INNER-CITY ASTHMA CONSORTIUM

PROTOCOL ICAC-27

A Pilot Study to Assess Safety and Feasibility of Cockroach Nasal Allergen Challenge in Cockroach Sensitive Children and Adults with Asthma

Cockroach Nasal Allergen Challenge Pilot

5.0 /9 September 2016

IND# 16512

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

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PROTOCOL CHAIR- [redacted]

MEDICAL MONITOR- [redacted]

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PROJECT MANAGER- [redacted]

REGULATORY OFFICER- [redacted]

INVESTIGATOR SIGNATURE PAGE	
Protocol: ICAC - 27	**Version/Date: 5.0 / 9 September2016**
Title: A Pilot Study to Assess Safety and Feasibility of Cockroach Nasal Allergen Challen in Cockroach Sensitive Children and Adults with Asthma	
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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
[redacted]

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.

_____

Site Principal Investigator (Print)

_____ _____

Site Principal Investigator (Signature) **Date**

Protocol Synopsis

Title	A Pilot Study to Assess Safety and Feasibility of Cockroach Nasal Allergen Challenge in Cockroach Sensitive Children and Adults with Asthma
Short Title	Cockroach Nasal Allergen Challenge Pilot
Clinical Phase	I/IIa
Number of Sites	Multiple
Study Objectives	The primary objectives of the study are to: 1.) establish a range of German cockroach allergenic extract doses that, when delivered intranasally, can induce a threshold of nasal symptoms in adults (defined as a Total Nasal Symptom Score (TNSS) ≥8 out of 12 or a sneezing score of 3) and subsequently in 8-14 year old children (defined as a TNSS ≥6 out of 12 or a sneezing score of 3) with asthma and allergic sensitization to German cockroach and 2.) To document the safety profile of nasal challenge with German cockroach allergenic extract first in adults and subsequently in 8-14 year old children with asthma and allergic sensitization to German cockroach. Secondary objectives are: 1. To test the validity of objective outcomes of nasal challenge with German cockroach allergenic extract in 8-14 year old children with allergic sensitization to German cockroach including peak nasal inspiratory flow (PNIF). 2. To test the validity of objective outcomes of nasal challenge with German cockroach allergenic extract in 8-14 year old children with allergic sensitization to German cockroach including allergic reaction biomarkers in blood and nasal secretions. 3. To assess reproducibility of the Nasal Allergen Challenge (NAC) with German cockroach allergenic extract in adults with asthma who are sensitized to German cockroach.
Study Design	This is a multi-center, open label pilot study to assess the safety and determine the feasibility of cockroach nasal allergen challenge in children with asthma. This pilot study will occur in two phases. Phase 1 will enroll 10 cockroach sensitive adults with asthma who will undergo a nasal allergen challenge with increasing doses of cockroach allergen. Phase 1 will consist of two parts, Phase 1a and Phase 1b. In Phase 1a, participants will undergo a nasal allergen challenge. In Phase 1b, participants will undergo a repeat nasal allergen challenge to assess reproducibility of the NAC with cockroach allergen in a population with asthma. The data from Phase 1a will be used to identify a range of doses that is safe and elicits a threshold of nasal symptoms (TNSS ≥8 or a sneezing score of 3). Phase 2 will enroll 25 cockroach sensitive children with

	asthma ages 8-14 years who will undergo a nasal allergen challenge using the dose range identified in Phase 1a. The threshold for a positive response to the NAC in Phase 2 will be lowered to a TNSS ≥6; the sneezing score of 3 will remain the same.
Primary Outcomes	1. Prevalence of a positive response to NAC, defined at each dose as any sneezing score of 3 or a Total Nasal Symptom Score (TNSS) ≥8 out of 12 in Phase 1 or a TNSS ≥6 out of 12 in Phase 2. 2. The number of reported adverse events and serious adverse events, including their severity, seriousness, and relatedness
Secondary Outcomes	1. Number of Sneezes 2. TNSS – highest score out of all doses received 3. TNSS – change from baseline 4. Change in PNIF from baseline 5. Change in PEF from baseline 6. Visual Analog Scale (VAS) - change from baseline 7. Change in tryptase in nasal secretions 8. Change in albumin in nasal secretions
Exploratory Outcomes	1. Change in chemokines and other biomarkers in nasal secretions 2. Change in cockroach-specific T-cell epitopes in peripheral blood
Accrual Objective	*35 (Phase 1 - 10 adults, Phase 2 - 25 children)*
Study Duration	*1 year*
Treatment Description	Participants will receive escalating doses of glycerinated German cockroach allergenic extract administered via the intranasal route.
Inclusion Criteria	Individuals who meet all of the following criteria are eligible for enrollment as study participants for Phase 1a and Phase 2: 1. Subject and/or parent guardian must be able to understand and provide informed consent 2. Male or female adults, 18 through 55 years of age at recruitment (Phase 1) or male or female children, 8-14 years of age at recruitment (Phase 2). 3. Have a history of asthma for a minimum of 1 year before study entry. 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 physician over a year ago. b. The participant must have persistent asthma

	defined by the current need for at least 100 microgram (mcg) fluticasone per day or the equivalent of another inhaled corticosteroid. c. The participant's asthma must be well controlled as defined by: i. A FEV1 greater than or equal to 80% predicted (see Section 8.2). ii. An Asthma Control Test (ACT) score ≥ 20. 4. Are sensitive to German cockroach (CR) as documented by a positive (≥ 3 mm greater than negative control) skin prick test result and a positive German CR specific IgE (≥0.35 kUA/L). 5. Have no known contraindications to the allergenic extracts or diluents. Individuals who meet the following criteria are eligible for enrollment as study participants in Phase 1b after completion of Phase 1a: 1. The participant's asthma must be well controlled as defined by: a. A FEV1 greater than or equal to 80% predicted (see Section 8.2). b. An Asthma Control Test (ACT) score ≥ 20. 2. The participant tolerated the NAC during Phase 1a with no AEs grade 2 or higher as determined by Table 12.3.1a Grading of Local Reactions to Study Procedures.
Exclusion Criteria	Individuals who meet any of these criteria are not eligible for enrollment as study participants in Phase 1a and Phase 2: 1. Are pregnant or lactating. Post-menarcheal 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 Recruitment 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 or one course within the last 3 months. c. Have been treated with depot corticosteroids

within the last 12 months.

d. Have been hospitalized for asthma within the 12 months prior to recruitment.

e. Have had an emergency room visit for asthma within the 3 months prior to recruitment.

f. Have had a life-threatening asthma exacerbation that required intubation, mechanical ventilation, or that resulted in a hypoxic seizure within 2 years prior to recruitment.

4. Have nasal polyps or other major structural abnormalities in their nasal cavities as assessed by anterior rhinoscopy.
5. Have active rhinitis symptoms prior to the nasal allergen challenge, defined as a Baseline TNSS >3, with no individual symptom score >1.
6. Do not have access to a phone (needed for scheduling appointments).
7. Have received allergen immunotherapy (SLIT or SCIT) in the last 12 months prior to recruitment or who plan to initiate or resume allergen immunotherapy during the study.
8. Have previously been treated with anti-IgE therapy in the 12 months prior to recruitment.
9. Are currently receiving oral or nasal antihistamines, nasal corticosteroids, nasal decongestants, nasal anticholinergics or cromolyn, which cannot be suspended for the required washout periods prior to skin prick testing and the nasal allergen challenge.
10. Have received an investigational drug in the 30 days prior to recruitment or who plan to use an investigational drug during the study.
11. Past or current medical problems or findings from physical examination or laboratory testing that are not listed above, which, in the opinion of the investigator, may pose additional risks from participation in the study, may interfere with the participant's ability to comply with study requirements or that may impact the quality or interpretation of the data obtained from the study.

Individuals are not eligible for enrollment as study participants in Phase 1b after completion of Phase 1a if any of the following criteria are met:

1. Are pregnant or lactating.
2. Have an asthma severity classification 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 or one course within the last 3 months.

c. Have been treated with depot corticosteroids within the last 12 months.

d. Have been hospitalized for asthma within the 12 months prior to their participation in Phase 1b.

e. Have had an emergency room visit for asthma within the 3 months prior to their participation in Phase 1b.

f. Have had a life-threatening asthma exacerbation that required intubation, mechanical ventilation, or that resulted in a hypoxic seizure within 2 years prior to their participation in Phase 1b.

3. Have received allergen immunotherapy (SLIT or SCIT) in the last 12 months prior to their participation in Phase 1b.

4. Have previously been treated with anti-IgE therapy in the 12 months prior to their participation in Phase 1b.

5. Are currently receiving oral or nasal antihistamines, nasal corticosteroids, nasal decongestants, nasal anticholinergics or cromolyn, which cannot be suspended for the required washout periods prior to the nasal allergen challenge in Phase 1b.

6. Have received an investigational drug in the 30 days prior to their participation in Phase 1b.

7. Have past or current medical problems or findings from physical examination or laboratory testing that are not listed above, which, in the opinion of the investigator, may pose additional risks from participation in the study, may interfere with the participant's ability to comply with study requirements or that may impact the quality or interpretation of the data obtained from the study.

