

**INNER-CITY ASTHMA CONSORTIUM****PROTOCOL ICAC-26****A BIOMARKER-BASED PILOT STUDY OF MOUSE SUBCUTANEOUS  
IMMUNOTHERAPY IN MOUSE-SENSITIVE ADULTS WITH ASTHMA****VERSION 2.0 / January 22, 2016****IND # Exempt**

**Study Sponsor:** The Division of Allergy, Immunology, and Transplantation, National Institute of Allergy and Infectious Diseases (NIAID)

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**Study Drug Manufacturer/Provider:** Greer Laboratories

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**Confidentiality Statement**

The information contained within this document is not to be disclosed in any way without the prior permission of the Protocol Chair, or the Division of Allergy, Immunology and Transplantation, National Institute of Allergy and Infectious Diseases of the National Institutes of Health.



## INVESTIGATOR SIGNATURE PAGE

Protocol: ICAC-26

Version/Date: 2.0 / 22 Jan 2016

Site Principal Investigator:

Title: A Biomarker-Based Pilot Study of Mouse Subcutaneous Immunotherapy in Mouse- Sensitive Adults with Asthma and / or Perennial Allergic Rhinitis

Study Sponsor: The National Institute of Allergy and Infectious Diseases (NIAID)

**INSTRUCTIONS:** The site Principal Investigator should print, sign, and date at the indicated location below. A copy should be kept for your records and the original signature page sent. After signature, please return the original of this form by surface mail to:

**DAIT Regulatory Management Center  
Pharmaceutical Product Development  
3900 Paramount Parkway  
Morrisville, NC 27560**

I confirm that I have read the above protocol in the latest version. I understand it, and I will work according to the principles of Good Clinical Practice (GCP) as described in the United States Code of Federal Regulations (CFR) – 45 CFR part 46 and 21 CFR parts 50, 56, and 312, and in the International Conference on Harmonization (ICH) document *Guidance for Industry: E6 Good Clinical Practice: Consolidated Guidance* dated April 1996. Further, I will conduct the study in keeping with local legal and regulatory requirements.

As the site Principal Investigator, I agree to carry out the study by the criteria written in the protocol and understand that no changes can be made to this protocol without the written permission of the IRB and NIAID.

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Site Principal Investigator (Print)

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Site Principal Investigator (Signature)

Date

## Protocol Synopsis

Title	A Biomarker-Based Pilot Study of Mouse Subcutaneous Immunotherapy in Mouse Sensitive Adults with Asthma
Short Title	Subcutaneous Immunotherapy for Mouse in Adults (SCITMO)
Clinical Phase	I/IIa
Number of Sites	Multiple
Study Objectives	<p>The primary objective of the study is to assess if treatment with mouse SCIT, using the per protocol allergenic extract doses, is safe. This will be done by determining the rate of related adverse events and serious adverse events in the course of treatment.</p> <p>Secondary objectives are:</p> <ol style="list-style-type: none"> <li>1. To determine whether a 24 week treatment with mouse SCIT, using the per protocol allergenic extract doses, will induce a 3-fold increase in mouse-specific serum IgE.</li> <li>2. To determine whether a 24 week treatment with mouse SCIT, using the per protocol allergenic extract doses, will induce changes in the serum levels of mouse-specific IgG and IgG4.</li> <li>3. To determine whether a 24 week treatment with mouse SCIT, using the per protocol allergenic extract doses, will inhibit the in the in-vitro mouse antigen binding to B-cells.</li> </ol>
Study Design	This is an open label trial of mouse allergenic extract administered by subcutaneous injection in 10 adults ages 18 to 55 years with asthma and mouse sensitivity. It is designed to study the safety of this therapy as well as biomarkers of the immune response.
Primary Endpoint(s)	The number of reported adverse events and serious adverse events, including their severity, seriousness, and treatment relatedness.
Secondary Endpoint(s)	<ol style="list-style-type: none"> <li>1. Changes in levels of mouse specific IgE observed after initiation of study treatment.</li> <li>2. Changes in mouse specific IgG and IgG4.</li> <li>3. Change in in-vitro mouse antigen binding to B-cells</li> </ol>
Accrual Objective	Approximately 10 - 12
Study Duration	12 months

Treatment Description	Nonstandardized glycerinated mouse epithelial allergenic extract by subcutaneous administration in escalating doses up to 0.4 ml of 1:20 wt/vol.
Inclusion Criteria	<ol style="list-style-type: none"> <li>1. Male or female adults, 18 through 55 years of age at recruitment.</li> <li>2. Have a history of asthma for a minimum of 1 year before study entry.             <ol style="list-style-type: none"> <li>a. A diagnosis of asthma will be defined as a report by the participant that they have had a clinical diagnosis of asthma made by a clinician over a year ago.</li> <li>b. The participant must have persistent asthma defined by the current need for at least 100 mcg fluticasone per day or the equivalent of another inhaled corticosteroid.</li> <li>c. The participant's asthma must be well controlled as defined by:                     <ol style="list-style-type: none"> <li>i. A FEV1 greater than or equal to 70% predicted with or without controller medication (see Section 8.2).</li> <li>ii. An Asthma Control Test (ACT) score <math>\geq 20</math>.</li> </ol> </li> </ol> </li> <li>3. Are sensitive to mouse as documented by a positive (<math>\geq 3</math> mm greater than negative control) skin prick test result (using the same extract used for immunotherapy) and detectable mouse specific IgE (<math>\geq 0.10</math> kUA/L).</li> <li>4. Have no known contraindications to therapy with glycerinated mouse allergenic extract or placebo.</li> <li>5. Are willing to sign the written Informed Consent prior to initiation of any study procedure.</li> </ol>
Exclusion Criteria	<ol style="list-style-type: none"> <li>1. Are pregnant or lactating. Females must be abstinent or use a medically acceptable birth control method throughout the study (e.g. oral, subcutaneous, mechanical, or surgical contraception).</li> <li>2. Cannot perform spirometry at Screening.</li> <li>3. Have an asthma severity classification at Screening of severe persistent, using the NAEPP classification, as evidenced by at least one of the following:             <ol style="list-style-type: none"> <li>a. Require a dose of greater than 500 mcg of fluticasone per day or the equivalent of another inhaled corticosteroid.</li> <li>b. Have received more than 2 courses of oral or parenteral corticosteroids within the last 12</li> </ol> </li> </ol>

	<p>months.</p> <ul style="list-style-type: none"><li>c. Have been treated with depot steroids within the last 3 months.</li><li>d. Have been hospitalized for asthma within the 6 months prior to Screening.</li><li>e. Have had a life-threatening asthma exacerbation that required intubation, mechanical ventilation, or that resulted in a hypoxic seizure within 2 years prior to Screening.</li></ul> <ul style="list-style-type: none"><li>4. Do not have access to a phone (needed for scheduling appointments).</li><li>5. Have received allergen immunotherapy (SLIT or SCIT) in the last 12 months prior to Screening or who plan to initiate or resume allergen immunotherapy during the study.</li><li>6. Have previously been treated with anti-IgE therapy within 1 year of Screening.</li><li>7. Have received an investigational drug in the 30 days prior to Screening or who plan to use an investigational drug during the study.</li><li>8. Refuse to sign the Epinephrine Auto-injector Training Form.</li></ul> <p>Participants who meet any of the following criteria are not eligible for enrollment and may not be reassessed. Participants are ineligible if they:</p> <ul style="list-style-type: none"><li>9. Do not primarily speak English.</li><li>10. Plan to move from the area during the study period.</li><li>11. Have a history within the past 5 years of idiopathic anaphylaxis or anaphylaxis grade 2 or higher as defined in section 9.2.4.2, Grading Criteria for Anaphylaxis.</li><li>12. Have unstable angina, significant arrhythmia, uncontrolled hypertension, history of autoimmune disease, or other chronic or immunological diseases that in the opinion of the investigator might interfere with the evaluation of the investigational agent or pose additional risk to the participant.</li><li>13. Are using tricyclic antidepressants or beta-adrenergic blocker drugs (both oral and topical).</li><li>14. Have not received and refuse to receive the Flu Vaccine</li></ul>
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Study Stopping Rules	<p>Study enrollment and treatment will be suspended pending expedited review of all pertinent data after the occurrence of:</p> <ol style="list-style-type: none"><li>1) 1 death regardless of relationship to the investigational agent</li><li>2) 1 anaphylactic reaction grade 3 possibly related to the investigational agent</li><li>3) Either of the following events, if considered related to the study procedures or treatments, <b><u>in at least 2 participants</u></b>:<ol style="list-style-type: none"><li>a) Anaphylactic reaction grade 2.</li><li>b) Hypotensive shock: Drop in blood pressure: Systolic &lt; 90 mm Hg or &lt; 80% of baseline, whichever is higher, and diastolic blood pressure &lt; 60 mm Hg-absolute.</li></ol></li></ol>
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## Glossary of Abbreviations

