinded treatment information.
26. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix D Allergen skin prick testing and interpretation methodology

Allergen is indirectly transferred to the skin by first dipping a disposable skin test device into a well containing allergen extract material. Six Multi-Test PC devices will be required for each subject (48 individual tests).

Skin prick testing proceeds as follows:

1. Gather the materials required for skin testing
2. Discuss with the patient what will be done and what to expect
3. Ensure that antihistamines have been avoided for at least 7 days
4. Put on gloves
5. Clean the work space with alcohol and prep the patients skin
6. Mark the skin on the forearm (or back) with a skin safe marker
7. Place negative then positive histamine control tests first
8. Then place the remaining allergens on the skin sequentially
9. Set a 15-minute timer

Allergens are usually placed at least 2cm apart from each other. The wrist and antecubital fossa should be avoided. To ensure reproducibility it is essential that the technician take care to use the exact same methods every time a chosen device is used. If for example, the histamine control were to be placed with hard pressure but the allergens are placed with light pressure this could lead to a false negative result. In some cases where the identification of allergens suspected of causing anaphylaxis, misreading a test as negative could have serious implications.

Measurement of Wheal

Patients are asked to avoid scratching while skin tests are developing. Gentle blowing may alleviate some of the discomfort. Once the 15-minute timer rings measurements may begin using a clean ruler or disposable caliper with 1mm increments. Digital image of the skin tests will also be recorded using the Flare Diagnostics (Baltimore, MD) automated skin test reading device. A positve result is defined as an average wheal diameter greater than or equal 5mm and at least 2mm greater than negative control. Readings must be performed in a rotation consistent with the pattern of placement. Careful measurements may take several minutes and therefore allergens placed last should subsequently be read last so that all allergens have had the same amount of time to develop.

Appendix E FDA Approved Allergens to be Used for Treatment

(Note: Only a proprietary selection of allergens will be used for treatment.)

Type	Allergen	Stock Concentration	Manufacturer
Cat Std	Standardized Cat Hair	10,000 BAU/ml	Greer Labs
Mite Std	Dermatophagoides farinae	10,000 BAU/ml	Greer Labs
Mite Std	Dermatophagoides pteronyssinus	10,000 BAU/ml	Greer Labs
Mite Std	Mite Mix, Standardized	10,000 BAU/ml	Greer Labs
Grass Std	Bermuda Cynodon dactylon	100,000 BAU/ml	Greer Labs
Grass Std	Kentucky Blue/JunePoa pratensis	100,000 BAU/ml	Greer Labs
Grass Std	Meadow FescueLolium pratensis	100,000 BAU/ml	Greer Labs
Grass Std	Orchard Dactylis glomerata	100,000 BAU/ml	Greer Labs
Grass Std	Red Top Agrostis gigantean	100,000 BAU/ml	Greer Labs
Grass Std	Ryegrass, Perennial Lolium perenne	100,000 BAU/ml	Greer Labs
Grass Std	Sweet Vernal Anthoxanthum odoratum	100,000 BAU/ml	Greer Labs
Grass Std	Timothy Phleum pratense	100,000 BAU/ml	Greer Labs
Grass Std	Timothy/Orchard Grass Mix	100,000 BAU/ml	Greer Labs
Grass Std	7 Grass Mix	100,000 BAU/ml	Greer Labs
Grass Std	9 Southern Grass Mix (Concentrate)	100,000 BAU/ml	Greer Labs
Weed Std	Ragweed, Short Ambrosia artemisiifolia	100,000 BAU/ml	Greer Labs
Weed Std	National Weed Mix	100,000 BAU/ml	Greer Labs
Weed Std	Ragweed Mix	100,000 BAU/ml	Greer Labs
Tree	Acacia Acacia spp	40,000 PNU/ml	Greer Labs
Tree	Alder, Red	40,000 PNU/ml	Greer Labs
Tree	Alnus rubra	40,000 PNU/ml	Greer Labs
Tree	Alder, Hazel	40,000 PNU/ml	Greer Labs
Tree	Alder, White	40,000 PNU/ml	Greer Labs
Tree	Ash, Arizona	40,000 PNU/ml	Greer Labs
Tree	Ash, Oregon	40,000 PNU/ml	Greer Labs
Tree	Ash, Red/Green	40,000 PNU/ml	Greer Labs
Tree	Ash, White	40,000 PNU/ml	Greer Labs
Tree	Aspen	40,000 PNU/ml	Greer Labs
Tree	Bayberry/Wax Myrtle	40,000 PNU/ml	Greer Labs
Tree	Beech, American	40,000 PNU/ml	Greer Labs
Tree	Beefwood/Australian Pine	40,000 PNU/ml	Greer Labs
Tree	Birch, Black/Sweet	40,000 PNU/ml	Greer Labs
Tree	Birch, River	40,000 PNU/ml	Greer Labs
Tree	Birch, Spring	40,000 PNU/ml	Greer Labs

Tree	Birch, White	40,000 PNU/ml	Greer Labs
Tree	Box Elder	40,000 PNU/ml	Greer Labs
Tree	Cedar, Mountain	40,000 PNU/ml	Greer Labs
Tree	Cedar, Red	40,000 PNU/ml	Greer Labs
Tree	Cedar, Salt/Tamarisk	40,000 PNU/ml	Greer Labs
Tree	Cottonwood, Black	40,000 PNU/ml	Greer Labs
Tree	Cottonwood, Eastern	40,000 PNU/ml	Greer Labs
Tree	Cottonwood, Fremont	40,000 PNU/ml	Greer Labs
Tree	Cottonwood, Western	40,000 PNU/ml	Greer Labs
Tree	Cypress, Arizona	40,000 PNU/ml	Greer Labs
Tree	Cypress, Bald	40,000 PNU/ml	Greer Labs
Tree	Elm, American	40,000 PNU/ml	Greer Labs
Tree	Elm, Cedar/Fall Blooming	40,000 PNU/ml	Greer Labs
Tree	Elm, Siberian	40,000 PNU/ml	Greer Labs
Tree	Eucalyptus	40,000 PNU/ml	Greer Labs
Tree	Hackberry	40,000 PNU/ml	Greer Labs
Tree	Hazelnut, American	40,000 PNU/ml	Greer Labs
Tree	Hickory, Shagbark	40,000 PNU/ml	Greer Labs
Tree	Hickory, Shellbark	40,000 PNU/ml	Greer Labs
Tree	Hickory, White	40,000 PNU/ml	Greer Labs
Tree	Juniper, Oneseed	40,000 PNU/ml	Greer Labs
Tree	Juniper, Pinchot	40,000 PNU/ml	Greer Labs
Tree	Juniper, Rocky Mountain	40,000 PNU/ml	Greer Labs
Tree	Juniper, Utah	40,000 PNU/ml	Greer Labs
Tree	Juniper, Western	40,000 PNU/ml	Greer Labs
Tree	Locust Blossom, Black	40,000 PNU/ml	Greer Labs
Tree	Mango Blossom	40,000 PNU/ml	Greer Labs
Tree	Maple, Red	40,000 PNU/ml	Greer Labs
Tree	Maple, Soft/Silver	40,000 PNU/ml	Greer Labs
Tree	Maple, Sugar/Hard	40,000 PNU/ml	Greer Labs
Tree	Melaleuca	40,000 PNU/ml	Greer Labs
Tree	Mesquite	40,000 PNU/ml	Greer Labs
Tree	Mulberry, Paper	40,000 PNU/ml	Greer Labs
Tree	Mulberry, Red	40,000 PNU/ml	Greer Labs
Tree	Mulberry, White	40,000 PNU/ml	Greer Labs
Tree	Oak, Arizona/Gambel	40,000 PNU/ml	Greer Labs
Tree	Oak, Black	40,000 PNU/ml	Greer Labs
Tree	Oak, Bur	40,000 PNU/ml	Greer Labs
Tree	Oak, California Black	40,000 PNU/ml	Greer Labs