8. Meet any of the Participant Stopping Rules and Withdrawal Criteria during Phase 1a

a. The participant elected to withdraw consent from all future study activities, including follow-up.

b. The participant died.

c. The Investigator no longer believes participation is in the best interest of the participant.

d. SAE related to investigational product

e. Anaphylactic reaction grade 2 or 3 (see Table 12.3.1c)

f. Inability to tolerate the NAC prior to reaching a TNSS ≥8 or

	sneezing score of 3 due to excessive discomfort or symptoms g. Epistaxis occurring during the Challenge Visit h. The need to start immunotherapy or any chronic immunosuppressive medications in the period between Phase 1a and Phase 1b i. Require a dose of greater than 500 mcg of fluticasone per day or the equivalent of another inhaled corticosteroid to maintain asthma control in the period between Phase 1a and Phase 1b j. Inability to restrict use of antihistamines, nasal steroids, nasal decongestants, nasal anticholinergics or cromolyn prior to the NAC according to the period specified in the ICAC medication washout guidelines described in the MOP for Protocol ICAC-27 k. Development of any serious medical illness whose natural history, sequela, or treatment would be worsened or impaired by continuation in the protocol l. Participant is "lost to follow-up," as defined in the MOP for Protocol ICAC-27. 9. The participant's initial TNSS at the Repeat Challenge Visit must be within 1 point of the initial TNSS at the Challenge Visit in Phase 1a. If the participant's initial TNSS is outside the 1 point range, then the participant may be reevaluated for the Repeat Challenge Visit up to 3 additional times. Participants who meet any of the following criteria are not eligible for enrollment and may not be reassessed. Participants are ineligible if they: 1. Plan to move from the area during the study period. 2. Have a history of idiopathic anaphylaxis or anaphylaxis grade 2 or higher as defined in Table 12.3.1c 3. 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 product or pose additional risk to the participant. 4. Are using tricyclic antidepressants or beta-adrenergic blocker drugs (both oral and topical).
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 product 2) 1 anaphylactic reaction grade 3 or higher possibly related

	to the investigational product 3) ≥ 1 nonfatal SAE possibly related to the investigational product 4) If considered related to the study procedures or treatments, **in at least 2 participants**: a. Anaphylactic reaction grade 2 or higher b. Reduction of FEV1 by more than 15% from baseline and/or reduction of PEF by more than 20% from baseline and inability to perform spirometry due to administration of rescue medications in Phase 1 or Phase 2.

Table of Contents

Glossary of Abbreviations

ACT	Asthma Control Test
AE	Adverse Event
CFR	Code of Federal Regulations
CR	Cockroach
eCRF	Electronic 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
FENO	Fractional Exhaled Nitric Oxide
GCP	Good Clinical Practice
HIPPA	Health Insurance Portability and Accountability Act
IB	Investigator Brochure
ICAC	Inner-City Asthma Consortium
ICH	International Conference on Harmonization
IND	Investigational New Drug
IRB	Institutional Review Board
MCG	Microgram
MCL	Microliter
MOP	Manual of Procedures
NAC	Nasal Allergen Challenge
NAEPP	The National Asthma Education and Prevention Program
NCI	National Cancer Institute
NIAID	National Institute of Allergy and Infectious Diseases
PD	Protocol Deviation
PEF	Peak Expiratory Flow
PI	[Site] Principal Investigator
PNIF	Peak Nasal Inspiratory Flow
SACCC	Statistical and Clinical Coordinating Center
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Suspected Adverse Reaction
SCIT	Subcutaneous Immunotherapy

SLIT	Sublingual Immunotherapy
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TLC	Total Lung Capacity
TNSS	Total Nasal Symptom Score
VAS	Visual Analog Scale
WAO	World Allergy Organization

1. Background and Rationale

1.1. Background and Scientific Rationale

Cockroach allergen has been established as one of the leading causative agents for morbidity in inner-city children with asthma.[1] Although the negative effects of cockroach exposure have been known for almost 20 years, eradication and avoidance, which can be unrealistic to achieve in the environment of a lower socioeconomic urban population, is still the mainstay of treatment.[2] The Inner-City Asthma Consortium (ICAC) has been working on developing and conducting a clinical study to determine whether subcutaneous immunotherapy (SCIT) with German cockroach extract could induce a beneficial immunomodulatory effect on cockroach allergy-associated asthma, in children.

Unlike pollen allergy, where symptoms characteristically peak during a particular season, or allergy to animals (e.g., cat, dog), where symptoms are induced upon exposure, there is no specific period during the year at which assessment of the efficacy of SCIT on natural cockroach allergen exposure can be undertaken. This only leaves the option of year-round clinical evaluations of symptoms, medication use, lung function and asthma exacerbations as clinical outcomes of a cockroach allergen immunotherapy study. Although these are very relevant outcomes, their specificity or sensitivity as surrogates of the effect of single allergen immunotherapy in polysensitized individuals is low and the need for a "positive control" approach becomes pertinent. In this context, provocation testing with cockroach allergen could be used to objectively evaluate the efficacy of SCIT. Nasal allergen challenge is an established type of provocation testing commonly used in the research setting to assess early stage efficacy of nasal allergy treatments, including allergen immunotherapy, and to study the pathophysiology of allergic reactions in an accessible part of the respiratory tract.[3,4] The outcomes of nasal allergen challenge do not, obviously, match lower airway outcomes, but the purpose of using this form of assessment in the context of a trial of allergen immunotherapy in asthma is only to establish that treatment is effective against mucosal reactions to the allergen in question and not to substitute for asthma outcomes. Yet, it is important to note that the vast majority of children with allergic asthma also have allergic rhinitis and that systemic treatment with allergen immunotherapy should impact upper airway disease, as well. Therefore, the outcomes of nasal allergen challenge may also have clinical relevance in a study of allergen immunotherapy in asthma. An alternative approach would have been to establish a bronchial cockroach allergen provocation[3], but this procedure raises more safety concerns and is more complicated and time consuming than nasal allergen challenge.

Very few studies examining nasal challenge with cockroach allergen have been reported, and no study provides adequate information on safety and dosing in adults or children.[5-7] For further details, please refer to the Investigator Brochure for German Cockroach Allergenic Extract for Nasal Allergen Challenge.

The purpose of this pilot study is to examine the safety and establish the correct dosing of cockroach extract for nasal allergen challenge in adults and then in children, in order to determine whether and how this procedure can be utilized in a subsequent large cockroach allergen SCIT trial.

1.2. Rationale for Selection of Investigational Product or Intervention

The cockroach extract utilized for this study will be obtained from Greer laboratories, Lenoir NC. The selection of this particular extract was based on the potency of German cockroach extracts available for skin testing and allergen immunotherapy on the market. The dosing regimen will be determined based on established protocols set forth by experience with nasal allergen challenges using cat and grass extract.

1.3. Preclinical Experience

Not applicable.

1.4. Clinical Studies

There have been three reports of nasal allergen challenge with cockroach extract in the literature.[5-7]

In the Hosen study, 174 patients of unreported ages underwent nasal provocation testing to insects common to Texas. An unclear number of these patients underwent nasal provocation testing specifically to cockroach. The extract used as the diagnostic agent was a powdered concentration of cockroach, which was directly inhaled by the patients in the setting of nasal allergen challenge with multiple allergen extracts in powdered form. Participants would be treated with phenylephrine hydrochloride and, if needed, a bronchodilator in between allergen challenges. Sixty nine patients were reported to have had a systemic reaction to 1 of the allergen extracts. For cockroach in particular, 16 total reactions were reported, of which 11 were nasal, 2 were listed as bronchial asthma, and 3 were listed as post-nasal and upper bronchial.[7]

In the Okuda study, 560 patients from the ages of 4 to 80 years old (mean 31.3 years; 112 participants were 19 years old or younger) with allergic rhinitis were recruited to undergo an evaluation for insect allergy. Sixty-five participants of unknown ages were selected by unspecified means from the pool of 560 patients to undergo nasal allergen challenge with a mixture of German cockroach, *Chironomus yoshimatsui*, and silkworm moth. The publication did not mention whether there were any adverse reactions from the nasal allergen challenge.[5]

The most recent and informative study evaluated the concept of localized allergy in patients with nonallergic rhinitis. In that study, 16 adult volunteers underwent sequential nasal allergen testing with a variety of aeroallergens, including a cockroach extract mix. The cockroach mix nasal allergen testing was done with an arbitrarily chosen single dose of 100 µL of 1:5000 (w/v), and no testing was conducted prior to the challenge to establish a dose. No adverse events were reported in this published report.[6]

For further details, please refer to the Investigator Brochure for German Cockroach Allergenic Extract for Nasal Allergen Challenge.

2. Study Hypotheses/Objectives

2.1. Hypotheses

The two hypotheses tested by this study are: intranasal delivery of cockroach allergen via a nasal allergen challenge 1) can induce significant changes in nasal symptoms and 2) can be safely administered in adults and children with asthma.

2.2. Primary Objective

The primary objectives of this pilot study are:

1. To establish a range of German cockroach allergenic extract doses that, when delivered intranasally, can induce a threshold of nasal symptoms in most adults (TNSS ≥8 out of 12 or a sneezing score of 3) and subsequently in most 8-14 year old children (TNSS ≥6 out of 12 or a sneezing score of 3) with asthma and allergic sensitization to German cockroach.

2. To document the safety profile of nasal challenge with German cockroach allergenic extract first in adults and subsequently in 8-14 year old children with asthma and allergic sensitization to German cockroach.

2.3 Secondary Objectives

1. To test the validity of objective outcomes of nasal challenge with German cockroach allergenic extract in 8-14 year old children with allergic sensitization to German cockroach including peak nasal inspiratory flow (PNIF).
2. To test the validity of objective outcomes of nasal challenge with German cockroach allergenic extract in 8-14 year old children with allergic sensitization to German cockroach including allergic reaction biomarkers in nasal secretions.
3. To assess reproducibility of the Nasal Allergen Challenge (NAC) with German cockroach allergenic extract in adults with asthma who are sensitized to German cockroach.