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DAIT	Division of Allergy, Immunology, and Transplantation
DSMB	Data Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonization
IND	Investigational New Drug
IRB	Institutional Review Board
MOP	Manual of Procedures
MSD	Maximum Study Dose
NAEPP	The National Asthma Education and Prevention Program
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PHI	Protected Health Information
PI	Principal Investigator
SACCC	Statistical and Clinical Coordinating Center
SAE	Serious Adverse Event
SAR	Suspected Adverse Reaction
SCIT	Subcutaneous Immunotherapy
SLIT	Sublingual Immunotherapy
SUSAR	Suspected Unexpected Serious Adverse Reaction

## 1 Background and Rationale

### 1.1 Background and Scientific Rationale

Mouse allergen has received much less attention than cockroach allergen, despite the fact that findings to date suggest that exposure to this pest allergen also plays an important role in asthma morbidity.<sup>1-4</sup> Like Bla g 1, the major mouse allergen, Mus m 1, is detectable in a very high proportion of inner-city homes and is present in 100-fold higher concentrations in inner-city homes compared to suburban homes.<sup>5,6</sup> Mouse allergen exposure is also a well-recognized risk factor for occupational asthma, with 30-50% of laboratory mouse workers experiencing mouse-related allergic symptoms, and 20% with skin test sensitivity to mouse.<sup>7</sup> More compelling with regard to inner-city asthma is the fact that Mus m 1 levels in many inner-city homes are comparable to levels found in occupational settings, where mouse allergen is known to cause both acute and chronic asthma. In addition, the prevalence rate of mouse skin test sensitivity in patients with asthma living in the inner-city is similar to that found in occupational settings. In fact, cross-sectional studies of inner-city asthmatics have found mouse skin test sensitization rates of 17-50%.<sup>2,8-10</sup> The fact that both the prevalence of mouse sensitization and the intensity of Mus m 1 exposure in the inner-city are similar to that observed in occupational settings – where mouse allergen is a known cause of asthma symptoms – provides a compelling rationale for a causal link between mouse allergen exposure and asthma in the inner-city.

As with cockroach allergen, the only currently available treatment for mouse allergy is avoidance and eradication. Studies aimed at the eradication of mice in home environments have had some success; however, the fact remains that multifaceted environmental eradication programs are extremely difficult to implement in inner city environments with limited resources. As such, a more definitive treatment may be desensitization of patients with mouse allergy using allergen immunotherapy.

Given these data, a major ICAC goal is to conduct a large multi-center efficacy trial of immunotherapy, including mouse allergen, in inner-city asthma. While we have pursued the possibility of using sublingual immunotherapy (SLIT) given its excellent safety profile, data from the BioCSI and BioCSI2 studies (ICAC-12 and ICAC-17) of cockroach SLIT have raised the possibility that SLIT for cockroach may not be effective due to limitations in the maximum doses that can be provided with currently available extracts. These studies have also generated concerns about the likelihood of compliance with daily SLIT therapy, an issue that may both reduce efficacy and potentially increase risk. Given those concerns, a pilot study of cockroach SCIT was also conducted in 10 adults (SCITCO, ICAC-18) with a primary focus on safety in an effort to lay the groundwork for an efficacy study using SCIT. The SCITCO study demonstrated an excellent safety profile, as well as robust biomarkers of immunologic response. Given that mouse allergen is also a key inner-city allergen, and that there is a paucity of experience with mouse immunotherapy, the current study is designed to provide similar safety and immunologic data for mouse that SCITCO provided for cockroach.

While studies of cockroach and mouse are limited, there is a vast clinical and research experience with the use of SCIT for the treatment of asthma and allergic rhinitis, as well as stinging insect hypersensitivity.<sup>11,12</sup> While there is a higher risk of systemic reactions with SCIT compared to SLIT, the overall safety profile of SCIT is very favorable, as is the overall SCIT risk benefit ratio given the marked improvements in disease activity demonstrated in most studies. As with SLIT, the efficacy of SCIT depends on the use of adequate dosages, but we are confident that for SCIT the available extracts will prove adequate in this regard.<sup>11,13</sup>

The rationale for this study is therefore that immunotherapy, focused on key indoor allergens, will be effective for the treatment of inner-city asthma, and that SCIT is the best option. This preliminary study is a logical next step, necessary to provide data regarding both safety and immunogenicity before proceeding to an efficacy trial.

### **1.2 Rationale for Selection of Investigational Product or Intervention**

The study agent for this protocol is 1:20 w/v glycerinated mouse epithelial allergenic extract administered by the subcutaneous route purchased from Greer Laboratories (Lenoir, NC). Mouse Epithelia (*Mus musculus*) allergic extract is approved in the United States for diagnostic skin testing and immunotherapy by subcutaneous injection (US License NO. 308). While mouse SCIT has undergone little prior study and specific dosing guidelines have not been established, there is a large body of literature for other allergens that can be applied to choose a dose schedule for this protocol that should maximize safety and efficacy. For other allergens, maintenance doses of major allergens ranging from 5 to 15 micrograms have proven effective and our dosing strategy will seek to achieve a maintenance dose within this range, with a secondary goal of minimizing injection volume so that this same dose could eventually be applied to a multi-allergen protocol in pediatric patients.

### **1.3 Preclinical Experience**

Not applicable.

### **1.4 Clinical Studies**

Only one study of mouse immunotherapy has previously been published.<sup>14</sup> That study was conducted in 23 laboratory animal workers, 11 of whom received immunotherapy with 12 different extracts (five mouse, six rat, one rabbit), and 12 were matched untreated controls. The maximum weekly immunotherapy dose for the different allergens ranged from 2,000 to 10,000 protein nitrogen units (PNU). Among the treated patients, nine of 11 subjectively improved with immunotherapy and blocking antibody titers were significantly elevated in the treated subjects compared to the controls (specific data on mouse were not provided). There were no systemic reactions reported, nor any need to discontinue dosing due to adverse reactions.

It is important to recognize, however, that even though there are a minimal data regarding mouse, there is a vast body of literature and clinical experience with the use of SCIT for other allergens. A recent practice parameter detailed the use of SCIT for inhalant allergens as well as stinging insects.<sup>11</sup> In addition, meta-analyses have confirmed the effectiveness of SCIT for the treatment of asthma, allergic rhinitis, and stinging insect hypersensitivity.<sup>15-18</sup> A 2003 Cochrane review of 75 trials, including 3188 patients with asthma, found that overall SCIT led to a significant reduction in asthma symptoms, medication use, and bronchial hyperreactivity.<sup>16</sup> For example, in that review, it was determined that it would have been necessary to treat 4 patients with immunotherapy to avoid 1 deterioration in asthma symptoms and 5 patients to avoid 1 requiring increased asthma medication.

## **2 Study Hypotheses/Objectives**

### **2.1 Hypotheses**

The two hypotheses tested by this study are 1) Subcutaneous treatment with mouse extract can be safely administered in adults with mouse sensitivity and 2) Subcutaneous treatment with mouse extract can induce significant changes in serum biomarkers indicative of immunologic activity.

### **2.2 Primary Objectives**

The primary objective of this pilot study is to assess if treatment with mouse SCIT, using the per protocol allergenic extract doses, is safe. This will be done by determining the rate of related adverse events and serious adverse events in the course of treatment.

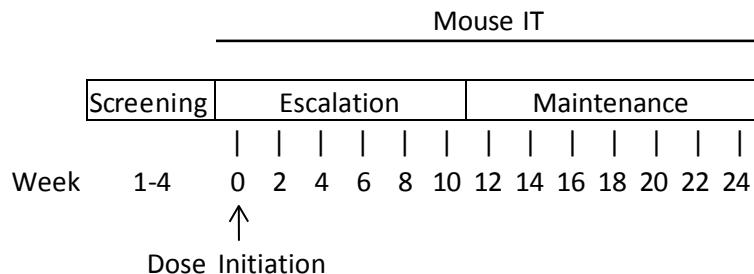
### 2.3 Secondary Objective(s)

1. To determine whether a 24 week treatment with mouse SCIT, using the per protocol allergenic extract doses, will induce a 3-fold increase in mouse-specific serum IgE.
2. To determine whether a 24 week treatment with mouse SCIT, using the per protocol allergenic extract doses, will induce changes in the serum levels of mouse-specific IgG and IgG4.
3. To determine whether a 24 week treatment with mouse SCIT, using the per protocol allergenic extract doses, will inhibit the in-vitro mouse antigen binding to B-cells.