Tree	Oak, California Live	40,000 PNU/ml	Greer Labs
Tree	Oak, California White	40,000 PNU/ml	Greer Labs
Tree	Oak, Post	40,000 PNU/ml	Greer Labs
Tree	Oak, Red	40,000 PNU/ml	Greer Labs
Tree	Oak, Virginia Live	40,000 PNU/ml	Greer Labs
Tree	Oak, Water	40,000 PNU/ml	Greer Labs
Tree	Oak, Western White	40,000 PNU/ml	Greer Labs
Tree	Oak, White	40,000 PNU/ml	Greer Labs
Tree	Olive	40,000 PNU/ml	Greer Labs
Tree	Olive, Russian	40,000 PNU/ml	Greer Labs
Tree	Orange Pollen	40,000 PNU/ml	Greer Labs
Tree	Palm, Queen	40,000 PNU/ml	Greer Labs
Tree	Pecan	40,000 PNU/ml	Greer Labs
Tree	Pepper Tree	40,000 PNU/ml	Greer Labs
Tree	Pine, Loblolly	40,000 PNU/ml	Greer Labs
Tree	Pine, Longleaf	40,000 PNU/ml	Greer Labs
Tree	Pine, Ponderosa	40,000 PNU/ml	Greer Labs
Tree	Pine, Virginia Scrub	40,000 PNU/ml	Greer Labs
Tree	Pine, White/Eastern	40,000 PNU/ml	Greer Labs
Tree	Pine, White/Western	40,000 PNU/ml	Greer Labs
Tree	Pine, Yellow	40,000 PNU/ml	Greer Labs
Tree	Poplar, Lombardy	40,000 PNU/ml	Greer Labs
Tree	Poplar, White	40,000 PNU/ml	Greer Labs
Tree	Privet, Common	40,000 PNU/ml	Greer Labs
Tree	Sweet Gum	40,000 PNU/ml	Greer Labs
Tree	Sycamore, American/Eastern	40,000 PNU/ml	Greer Labs
Tree	Sycamore, Western	40,000 PNU/ml	Greer Labs
Tree	Walnut, Black	40,000 PNU/ml	Greer Labs
Tree	Willow, Arroyo	40,000 PNU/ml	Greer Labs
Tree	Willow, Black	40,000 PNU/ml	Greer Labs
Weed	Allscale	20,000 PNU/ml	Greer Labs
Weed	Baccharis	20,000 PNU/ml	Greer Labs
Weed	Burrobrush	20,000 PNU/ml	Greer Labs
Weed	Careless Weed,Amaranth/Green	20,000 PNU/ml	Greer Labs
Weed	Cocklebur	20,000 PNU/ml	Greer Labs
Weed	Dock, Yellow/Curly	20,000 PNU/ml	Greer Labs
Weed	Dog Fennel	20,000 PNU/ml	Greer Labs
Weed	Firebush/Kochia	20,000 PNU/ml	Greer Labs
Weed	Goldenrod	20,000 PNU/ml	Greer Labs

Weed	Hemp, Water	20,000 PNU/ml	Greer Labs
Weed	Iodine Bush	20,000 PNU/ml	Greer Labs
Weed	Lamb's Quarter	20,000 PNU/ml	Greer Labs
Weed	Lenscale/Quailbrush	20,000 PNU/ml	Greer Labs
Weed	Marsh Elder, Burweed/Giant Poverty	20,000 PNU/ml	Greer Labs
Weed	Marsh Elder, True/Rough	20,000 PNU/ml	Greer Labs
Weed	Mugwort, Common	20,000 PNU/ml	Greer Labs
Weed	Mugwort, Darkleaved/ Sagebrush, Prairie	20,000 PNU/ml	Greer Labs
Weed	Nettle	20,000 PNU/ml	Greer Labs
Weed	Palmer's Amaranth	20,000 PNU/ml	Greer Labs
Weed	Pigweed, Rough/Redroot	20,000 PNU/ml	Greer Labs
Weed	Pigweed, Spiny	20,000 PNU/ml	Greer Labs
Weed	Plantain, English	20,000 PNU/ml	Greer Labs
Weed	Rabbit Bush	20,000 PNU/ml	Greer Labs
Weed	Ragweed, Desert	20,000 PNU/ml	Greer Labs
Weed	Ragweed, False	20,000 PNU/ml	Greer Labs
Weed	Ragweed, Giant	20,000 PNU/ml	Greer Labs
Weed	Ragweed, Short	20,000 PNU/ml	Greer Labs
Weed	Ragweed, Slender	20,000 PNU/ml	Greer Labs
Weed	Ragweed, Southern	20,000 PNU/ml	Greer Labs
Weed	Ragweed, Western	20,000 PNU/ml	Greer Labs
Weed	Russian Thistle	20,000 PNU/ml	Greer Labs
Weed	Sagebrush, Coast	20,000 PNU/ml	Greer Labs
Weed	Sagebrush, Common	20,000 PNU/ml	Greer Labs
Weed	Sagebrush, Pasture	20,000 PNU/ml	Greer Labs
Weed	Saltbush, Annual	20,000 PNU/ml	Greer Labs
Weed	Sorrel, Sheep/Red	20,000 PNU/ml	Greer Labs
Weed	Wingscale	20,000 PNU/ml	Greer Labs
Grass	Bahia Grass	20,000 PNU/ml	Greer Labs
Grass	Bermuda Grass	10,000 PNU/ml	Greer Labs
Grass	Brome Grass, Smooth	40,000 PNU/ml	Greer Labs
Grass	Canarygrass, Reed	40,000 PNU/ml	Greer Labs
Grass	Corn, Cultivated	40,000 PNU/ml	Greer Labs
Grass	Couch/Quack Grass	40,000 PNU/ml	Greer Labs
Grass	Johnson Grass	40,000 PNU/ml	Greer Labs
Grass	Kentucky Blue/June	40,000 PNU/ml	Greer Labs
Grass	Meadow Fescue	40,000 PNU/ml	Greer Labs
Grass	Oats, Common/Cultivated	40,000 PNU/ml	Greer Labs
Grass	Orchard	40,000 PNU/ml	Greer Labs