3. Study Design

3.1. Description of Study Design

This is a multi-center, open label pilot study to assess the safety and determine the feasibility of cockroach nasal allergen challenge (NAC) in children with asthma. This pilot study will occur in two phases. Phase 1 will enroll 10 cockroach sensitive adults with asthma who will undergo a nasal allergen challenge with increasing doses of cockroach allergen. This phase will consist of two parts, Phase 1a and Phase 1b. In Phase 1a, the cockroach sensitive adults will undergo the initial NAC. In Phase 1b, the adult participants will undergo a repeat challenge 30-365 days after the Phase 1a NAC. The purpose of Phase 1b is to assess reproducibility of the NAC with cockroach allergen in a population with asthma. Phase 2 will enroll 25 cockroach sensitive children with asthma who will undergo a NAC with increasing doses of cockroach allergen. Progressing to Phase 2 will not be dependent upon the results of Phase 1b, and Phase 2 will proceed immediately after the completion of Phase 1a. After the completion of Phase 1a, the primary outcome data (positive response to NAC, defined as TNSS≥8 out of 12 or a sneezing score of 3) for the participants in Phase 1a will be reviewed to determine the optimal dose range to be used in Phase 2. Considerations for choosing the most appropriate dose range will include tolerability and the aim of eliciting a threshold of nasal symptoms. The investigators planned to use the results of the primary outcome analysis (Section 13.4.2) to determine the optimal dose to be used in Phase 2, with the combination of the optimal dose, one dose above, and 2 doses below the optimal dose to be selected as the four doses to be used in Phase 2. However, an optimal dose was not determined in Phase 1a. It was noted that no adult reacted to the first dose of allergen (challenge dose 2).

Phase 2 will enroll 25 cockroach sensitive children with asthma, ages 8-14 years, who will undergo a nasal allergen challenge with all 8 allergen doses used in Phase 1a in at least the first 5 participants to ensure a similar pattern of response. If none of these 5 children react to the first dose of allergen (challenge dose 2), then that dose will be dropped from subsequent challenges. The threshold for a positive response to the NAC in Phase 2 will be defined as a TNSS ≥6; the sneezing score of 3 will remain the same.

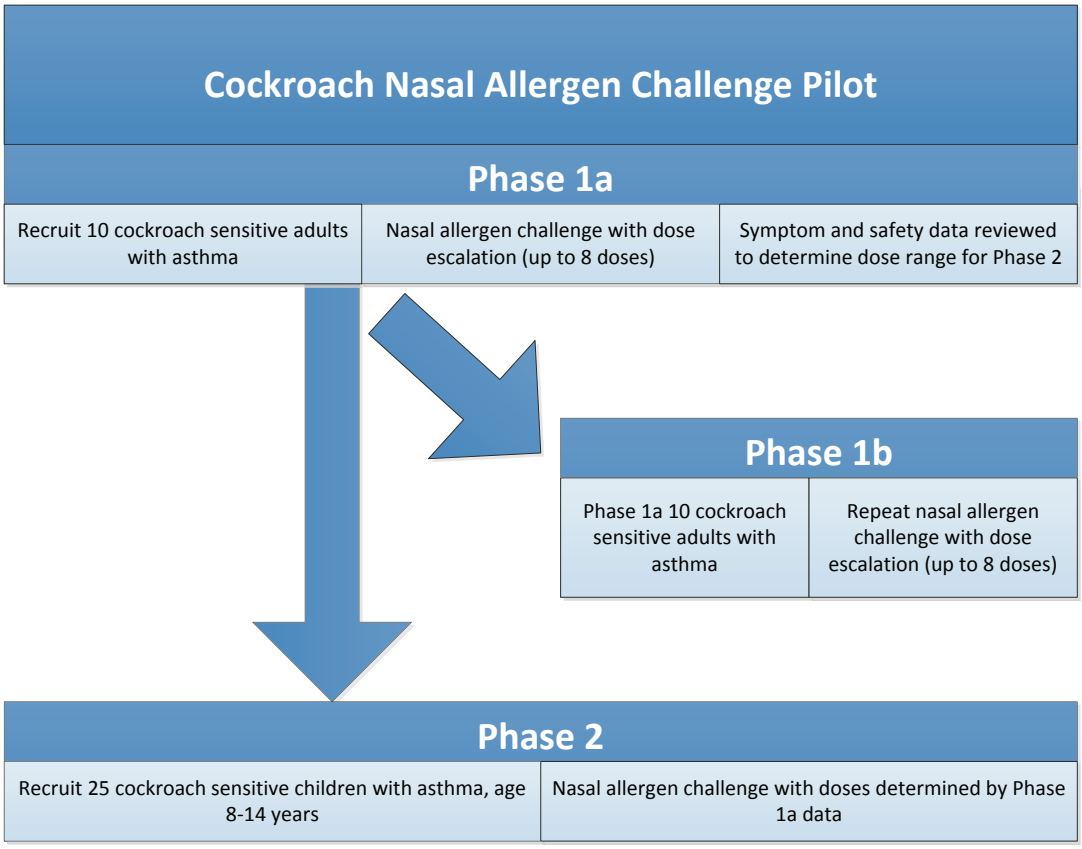


Figure 3.1 Cockroach Nasal Allergen Challenge Study Design

In Phase 1a and Phase 2, there will be a Screening Visit followed by a Challenge Visit, at which the subject will undergo the Nasal Allergen Challenge. In Phase 1a, up to 8 escalating doses of cockroach allergen will be administered intranasally. In Phase 2, the number and concentration of doses given will be determined by the data collected in Phase 1a. Outcomes will be assessed during an approximately 20 minute rest period after each dose. Prior to the commencement of the NAC, participants will have blood drawn for mechanistic studies. The day after the Challenge Visit, each participant will receive a follow-up phone call to assess if the participant is experiencing any late-onset respiratory symptoms. Each participant will be given the peak flow meter they used during the Challenge Visit to take home in order to report their peak expiratory flow (PEF) during the phone visit. Adverse Events (AE) and concomitant medications will also be assessed. The investigator will determine, based on the participant's reported symptoms, medication use, and PEF, if the participant will be asked to return to the site for evaluation and possible treatment or referred to urgent/emergency care if the site is not open (i.e., on a weekend or holiday). Approximately 6-10 days after the Challenge Visit (or as specified in the Manual of Procedures (MOP) for Protocol ICAC-27), participants will return to the site for a blood draw for mechanistic studies and an assessment of adverse events occurring after the challenge. If the participant opted not to have mechanistic studies done, then the assessment of adverse events occurring after the challenge will be done via a Second Follow-Up Phone Call. Additionally, Phase 2 participants will have an option to return to the site for another blood draw for mechanistic studies 30 days after the Challenge Visit.

In Phase 1b, the 10 adult participants will return for the Repeat Challenge Visit in which up to 8 escalating doses of cockroach allergen will be administered intranasally, as described in Phase 1a. Prior to the commencement of the NAC, participants will have blood drawn for mechanistic studies. Participants also will have a mechanistic blood draw 6 hours after the start of the challenge for mechanistic studies. The day after the Repeat Challenge Visit, each participant will receive a follow-up phone call to assess if the participant is experiencing any late-onset respiratory symptoms. Each participant will be given the peak flow meter they used during the Repeat Challenge Visit to take home in order to report their PEF during the phone visit. Adverse Events (AE) and concomitant medications will also be assessed. The investigator will determine, based on the participant's reported symptoms, medication use, and PEF, if the participant will be asked to return to the site for evaluation and possible treatment or referred to urgent/emergency care if the site is not open (i.e., on a weekend or holiday). The participant will return 6-10 days after the Repeat Challenge Visit (or as specified in the Manual of Procedures (MOP) for Protocol ICAC-27) for a blood draw for mechanistic studies. If the participant opted not to have mechanistic studies done, then the assessment of adverse events occurring after the challenge will be done via a Second Follow-Up Phone Call. Approximately 30 days after the Repeat Challenge Visit , Phase 1b participants will return to the site for a blood draw for mechanistic studies.

3.2. Primary Outcomes

1) Prevalence of a positive response to NAC, defined at each dose as any sneezing score of 3 or a TNSS ≥8 out of 12 in Phase 1 or a TNSS ≥6 out of 12 in Phase 2.
2) Safety - number of reported adverse events and serious adverse events, including their severity, seriousness, and relatedness to study procedures.