## 3 Study Design

### 3.1 Description of Study Design

This study is an open label multi-site trial of mouse allergenic extract administered by subcutaneous injection in approximately 10 - 12 adults ages 18 to 55 years with asthma. The study will be based on a continuous treatment schedule with mouse allergenic extract for a period of approximately 24 weeks. It is primarily designed to study the safety of this therapy.



There will be a Screening Visit followed by a Dose Initiation Visit, at which the subject will receive their first injection. Up to 2 doses of SCIT will be given weekly during dose escalation, separated by a minimum of 2 days. Dose escalation will occur over a minimum of 11 weeks. Dose escalation can be delayed at any point if there are excessive large local reactions or other concerns, although to continue on to maintenance each subject will need to reach the maintenance dose in a maximum of 18 weeks. Once the maintenance dose is achieved, bi-weekly visits will continue to complete a total of 24 weeks of treatment.

Blood will be collected at baseline and then monthly for assessment of biomarkers of allergen immunotherapy, including mouse specific IgE, IgG, IgG4, and inhibition of mouse antigen binding to B-cells. Mouse skin testing will be performed at screening. (See Visit Activities Summary, Appendix A)

Adverse events (AEs) will be assessed at each study visit. Allergy and asthma symptom questionnaires will also be administered throughout the study.

### 3.2 Primary Endpoints

The primary endpoint is the number of reported adverse events and serious adverse events, including their severity, seriousness, and treatment relatedness.

### 3.3 Secondary Endpoints

1. Change in mouse specific IgE.
2. Change in mouse specific IgG and IgG4.
3. Change in in-vitro mouse antigen binding to B-cells

## 4 Selection of Participants and Clinical Sites/Laboratories

### 4.1 Rationale for Study Population

Because the combination of mouse allergy and mouse exposure is one of the most important factors contributing to the asthma morbidity seen in inner city children with asthma, a major ICAC goal is to conduct an immunotherapy efficacy trial that will include mouse allergen. Given that there has been so little study of mouse immunotherapy, adults will be studied in this safety trial.

### 4.2 Participant Inclusion Criteria

Participants who meet all of the following criteria are eligible for enrollment. Participants may be reassessed if not initially eligible. Participants are eligible if they:

1. Are male or female adults, 18 through 55 years of age at recruitment.
2. Have a history of asthma for a minimum of 1 year before study entry.
  - i. A diagnosis of asthma will be defined as a report by the participant that they have had a clinical diagnosis of asthma made by a clinician over a year ago.
  - ii. The participant must have persistent asthma defined by the current need for at least 100 mcg of fluticasone per day or the equivalent of another inhaled corticosteroid.
  - iii. The participant's asthma must be well controlled as defined by:
    1. A FEV<sub>1</sub> greater than or equal to 70% predicted with or without controller medication. (see Section 8.2).
    2. An Asthma Control Test (ACT) score  $\geq 20$ .
3. Are sensitive to mouse as documented by a positive ( $\geq 3$  mm greater than negative control) skin prick test result (using the same extract used for immunotherapy) and detectable mouse specific IgE ( $\geq 0.10$  kU<sub>A</sub>/L).
4. Have no known contraindications to therapy with glycerinated mouse allergenic extract.
5. Are willing to sign the written Informed Consent prior to initiation of any study procedure.

### 4.3 Participant Exclusion Criteria

Participants who meet any of the following criteria are not eligible for enrollment but may be reassessed. Participants are ineligible if they:

1. Are pregnant or lactating. Females must be abstinent or use a medically acceptable birth control method throughout the study (e.g. oral, subcutaneous, mechanical, or surgical contraception).
2. Cannot perform spirometry at Screening.
3. Have an asthma severity classification at Screening of severe persistent, using the NAEPP classification, as evidenced by at least one of the following:
  - a. Require a dose of greater than 500 mcg of fluticasone per day or the equivalent of another inhaled corticosteroid.
  - b. Have received more than 2 courses of oral or parenteral corticosteroids within the last 12 months.
  - c. Have been treated with depot steroids within the last 3 months.
  - d. Have been hospitalized for asthma within the 6 months prior to Screening.

- e. Have had a life-threatening asthma exacerbation that required intubation, mechanical ventilation, or that resulted in a hypoxic seizure within 2 years prior to Screening.
4. Do not have access to a phone (needed for scheduling appointments).
5. Have received allergen immunotherapy (SLIT or SCIT) in the last 12 months prior to Screening or who plan to initiate or resume allergen immunotherapy during the study.
6. Have previously been treated with anti-IgE therapy within 1 year of Screening.
7. Have received an investigational drug in the 30 days prior to Screening or who plan to use an investigational drug during the study.
8. Refuse to sign the Epinephrine Auto-injector Training Form.

Participants who meet any of the following criteria are not eligible for enrollment and may not be reassessed.

Participants are ineligible if they:

1. Do not primarily speak English.
2. Plan to move from the area during the study period.
3. Have a history of idiopathic anaphylaxis within the past 5 years or anaphylaxis grade 2 or higher as defined in section 12.3.2, Grading Criteria for Anaphylaxis.
4. Have unstable angina, significant arrhythmia, uncontrolled hypertension, history of autoimmune disease, or other chronic or immunological diseases that in the opinion of the investigator might interfere with the evaluation of the investigational agent or pose additional risk to the participant.
5. Are using tricyclic antidepressants or beta-adrenergic blocker drugs (both oral and topical).
6. Have not received and refuse to receive the Flu Vaccine.

## 5 Known and Potential Risks and Benefits to Participants

### 5.1 Risks of Study Procedures

Risks of exposing participants to allergens via immunotherapy include, but are not limited to: itching of the mouth, ears, and throat, itching or swelling of the eyes, nasal congestion, sneezing, rhinorrhea, oral or throat angioedema, cough, chest tightness, wheezing, gastrointestinal symptoms (vomiting, diarrhea, abdominal pain), skin symptoms (rash, hives, swelling, itching), and anaphylaxis. We expect that the main sign/symptom experienced by participants will be localized swelling at the injection site occurring within 30 minutes after administration of the immunotherapy injection. Large local reactions associated with allergen immunotherapy are common, with a frequency ranging from 26% to 86% of injections.<sup>19</sup>

In published studies of SCIT, systemic anaphylactic reactions with other inhalant allergens have been reported to occur in from 1% of patients to as many as 36% of patients receiving SCIT using a rush schedule.<sup>20,21</sup> This study does not involve a rush immunotherapy schedule. Fatalities are very rare but have been reported, as have specific risk factors for fatal reactions, which include unstable asthma, beta-blocker therapy, rush immunotherapy, and use of high doses of potent standardized extracts.<sup>20</sup> In our SCITCO study, in 10 adults undergoing six months of SCIT, there were 2 serious adverse events reported, neither of which were considered related to the therapy.<sup>22</sup>

The risks to a fetus are unknown and SCIT is generally not initiated during pregnancy. Pregnant females will be excluded from the present protocol. Urine pregnancy testing will be performed at the Screening Visit and monthly

thereafter to ensure no pregnant female will be entered into the study and any female becoming pregnant during the course of the study will be discontinued.

## **5.2 Potential Benefits**

There are no known potential benefits for the participant in this trial. The participant's allergic rhinitis or asthma may or may not improve while in this study. In the longer term, this study may promote the further development of mouse SCIT for asthma and allergic rhinitis, which could be a major advance in the care of individuals with these conditions who are allergic to mouse antigens.

# **6 Investigational Agent**

## **6.1 Investigational Agent**

Participants will receive escalating doses of glycerinated mouse allergenic extract or placebo administered via the subcutaneous route up to a Maximum Study Dose (MSD) of 0.4 ml of extract at a concentration of 1:20 wt/vol.

### **6.1.1 Formulation, Packaging, and Labeling**

The investigational agent is glycerinated mouse allergenic extract (50% Glycerin). The active ingredient of the investigational agent is a non-standardized allergen derived from the extraction and purification of proteins from mouse epithelia (*mouse epithelial extract*).