Grass	Redtop	40,000 PNU/ml	Greer Labs
Grass	Rye, Cultivated	40,000 PNU/ml	Greer Labs
Grass	Ryegrass, Giant Wild	40,000 PNU/ml	Greer Labs
Grass	Ryegrass, Italian	40,000 PNU/ml	Greer Labs
Grass	Ryegrass, Perennial	40,000 PNU/ml	Greer Labs
Grass	Sweet Vernal	40,000 PNU/ml	Greer Labs
Grass	Timothy	40,000 PNU/ml	Greer Labs
Grass	Velvetgrass	40,000 PNU/ml	Greer Labs
Grass	Wheat, Cultivated	40,000 PNU/ml	Greer Labs
Grass	Wheatgrass, Western	40,000 PNU/ml	Greer Labs
Mold	Acremonium strictum	40,000 PNU/ml	Greer Labs
Mold	Alternaria alternat	40,000 PNU/ml	Greer Labs
Mold	Aspergillus amstelodami	40,000 PNU/ml	Greer Labs
Mold	Aspergillus flavus	40,000 PNU/ml	Greer Labs
Mold	Aspergillus fumigatus	40,000 PNU/ml	Greer Labs
Mold	Aspergillus nidulans	40,000 PNU/ml	Greer Labs
Mold	Aspergillus nige	40,000 PNU/ml	Greer Labs
Mold	Aureobasidium pullulan	40,000 PNU/ml	Greer Labs
Mold	Bipolaris sorokinian	40,000 PNU/ml	Greer Labs
Mold	Botrytis cinere	40,000 PNU/ml	Greer Labs
Mold	Candida albican	40,000 PNU/ml	Greer Labs
Mold	Chaetomium globosu	40,000 PNU/ml	Greer Labs
Mold	Cladosporium herbarum	40,000 PNU/ml	Greer Labs
Mold	Cladosporium sphaerospermum	40,000 PNU/ml	Greer Labs
Mold	Drechslera spicifera	40,000 PNU/ml	Greer Labs
Mold	Epicoccum nigrum	40,000 PNU/ml	Greer Labs
Mold	Epidermophyton floccosum	40,000 PNU/ml	Greer Labs
Mold	Fusarium moniliform	40,000 PNU/ml	Greer Labs
Mold	Fusarium solani	40,000 PNU/ml	Greer Labs
Mold	Geotrichum candidum	40,000 PNU/ml	Greer Labs
Mold	Gliocladium viride	40,000 PNU/ml	Greer Labs
Mold	Helminthosporium solani	40,000 PNU/ml	Greer Labs
Mold	Microsporum canis	40,000 PNU/ml	Greer Labs
Mold	Mucor circinelloides f. circinelloides	40,000 PNU/ml	Greer Labs
Mold	Mucor circinelloides f. lusitanicus	40,000 PNU/ml	Greer Labs
Mold	Mucor plumbeus	40,000 PNU/ml	Greer Labs
Mold	Mycogone perniciosa	40,000 PNU/ml	Greer Labs
Mold	Neurospora intermedia	40,000 PNU/ml	Greer Labs
Mold	Nigrospora oryzae	40,000 PNU/ml	Greer Labs

Mold	Paecilomyces variotii	40,000 PNU/ml	Greer Labs
Mold	Penicillium digitatum	40,000 PNU/ml	Greer Labs
Mold	Penicillium chrysogenum	40,000 PNU/ml	Greer Labs
Mold	Phoma betae	40,000 PNU/ml	Greer Labs
Mold	Rhizopus oryzae	40,000 PNU/ml	Greer Labs
Mold	Rhizopus stolonife	40,000 PNU/ml	Greer Labs
Mold	Rhodotorula mucilaginosa	40,000 PNU/ml	Greer Labs
Mold	Saccharomyces cerevisiae	40,000 PNU/ml	Greer Labs
Mold	Stemphylium solani	40,000 PNU/ml	Greer Labs
Mold	Trichoderma harzianum	40,000 PNU/ml	Greer Labs
Mold	Trichophyton mentagrophytes	40,000 PNU/ml	Greer Labs
Mold	Trichophyton rubrum	40,000 PNU/ml	Greer Labs
Mold	Trichothecium roseum	40,000 PNU/ml	Greer Labs
Animal	Cattle Epithelia	20,000 PNU/ml	Greer Labs
Animal	Dog Epithelia	20,000 PNU/ml	Greer Labs
Animal	Gerbil Epithelia	20,000 PNU/ml	Greer Labs
Animal	Goat Epithelia	20,000 PNU/ml	Greer Labs
Animal	Guinea Pig Epithelia	20,000 PNU/ml	Greer Labs
Animal	Hamster Epithelia	20,000 PNU/ml	Greer Labs
Animal	Hog Epithelia	20,000 PNU/ml	Greer Labs
Animal	Horse Epithelia	20,000 PNU/ml	Greer Labs
Animal	Mouse Epithelia	20,000 PNU/ml	Greer Labs
Animal	Rabbit Epithelia	20,000 PNU/ml	Greer Labs
Animal	Rat Epithelia	20,000 PNU/ml	Greer Labs
Animal	2 Cockroach Mix	40,000 PNU/ml	Greer Labs
Tree	ACACIA Acacia spp.	40,000 PNU/ml	Allergy Laboratories
Tree	ALDER, RED Alnus rubra	40,000 PNU/ml	Allergy Laboratories
Tree	ALDER, SMOOTH Alnus rugosa	40,000 PNU/ml	Allergy Laboratories
Tree	ASH, ARIZONA Fraxinus velutina	40,000 PNU/ml	Allergy Laboratories
Tree	ASH, GREEN (RED) Fraxinus pennsylvanica	40,000 PNU/ml	Allergy Laboratories
Tree	ASH, WHITE Fraxinus Americana	40,000 PNU/ml	Allergy Laboratories
Tree	ASH MIX (Green & White)	40,000 PNU/ml	Allergy Laboratories
Tree	ASPEN, QUAKING Populus tremuloides	40,000 PNU/ml	Allergy Laboratories
Tree	BAYBERRY Myrica cerifera	40,000 PNU/ml	Allergy Laboratories
Tree	BEECH, AMERICAN Fagus grandifolia	40,000 PNU/ml	Allergy Laboratories
Tree	BIRCH, RIVER Betula nigra	40,000 PNU/ml	Allergy Laboratories
Tree	BIRCH MIX (River, Paper, Sweet & White)	40,000 PNU/ml	Allergy Laboratories
Tree	BIRCH, WHITE (GRAY) Betula populifolia	40,000 PNU/ml	Allergy Laboratories
Tree	BOX ELDER Acer negundo	40,000 PNU/ml	Allergy Laboratories