3.3. Secondary Outcomes

1) Number of Sneezes – summarized across all participants at each dose
2) TNSS – highest score out of all doses received
3) TNSS – change from baseline
4) Change in PNIF from baseline
5) Change in PEF from baseline
6) Visual Analog Scale (VAS) - change from baseline
7) Change in tryptase in nasal secretions
8) Change in albumin in nasal secretions

3.4. Exploratory Outcomes

1) Change in chemokines and other biomarkers in nasal secretions
2) Change in cockroach-specific T-cell epitopes in peripheral blood

3.5. Symptom scoring

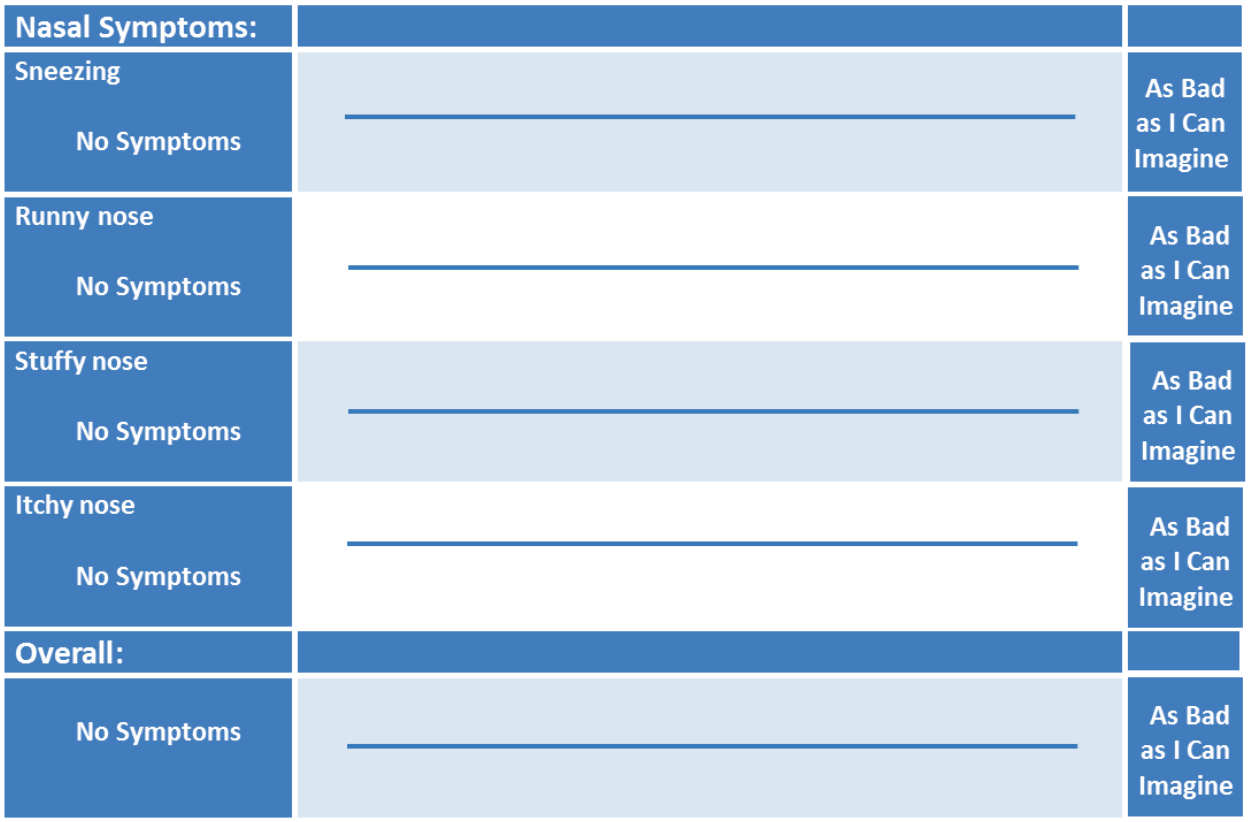
The systems for symptom scoring for use in tabulating clinical responses before or after allergen exposure are described in Table 3.5 and Figure 3.5.
Symptom scores will be assessed at the following time points or as described in the MOP for Protocol ICAC-27:

- Baseline – pre and post nasal rinse
- After each NAC dose administration

Table 3.5. Total Nasal Symptom Score (TNSS)

Category	Measurement	Points
Sneezing **Sneeze Count = __**	none	0
	1-2	1
	3-4	2
	5 or more	3
Runny nose	None - my nose feels fine and not runny at all	0
	Mild - my nose is a little runny; I might be able to blow a little snot or mucous out	1
	Moderate - my nose is very runny; I could definitely blow out some snot or mucous	2
	Severe - my nose is extremely runny; I could blow out a lot of snot or mucous	3
Stuffy nose	None - my nose feels fine; I am not at all stuffy or congested	0
	Mild - my nose feels a little stuffy	1
	Moderate - my nose feels very stuffy; it is hard to breathe through my nose	2
	Severe - my nose is completely stuffy; I cannot even breathe through my nose	3
Itchy Nose	None - my nose does not itch at all	0
	Mild - my nose feels a little itchy	1
	Moderate - my nose feels very itchy	2
	Severe - my nose is extremely itchy	3
TNSS		/12

Figure 3.5. Visual Analog Scale (VAS)



Please mark with a single vertical (up and down) line for how you feel RIGHT NOW for each symptom, as shown to you by the staff.

4. Selection of Participants and Clinical Sites/Laboratories

4.1. Rationale for Study Population

Because the combination of cockroach allergy and cockroach exposure is one of the most important factors contributing to the dramatically increased asthma morbidity seen in inner city children with asthma, a major ICAC goal is to conduct a large multi-center efficacy trial of cockroach immunotherapy in this population. Direct instillation of allergen to the nose via a NAC has been studied as a surrogate measure of allergic reactivity. Another DAIT NIAID-sponsored clinical trial (Protocol ITN 057AD, IND #117,529) conducted in conjunction with the Immune Tolerance Network, incorporated a NAC followed by measurement of nasal responses as a way of quantifying treatment efficacy for individuals with cat allergy. However, cockroach allergen has not been previously used in a NAC, and the tolerability and appropriate dose range for administration to children with asthma is unknown. The first phase of this study will recruit adults in order to establish a range of doses of cockroach allergen that can be safely administered to cockroach sensitive children with asthma.

4.2. Inclusion Criteria

Individuals who meet all of the following criteria are eligible for enrollment as study participants for Phase 1a and Phase 2:

1. Subject and/or parent guardian must be able to understand and provide informed consent

2. Male or female adults, 18 through 55 years of age at recruitment (Phase 1) or male or female children, 8-14 years of age at recruitment (Phase 2)
3. Have a history of asthma for a minimum of 1 year before study entry:
    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 physician over a year ago.
    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.
    c. The participant's asthma must be well controlled as defined by:
        i. A FEV1 greater than or equal to 80% predicted (see Section 8.2).
        ii. An Asthma Control Test (ACT) score ≥ 20.
4. Are sensitive to German Cockroach as documented by a positive (≥ 3 mm greater than negative control) skin prick test result and a positive German Cockroach specific IgE (≥0.35 kUA/L).
5. Have no known contraindications to the allergenic extracts or diluents.

Individuals who meet the following criteria are eligible for enrollment as study participants in Phase 1b after completion of Phase 1a:

1. The participant's asthma must be well controlled as defined by:
    a. A FEV1 greater than or equal to 80% predicted (see Section 8.2).
    b. An Asthma Control Test (ACT) score ≥ 20.
2. The participant tolerated the NAC during Phase 1a with no AEs grade 2 or higher as determined by Table 12.3.1a Grading of Local Reactions to Study Procedures.

4.3. Exclusion Criteria

Individuals who meet any of these criteria are not eligible for enrollment as study participants in Phase 1a and Phase 2:

1. Are pregnant or lactating. Post-menarcheal 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 Recruitment 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 or one course within the last 3 months.
    c. Have been treated with depot corticosteroids within the last 12 months.
    d. Have been hospitalized for asthma within the 12 months prior to recruitment.
    e. Have had an emergency room visit for asthma within the 3 months prior to recruitment.
    f. Have had a life-threatening asthma exacerbation that required intubation, mechanical ventilation, or that resulted in a hypoxic seizure within 2 years prior to recruitment.
4. Have nasal polyps or other major structural abnormalities in their nasal cavities as assessed by anterior rhinoscopy.
5. Have active rhinitis symptoms prior to the nasal allergen challenge, defined as a Baseline TNSS >3, with no individual symptom score >1.

6. Do not have access to a phone (needed for scheduling appointments).
7. Have received allergen immunotherapy (SLIT or SCIT) in the last 12 months prior to recruitment or who plan to initiate or resume allergen immunotherapy during the study.
8. Have previously been treated with anti-IgE therapy in the 12 months prior to recruitment.
9. Are currently receiving oral or nasal antihistamines, nasal corticosteroids, nasal decongestants, nasal anticholinergics or cromolyn, which cannot be suspended for the required washout periods prior to skin prick testing and the nasal allergen challenge.
10. Have received an investigational drug in the 30 days prior to recruitment or who plan to use an investigational drug during the study.
11. Past or current medical problems or findings from physical examination or laboratory testing that are not listed above, which, in the opinion of the investigator, may pose additional risks from participation in the study, may interfere with the participant's ability to comply with study requirements or that may impact the quality or interpretation of the data obtained from the study.

Individuals are not eligible for enrollment as study participants in Phase 1b after completion of Phase 1a if any of the following criteria are met:

1. Are pregnant or lactating.
2. Have an asthma severity classification 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 or one course within the last 3 months.
    c. Have been treated with depot corticosteroids within the last 12 months.
    d. Have been hospitalized for asthma within the 12 months prior to their participation in Phase 1b.
    e. Have had an emergency room visit for asthma within the 3 months prior to their participation in Phase 1b.
    f. Have had a life-threatening asthma exacerbation that required intubation, mechanical ventilation, or that resulted in a hypoxic seizure within 2 years prior to their participation in Phase 1b.
3. Have received allergen immunotherapy (SLIT or SCIT) in the last 12 months prior to their participation in Phase 1b.
4. Have previously been treated with anti-IgE therapy in the 12 months prior to their participation in Phase 1b.
5. Are currently receiving oral or nasal antihistamines, nasal corticosteroids, nasal decongestants, nasal anticholinergics or cromolyn, which cannot be suspended for the required washout periods prior to the nasal allergen challenge in Phase 1b.
6. Have received an investigational drug in the 30 days prior to their participation in Phase 1b.
7. Have past or current medical problems or findings from physical examination or laboratory testing that are not listed above, which, in the opinion of the investigator, may pose additional risks from participation in the study, may interfere with the participant's ability to comply with study requirements or that may impact the quality or interpretation of the data obtained from the study.