The investigational agent will be manufactured Greer laboratories, Lenoir NC. Glycerinated Mouse Epithelia (*Mus musculus*) allergic extract is approved in the United States for diagnostic skin testing and immunotherapy by subcutaneous injection (US License NO. 308). It has been used in humans for at least 35 years. Dosage, Preparation, and Administration

Initial dilutions of the mouse allergenic extract needed for dose escalation will be prepared by a research pharmacy. Complete details can be found in the Manual of Operations (MOP), which is based on the DAIT Pharmacy manual and AAAAI practice parameters.

Participants will receive escalating doses of glycerinated mouse allergenic extract administered via the subcutaneous route up to a MSD of 0.4 ml of extract at a concentration of 1:20 wt/vol. See Section 8.45 for the dose escalation schedule.

The investigational agent will be shipped by the manufacturer as per their approved method. On site the investigational agent will be stored at -2° C.

## **6.2 Drug Accountability**

Under Title 21 of the Code of Federal Regulations (21CFR §312.62) the investigator will maintain adequate records of the disposition of the investigational agent, including the date and quantity of the drug received, to whom the drug was dispensed (participant-by-participant accounting), and a detailed accounting of any drug accidentally or deliberately destroyed.

Records for receipt, storage, use, and disposition will be maintained by the study site. A drug-dispensing log will be kept current for each participant. This log will contain the identification of each participant and the date and quantity of drug dispensed.

All records regarding the disposition of the investigational product will be available for inspection.

Unused product will be destroyed by the study site after accountability requirements have been met and approval has been received from DAIT/NIAID.

### **6.3 Assessment of Participant Compliance with Investigational Agent**

As participants will receive their injections in the clinic, compliance will be monitored by assessing the number of completed and missed clinic visits.

### **6.4 Toxicity Prevention and Management**

In the case of a reaction to the study medication, dosing will be altered in the following manner:

- For local reactions 6-11 cm in diameter, the dose will be repeated.
- For local reactions greater than 12 cm, the dose will be reduced to the prior dose during escalation and cut by 50% while on maintenance with re-escalation the following week.
- For mild systemic symptoms (Grade 1 anaphylaxis), the dose will be reduced by 2 doses during escalation or reduced cut by 75% while on maintenance with re-escalation over the next 2 weeks.

### **6.5 Premature Discontinuation of Investigational Agent**

Participants who are unable to complete the first 8 injections following the Dose Initiation Visit will be unable to proceed to the maintenance period and may be replaced (see Section 11.2, Participant Stopping Rules and Withdrawal Criteria). Subjects unable to continue beyond that point will not be replaced. A final blood sample will be drawn on participants who need to discontinue therapy.

Study therapy may be prematurely discontinued for any participant for any of the following reasons:

1. SAE related to investigational agent
2. Anaphylactic reaction grade 2 or 3 (see Section 12.3.2, Grading Criteria for Anaphylaxis)
3. Inability to tolerate the build up to or the MSD due to excessive discomfort/symptoms or large local reactions after a second attempt at dose escalation
4. Development of any serious medical illness whose natural history, sequela, or treatment would be worsened or impaired by continuation in the protocol
5. The study treatment is no longer in the best interest of the participant
6. Pregnancy

## **7 Other Medications**

### **7.1 Concomitant Medications**

#### **7.1.1 Protocol-mandated**

Not applicable.

#### **7.1.2 Other permitted concomitant medications**

During the study, after the initial skin testing, rhinitis and asthma medications will be permitted along with other maintenance medications, aside from those excluded in Section 4.3, Participant Exclusion Criteria. A dose of greater than 500 mcg of fluticasone per day or the equivalent of another inhaled corticosteroid may be used short-term to control an asthma exacerbation.

## **7.2 Prophylactic Medications**

Not applicable.

## **7.3 Prohibited Medications**

1. A regular dose of greater than 500 mcg of fluticasone per day or the equivalent of another inhaled corticosteroid.
2. Allergen immunotherapy (SLIT or SCIT)
3. Anti-IgE therapy
4. Tricyclic antidepressants
5. Beta-adrenergic blocker drugs (both oral and topical)
6. Any investigational drug

Antihistamines will need to be suspended prior to skin testing at the screening and final visits.

## **7.4 Rescue Medications**

Participants may use antihistamines as needed for large local reactions to the injections. In the event of a rare, but severe reaction to the glycerinated mouse allergenic extract away from the study site, participants will receive 2 epinephrine auto-injectors during the Dose Initiation Visit. Participants must sign the epinephrine auto-injector training form and understand its use before they can be enrolled in the study and receive the investigational agent.

# **8 Study Procedures**

## **8.1 Recruitment**

The study center may use any IRB-approved means to identify potential participants. Examples include hospital, clinic, or emergency department admission records; investigators' specialty clinic records; and advertising (in public locations and on the radio). Potential participants will be screened and recruited using a standardized questionnaire that collects contact information and inclusion/exclusion criteria information. Participants may be recruited by phone or in person.

Retention methods involve a number of different approaches. Appointment reminder cards are given at each visit. We will use an appointment reminder system that consists of phone calls and/or text messages several days and one day prior to scheduled appointments for confirmation. To facilitate telephone contact with subjects whose phone service may change during the study, at least three telephone contact numbers (relatives, neighbors, friends) will be collected for each subject. This has proven to be an effective strategy in previous ICAC studies. Those who have no obvious characteristics making them ineligible and who are interested will be invited to the clinic for a Screening Visit.

## **8.2 Screening/Baseline Visit**

This research study will be explained in lay terms to each potential research participant. The potential participant will provide informed consent before he or she undergoes any screening study procedures. Written informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization will be obtained from all participants at the beginning of this visit. Study procedures will be stopped and the participant will be deemed ineligible for the study at any point during the Screening Visit if and when they fail to meet eligibility criteria.

After the consent is signed, participants will undergo screening study procedures, including prick skin tests with mouse allergenic extract to ensure participants are sensitive to the test product, since those who do not react to mouse are excluded from the remainder of the study. In addition, participants will be tested with: American cockroach, German

cockroach, cat, dog, Alternaria, house dust mite, and selected seasonal aeroallergen allergenic extracts, as specified in the study MOP, to characterize the study population.

A medical history will be taken and a targeted physical examination will be performed to verify the participant's suitability for inclusion in the study. A urine pregnancy test will also be performed on all female participants.

Spirometry will be performed by all participants to verify the participant's suitability for inclusion in the study. Candidates whose FEV1 is less than 70% of predicted normal will be excluded; however, if their asthma can be brought under control within 2 months, as described in Section 8.3, they are eligible for rescreening.

Blood will be collected by venipuncture for mouse-specific IgE antibody testing.

Participants must agree to receive a flu vaccine if they are in the study during flu season. Participants will be offered a flu vaccine when it becomes available. Participants may choose to receive the flu vaccine outside of the study.

Participants who have both a positive skin prick test to mouse allergenic extract and a mouse-specific IgE  $\geq 0.10$  kU/L and are considered eligible for the study, and at the discretion of the study clinician, will be invited to proceed to the Dose Initiation Visit.

### **8.3      Asthma Control Optional Visits**

Participants whose FEV1 is less than 70% of predicted normal or whose asthma is not well controlled as defined by the inclusion and exclusion criteria may qualify for rescreening if their condition improves while recruitment is ongoing.

### **8.4      Dose Initiation**

The Dose Initiation Visit will be scheduled according to the guidelines in the MOP.

Written instructions on the proper use, storage, and administration of the epinephrine auto-injector will be given to participants at the Dose Initiation Visit. Participants must sign the epinephrine auto-injector training form and understand its use before being enrolled in the study and receiving the investigational agent. Participants will receive 2 epinephrine auto-injectors during the Dose Initiation Visit.

Blood will be collected by venipuncture and will be tested for assessment of biomarkers of allergen immunotherapy, such as mouse-specific IgE and IgG4 antibodies.

The first injection will contain 0.05 mL of 1:10,000 concentration of 1:20 w/v glycerinated mouse allergenic extract as detailed in the Dose Escalation Table 8.5.1. Each injection will be administered by the research staff along with any rescue medications, as required. Refer to the MOP for information on handling treatment-related reactions. Prior to the administration of each dose of allergenic extract, the study clinician will assess the eligibility of the participant to receive the allergenic extract injection and will review any side-effects or adverse reactions experienced by the participant. Participants will report symptoms, using a questionnaire, 30 minutes after each injection is administered in order to identify side effects. During all dosing visits, a clinician and appropriate emergency supplies will be readily available to treat any adverse reactions. Study participants will remain at the clinic for observation for at least 30 minutes after each allergenic extract injection.