Tree	CEDAR, MOUNTAIN Juniperus sabinoides	40,000 PNU/ml	Allergy Laboratories
Tree	CEDAR, PINCHOT Juniperus pinchotii	40,000 PNU/ml	Allergy Laboratories
Tree	CEDAR, RED Juniperus virginiana	40,000 PNU/ml	Allergy Laboratories
Tree	COTTONWOOD, EASTERN Populus deltoids	40,000 PNU/ml	Allergy Laboratories
Tree	COTTONWOOD, WESTERN Populus sargentii	40,000 PNU/ml	Allergy Laboratories
Tree	COTTONWOOD MIX, EASTERN/WESTERN	40,000 PNU/ml	Allergy Laboratories
Tree	CYPRESS, ARIZONA Cupressus arizonica	40,000 PNU/ml	Allergy Laboratories
Tree	CYPRESS, BALD Taxodium distichum	40,000 PNU/ml	Allergy Laboratories
Tree	ELM, AMERICAN Ulmus americana	40,000 PNU/ml	Allergy Laboratories
Tree	ELM, CEDAR (FALL BLOOMING) Ulmus crassifolia	40,000 PNU/ml	Allergy Laboratories
Tree	ELM, CHINESE (SIBERIAN) Ulmus pumila	40,000 PNU/ml	Allergy Laboratories
Tree	ELM MIX (American, Chinese & Slippery)	40,000 PNU/ml	Allergy Laboratories
Tree	EUCALYPTUS (BLUE GUM) Eucalyptus globulus	40,000 PNU/ml	Allergy Laboratories
Tree	FIR, DOUGLAS Pseudotsuga taxifolia	40,000 PNU/ml	Allergy Laboratories
Tree	SWEETGUM Liquidambar styraci ua	40,000 PNU/ml	Allergy Laboratories
Tree	HACKBERRY Celtis occidentalis	40,000 PNU/ml	Allergy Laboratories
Tree	HICKORY, SHAGBARK Carya ovata	40,000 PNU/ml	Allergy Laboratories
Tree	HICKORY, WHITE Carya tomentosa	40,000 PNU/ml	Allergy Laboratories
Tree	HICKORY MIX (Pignut, Shagbark, Shellbar, White)	40,000 PNU/ml	Allergy Laboratories
Tree	JUNIPER, ONE SEED Juniperus monosperma	40,000 PNU/ml	Allergy Laboratories
Tree	JUNIPER, ROCKY MOUNTAIN	40,000 PNU/ml	Allergy Laboratories
Tree	LOCUST, BLACK Robinia pseudoacacia	40,000 PNU/ml	Allergy Laboratories
Tree	MAPLE, SUGAR (HARD) Acer saccharum	40,000 PNU/ml	Allergy Laboratories
Tree	MAPLE MIX (Red, Silver & Sugar)	40,000 PNU/ml	Allergy Laboratories
Tree	MESQUITE Prosopis spp.	40,000 PNU/ml	Allergy Laboratories
Tree	MULBERRY, PAPER Broussonetia papyrifera	40,000 PNU/ml	Allergy Laboratories
Tree	MULBERRY, RED Morus rubra	40,000 PNU/ml	Allergy Laboratories
Tree	MULBERRY, WHITE Morus alba	40,000 PNU/ml	Allergy Laboratories
Tree	OAK, BLACK Quercus velutina	40,000 PNU/ml	Allergy Laboratories
Tree	OAK, BLACKJACK Quercus marilandica	40,000 PNU/ml	Allergy Laboratories
Tree	OAK, BUR Quercus macrocarpa	40,000 PNU/ml	Allergy Laboratories
Tree	OAK, LIVE Quercus virginiana	40,000 PNU/ml	Allergy Laboratories
Tree	2-OAK MIX (Red & White)	40,000 PNU/ml	Allergy Laboratories
Tree	3-OAK MIX (Black, Blackjack & Post)	40,000 PNU/ml	Allergy Laboratories
Tree	5-OAK MIX (Blackjack, Bur, Post, Red & White)	40,000 PNU/ml	Allergy Laboratories
Tree	OAK, POST Quercus stellata	40,000 PNU/ml	Allergy Laboratories
Tree	OAK, WHITE Quercus alba	40,000 PNU/ml	Allergy Laboratories
Tree	OLIVE, EUROPEAN Olea europaea	40,000 PNU/ml	Allergy Laboratories
Tree	OSAGE ORANGE Maclura pomifera	40,000 PNU/ml	Allergy Laboratories

Tree	PALM, DATE Phoenix dactylifera	40,000 PNU/ml	Allergy Laboratories
Tree	PALM QUEEN, Arecastrum spp.	40,000 PNU/ml	Allergy Laboratories
Tree	PECAN POLLEN Carya illinoinensis	40,000 PNU/ml	Allergy Laboratories
Tree	PINE, WHITE Pinus strobus	40,000 PNU/ml	Allergy Laboratories
Tree	4 PINE MIX (Austrian, Loblolly, Scotch & White)	40,000 PNU/ml	Allergy Laboratories
Tree	POPLAR, LOMBARDY Populus nigra	40,000 PNU/ml	Allergy Laboratories
Tree	POPLAR, WHITE Populus alba	40,000 PNU/ml	Allergy Laboratories
Tree	PRIVET Ligustrum spp.	40,000 PNU/ml	Allergy Laboratories
Tree	SPRUCE, BLUE Picea pungens	40,000 PNU/ml	Allergy Laboratories
Tree	SUMAC, UPLAND Rhus glabra	40,000 PNU/ml	Allergy Laboratories
Tree	SYCAMORE Platanus occidentalis	40,000 PNU/ml	Allergy Laboratories
Tree	TREE OF HEAVEN Ailanthus altissima	40,000 PNU/ml	Allergy Laboratories
Tree	WALNUT, BLACK (POLLEN) Juglans nigra	40,000 PNU/ml	Allergy Laboratories
Tree	WILLOW, BLACK Salix nigra	40,000 PNU/ml	Allergy Laboratories
Grass	ALFALFA Medicago sativa	40,000 PNU/ml	Allergy Laboratories
Grass	BAHIA GRASS Paspalum notatum	40,000 PNU/ml	Allergy Laboratories
Grass	BARLEY, CULTIVATED Hordeum vulgare	40,000 PNU/ml	Allergy Laboratories
Grass	SUGAR BEET POLLEN Beta vulgaris	40,000 PNU/ml	Allergy Laboratories
Grass	BENT GRASS, CREEPING Agrostis stolonifera	40,000 PNU/ml	Allergy Laboratories
Grass Std	BERMUDA GRASS	10,000 PNU/ml	Allergy Laboratories
Grass	BLUEGRASS, ANNUAL Poa annua	40,000 PNU/ml	Allergy Laboratories
Grass	BROME, HUNGARIAN (SMOOTH) Bromus inermis	40,000 PNU/ml	Allergy Laboratories
Grass	CANARY GRASS Phalaris minor	40,000 PNU/ml	Allergy Laboratories
Grass	CORN, CULTIVATED Zea mays	40,000 PNU/ml	Allergy Laboratories
Grass	JOHNSON GRASS Sorghum halepense	40,000 PNU/ml	Allergy Laboratories
Grass	KENTUCKY (JUNEGRASS) BLUEGRASS	100,000 PNU/ml	Allergy Laboratories
Grass Std	MEADOW FESCUE GRASS	100,000 PNU/ml	Allergy Laboratories
Grass	OAT GRASS, TALL Arrhenatherum elatius	40,000 PNU/ml	Allergy Laboratories
Grass	OATS, CULTIVATED Avena sativa	40,000 PNU/ml	Allergy Laboratories
Grass Std	ORCHARD GRASS	100,000 PNU/ml	Allergy Laboratories
Grass Std	PERENNIAL RYEGRASS	100,000 PNU/ml	Allergy Laboratories
Grass	REDTOP GRASS, STANDARDIZED Agrostis alba	100,000 BAU/ml	Allergy Laboratories
Grass	RYEGRASS, ITALIAN Lolium multi orum	40,000 PNU/ml	Allergy Laboratories
Grass	SORGHUM, GRAIN Sorghum vulgare	40,000 PNU/ml	Allergy Laboratories
Grass	SUDAN GRASS Sorghum vulagare var. sudanense	40,000 PNU/ml	Allergy Laboratories
Grass	SWEET VERNAL GRASS	100,000 PNU/ml	Allergy Laboratories
Grass	TIMOTHY GRASS	100,000 PNU/ml	Allergy Laboratories
Grass	WHEAT, CULTIVATED Triticum aestivum	40,000 PNU/ml	Allergy Laboratories
Weed	BROOMWEED Gutierrezia dracunculoides	20,000 PNU/ml	Allergy Laboratories