8. Meet any of the Participant Stopping Rules and Withdrawal Criteria during Phase 1a
    a. The participant elected to withdraw consent from all future study activities, including follow-up.
    b. The participant died.
    c. The Investigator no longer believes participation is in the best interest of the participant.
    d. SAE related to investigational product
    e. Anaphylactic reaction grade 2 or 3 (see Table 12.3.1c)
    f. Inability to tolerate the NAC prior to reaching a TNSS ≥8 or a sneezing score of 3 due to excessive discomfort or symptoms
    g. Epistaxis occurring during the Challenge Visit
    h. The need to start immunotherapy or any chronic immunosuppressive medications in the period between Phase 1a and Phase 1b
    i. Require a dose of greater than 500 mcg of fluticasone per day or the equivalent of another inhaled corticosteroid to maintain asthma control in the period between Phase 1a and Phase 1b
    j. Inability to restrict use of antihistamines, nasal steroids, nasal decongestants, nasal anticholinergics or cromolyn prior to the NAC according to the period specified in the ICAC medication washout guidelines described in the MOP for Protocol ICAC-27
    k. Development of any serious medical illness whose natural history, sequela, or treatment would be worsened or impaired by continuation in the protocol
    l. Participant is “lost to follow-up,” as defined in the MOP for Protocol ICAC-27.
9. The participant’s initial TNSS at the Repeat Challenge Visit must be within 1 point of the initial TNSS at the Challenge Visit in Phase 1a. If the participant’s initial TNSS is outside the 1 point range, then the participant may be reevaluated for the Repeat Challenge Visit up to 3 additional times.

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

1. Plan to move from the area during the study period.
2. Have a history of idiopathic anaphylaxis or anaphylaxis grade 2 or higher as defined in Table 12.3.1c
3. 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.
4. Are using tricyclic antidepressants or beta-adrenergic blocker drugs (both oral and topical).

5. Known and Potential Risks and Benefits to Participants

5.1. Risks of Study Procedures

5.1.1. Nasal Allergen Challenge

This involves the direct application of one or more defined doses of allergen onto the participant’s nasal mucosa using a nasal drug delivery system (LMA® MAD Nasal delivery system LMA/Teleflex, San Diego, CA) . Challenge is expected to cause allergic symptoms such as nasal congestion, sneezing, nasal discharge, and itchy, watery eyes which may last up to several hours after the last dose is administered.

If nasal and/or ocular symptoms persist after the period of observation in the clinical unit, participants will be offered treatment with oral antihistamines. There is a theoretical risk of provoking asthma symptoms. If a participant begins exhibiting asthma symptoms during the NAC, or the PEF is reduced by more than 20% from baseline, the challenge will be suspended, and the participant will be evaluated by the study clinician. If it is determined treatment is needed based on clinical judgment, then the challenge will not be continued. In the absence of an immediate need for treatment, spirometry will be performed to confirm a change in lung function. If the FEV1 is < 85% of baseline value, the challenge will be stopped. If spirometry is performed because of a low PEF and the FEV1 is ≥ 85% of baseline value, the challenge can continue at the clinician's discretion. To minimize this risk, individuals with a pre-bronchodilator FEV1 of less than 80% of predicted are excluded from this trial. In addition, the allergen will be delivered to the nose while subjects are breath holding at Total Lung Capacity (TLC) and will be asked to exhale through their nose thereafter thus minimizing the potential for allergen to reach the lower airways. As for any intervention with allergen to which the patient is sensitive there is the theoretical risk of developing an anaphylactic reaction. Trained personnel, including a physician, as well as medications and equipment, will be immediately available to treat any reaction.

No previous studies have reported on the safety or efficacy of cockroach nasal allergen challenge in children with asthma. Nasal allergen challenge has been performed with other allergens (perennial and seasonal) in children with asthma and found to be low risk. Mild cough or wheezing developed shortly after the nasal challenge in 2 out of 25 children,[8] while in another study a slight drop (10%) in FEV1 was noted in 1 out of 50 children immediately following nasal allergen challenge.[9] Twenty-four hours after the nasal allergen challenge, 1 out of 50 children had an asthma exacerbation with a febrile viral infection.[9] Pedroletti et al. demonstrated that a single nasal allergen challenge with cat allergen was not associated with increased bronchial inflammation, as assessed by F_ENO, among cat allergic children with asthma.[10] For further details, please refer to the Investigator Brochure for German Cockroach Allergenic Extract for Nasal Allergen Challenge.

5.1.2. Skin Prick Tests

Participants may experience mild to moderate pruritus or local discomfort at the sites of skin pricks with allergen and the positive control (histamine dihydrochloride 10 mg/mL). The symptoms are not bothersome. Usually, the allergen-induced wheal and flare responses resolve within 1–2 hours, but rarely a participant may have local swelling that takes 2-3 days to clear entirely. Rarely skin testing will cause the participant being tested to have systemic allergic symptoms. These symptoms may include sneezing, ocular pruritus and tearing, rhinorrhea and/or generalized pruritus or urticaria. Treatment with oral antihistamines is available and is effective although almost never required. A physician is always present and drugs and equipment for treatment of anaphylactic reactions are available.

There is also a very rare chance that the participant may experience a systemic allergic reaction or fainting. A study clinician will be available to provide immediate treatment, if needed. To date, aeroallergen skin prick test procedures, conducted according to our manual of operations by trained and certified site personnel, have NEVER resulted in a systemic adverse reaction. Further, we believe that performance of such allergen evaluation is consistent with national asthma guidelines, and provides direct benefits to participants. The results of the skin tests are provided to participants.

5.1.3. Venipuncture

The risks associated with taking blood include possible pain from the stick, as well as bleeding, bruising, and infection of the skin. Lightheadedness and fainting rarely occur. To minimize these risks, a staff

member who is trained to draw blood from children will collect the samples in Phase 2. Additionally, investigative sites may apply a topical anesthetic such as EMLA® to the skin before the blood draw to reduce the pain of the stick. Side effects from the topical anesthetic include erythema, burning, paleness at the skin site, edema, and alterations in temperature. Reactions are mild and transient. There is a potential for allergic reactions.

5.1.4. Spirometry

Spirometry can cause coughing or lightheadedness, which will go away shortly after the test is finished.

5.1.5. Questionnaires

There is a possibility that participants may find the questions too personal. Participants may refuse to answer any questions that make them feel uncomfortable.

5.2. Potential Benefits

The results of the skin testing will be provided to participants at the end of the study visit. A copy of the spirometry test results will also be provided. The participant may choose to share these results with their primary care physician to facilitate further medical care.

The Inner-City Asthma Consortium (ICAC) has been working on developing and conducting a clinical study to determine whether SCIT with German cockroach extract could induce a beneficial immunomodulatory effect on cockroach allergy-associated asthma, in children. Unlike pollen allergy, where symptoms characteristically peak during a particular season, or allergy to animals (e.g., cat, dog), where symptoms are induced upon exposure, there is no specific period during the year at which assessment of the efficacy of SCIT on natural cockroach allergen exposure can be undertaken. This only leaves the option of year-round clinical evaluations of symptoms, medication use, lung function and asthma exacerbations as clinical outcomes of a cockroach allergen immunotherapy study. Although these are very relevant outcomes, their specificity or sensitivity as surrogates of the effect of single allergen immunotherapy in polysensitized individuals is low and the need for a "positive control" approach becomes pertinent. In this context, provocation testing with cockroach allergen could be used to objectively evaluate the efficacy of SCIT. An alternative approach would have been to establish a bronchial cockroach allergen provocation,[3] but this procedure raises more safety concerns and is more complicated and time consuming than nasal allergen challenge.

6. Investigational Product /Delivery System/Intervention

6.1. Investigational Product

6.1.1. Formulation, Packaging, and Labeling

The investigational product is AllerMed non-standardized glycerinated German cockroach allergenic extract (50% Glycerin) distributed by Greer Laboratories, Inc. (Lenoir, NC). The active ingredient of the investigational product is a non-standardized allergen derived from the extraction and purification of proteins from German cockroach (*Blatella germanica*).

AllerMed non-standardized glycerinated German cockroach allergenic extract is approved in the United States for diagnostic skin testing and immunotherapy by subcutaneous injection (U.S. License 467). It has been used in humans for at least 35

years. This product will be further diluted in a manner appropriate for nasal administration as described in the MOP for Protocol ICAC-27.

6.1.2. Dosage, Preparation, and Administration

Dilutions of the German cockroach allergenic extract needed for NAC dose escalation will be prepared by the site research pharmacy.

Participants will receive escalating doses of glycerinated German cockroach allergenic extract administered via the intranasal route. Each dose will be administered as a nasal spray with the use of a nasal drug delivery system (LMA/Teleflex, San Diego, CA), which delivers 0.1 mL per activation (spray). One spray will be delivered in each nostril for a total delivered volume of 0.2 mL. Nine doses will be given. Dose 1 will be a diluent control. Doses 2 through 9 will have a Bla g 1 dose range of approximately 0.002 mcg to 5 mcg.

All 8 allergen doses will be used in the first 5 children in Phase 2 to ensure a similar response pattern to that seen in the adults. If, like in the adults in Phase 1, none of these 5 children react to the first allergen dose, this dose will be dropped from the subsequent challenges. The threshold for a positive response to the NAC in Phase 2 will be defined as a TNSS ≥6; the sneezing score of 3 will remain the same.

The proposed NAC dose escalation for Phase 2 was reviewed and approved by the NIAID Allergy and Asthma DSMB.

Complete details of the dilutions can be found in the MOP for Protocol ICAC-27, which is based on the DAIT Pharmacy manual.