All participants receiving the initial dose will have information gathered and assessed on any delayed reactions or side effects experienced, regardless of whether or not they continue on to the 24 week treatment course.

## 8.5 Follow-up

### 8.5.1 Dose Escalation

Dose escalation will be conducted by the following schedule:

**Table 8.5.1 Dose Escalation**

Dose #	Week* #	Concentration	Volume	Approximate Dose	Mus m 1
1	1	1:10,000	0.05 ml		
2	1	1:10,000	0.10 ml		
3	2	1:10,000	0.20 ml		
4	2	1:10,000	0.40 ml		
5	3	1:1,000	0.05 ml		
6	3	1:1,000	0.10 ml		
7	4	1:1,000	0.20 ml		
8	4	1:1,000	0.40 ml		
9	5	1:100	0.05 ml		
10	5	1:100	0.10 ml		
11	6	1:100	0.20 ml		
12	6	1:100	0.40 ml		
13	7	1:10	0.05 ml		
14	7	1:10	0.10 ml		
15	8	1:10	0.20 ml		
16	8	1:10	0.40 ml		
17	9	1:1	0.05 ml		
18	9	1:1	0.10 ml		
19	10	1:1	0.15 ml		
20	10	1:1	0.20 ml		
21	11**	1:1	0.30 ml		
22	11	1:1	0.40 ml		
Maint.***	12-24	1:1	0.40 ml		6.2 mcg

\* During dose escalation, 2 injections will be given each week separated by at least 2 days

\*\* Dose escalation may be accomplished over a maximum of 18 weeks

\*\*\* During maintenance, doses will be given every 2 weeks

For the first 11 weeks of the 24-week treatment course participants will receive two injections per week, separated by at least 2 days, at the escalating doses as described in Table 8.5.1. Dose escalation can be delayed at any point if there are excessive large local reactions or other concerns, although to continue on to maintenance each subject will need to reach the maximum study dose in a maximum of 18 weeks. A clinician and appropriate emergency supplies will be readily available to treat any adverse reactions. Participants will be discharged after the 30 minute waiting period if they show no signs or symptoms greater than mild, as defined in Section 12.3.1, or at the discretion of the study clinician.

Dose escalation will continue according to the schedule unless there are lapses in dosing or reactions occur. Dosing will be modified as follows for lapses in dosing or reactions:

- For a lapse in dosing of more than two weeks during escalation, the dose from the previous visit will be repeated.
- For a lapse in dosing of more than three weeks during escalation, the subject will be discontinued from the protocol.
- For one missed dosing visit while on maintenance, the maintenance dose will be continued.
- For two missed maintenance doses while on maintenance, the dose will be reduced by 50% and re-escalated the following week.
- For more than two consecutive missed dosing visits while on maintenance, the subject will be discontinued from the protocol.
- For local reactions 6-11 cm in diameter, the dose will be repeated.
- For local reactions greater than 12 cm, the dose will be reduced to the prior dose during escalation and cut by 50% while on maintenance with re-escalation the following week.
- For mild systemic symptoms (Grade 1 anaphylaxis), the dose will be reduced by 2 doses during escalation or reduced cut by 75% while on maintenance with re-escalation over the next 2 weeks.

Participants who are unable to reach the Maximum Study Dose by 18 weeks following the Dose Initiation Visit will be unable to proceed to the maintenance period and may be replaced (see Section 11.2, Participant Stopping Rules and Withdrawal Criteria).

### **8.5.2 Maintenance Visits**

For the remaining time of the 24 week treatment course, participants will receive one injection of investigational agent every 2 weeks.

Participants will be instructed to immediately report any severe sign or symptom possibly related to the subcutaneous administration of the investigational agent and to contact the study site when they need medical advice. For those participants with asthma, exacerbations will be handled through an approach consistent with standard clinical practice as described in the MOP.

### **8.6 Final Study Visit**

A final study visit will be performed for all participants who began study treatment, regardless of whether or not they entered or completed the 24 week treatment course. The final visit will include:

- Final physical exam
- Blood draw
- Spirometry
- Pregnancy test (females only)

Participants recording only mild or no symptoms at the last office visit will be discharged from the study. Participants recording moderate or severe symptoms at the last office visit will require follow-up as described in 12, Safety Monitoring and Reporting.

### **8.7 Early Termination Visit**

Participants may withdraw or be dropped from the study during or between study visits, according to the criteria in Section 11.2, Participant Stopping Rules and Withdrawal Criteria. For participants who withdraw or are dropped during a study visit, the visit will be terminated. The study clinician will perform a final clinical assessment, including blood collection and a targeted physical exam, as described in Section 8.6.

Participants who withdraw or are dropped from the study between visits will be contacted by phone and will be invited to the study center for a final assessment as described in Section 8.6 above. For participants who refuse to come to the clinic, the final clinical assessment as described above may be conducted over the phone. Besides this visit, no further follow-up will be made, except for participants who are discontinued due to pregnancy or SAEs. These participants will be contacted to determine the outcome of the pregnancy or the SAE. Refer to Section 12.6, Pregnancy Reporting, for more information on AE reporting for pregnancy.

### **8.8 Pregnancy Visit**

Females who become pregnant during the study will be discontinued immediately and no further study procedures will be performed. These participants will be followed to determine the outcome of the pregnancy; otherwise no further follow-up will be made.

### **8.9 Unscheduled Visits**

Study participants may attend unscheduled visits for a medical evaluation if they experience moderate to severe symptoms.

### **8.10 Visit Windows**

During dose escalation, 2 injections will be given each week separated by at least 2 days. Dose escalation may be accomplished over a maximum of 18 weeks.

Bi-weekly maintenance visits will be scheduled within the second calendar week following the previous maintenance visit. See the MOP for details regarding visit scheduling.

## **9 Mechanistic Assays**

Whole blood will be collected by venipuncture every month during the maintenance period, and will be processed according to the MOP. The blood will be tested for biomarkers of allergen immunotherapy, such as mouse-specific IgE, IgG, IgG4 antibodies, and in-vitro mouse antigen binding to B-cells (see Appendix A).

## **10 Biospecimen Storage**

Unused samples of biological specimens (blood) collected during the course of the study will be stored (described in the MOP) for future use for tests that may or may not be planned. These tests may or may not be related to the study of asthma and allergy. Participants will be asked to give permission for long-term storage and future use during the consent process. Samples may be stored indefinitely.

## **11 Criteria for Participant and Study Completion and Premature Study Termination**

### **11.1 Participant Completion**

The participants are considered to have completed the study once they have completed the Final Study Visit.

### **11.2 Participant Stopping Rules and Withdrawal Criteria**

Participants will be withdrawn from the study if the following events occur:

1. SAE related to investigational agent
2. Anaphylactic reaction grade 2 or 3 (see Section 12.3.2, Grading Criteria for Anaphylaxis)
3. Inability to tolerate the build up to or the MSD due to excessive discomfort/symptoms or large local reactions after a second attempt at dose escalation
4. The need to start immunotherapy or any chronic immunosuppressive medications (e.g., greater than 2 courses of oral or parenteral corticosteroids)
5. Require a dose of greater than 500 mcg of fluticasone per day or the equivalent of another inhaled corticosteroid to maintain asthma control
6. Development of any serious medical illness whose natural history, sequela, or treatment would be worsened or impaired by continuation in the protocol
7. The study treatment is no longer in the best interest of the participant
8. Participant is “lost to follow-up,” as defined in the MOP
9. Pregnancy
10. A lapse in dosing of more than 3 weeks during escalation
11. Missing more than 2 consecutive treatment visits during maintenance
12. Missing 25% or more of all maintenance visits (miss more than 2 maintenance visits)

### **11.3 Participant Replacement**

Participants who withdraw or are withdrawn will be replaced until the desired sample size is reached.

### **11.4 Follow-up after Early Study Withdrawal**

Participants who withdraw from the study after receiving dose 1 will be followed as described in Section 6.5 Premature Discontinuation of Investigational Agent.

### **11.5 Study Stopping Rules**

Study enrollment and treatment will be suspended pending expedited review of all pertinent data after the occurrence of:

1. 1 death regardless of relationship to the investigational agent
2. 1 anaphylactic reaction grade 3 (see Section 12.3.2, Grading Criteria for Anaphylaxis) possibly related to the investigational agent
3. Either of the following events, which are considered related to the study procedures or treatments, in at least 2 participants:
  - a. Anaphylactic reaction grade 2 (see Section 12.3.2, Grading Criteria for Anaphylaxis).
  - b. Hypotensive shock: Drop in blood pressure: Systolic < 90 mm Hg or < 80% of baseline, whichever is higher, and diastolic blood pressure < 60 mm Hg-absolute.