Weed	CARELESS WEED Amaranthus palmeri	20,000 PNU/ml	Allergy Laboratories
Weed	COCKLEBUR Xanthium commune	20,000 PNU/ml	Allergy Laboratories
Weed	DOCK, SOUR (SHEEP SORREL) Rumex acetosella	20,000 PNU/ml	Allergy Laboratories
Weed	DOCK, YELLOW (CURLY) Rumex crispus	20,000 PNU/ml	Allergy Laboratories
Weed	DOCK MIX, SOUR (SHEEP SORREL)/YELLOW	20,000 PNU/ml	Allergy Laboratories
Weed	FIREBUSH (KOCHIA) Kochia scoparia	20,000 PNU/ml	Allergy Laboratories
Weed	GOLDENROD Solidago spp.	20,000 PNU/ml	Allergy Laboratories
Weed	GREASEWOOD Sarcobatus vermiculatus	20,000 PNU/ml	Allergy Laboratories
Weed	GROUNDSEL TREE Baccharis halimifolia	20,000 PNU/ml	Allergy Laboratories
Weed	LAMB'S QUARTERS Chenopodium album	20,000 PNU/ml	Allergy Laboratories
Weed	MARSHELDER, BURWEED Iva xanthifolia	20,000 PNU/ml	Allergy Laboratories
Weed	MARSHELDER, NARROWLEAF Iva angustifolia	20,000 PNU/ml	Allergy Laboratories
Weed	MARSHELDER, ROUGH Iva ciliata	20,000 PNU/ml	Allergy Laboratories
Weed	MUGWORT, COMMON Artemisia vulgaris	20,000 PNU/ml	Allergy Laboratories
Weed	NETTLE Urtica dioica	20,000 PNU/ml	Allergy Laboratories
Weed	PIGWEED MIX (Rough/Spiny)	20,000 PNU/ml	Allergy Laboratories
Weed	PIGWEED, ROUGH (REDROOT)	20,000 PNU/ml	Allergy Laboratories
Weed	PIGWEED, SPINY Amaranthus spinosus	20,000 PNU/ml	Allergy Laboratories
Weed	PLANTAIN, ENGLISH Plantago lanceolata	20,000 PNU/ml	Allergy Laboratories
Weed	RAGWEED, FALSE (BUR) Ambrosia acanthicarpa	20,000 PNU/ml	Allergy Laboratories
Weed	RAGWEED, GIANT Ambrosia trida	20,000 PNU/ml	Allergy Laboratories
Weed Std	SHORT RAGWEED	100,000 PNU/ml	Allergy Laboratories
Weed	RAGWEED, WESTERN Ambrosia psilostachya	20,000 PNU/ml	Allergy Laboratories
Weed	3-RAGWEED MIX (Giant/Short/ Western)	20,000 PNU/ml	Allergy Laboratories
Weed Std	RAGWEED MIX, GIANT/SHORT	100,000 PNU/ml	Allergy Laboratories
Weed	RUSSIAN THISTLE Salsola kali	20,000 PNU/ml	Allergy Laboratories
Weed	SAGEBRUSH, COMMON (BIG) Artemisia tridentata	20,000 PNU/ml	Allergy Laboratories
Weed	SAGE, PRAIRIE (DARK-LEAVED)	20,000 PNU/ml	Allergy Laboratories
Weed	SALTBUSH, ANNUAL Atriplex wrightii	20,000 PNU/ml	Allergy Laboratories
Weed	SHADSCALE Atriplex confertifolia	20,000 PNU/ml	Allergy Laboratories
Weed	WATER-HEMP Acnida tamariscina	20,000 PNU/ml	Allergy Laboratories
Weed	WINGSCALE Atriplex canescens	20,000 PNU/ml	Allergy Laboratories
Weed	WORMWOOD, ANNUAL Artemisia annua	20,000 PNU/ml	Allergy Laboratories
Weed	WORMWOOD, COMMON Artemisia absinthium	20,000 PNU/ml	Allergy Laboratories
Mold	ALTERNARIA TENUIS (ALTERNATA)	40,000 PNU/ml	Allergy Laboratories
Mold	ASPERGILLUS FUMIGATUS	40,000 PNU/ml	Allergy Laboratories
Mold	ASPERGILLUS NIGER	40,000 PNU/ml	Allergy Laboratories
Mold	BOTRYTIS CINEREA	40,000 PNU/ml	Allergy Laboratories
Mold	CANDIDA (MONILA) ALBICANS	40,000 PNU/ml	Allergy Laboratories

Mold	CEPHALOSPORIUM ACREMONIUM	40,000 PNU/ml	Allergy Laboratories
Mold	CHAETOMIUM GLOBOSUM	40,000 PNU/ml	Allergy Laboratories
Mold	CLADOSPORIUM FULVUM	40,000 PNU/ml	Allergy Laboratories
Mold	CURVULARIA SPICIFERA	40,000 PNU/ml	Allergy Laboratories
Mold	EPICOCCUM NIGRUM	40,000 PNU/ml	Allergy Laboratories
Mold	EPIDERMOPHYTON FLOCCOSUM	40,000 PNU/ml	Allergy Laboratories
Mold	FUSARIUM VASINFECTUM (OXYSPORUM)	40,000 PNU/ml	Allergy Laboratories
Mold	FUSARIUM SOLANI	40,000 PNU/ml	Allergy Laboratories
Mold	GEOTRICHUM CANDIDUM	40,000 PNU/ml	Allergy Laboratories
Mold	HELMINTHOSPORIUM SATIVUM	40,000 PNU/ml	Allergy Laboratories
Mold	HORMODENDRUM (CLADOSPORIUM)	40,000 PNU/ml	Allergy Laboratories
Mold	MUCOR PLUMBEUS	40,000 PNU/ml	Allergy Laboratories
Mold	MUCOR RACEMOSUS	40,000 PNU/ml	Allergy Laboratories
Mold	NEUROSPORA SITOPHILA	40,000 PNU/ml	Allergy Laboratories
Mold	NIGROSPORA SPHAERICA	40,000 PNU/ml	Allergy Laboratories
Mold	PENICILLIUM NOTATUM (CHRYSOGENUM)	40,000 PNU/ml	Allergy Laboratories
Mold	PHOMA DESTRUCTIVA	40,000 PNU/ml	Allergy Laboratories
Mold	PULLULARIA PULLULANS	40,000 PNU/ml	Allergy Laboratories
Mold	RHIZOPUS NIGRICANS	40,000 PNU/ml	Allergy Laboratories
Mold	RHODOTORULA MUCILAGINOSA	40,000 PNU/ml	Allergy Laboratories
Mold	RINKEL MOLD MIX A	40,000 PNU/ml	Allergy Laboratories
Mold	RINKEL MOLD MIX B	40,000 PNU/ml	Allergy Laboratories
Mold	RINKEL MOLD MIX C	40,000 PNU/ml	Allergy Laboratories
Mold	STEMPHYLLIUM SARCINAEFORME	40,000 PNU/ml	Allergy Laboratories
Mold	TRICHODERMA LIGNORUM	40,000 PNU/ml	Allergy Laboratories
Mold	TRICHOPYHTON MENTAGROPHYTES	40,000 PNU/ml	Allergy Laboratories
Mold	TRICHOPYHTON RUBRUM	40,000 PNU/ml	Allergy Laboratories
Mold	TRICHOPYHTON TONSURANS	40,000 PNU/ml	Allergy Laboratories
Smut	VERTICILLIUM ALBO-ATRUM	40,000 PNU/ml	Allergy Laboratories
Smut	BERMUDA GRASS SMUT	20,000 PNU/ml	Allergy Laboratories
Smut	CORN SMUT	20,000 PNU/ml	Allergy Laboratories
Smut	JOHNSON GRASS SMUT	20,000 PNU/ml	Allergy Laboratories
Smut	WHEAT RUST	20,000 PNU/ml	Allergy Laboratories
Flower	DANDELION Taraxacum of cinale	40,000 PNU/ml	Allergy Laboratories
Flower	SUNFLOWER Helianthus annuus	40,000 PNU/ml	Allergy Laboratories
Environmental	COTTON LINTERS Gossypium hirsutum	40,000 PNU/ml	Allergy Laboratories
Environmental	COTTON SEED	40,000 PNU/ml	Allergy Laboratories
Environmental	FLAX SEED	40,000 PNU/ml	Allergy Laboratories
Environmental	KAPOK Ceiba pentandra	40,000 PNU/ml	Allergy Laboratories