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 product, 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, the IND sponsor.

6.3. Toxicity Prevention and Management

Non-applicable

6.4. Premature Discontinuation of Investigational Product

Participants, who are prematurely discontinued for safety reasons after receiving at least one dose of investigational product during the Challenge Visit, will not be replaced. Participants who are prematurely discontinued, but who did not receive a dose of investigational product may be replaced.

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

1. SAE related to investigational product
2. Anaphylactic reaction grade 2 or 3 (see Table 12.3.1c)
3. Inability to tolerate the dose escalation during the NAC due to excessive discomfort/symptoms
4. Reduction in FEV_1 of more than 15% from baseline and/or reduction of PEF by more than 20% from baseline and inability to perform spirometry due to administration of rescue medications during the course of the nasal allergen challenge.
5. Development of any serious medical illness whose natural history, sequela, or treatment would be worsened or impaired by continuation in the protocol

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 7.3. 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 visit. Antihistamines, nasal corticosteroids, nasal decongestants, nasal anticholinergics and cromolyn will need to be suspended prior to any Challenge Visit. See MOP for Protocol ICAC-27 for medication washout periods.

Leukotriene receptor antagonists (e.g., Montelukast) are permitted only as existing concomitant medications at screening and should not be started during the duration of study participation.

7.4. Rescue Medications

Participants may use antihistamines and/or a nasal steroid as needed for persistent nasal and/or ocular symptoms following the nasal allergen challenge. If at any time during the nasal challenge a participant experiences asthma symptoms or anaphylaxis, treatment with inhaled short-acting bronchodilators, corticosteroids and epinephrine will be immediately available. Participants will be instructed to bring an albuterol inhaler to any Challenge Visit and carry it with them for the first 24 hours after the challenge. Participants who do not bring an albuterol inhaler to a Challenge Visit will be provided one.

8. Study Procedures

8.1. Recruitment

The study centers 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 Visit

The research study will be explained in lay terms to each potential research participant. The potential participant will sign an informed consent form before undergoing any study procedures. Written informed consent (and assent, if applicable) 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 (and assent, if applicable) is signed, participants will undergo screening study procedures, including prick skin tests with German cockroach allergenic extract to ensure participants are sensitive to the test product. In addition, 8-14 year old participants will undergo prick skin tests to a panel of allergens detailed in the MOP for Protocol ICAC-27. Participants who have valid skin test results within the previous year under another ICAC protocol will not need to be re-tested.

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 post-menarcheal female participants prior to any procedures that entail any risk, such as skin prick testing and the NAC.

For participants with a positive skin prick test to cockroach, blood will be collected by venipuncture for cockroach specific IgE antibody testing. For participants with a negative skin prick test to cockroach, 60 mL of blood (Phase 1a) or the maximum volume allowed up to 60 mL (Phase 2) will be collected at the screening visit for mechanistic assays if the participant agrees. Participants who have valid IgE test results within the previous year under another ICAC protocol will not need to be re-tested.

Participants, who have both a positive skin prick test to cockroach allergenic extract and a cockroach-specific IgE ≥0.35 kU_A/L and are considered eligible for the study, and at the discretion of the study physician, will be invited to proceed to the Challenge Visit.

Spirometry will be performed by all participants to verify the participant's suitability for inclusion in the study. Candidates whose FEV1 is less than 80% of predicted normal will be excluded; however, while

recruitment is ongoing, if their asthma can be brought under control, based on albuterol use, they are eligible for rescreening.

Participants may also qualify for rescreening if they are ineligible due to nasal symptoms or other reversible illness if their condition improves while recruitment is ongoing.

8.3. Challenge Visit

Participants who are deemed eligible based on results from tests conducted at the Screening Visit will be invited to proceed to the Challenge Visit in Phase 1a and Phase 2.

The following procedures, assessments, and laboratory measures will be conducted:

1. Concomitant medications
2. Adverse events
3. Assessment of nasal and pulmonary symptoms (including spirometry)
4. Brief Physical Exam - includes Vital signs, height, weight and nasal and lung exam (or as specified in the MOP for Protocol ICAC-27)
5. Urine pregnancy test (female participants; if more than 28 days after the screening visit)
6. Initial nasal rinses – approximately 200mcl of isotonic saline solution (2 sprays) will be sprayed into each nostril and the participant will be asked to blow their nose; this process will be repeated 3 times (as specified in the MOP for Protocol ICAC-27). The fluids from the 2^{nd} and 3^{rd} rinses will be collected and processed for analysis as specified in the MOP for Protocol ICAC-27– the outcomes from these fluids will be considered baseline for the ensuing nasal challenge procedure. A nasal rinse will be repeated 10 minutes after the diluent control is administered and after each dose of allergen during the NAC, as specified in the MOP for Protocol ICAC-27.
7. Nasal symptoms – TNSS and VAS and will be assessed pre and post the initial nasal rinses, and then 10 -20 minutes after each NAC dose administration and before the nasal rinse. (as specified in the MOP for Protocol ICAC-27) If the participant does not qualify for the Challenge because of the TNSS score, they may be rescheduled as per the MOP for Protocol ICAC-27.
8. Peak nasal inspiratory flow (PNIF) - assessed pre and post the initial nasal rinses, and then 10-20 minutes after each NAC dose administration (as specified in the MOP for Protocol ICAC-27)
9. Peak expiratory flow (PEF) - will be assessed pre and post the initial nasal rinses and then 10-20 minutes after each NAC dose administration as specified in the MOP for Protocol ICAC-27. If PEF is reduced by more than 20% from baseline, the challenge will be suspended, and the participant will be evaluated by the study clinician. If it is determined treatment is needed based on clinical judgment, then the challenge will not be continued. In the absence of an immediate need for treatment, spirometry will be performed to confirm a change in lung function. If the FEV1 is < 85% of baseline value, the challenge will be stopped. If spirometry is performed because of a low PEF and the FEV1 is ≥ 85% of baseline value, the challenge can continue at the clinician's discretion.
10. Blood draw – Prior to the commencement of the NAC, Phase 1a, Phase 1b, and Phase 2 participants will have blood drawn for mechanistic studies - 60 mL of blood (Phase 1a/b) or the maximum volume allowed up to 60 mL (Phase 2).

11. Nasal allergen challenge (NAC) - increasing doses of allergen in defined time intervals (every 20 minutes) up to a specified maximum dose or symptom level, will be given as described in an accompanying MOP for Protocol ICAC-27. Briefly, one spray (100mcL) of diluent or diluted allergen solution is applied to each of the participant's nostrils using a nasal drug delivery system while the participant breath-holds at TLC. After the dose is delivered, the participant is asked to exhale through the nose and then to avoid sniffing or swallowing in the immediate 1 minute after application. In Phase 1, the challenge will begin with a 0 mcg/ml (negative control – 50% glycerin, 50% COCAS with 0.2% phenol) dose followed by up to 8 doses of increasing concentration, until the participant reaches a TNSS score of 8 or more, has a sneezing score of 3 or their symptoms become intolerable. In Phase 2, the challenge will begin with a 0mcg/ml (diluent control) dose followed by a number of doses of increasing concentration, until the participant reaches a TNSS score of ≥6, has a sneezing score of 3 or their symptoms become intolerable. All 8 allergen doses will be used in the first 5 children in Phase 2 to ensure a similar response pattern to that seen in the adults. If, like in Phase 1 in adults, none of these 5 children react to the first allergen dose, this dose will be dropped from the subsequent challenges. Nasal secretions will be collected for approximately 10 minutes immediately following administration of each diluent and allergen dose and a nasal rinse (two 100mcL sprays of isotonic saline solution per nostril) will be performed at 10 minutes, as described above. The fluids from each rinse will be mixed with the nasal secretions collected during the preceding 10 minutes and processed for analysis as specified in the MOP for Protocol ICAC-27. Collection of other outcomes will begin 10 minutes after each diluent or allergen dose is administered. If a participant begins exhibiting asthma symptoms during the NAC, or the PEF is reduced by more than 20% from baseline, the challenge will be suspended, and the participant will be evaluated by the study clinician. If it is determined treatment is needed based on clinical judgment, then the challenge will not be continued. In the absence of an immediate need for treatment, spirometry will be performed to confirm a change in lung function. If the FEV1 is < 85% of baseline value, the challenge will be stopped. If spirometry is performed because of a low PEF and the FEV1 is ≥ 85% of baseline value, the challenge can continue at the clinician's discretion.
12. In a subset of sites in Phase 1a, Phase 1b, and Phase 2, additional blood will be drawn (60 mL or the maximum volume allowed up to 60 mL) once immediately preceding the NAC for mechanistic studies. Details of these studies are specified in the MOP for Protocol ICAC-27.

8.4. Repeat Challenge Visit – Phase 1b

In order to participate in the Repeat Challenge Visit, Phase 1a participants must meet the following evaluation criteria:

- The participant's asthma must be well controlled as defined by:
  - A FEV1 greater than or equal to 80% predicted (see Section 8.2).
  - An Asthma Control Test (ACT) score ≥ 20.
- The participant tolerated the NAC during Phase 1a with no AEs grade 2 or above as determined by Table 12.3.1a Grading of Local Reactions to Study Procedures.

Phase 1a participants will be excluded from participation in the Repeat Challenge Visit if any of the following criteria are met:

- Are pregnant or lactating.