If the study is stopped due to meeting the above criteria, it may not be resumed until all pertinent information is discussed with DAIT NIAID, NIAID Asthma and Allergy DSMB, and the site IRBs, and all parties concur with the resumption of the study.

The study may be terminated by DAIT/NIAID or the NIAID DSMB upon review of any observations, events, or new information that merit such action.

## 12 Safety Monitoring and Reporting

### 12.1 Overview

This section defines the types of safety data that will be collected under this protocol and outlines the procedures for appropriately collecting, grading, recording, and reporting those data. Adverse events that are classified as serious according to the definition of the FDA must be reported promptly (per Section 12.5, Reporting of Serious Adverse Events and Adverse Events) to DAIT/NIAID. Appropriate notifications will also be made to site principal investigators, and to the Institutional Review Boards (IRBs).

Information in this section complies with ICH Guideline E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, ICH Guideline E-6: Guideline for Good Clinical Practice, 21CFR Parts 312 and 320, and applies the standards set forth in the National Cancer Institute (NCI), Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03, June 14, 2010: <http://ctep.cancer.gov/reporting/ctc.html>.

### 12.2 Definitions

#### 12.2.1 Adverse Event (AE)

An adverse event is any untoward or unfavorable medical occurrence associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice) (from OHRP "Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events (1/15/07)" (<http://www.hhs.gov/ohrp/policy/advevntguid.html#Q2>)

For this study, a related adverse events will include any untoward or unfavorable medical occurrence associated with:

**Study therapy regimen:** Mouse Allergenic Extract Administered by the Subcutaneous Route

- Eye symptoms (itchy, runny, swelling)
- Nose symptoms (sneezing, itching, runny, stuffy)
- Mouth/ears/throat symptoms (itchy mouth, throat irritation, oral or throat angioedema, cough, itchy ears)
- Skin symptoms (angioedema, urticaria, generalized itching, rash)
- Gastrointestinal symptoms (vomiting, diarrhea, cramps, nausea)
- Chest (cough, tightness, wheezing)
- Anaphylaxis
- Injection site reaction  $\geq 6$  cm in diameter

**Study mandated procedures:**

**Allergen Scratch Skin Testing**

- Prolonged (>24 hours) itching at test site
- Swelling (> 10 cm ) at site of test lasting more than 24 hours

- Nasal allergic symptoms within 30 minutes of the procedure
- Fainting/Vasovagal event within 30 minutes of the procedure
- Anaphylaxis

### **Blood Draws**

- Fainting/Vasovagal events
- Bruising at puncture site larger than 2 cm diameter
- Bleeding from puncture site lasting more than 30 minutes
- Swelling at puncture site larger than 2 cm

### **Pulmonary Function Testing**

- Wheezing or bronchoconstriction requiring treatment with bronchodilators within 30 minutes from the procedure
- Coughing requiring treatment with bronchodilators within 30 minutes from the procedure

#### **12.2.2 Suspected Adverse Reaction (SAR)**

Suspected adverse reaction (SAR) means any adverse event for which there is a reasonable possibility that the investigational study therapy regimen caused the adverse event. For the purposes of safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug (21 CFR 312.32(a)).

#### **12.2.3 Unexpected Adverse Event**

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the safety information of Greer's package insert for allergenic extracts or is not listed at the specificity, severity or rate of occurrence that has been observed; or is not consistent with the risk information described in the protocol.

"Unexpected" also refers to adverse events or suspected adverse reactions that are mentioned in the package insert as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation (21 CFR 312.32(a)).

#### **12.2.4 Serious Adverse Event (SAE)**

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or DAIT/NIAID, it results in any of the following outcomes (21 CFR 312.32(a)):

1. Death: A death that occurs during the study or that comes to the attention of the investigator during the protocol-defined follow-up period must be reported whether it is considered treatment related or not.
2. A life-threatening event: An AE or SAR is considered "life-threatening" if, in the view of either the investigator or DAIT/NIAID, its occurrence places the subject at immediate risk of death. It does not include an AE or SAR that, had it occurred in a more severe form, might have caused death.
3. Inpatient hospitalization or prolongation of existing hospitalization.
4. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5. Congenital anomaly or birth defect.

6. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Elective hospitalizations or hospital admissions for the purpose of conduct of protocol mandated procedures are not to be reported as an SAE unless hospitalization is prolonged due to complications.

### **12.3 Grading and Attribution of Adverse Events**

#### **12.3.1 Grading Criteria**

The study site will grade the severity of adverse events experienced by the study subjects according to the criteria set forth in the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) (Version 4.03, June 14, 2010). This document (referred to herein as the NCI-CTCAE manual) provides a common language to describe levels of severity, to analyze and interpret data, and to articulate the clinical significance of all adverse events. The NCI-CTCAE has been reviewed by the Protocol Chair and has been deemed appropriate for the subject population to be studied in this protocol.

Adverse events will be graded on a scale from 1 to 5 according to the following standards in the NCI-CTCAE manual:

Grade 1 = mild adverse event.

Grade 2 = moderate adverse event.

Grade 3 = severe and undesirable adverse event.

Grade 4 = life-threatening or disabling adverse event.

Grade 5 = death.

For grading an abnormal value or result of a clinical or laboratory evaluation (including, but not limited to, a radiograph, an ultrasound, an electrocardiogram etc.), a treatment-emergent adverse event is defined as an increase in grade from baseline or from the last post-baseline value that doesn't meet grading criteria. Changes in grade from screening to baseline will also be recorded as adverse events, but are not treatment-emergent. If a specific event or result from a given clinical or laboratory evaluation is not included in the NCI-CTCAE manual, then an abnormal result would be considered an adverse event if changes in therapy or monitoring are implemented as a result of the event/result.

#### **12.3.2 Grading Criteria for Anaphylaxis**

This study will grade anaphylaxis as defined by the following table, adapted from the grading scale of Dr. Simon Brown.<sup>23</sup>

**Table 12.3.2 Grading System of Severity of Anaphylaxis**

Grade	Defined By
1. Mild (skin & subcutaneous tissues, GI, &/or mild respiratory)	Flushing, urticaria, periorbital or facial angioedema; mild dyspnea, wheeze or upper respiratory symptoms; mild abdominal pain and/or emesis
2. Moderate (mild symptoms + features suggesting moderate respiratory, cardiovascular or GI symptoms)	Marked dysphagia, hoarseness, and/or stridor; SOB, wheezing & retractions; crampy abdominal pain, recurrent vomiting and/or diarrhea; and/or mild dizziness
3. Severe (hypoxia, hypotension, or neurological compromise)	Cyanosis or SpO <sub>2</sub> < 92% at any stage, hypotension, confusion, collapse, loss of consciousness; or incontinence

**12.3.3 Attribution Definitions**

The relationship, or attribution, of an adverse event to study procedure(s) will initially be determined by the site investigator and recorded on the appropriate AE/SAE paper case report form. Final determination of attribution for safety reporting will be determined by DAIT/NIAID. The relationship of an adverse event to study procedures will be determined using the descriptors and definitions provided in Table 12.3.3.

For additional information and a printable version of the NCI-CTCAE manual, consult the NCI-CTCAE web site: <http://ctep.cancer.gov/reporting/ctc.html>.

**Table 12.3.3 Attribution of Adverse Events**

Code	Descriptor	Relationship (to primary investigational product and/or other concurrent mandated study therapy or study procedure)
Unrelated Category		
1	Unrelated	The adverse event is clearly not related.
Related Categories		
2	Possible	The adverse event has a reasonable possibility to be related; there is evidence to suggest a causal relationship.
3	Definite	The adverse event is clearly related.

**12.4 Collection and Recording of Adverse Events**

Adverse events (including SAEs) will be collected from the time of consent until a subject completes study participation or until 30 days after he/she prematurely withdraws (without withdrawing consent) or is withdrawn from the study.

**12.4.1 Collecting Adverse Events**

Adverse events (including SAEs) may be discovered through any of these methods:

- Observing the participant.

- Interviewing the participant.
- Receiving an unsolicited complaint from the participant.
- In addition, an abnormal value or result from a clinical or laboratory evaluation can also indicate an adverse event, as defined in Section 12.3, Grading and Attribution of Adverse Events.