Environmental	ORRIS ROOT Iris orentina	40,000 PNU/ml	Allergy Laboratories
Environmental	PYRETHRUM Chrysanthemum	40,000 PNU/ml	Allergy Laboratories
Environmental	SILK	40,000 PNU/ml	Allergy Laboratories
Cat Hair Std	Felis domesticus	40,000 PNU/ml	Allergy Laboratories
Animal	CATTLE HAIR & EPITHELIA Bos taurus	20,000 PNU/ml	Allergy Laboratories
Animal	DOG HAIR & EPITHELIA Canis familiaris	20,000 PNU/ml	Allergy Laboratories
Animal	GUINEA PIG HAIR & EPITHELIA Cavia porcellus	20,000 PNU/ml	Allergy Laboratories
Animal	HAMSTER HAIR & EPITHELIA Cricetus cricetus	20,000 PNU/ml	Allergy Laboratories
Animal	COCKROACH, AMERICAN	20,000 PNU/ml	Allergy Laboratories
Animal	HOG HAIR & EPITHELIA Sus scrofa	20,000 PNU/ml	Allergy Laboratories
Animal	HORSE HAIR & DANDER Equus caballus	20,000 PNU/ml	Allergy Laboratories
Animal	MOUSE HAIR & EPITHELIA Mus musculus	20,000 PNU/ml	Allergy Laboratories
Animal	RABBIT HAIR & EPITHELIA Oryctolagus cuniculus	20,000 PNU/ml	Allergy Laboratories
Feathers	CHICKEN FEATHERS Gallus gallus	20,000 PNU/ml	Allergy Laboratories
Feathers	DUCK FEATHERS Anas platyrhynchos	20,000 PNU/ml	Allergy Laboratories
Feathers	GOOSE FEATHERS Anser anser	20,000 PNU/ml	Allergy Laboratories
Feathers	FEATHER MIX (Chicken, Duck, & Goose)	20,000 PNU/ml	Allergy Laboratories
Mite Std	Dermatophagoides farinae	10,000 AU/ml	Allergy Laboratories
Mite Std	Dermatophagoides pteronyssinus	10,000 AU/ml	Allergy Laboratories

Appendix F Immunotherapy efficacy assessment instruments

Mini-RQLQ

Please complete all questions by circling the number that best describes how troubled you have been during the last week as a result of your nose/eye symptoms.

	Not troubled	Hardly troubled at all	Somewhat troubled	Moderately troubled	Quite a bit troubled	Very troubled	Extremely troubled
Activities							
1. Regular activities at home and at work (your occupation or tasks that you have to do regularly around your home and/or garden)	0	1	2	3	4	5	6
2. Recreational activities (indoor and outdoor activities with friends and family, sports, social activities, hobbies)	0	1	2	3	4	5	6
3. Sleep (difficulties getting a good night's sleep and/or getting to sleep at night)	0	1	2	3	4	5	6
Practical problems							
4. Need to rub nose/eyes	0	1	2	3	4	5	6
5. Need to blow nose repeatedly	0	1	2	3	4	5	6
Nose symptoms							
6. Sneezing	0	1	2	3	4	5	6
7. Stuffy blocked nose	0	1	2	3	4	5	6
8. Runny nose	0	1	2	3	4	5	6
Eye symptoms							
9. Itchy eyes	0	1	2	3	4	5	6
10. Sore eyes	0	1	2	3	4	5	6
11. Watery eyes	0	1	2	3	4	5	6
Other symptoms							
12. Tiredness and/or fatigue	0	1	2	3	4	5	6
13. Thirst	0	1	2	3	4	5	6
14. Feeling irritable	0	1	2	3	4	5	6

Total Nasal Symptoms Score (TNSS)

The Total Nasal Symptom Score (TNSS; possible score of 0-12) is the sum of 4 individual participant-assessed symptom scores for rhinorrhea, nasal congestion, nasal itching, and sneezing, each evaluated using a scale of 0=None, 1=Mild, 2=Moderate, or 3=Severe.

Appendix G Allergens used for skin prick testing

Type	Allergen	Stock Concentration	Manufacturer
Tree	Oak	20,000 PNU/ml	Greer
Tree	Birch	20,000 BAU/ml	Greer
Tree	Beech	20,000 BAU/ml	Greer
Tree	Elm	20,000 BAU/ml	Greer
Tree	Ash	20,000 BAU/ml	Greer
Tree	Sycamore	20,000 BAU/ml	Greer
Tree	Poplar	20,000 BAU/ml	Greer
Tree	Hickory	20,000 BAU/ml	Greer
Tree	Walnut	20,000 BAU/ml	Greer
Tree	Mulberry	20,000 BAU/ml	Greer
Tree	Pine	20,000 BAU/ml	Greer
Tree	Willow	20,000 BAU/ml	Greer
Grass	Timothy	100,000 BAU/ml	Greer
Grass	Orchard	100,000 BAU/ml	Greer
Grass	Johnson	100,000 BAU/ml	Greer
Grass	June	100,000 BAU/ml	Greer
Grass	Rye	100,000 BAU/ml	Greer
Grass	Fescue	100,000 BAU/ml	Greer
Grass	Bermuda	10,000 BAU/ml	Greer
Weed	Ragweed	100,000 AU/ml	Greer
Weed	Plantain	40,000 PNU/ml	Greer
Weed	Pigweed	40,000 PNU/ml	Greer
Weed	Lambsquarter	40,000 PNU/ml	Greer
Weed	Sage/Mugwart	40,000 PNU/ml	Greer
Weed	Sheep Sorrel	40,000 PNU/ml	Greer
Weed	Cocklebur	40,000 PNU/ml	Greer
Mold	Aspergillus	40,000 PNU/ml	Greer
Mold	Penicillium	40,000 PNU/ml	Greer
Mold	Mucor	40,000 PNU/ml	Greer
Mold	Fusarium	40,000 PNU/ml	Greer
Mold	Alternaria	40,000 PNU/ml	Greer
Mold	Helminthosporium	40,000 PNU/ml	Greer
Mold	Botrytis	40,000 PNU/ml	Greer
Mold	Cladosporium	40,000 PNU/ml	Greer
Mold	Curvularia	40,000 PNU/ml	Greer
Animal	Cat Hair	10,000 BAU/ml	Greer