- Have an asthma severity classification of severe persistent, using the NAEPP classification, as evidenced by at least one of the following:
    - Require a dose of greater than 500 mcg of fluticasone per day or the equivalent of another inhaled corticosteroid.
    - Have received more than 2 courses of oral or parenteral corticosteroids within the last 12 months or one course within the last 3 months.
    - Have been treated with depot corticosteroids within the last 12 months.
    - Have been hospitalized for asthma within the 12 months prior to their participation in Phase 1b.
    - Have had an emergency room visit for asthma within the 3 months prior to their participation in Phase 1b.
    - Have had a life-threatening asthma exacerbation that required intubation, mechanical ventilation, or that resulted in a hypoxic seizure within 2 years prior to their participation in Phase 1b.
- Have received allergen immunotherapy (SLIT or SCIT) in the last 12 months prior to their participation in Phase 1b.
- Have previously been treated with anti-IgE therapy in the 12 months prior to their participation in Phase 1b.
- Are currently receiving oral or nasal antihistamines, nasal corticosteroids, nasal decongestants, nasal anticholinergics or cromolyn, which cannot be suspended for the required washout periods prior to the nasal allergen challenge in Phase 1b.
- Have received an investigational drug in the 30 days prior to their participation in Phase 1b.
- Have past or current medical problems or findings from physical examination or laboratory testing that are not listed above, which, in the opinion of the investigator, may pose additional risks from participation in the study, may interfere with the participant's ability to comply with study requirements or that may impact the quality or interpretation of the data obtained from the study.
- Meet any of the Participant Stopping Rules and Withdrawal Criteria during Phase 1a
    - The participant elected to withdraw consent from all future study activities, including follow-up.
    - The participant died.
    - The Investigator no longer believes participation is in the best interest of the participant.
    - SAE related to investigational product
    - Anaphylactic reaction grade 2 or 3 (see Table 12.3.1c)
    - Inability to tolerate the NAC prior to reaching a TNSS ≥8 or sneezing score of 3 due to excessive discomfort or symptoms
    - Epistaxis occurring during the Challenge Visit

- The need to start immunotherapy or any chronic immunosuppressive medications in the period between Phase 1a and Phase 1b
- Require a dose of greater than 500 mcg of fluticasone per day or the equivalent of another inhaled corticosteroid to maintain asthma control in the period between Phase 1a and Phase 1b
- Inability to restrict use of antihistamines, nasal steroids, nasal decongestants, nasal anticholinergics or cromolyn prior to the NAC according to the period specified in the ICAC medication washout guidelines described in the MOP for Protocol ICAC-27
- Development of any serious medical illness whose natural history, sequela, or treatment would be worsened or impaired by continuation in the protocol
- Participant is "lost to follow-up," as defined in the MOP for Protocol ICAC-27.

- The participant's initial TNSS at the Repeat Challenge Visit must be within 1 point of the initial TNSS at the Challenge Visit in Phase 1a. If the participant's initial TNSS is outside the 1 point range, then the participant may be reevaluated for the Repeat Challenge Visit up to 3 additional times.
- The Repeat Challenge Visit will proceed as described in Section 8.3, except that there will be an additional blood draw for mechanistic studies that will occur approximately 6 hours after the initiation of the challenge (or as specified in the MOP for Protocol ICAC-27). Nasal samples will be collected and processed for analysis as specified in the MOP for Protocol ICAC-27.

8.5. Follow-Up Phone Visit

The day after a Challenge Visit, each participant will receive a follow-up phone call to assess if the participant is experiencing any late-onset respiratory symptoms. Each participant will be given the peak flow meter they used during the Challenge Visit to take home in order to report their PEF during the phone visit. The participants (or their caretaker) will be asked to record two PEF measurements, one 4-8 hours after the completion of the challenge and one 24 hours after the completion of the challenge (or as soon as possible after the school day, if applicable). AEs and concomitant medications will also be assessed. The investigator will determine, based on the participant's symptoms, medication use, and PEF measurements, if the participant will be asked to return to the site for evaluation and possible treatment or referred to urgent/emergency care if the site is not open (i.e., on a weekend or holiday). Participants, who have significant asthma symptoms during the Follow-Up Phone Visit as determined by the physician, will receive additional follow-up to assess safety.

For participants who do not consent to the mechanistic blood draw at the Follow-Up Clinic Visit, a Second Follow-Up Phone Call will be made 6-10 days following the Challenge Visit to assess adverse events and concomitant medications.

8.6. Follow-Up Clinic Visits

All participants will be asked to return to the clinic 6-10 days after the Challenge Visit for an additional blood draw (60 mL or the maximum volume allowed up to 60 mL) for mechanistic studies. At this visit, adverse events and concomitant medications will also be assessed.

For participants who do not consent to the mechanistic blood draw, a Second Follow-Up Phone Call will be made in lieu of the Follow-Up Clinic Visit 6-10 days after the Challenge Visit to assess adverse events and concomitant medications.

In Phase 1b, participants will be asked to return to the clinic 30 days after the Repeat Challenge Visit for an additional blood draw (60 mL or the maximum volume allowed up to 60 mL) for mechanistic studies. At this visit, adverse events and concomitant medications will also be assessed.

In Phase 2, participants will be asked to return to the clinic 30 days after the Challenge Visit for an additional optional blood draw (60 mL or the maximum volume allowed by NIH guidelines based on weight up to 60 mL) for mechanistic studies. At this visit, adverse events and concomitant medications will also be assessed.

In a subset of sites in Phase 1a, Phase 1b, and Phase 2, additional blood (60 mL or the maximum volume allowed up to 60 mL) will be drawn once 24-72 hours after the NAC for mechanistic studies. An outcome assessment will be conducted (TNSS, VAS, PNIF and PEF), and AEs and concomitant medications will be assessed. If a participant's PEF is <80% of the Challenge Visit baseline value, the participant will be evaluated by the study clinician using clinical evaluation and/or spirometry. Nasal secretions will also be collected at this this visit involving two 100mcL sprays of isotonic saline solution per nostril and collecting secretions as described in the MOP for Protocol ICAC-27. This visit can be conducted in lieu of the Follow-Up Phone Visit if it occurs the day after the Challenge Visit.

Details of these mechanistic studies are specified in the MOP for Protocol ICAC-27.

8.7. Dust Sample Collection

The caretaker or participant will be given a dust collection kit, which includes instructions on how to collect a dust sample (Refer to the MOP for Protocol ICAC-27 for detailed instructions). A combined dust sample from the participant's bed and the participant's bedroom floor will be collected. The room where the participant sleeps most nights will be considered the participant's bedroom. Measuring templates will be used to delineate the areas to be vacuumed. Dust will be collected using a vacuum cleaner with a special dust collection filter attached. The dust collector will be placed into a sealable plastic bag and returned to the study center for temporary storage (frozen). Crude samples will be batched and shipped to a central laboratory by express mail for sieving, extraction, and analysis. The dust specimens will be assayed to measure the concentration allergens such as: Der p 1, Der f 1, Bla g 1, Fel d 1, Can f 1, Alt a 1, and Mus m 1. Additional allergens of interest and markers of fungal and microbial exposure may be measured. In addition, the caretaker/participant will complete a dust collection questionnaire, which will be returned with the dust collector.

The caretaker or participant will be given the dust collection kit at the screening visit and asked to return the dust sample and questionnaire either by mail or by bringing it to the challenge visit. Those participants that are eligible to have the challenge on the same day as the screening visit will be asked to return the sample and questionnaire either by mail or by bringing it to the Follow-Up Clinic Visit.

8.8. Unscheduled Visits

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

8.9. Visit Windows

Study visits should take place within the time limits specified below: the designated visit windows *(i.e. +/- n days)* for each scheduled visit are also indicated on the Schedule of Events. Additional details are provided in the MOP for Protocol ICAC-27.

The Challenge Visit should be conducted within 2 months of the screening visit. Participants unable to return for the Challenge Visit within 2 months of the Screening Visit will need to have the medical history, physical exam and urine pregnancy test (if applicable) repeated prior to initiation of the NAC. Participants may be reevaluated up to a maximum of 2 times for the Phase 1a and Phase 2 Challenge Visits if they are ineligible due to nasal symptoms or other reversible illness if their condition improves within 2 months of the Screening Visit.

A Follow-Up Phone Visit should occur approximately 24 hours after the end of a Challenge Visit (as described in the MOP for Protocol ICAC-27). In a subset of sites in Phase 1a, Phase 1b, and Phase 2, a Follow-Up Clinic Visit may occur in lieu of the phone call (see MOP for Protocol ICAC-27 for details). A Follow-Up Clinic Visit should occur 6 to 10 days after the Challenge Visit for participants who have agreed to participate in the mechanistic blood draw. Another Follow-up Phone Visit should occur 6 to 10 days following a challenge if the participant is not seen at the study site at this time (as described in the MOP for Protocol ICAC-27).

The optional Phase 2 30-day Follow-Up Visit should occur 30 days after the Challenge Visit (as described in the MOP for Protocol ICAC-27).

The Phase 1b Repeat Challenge Visit should be conducted within 30-365 days after the Challenge Visit. Participants may be reevaluated up to a maximum of 3 times for the Phase 1b Repeat Challenge Visit if they are ineligible due to nasal symptoms or other reversible illness if their condition improves during the 365 days after their initial Challenge Visit.

The Phase 1b 30-day Follow-Up Visit should occur 30 days after the Repeat Challenge Visit (as described in the MOP for Protocol ICAC-27).