#### **12.4.2 Recording Adverse Events**

Throughout the study, the investigator at the site will record adverse events and serious adverse events as described previously (Section 12.2, Definitions) on the appropriate AE/SAE eCRF regardless of the relationship to study procedure.

Once recorded, an AE/SAE will be followed until it resolves with or without sequelae, or until the end of study participation, or until 30 days after the subject prematurely withdraws (without withdrawing consent)/or is withdrawn from the study, whichever occurs first.

### **12.5 Reporting of Serious Adverse Events and Adverse Events**

#### **12.5.1 Reporting of Serious Adverse Events to DAIT/NIAID**

This section describes the responsibilities of the site investigator to report serious adverse events to the sponsor via the SAE CRF. Timely reporting of adverse events is required by 21 CFR and ICH E6 guidelines.

Site investigators will report to the SACCC (Rho, Inc.) and DAIT/NIAID all serious adverse events (see Section 12.2.4, Serious Adverse Event (SAE)), regardless of relationship or expectedness within 24 hours of discovering the event.

For serious adverse events, all requested information on the AE/SAE eCRF will be provided. However, unavailable details of the event will not delay submission of the known information. As additional details become available, the AE/SAE eCRF will be updated and submitted. Every time the SAE eCRF is submitted, it should be signed by the investigator.

For additional information regarding SAE reporting, contact Rho Product Safety:

Rho Product Safety  
6330 Quadrangle Drive, Suite 500  
Chapel Hill, NC 27517  
Toll-free: 1-888-746-7231  
SAE Fax Line: 1-888-746-3293  
Email: [rho\\_productsafety@rhoworld.com](mailto:rho_productsafety@rhoworld.com)

#### **12.5.2 Reporting to Health Authority**

This study will be conducted with an IND exemption; therefore no health authority reporting will be required. Annual and expedited reported, as described below, will be submitted to the DSMB and IRB, as appropriate.

##### **12.5.2.1 Annual Reporting**

DAIT/NIAID will include in the annual study report all adverse events classified as:

- Serious, expected, suspected adverse reactions (see Section 12.2.2, Suspected Adverse Reaction (SAR), and Section 12.2.3, Unexpected Adverse Event).
- Serious and not a suspected adverse reaction (see Section 12.2.2, Suspected Adverse Reaction (SAR)).

- Pregnancies not reported as serious adverse events.

Note that all adverse events (not just those requiring 24-hour reporting) will be reported annually.

#### 12.5.2.2 Expedited Safety Reporting

This option, with 2 possible categories, applies if the adverse event is classified as one of the following:

**Category 1: Serious and unexpected suspected adverse reaction [SUSAR]** (see Section 12.2.2, Suspected Adverse Reaction (SAR), and Section 12.2.3, Unexpected Adverse Event and 21 CFR 312.32(c)(1)i).

The sponsor must report any suspected adverse reaction that is both serious and unexpected. The DAIT/NIAID must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the study drug and the adverse event, such as:

1. A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., Grade 3 anaphylaxis as described in Table 12.3.2);
2. One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture);
3. An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

**Category 2: Any findings from studies that suggests a significant human risk**

The sponsor must report any findings from other epidemiological studies, analyses of adverse events within the current study or pooled analysis across clinical studies or animal or *in vitro* testing (e.g. mutagenicity, teratogenicity, carcinogenicity) that suggest a significant risk in humans exposed to the drug that would result in a safety-related change in the protocol, informed consent, investigator brochure or package insert or other aspects of the overall conduct of the study.

DAIT/NIAID must notify the DSMB, central IRB, and all participating investigators of expedited Safety Reports within 15 calendar days; unexpected fatal or immediately life-threatening suspected adverse reaction(s) shall be reported as soon as possible or within 7 calendar days.

#### 12.5.3 Reporting of Adverse Events to IRBs

All investigators will report adverse events, including expedited reports, in a timely fashion to their respective IRBs in accordance with applicable regulations and guidelines.

#### 12.6 Pregnancy Reporting

The investigator shall be informed immediately of any pregnancy in a study subject. A pregnant subject shall be instructed to stop taking study medication. The investigator shall counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the pregnant subject shall continue until the conclusion of the pregnancy.

The investigator shall report to the Statistical and Clinical Coordinating Center (SACCC) and DAIT/NIAID all pregnancies within 1 business day of becoming aware of the event using the Pregnancy eCRF. All pregnancies identified during the

study shall be followed to conclusion and the outcome of each must be reported. The Pregnancy eCRF shall be updated and submitted to the Statistical and Clinical Coordinating Center (SACCC) when details about the outcome are available.

Information requested about the delivery shall include:

- Gestational age at delivery
- Birth weight, length, and head circumference
- Gender
- Appearance, pulse, grimace, activity, and respiration (APGAR) score at 1 minute, 5 minutes, and 24 hours after birth, if available
- Any abnormalities.

Should the pregnancy result in a congenital abnormality or birth defect, an SAE must be submitted to the Statistical and Clinical Coordinating Center (SACCC) and DAIT/NIAID using the SAE reporting procedures described above.

### **12.7 Reporting of Other Safety Information**

An investigator shall promptly notify the site IRB as well as the SACCC and DAIT/NIAID via email when an “unanticipated problem involving risks to subjects or others” is identified, which is not otherwise reportable as an adverse event.

## **12.8 Review of Safety Information**

### **12.8.1 Medical Monitor Review**

The DAIT/NIAID Medical Monitor shall receive monthly reports from the SACCC compiling new and accumulating information on AEs, SAEs, and pregnancies recorded by the study site(s) on appropriate paper CRFs.

In addition, the Medical Monitor shall review and make decisions on the disposition of the SAE and pregnancy reports received by the SACCC (See Sections 12.5.1, Reporting of Serious Adverse Events to DAIT/NIAID and 12.6, Pregnancy Reporting).

### **12.8.2 DSMB Review**

The SACCC will provide the DSMB with listings of all SAEs on an ongoing basis, including quarterly reports of all SAEs. Furthermore, the DSMB will be informed of expedited reports of SAEs.

#### **12.8.2.1 Planned DSMB Reviews**

The NIAID Asthma and Allergy Data Safety and Monitoring Committee (DSMB) shall review safety data at least yearly during planned DSMB Data Review Meetings. Data for the planned safety reviews will include, at a minimum, a listing of all reported AEs and SAEs.

The DSMB will be informed of an Expedited Safety Report in a timely manner. An SAE which the Medical Monitor determines to be an unexpected safety risk will be sent to the DSMB immediately.

#### **12.8.2.2 Ad hoc DSMB Reviews**

In addition to the pre-scheduled data reviews and planned safety monitoring, the DSMB may be called upon for *ad hoc* reviews. The DSMB will review any event that potentially impacts safety at the request of the protocol chair or DAIT/NIAID. In addition, any occurrence of meeting one of the study stopping rules as described in Section 11.5 will

trigger an *ad hoc* comprehensive DSMB Safety Review. After review of the data, the DSMB will make recommendations regarding study conduct and/or continuation.

#### **12.8.2.3 Temporary Suspension of Enrollment and Drug Dosing for *ad hoc* DSMB Safety Review**

A temporary halt in both enrollment and drug dosing will be implemented if an *ad hoc* DSMB safety review is required.

### **13 Statistical Considerations and Analytical Plan**

#### **13.1 Overview**

The primary objective of this pilot study is to determine if treatment with this dose of mouse SCIT is safe. Other secondary objectives are to determine whether mouse SCIT will induce a 3-fold increase in mouse-specific IgE, a biomarker of allergen immunotherapy, when measured over 24 weeks, and to examine changes in levels of mouse-specific IgG and IgG4 over the same time period

#### **13.2 Endpoints**

##### **13.2.1 Primary Endpoints**

The primary endpoint is the number of reported adverse events and serious adverse events, including their severity, seriousness, and treatment relatedness.

##### **13.2.2 Secondary Endpoints**

1. Change in mouse-specific IgE.
2. Change in mouse-specific IgG and IgG4.
3. Change in in-vitro mouse antigen binding to B-cells.

#### **13.3 Measures to Minimize Bias**

This is a one arm open label study without randomization. All laboratory assays for serum IgE and IgG antibodies will be performed in a central laboratory.