Animal	AP Cat	10,000 BAU/ml	Hollister
Animal	Dog epithelia	20,000 PNU/ml	Greer
Animal	AP Dog	10,000 PNU/ml	Hollister
Animal	Mouse	20,000 PNU/ml	Greer
Animal	Cockroach Mix	20,000 PNU/ml	Greer
Animal	Rat	20,000 PNU/ml	Greer
Animal	Horse	20,000 PNU/ml	Greer
Animal	Rabbit	20,000 PNU/ml	Greer
Dust Mite	D. farinae	10,000 BAU/ml	Greer
Dust Mite	D. pteronyssinus	10,000 BAU/ml	Greer
Control	Saline		Hollister
Control	Histamine	1mg/ml	Hollister

Appendix H Immunotherapy Injection Schedule

Visit Day	Vial Number	Dilution	A, B, C (ml)	Injection Volume (ml)
2	#5	1:625	0.05	0.15
3	#5	1:625	0.10	0.30
4	#5	1:625	0.15	0.45
5	#5	1:625	0.20	0.60
6	#4	1:125	0.05	0.15
7	#4	1:125	0.10	0.30
8	#4	1:125	0.15	0.45
9	#4	1:125	0.20	0.60
10	#3	1:25	0.05	0.15
11	#3	1:25	0.10	0.30
12	#3	1:25	0.15	0.45
13	#3	1:25	0.20	0.60
14	#2	1:5	0.05	0.15
15	#2	1:5	0.10	0.30
16	#2	1:5	0.15	0.45
17	#2	1:5	0.20	0.60

Appendix I Allergy Rescue Medication Action Plan

Ask patient if symptoms are adequately controlled at each bi-weekly visit. The response dictates whether a medication is added or subtracted. Resuce medications will not be increased after week 10.

Symptoms Controlled?	Medication Action
no	Add medication
yes	Subtract medication

Step	Rescue Medication	Score
A	None	0 points
B	Loratadine 10mg PO Daily	1 point
C	Loratadine 10mg PO BID	2 points
D	Loratadine BID plus Triamcinolone Daily	4 points
E	Loratadine BID plus Triamcinolone BID	6 points
F	Loratadine BID plus Triamcinolone BID plus Prednisone 5mg Daily	9 points
G	Loratadine BID plus Triamcinolone BID plus Prednisone 5mg BID	12 points

Note: To calculate the daily medication score add the total points for all medications noted above. Any other allergy rescue medications inadvertently added will also be counted in a similar manner as follows; other oral antihistamines (1 points each tablet), ophthalmic allergy medications (1 points each use), other nasal steroids, cromolyn, azelastine (2 points daily, 4 points BID). Symptoms and medication use are recorded daily at home.

Appendix J Clinical Visit Summary

Subject ID **Date** **Visit #**

Initials

Allergy medications currently taking _____

_____

Daily symptom cards collected Y/N

Today's RQLQ _____

Baseline RQLQ _____

Symptoms controlled Y/N

Medication added _____

Medication removed _____

Initial Vitals P BP RR Temp Sats PFR Time Initials

Physical Exam _____ Time Initials

_____

_____

Vial ID _____ Vial # _____ Dose (ml) _____ Time Initials

Exit Vitals P BP Sats PFR Time Initials

Reactions or Other Notes _____

_____

Appendix K Symptom and Medication Card

Daily Symptoms and Medication Use Initials ID

Date

Symptoms	None	Mild	Mod	Severe
Runny nose	0	1	2	3
Nasal stuffiness	0	1	2	3
Nasal itching	0	1	2	3
Sneezing	0	1	2	3

Medications Taken	None	Once	Twice
Loratadine tablet	☐	☐	☐
Triamcinolone spray	☐	☐	☐
Prednisone tablet	☐	☐	☐

Other medications _________________________

Date

Symptoms	None	Mild	Mod	Severe
Runny nose	0	1	2	3
Nasal stuffiness	0	1	2	3
Nasal itching	0	1	2	3
Sneezing	0	1	2	3

Medications Taken	None	Once	Twice
Loratadine tablet	☐	☐	☐
Triamcinolone spray	☐	☐	☐
Prednisone tablet	☐	☐	☐

Other medications _________________________

Date

Symptoms	None	Mild	Mod	Severe
Runny nose	0	1	2	3
Nasal stuffiness	0	1	2	3
Nasal itching	0	1	2	3
Sneezing	0	1	2	3

Medications Taken	None	Once	Twice
Loratadine tablet	☐	☐	☐
Triamcinolone spray	☐	☐	☐
Prednisone tablet	☐	☐	☐

Other medications _________________________

Date

Symptoms	None	Mild	Mod	Severe
Runny nose	0	1	2	3
Nasal stuffiness	0	1	2	3
Nasal itching	0	1	2	3
Sneezing	0	1	2	3

Medications Taken	None	Once	Twice
Loratadine tablet	☐	☐	☐
Triamcinolone spray	☐	☐	☐
Prednisone tablet	☐	☐	☐

Other medications _________________________

Try to fill out this card every day at the same time before you go to bed.

If found please return to Dr Jody Tversky 5501 Hopkins Bayview Circle, Batimore, MD 21224

The purpose of this document is to provide a description of the statistical methods and procedures to be implemented for the analysis of data derived from the study entitled: "A double-blind, prospective, parallel group evaluation of a novel biologic therapy for perennial allergic rhinitis" sponsored by Relez Therapeutics, LLC, and conducted at the Johns Hopkins Bayview Medical Center, Baltimore, Maryland. The protocol version used for the plan is Version 6.9 dated February 10, 2017. At the time of development of this statistical analysis plan (SAP) the study Principal Investigator is Jody R. Tversky, MD, Johns Hopkins University School of Medicine, Baltimore, MD

Any revisions to the SAP (both alternative and additional methods) will be made prior to database lock and reasons for such revisions will be described in the final Clinical Study Report (CSR).

STUDY OVERVIEW

Endpoints

Primary Endpoints

The primary endpoint is to quantify and compare the clinical difference in signs and symptoms and medication usage as well as the global RQLQ index that may be apparent when subjects with active perennial allergic rhinitis (PAR) with or without seasonal symptoms (SAR) are treated in a double-blind, prospective, controlled eight weeks study with a proprietary mixture of FDA approved allergens (PMA) versus placebo.

Secondary Endpoint

The secondary endpoints include a symptom score trend analysis, drop out rates, and adverse events profile (AE). Serum will also be stored for measurement of immunoglobulins at a later time.

STUDY DESIGN AND METHODS

Study Design

This is a phase 2 proof of concept study. It is being undertaken to characterize and quantify the clinical difference in signs and symptoms that may evolve when subjects with active seasonal or perennial allergic rhinitis (SAR/PAR) are administered a sub-cutaneous form of immunotherapy in a double-blind, prospective, controlled six weeks study wherein a proprietary mixture of FDA approved allergens (PMA) is compared with saline placebo.

Randomization to active PMA versus placebo treatment is on a 1 to 1 ratio. A double-blind study design is used to minimize outcome bias. Randomization measures to minimize bias at study entry include computerized random assignment of treatment versus placebo vials.