#### **13.4 Analysis Plan**

##### **13.4.1 Analysis Population**

The study population consists of adults aged 18 through 55 years who have a history of asthma and are mouse sensitive. The study will examine the safety of the administration of non-standardized glycerinated mouse allergenic extract by subcutaneous injection. This is a phase I safety pilot with no efficacy measures; thus, only one analysis population, the safety population, will be defined for this study. The safety population will include all study participants who receive the initial injection during the Dose Initiation Visit. All statistical analyses will be performed on the Safety Population.

##### **13.4.2 Primary Analysis of Primary Endpoint(s)/Outcome(s)**

The primary objective of this pilot study is to assess if treatment with mouse SCIT, using the per protocol allergenic extract doses, is safe. This will be done by determining the rate of related adverse events and serious adverse events in the course of treatment. Frequency of AEs and SAEs will be tabulated by event, organ, seriousness, severity, and treatment relatedness.

##### **13.4.3 Analyses of Secondary Endpoints**

The secondary statistical analyses will include summary statistics for the secondary endpoints and correlation analyses. Endpoints that are proportions will be determined along with their exact 95% confidence intervals (Proc Freq, SAS).

Correlation analyses will test for associations between baseline allergy diagnoses (rhinitis, asthma), allergen sensitivity (mouse-specific IgE and IgG levels, skin test results), and increased risk of AEs. Changes from baseline levels of mouse-specific IgE, IgG, and IgG4 will be described in absolute and relative terms.

#### **13.4.4 Analyses of Exploratory Endpoint(s)/Outcome(s)**

Not applicable.

#### **13.4.5 Descriptive Analyses**

Not applicable.

#### **13.5 Interim Analyses**

Not applicable.

#### **13.6 Sample Size Considerations**

This is a single center, open-label, nonblinded, safety pilot study with the overall objective of demonstrating safety and determining the tolerability of glycerinated mouse allergenic extract via the subcutaneous route. The proposed sample size for this protocol is 10 mouse-sensitive participants, and each participant will receive approximately 28 injections. This study size will not provide for definitive assessment of safety parameters. Rather, if symptomatic response is sufficiently limited, this study group will permit larger subsequent studies for further evaluations of product safety and efficacy. Estimated event rates for these safety-related outcomes depend on the sample size and on the true underlying event rate. The table below summarizes the probabilities of observing at least one event given the sample size of 280 injections and the true event rate. For example, if the true event rate is 1%, the probability that we observe at least one event is 94%.

**Table 13.6** Probability of Observing Adverse Events According to the “True” Unknown Event Rates

“True” Unknown Probability of Event	Probability of Observing at Least One Event*
0.01%	2.7%
0.05%	13.1%
0.1 %	24.4 %
0.5 %	75.4 %
1 %	94.0 %
5 %	>99.9%
10 %	>99.9%
25 %	>99.9%
50 %	>99.9%

\* Assuming event probabilities are independent both within and between participants. Any correlation between event probabilities would reduce the probability of seeing at least one event.

## 14 Identification and Access to Source Data

### 14.1 Source Data

Source documents and source data are considered to be the original documentation where subject information, visits consultations, examinations and other information are recorded. Documentation of source data is necessary for the reconstruction, evaluation and validation of clinical findings, observations and other activities during a clinical trial.

### 14.2 Access to Source Data

The site investigators and site staff will make all source data available to the DAIT/NIAID, representatives of the sponsor, as well as to relevant health authorities. Authorized representatives as noted above are bound to maintain the strict confidentiality of medical and research information that may be linked to identified individuals.

## 15 Protocol Deviations

### 15.1 Protocol Deviation Definitions

#### 15.1.1 Protocol Deviation

The investigators and site staff will conduct the study in accordance to the protocol; no deviations from the protocol are permitted. Any change, divergence, or departure from the study design or procedures constitutes a protocol deviation. As a result of any deviation, corrective actions will be developed by the site and implemented promptly.

#### 15.1.2 Major Protocol Deviation (Protocol Violation)

A Protocol Violation is a deviation from the IRB-approved protocol that may affect the subject's rights, safety, or well-being and/or the completeness, accuracy and reliability of the study data. In addition, protocol violations include willful or knowing breaches of human subject protection regulations, or policies, any action that is inconsistent with the NIH Human Research Protection Program's research, medical, and ethical principles, and a serious or continuing noncompliance with federal, state, local or institutional human subject protection regulations, policies, or procedures.

#### 15.1.3 Non-Major Protocol Deviation

A non-major protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that does not have a major impact on the subject's rights, safety or well-being, or the completeness, accuracy and reliability of the study data.

### 15.2 Reporting and Managing Protocol Deviations

The study site principal investigator has the responsibility to identify, document and report protocol deviations. However, protocol deviations may also be identified during site monitoring visits or during other forms of study conduct review.

Upon determination that a protocol deviation (major or minor) has occurred, the study staff will a) notify the PI, b) notify the SACCC, and c) complete the Protocol Deviation form. The Protocol Deviation form will document at a minimum the date PD occurred, the date PD identified, a description of event, whether the deviation resulted in SAE/AE, the signature of PI, report to IRB, and documentation of a corrective action plan. The SACCC and DAIT/NIAID may request discussion with the PI to determine the effect of the protocol deviation on the study participant and his/her further study participation, the effect of the protocol deviation on the overall study, and corrective actions. The PI will complete and sign the Protocol Deviation form and submit it to the SACCC and to the site IRB, per IRB regulations. Major protocol deviations will be reported to the DSMB by the NIAID Medical Monitor at the Medical Monitor's discretion.

## 16 Ethical Considerations and Compliance with Good Clinical Practice

### 16.1 Statement of Compliance

This clinical study will be conducted using good clinical practice (GCP), as delineated in *Guidance for Industry: E6 Good Clinical Practice Consolidated Guidance*, and according to the criteria specified in this study protocol. Before study initiation, the protocol and the informed consent documents will be reviewed and approved by the local IRB. Any amendments to the protocol or to the consent materials will also be approved by the local IRB before they are implemented.

### 16.2 Informed Consent Process

The consent process will provide information about the study to a prospective participant and will allow adequate time for review and discussion prior to his/her decision. The principal investigator or designee listed on the delegation log will review the consent and answer questions. The consent designee must be listed on the delegation log, have knowledge of the study and received training (from the local IRB, PI, or study coordinator) in the consent process. The prospective participant will be told that being in the trial is voluntary and that he or she may withdraw from the study at any time, for any reason. All participants will read, sign, and date a consent form before undergoing any study procedures. Consent materials will be presented in participants' primary language. A copy of the signed consent form will be given to the participant.

The consent form will be revised when important new safety information is available, the protocol is amended, and/or new information becomes available that may affect participation in the study.

### 16.3 Privacy and Confidentiality

A participant's privacy and confidentiality will be respected throughout the study. Each participant will be assigned a unique identification number and these numbers rather than names will be used to collect, store, and report participant information. Site personnel will not transmit documents containing personal health identifiers (PHI) to the study sponsor or their representatives.

## 17 Publication Policy

Presentations and publication of the results of this trial will be governed by the ICAC Publication Policy.

## 18 References

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### Appendix A: Schedule of Procedures/Evaluations

Visit Number	Screening	Dose Initiation	Bi-Weekly Dose Escalation Visits	Bi-Monthly Maintenance Visits	Final Visit
Informed consent, screening	X				
Medical history	X				
Physical exam <sup>1</sup>	X	X	X	X	X
Vital signs <sup>2</sup>	X	X	X	X	X
Flu vaccine <sup>6</sup>	X				
Spirometry	X				X
Peak flow	X	X	X	X	X
Adverse event assessment		X	X	X	X
Symptom questionnaires	X	X	X	X	X
Allergen skin test	X				
Blood collection <sup>3</sup>	X	X		X	X
Pregnancy test <sup>4</sup>	X	X	X	X	X
Dose escalation <sup>5</sup>		X	X		
Injection		X	X	X	

<sup>1</sup> A detailed physical exam will occur at Screening and at the Final Visit. A more limited physical exam will be completed at every injection visit.

<sup>2</sup> Height and weight will be assessed at Screening only.

<sup>3</sup> Blood will be drawn at screening, at baseline and monthly after the maintenance dose has been reached for assessment of biomarkers of allergen immunotherapy such as IgE, IgG, and IgG4.

<sup>4</sup> Pregnancy testing will be done monthly after dose initiation in females.

<sup>5</sup> Dose Escalation will normally take 11 weeks, but can take place over up to 18 weeks, if needed.

<sup>6</sup> Flu vaccine will be given to participants when it becomes available if they have not already received the vaccine.