Subjects who are receiving nasal steroids for their SAR/PAR at screening may continue in the screening process if they agree to discontinue their therapy and commence a 14-day wash-out period of their medication prior to receiving active/placebo immunotherapy. Potential study subjects who, at screening, are not on active treatment for their SAR/PAR and asthma may enter directly into the investigation provided they fulfil entry and exclusion criteria and screening testing requirements.

The population to be studied consists of male and female adults aged 18 years to 65 years who are actively manifesting SAR/PAR have a score of at least 28 on the mini-RQLQ and 6 on the TNSS scale.

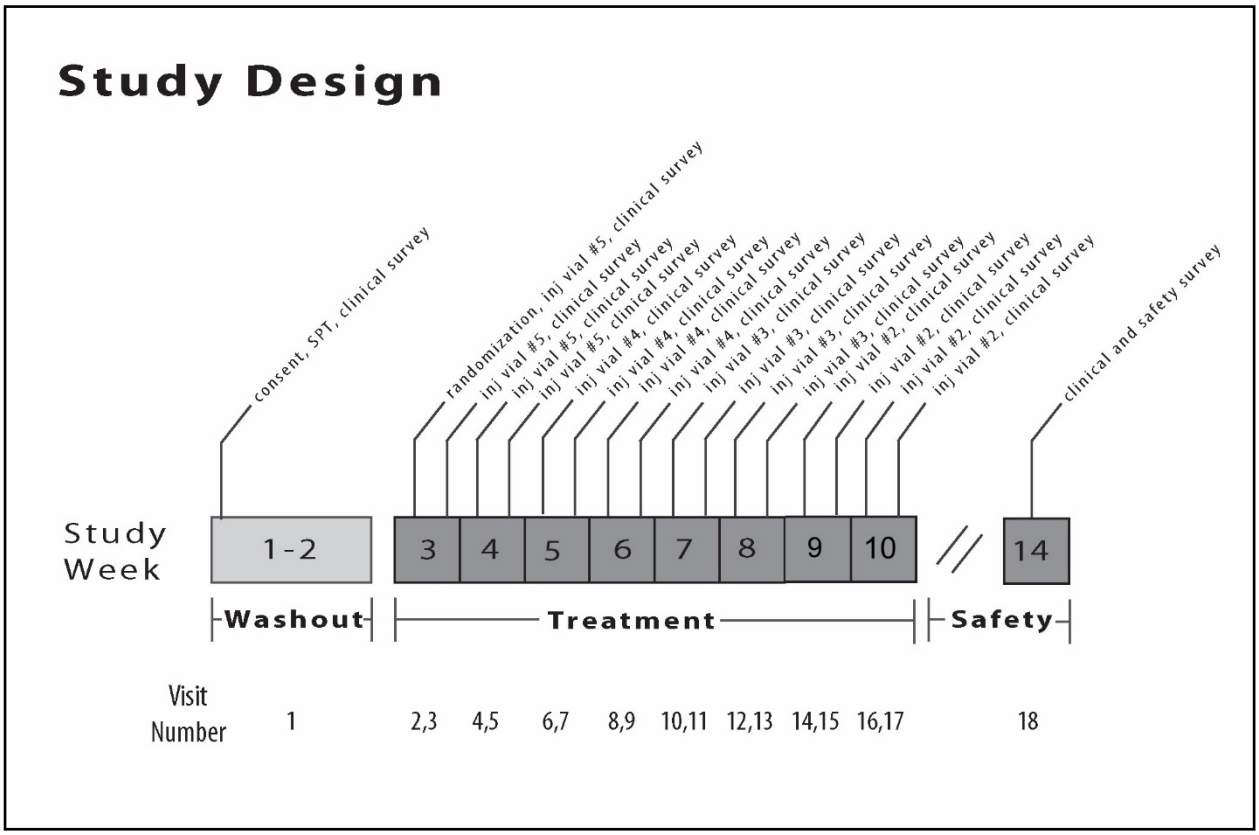
The active treatment phase of the study will be for six weeks with a safety follow-up assessment at 30 days post-treatment. No interim analysis is planned.

The study immunotherapy that will be evaluated in this study is a new innovative proprietary mixture of FDA approved allergens which has been clinically developed and evaluated, during the past three decades, in some 20,000 patients by the inventor of the mixture (see 3.2). In clinical evaluation this patented antigen mixture has provided clinical symptomatic relief to patients with SAR/PAR in as brief a period as three administrations of immunotherapy injections and has an observed overall success rate of approximately 80 to 90 percent of such treated subjects.

In this study approximately 36 study subjects will be equally randomized to active PMA or placebo. The duration of active PMA or placebo treatment will be 8 weeks with clinic visits twice-weekly during this period and a post-treatment safety follow up assessment at one month following the final administration of immunotherapy. All doses of immunotherapy will be administered in the study site clinic by the investigators or their designees.

A schematic of the study design is included in the Figure below. A schedule of assessments is listed in **Error! Reference source not found.** of the protocol.

Figure Schematic of Study Design



The SAP will follow the study protocol sections 12.1 to 12.3. Statistical methodology was developed in conjunction with the faculty of the Johns Hopkins Bloomberg School of Public Health Department of Biostatistics. Specific calculations include the following wherein “p" values as well as 95% confidence intervals will be calculated.

Primary Outcomes

1. Daily Combined Score (DCS) – Comparison of the delta visit 2 to visit 17 (change in score) between both treatment groups I and II using an unpaired t test.

2. Daily Combined Score (DCS) – Comparison of the delta visit 2 to visit 18 (change in score) between both treatment groups I and II using an unpaired t test.

3. mini-rhinoconjunctivitis quality of life questionnaire (RQLQ) - Comparison of the delta visit 2 to visit 17 (change in score) between both treatment groups I and II using an unpaired t test.

4. mini-RQLQ - Comparison of the delta visit 2 to visit 18 (change in score) between both treatment groups I and II using an unpaired t test.

Secondary Outcomes

1. Total nasal symptoms score (TNSS)- Comparison of the delta visit 2 to visit 17 (change in score) between both treatment groups I and II using an unpaired t test.

2. TNSS - Comparison of the delta visit 2 to visit 18 (change in score) between both treatment groups I and II using an unpaired t test.

3. Adverse Events - Adverse events (AEs) were to be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a patient. Comparison of the rates of adverse events between both treatment groups I and II will be evaluated using a one-tailed Fischer's exact test.

Other Comparisons and Outcomes

1. Baseline characteristics - Comparison of the rates of specific characteristics between both treatment groups I and II using a one-tailed Fischer's exact test and/or unpaired t test.

2. Use of epinephrine - Comparison of the rates of epinephrine rescue medication use between both treatment groups I and II using a one-tailed Fischer's exact test.

3. Mini-RQLQ - Kaplan-Meier or similar repeated measures test will also be used to calculate the effect of treatment over time between both groups I and II.

4. Drop out - Comparison of the drop out rates between both groups I and II using a one-tailed Fischer's exact test.

5. Trend tests - For these study data, representing a continuous response, an appropriate test, such as the Jonckheere-Terptsra trend test, based on a sum of Mann-Whitney-Wilcoxon tests may be sensitive and reveal a mild trend where pair-wise comparisons may not be able to find significant differences and not be as helpful. Other trend tests may also be used.