9. Mechanistic Assays

Blood samples will be drawn prior to the NAC at either the Screening visit or at the Challenge Visit, depending upon the method of recruitment. Additional blood will be drawn once in all phases 6-10 days after the Challenge Visit (or as specified in the MOP for Protocol ICAC-27). In Phase 1b, participants will undergo an additional blood draw at the Challenge Visit approximately 6 hours after the initiation of the challenge. In Phase 1b and Phase 2, participants will undergo an additional blood draw 30 days after the Challenge Visit, which will be optional for Phase 2 participants. These mechanistic blood samples will be evaluated for T-cell epitope repertoire against cockroach allergens. Nasal secretions will be collected during Challenge Visits. These secretions will be assayed for biomarkers to include tryptase and albumin. In a subset of sites in Phase 1a, Phase 1b, and Phase 2, additional blood will be drawn once immediately preceding the NAC and once 24-72 hours after the NAC for additional mechanistic studies focusing on changes in chemokines and other biomarkers in blood and nasal secretions. Details of these studies are specified in the MOP for Protocol ICAC-27.

10. Biospecimen Storage

10.1. Instructions for Specimen Storage

Extra specimens, including DNA, serum and nasal secretion samples remaining once the specified analyses are conducted will be stored long-term for future research in the field of asthma. Participants will be asked to give permission for long-term storage and future use during the consent process.

10.2. Specimen Shipment Preparation, Handling and Storage

Instructions for sample preparation, handling, storage, and shipping are included in the MOP for Protocol ICAC-27. Principal Investigators will be responsible for knowing about and observing all the regulations for classification, packaging and labeling, permits or authorizations, and personnel training for shipment of biological and hazardous materials required for the conduct of this study.

11. Criteria for Participant and Study Completion and Premature Study Termination

11.1. Participant Completion

Phase 1 participants are considered to have completed the study once they have completed either the Challenge Visit and 30-day Follow-Up Visit after Phase 1b, Challenge Visit and 6-10-day Follow-up visit for participants who did not consent to the 30-day Follow-up Visit, or the Challenge Visit and Second Follow-Up Phone Visit for participants who did not consent to the 6-10 or 30 day Follow-Up Visits. If participants refuse to participate in Phase 1b, they are considered to have completed the study after they have completed the Challenge Visit and Follow-Up Clinic Visit (or Additional Follow-Up Phone Visit for participants who do not consent to the mechanistic blood draw.) Phase 2 participants are considered to have completed the study once they have completed the Challenge Visit and 30-day Follow-Up Visit. If participants do not agree to the 30-day Follow-Up Visit, they are considered to have completed the study after the Follow-Up Clinic Visit after Phase 2 (or Additional Follow-Up Phone Visit for participants who do not consent to the mechanistic blood draw at 6-10 days.)

11.2. Participant Stopping Rules and Withdrawal Criteria

Participants may be prematurely terminated from the study for the following reasons:

1. The participant elects to withdraw consent from all future study activities, including follow-up.
2. The participant dies.
3. The Investigator no longer believes participation is in the best interest of the participant.
4. SAE related to investigational product
5. Anaphylactic reaction grade 2 or 3 (see Table 12.3.1c)
6. Inability to tolerate the NAC prior to reaching a sneezing score of 3 or a TNSS ≥8 (Phase 1) or a TNSS ≥6 (Phase 2) due to excessive discomfort or symptoms
7. Epistaxis occurring during the Challenge visit
8. The need to start immunotherapy or any chronic immunosuppressive medications in the period between the Screening and Challenge Visits
9. Require a dose of greater than 500 mcg of fluticasone per day or the equivalent of another inhaled corticosteroid to maintain asthma control in the period between the Screening and Challenge Visits

10. Inability to restrict use of antihistamines, nasal steroids, nasal decongestants, nasal anticholinergics or cromolyn prior to the NAC according to the period specified in the ICAC medication washout guidelines described in the MOP for Protocol ICAC-27
11. Development of any serious medical illness whose natural history, sequela, or treatment would be worsened or impaired by continuation in the protocol
12. Participant is "lost to follow-up," as defined in the MOP for Protocol ICAC-27.

11.3. Participant Replacement

Participants who withdraw or are withdrawn will not be replaced if they have received at least one dose of the investigational product.

11.4. Follow-up after Early Study Withdrawal

Participants who withdraw from the study after receiving one dose of investigational product will be followed as described in Section 6.4 Premature Discontinuation of Investigational Product.

11.5. Study Stopping Rules

The study may be prematurely terminated for the following reasons:

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 product
2. 1 anaphylactic reaction grade 3 or higher possibly related to the investigational product
3. ≥ 1 nonfatal SAE possibly related to the investigational product
4. If considered related to the study procedures or treatments, in at least 2 participants
    a. Anaphylactic reaction grade 2 or higher.
    b. Reduction of FEV1 by more than 15% from baseline and/or reduction of PEF by more than 20% from baseline and inability to perform spirometry due to administration of rescue medications in phase 1 or phase 2.

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 central IRB, and all parties concur with the resumption of the study. Local IRBs will be informed of the study stoppage and the DSMB/central IRB's decision on resumption of the study.

The study may be terminated by DAIT/NIAID or the NIAID Asthma and Allergy 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 the IND sponsor (DAIT/NIAID). Appropriate notifications will also be made to site principal investigators, Institutional Review Boards (IRBs) and health authorities.

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)

The investigator must report adverse events regardless of relationship to study therapy regimen or study mandated procedures.

Because some nasal and other local symptoms are expected to occur as a result of the nasal allergen challenge, only symptoms/signs described below as well as in Table 12.3.1.a will be recorded as AEs. However, if the investigator considers additional symptoms or signs, not covered under these lists, as AEs, they should be recorded and reported as described below.

Study mandated procedures and procedure-specific adverse events:

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

Nasal Allergen Challenge

- See table 12.3.1a

Allergen Skin Testing

- See table 12.3.1a

Peak Expiratory Flow

- See table 12.3.1b

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 drug or 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 the Investigator Brochure for German cockroach allergen extract, AllerMed'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 for study procedures described in the protocol.

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 the IND sponsor (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 Medical Monitor, 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

Information in this section complies with *ICH Guideline E-6: Guidelines for Good Clinical Practice;* and applies the standards:

- *Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (published September 2007)* for local reactions to study procedures.
- Grading System of Severity of Anaphylaxis adapted, from the grading scale of Brown et al.[11] for anaphylaxis and systemic reactions to study procedures.

- National Cancer Institute (NCI) *Common Terminology Criteria for Adverse Events Version 4.03* (published June 14, 2010) for all other reactions. (This document is referred to herein as the "NCI-CTCAE manual.")

12.3.1 Adverse Events Related to Nasal Allergen Challenge and Skin Testing

Excessive local reactions to nasal allergen challenge and skin testing not associated with systemic signs or symptoms will be graded according to Table 12.3.1a below; declines in PEF occurring during the Challenge Visit will be graded according to Table 12.3.1b below. If spirometry is performed because of a PEF less than 80% of baseline and the FEV1 is ≥ 85% of baseline value then the decline in PEF will not be considered an AE. All AEs should be recorded on the eCRF.

Table 12.3.1a. Grading of Local Reactions to Study Procedures

Grade	1	2	3	4
Nasal allergen challenge	Requiring antihistamines, decongestants or nasal steroids as rescue medication	Requiring oral steroids as rescue medication	Requiring a visit to a health care provider for treatment.	Life threatening and/or requiring hospitalization (e.g. upper airway obstruction)
Skin testing	Interfering with usual daily activities or sleep, but requiring no medication other than topical corticosteroids or antihistamines.	Interfering with usual daily activities or sleep and requiring oral steroids.	Requiring a visit to a health care provider for treatment	Not applicable

Table 12.3.1b. Grading of PEF Declines Occurring During the Challenge Visit

Grade	1	2	3	4	5
[1]**Peak Expiratory Flow**	79 - 75% of baseline[2] PEF value	74 - 70 % of baseline[2] value	69 - 50 % of baseline[2] value	< 50 % of baseline[2] value	Death

[1] If spirometry is performed because of a PEF less than 80% of baseline and the FEV1 is ≥ 85% of baseline value then the decline in PEF will not be considered an AE.

[2] Baseline refers to the PEF value (best of 3 efforts) prior to the initiation of the NAC.

All systemic reactions to skin testing or the NAC, regardless of severity grade, will be recorded as Adverse Events. Systemic reactions related to skin testing or nasal allergen challenge (including anaphylaxis) will be graded according to Table 12.3.1c Grading System of Severity of Anaphylaxis, adapted from the grading scale of Brown et al.[11]

Table 12.3.1c Grading System of Severity of Anaphylaxis

Grade	Defined By
1. Mild (skin & subcutaneous tissues, GI, &/or mild respiratory[1])	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 SpO2 ≤ 92% at any stage, hypotension, confusion, collapse, loss of consciousness; or incontinence

[1]During the Nasal Allergen Challenge, respiratory symptoms, upper or lower, will ONLY be considered as part of an anaphylaxis event if they appear together with other systemic symptoms, as described in the Table 12.3.1c, but not if they appear alone.

12.3.2 Rhinitis Symptoms

During the study it is anticipated that participants will experience allergic rhinitis symptoms related to the NAC including itching, sneezing, watery discharge, nasal congestion, and eye symptoms. These symptoms are consistent with moderate-severe allergic rhinitis caused by cockroach exposure in sensitized individuals. These symptoms therefore will not be reported as adverse events or grade 1 anaphylaxis. Only events with symptoms reaching the levels described in Table 12.3.1a will be recorded and reported as AEs.

12.3.3 Grading and Attribution of All Other Adverse Events

The study site will grade the severity of adverse events experienced by the study subjects not specified in 12.3.1 or 12.3.2, 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.

Events grade 1 or higher, not described in section 12.3.1 or 12.3.2, will be recorded on the appropriate AE case report form (eCRF) for this study.

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.

12.3.4 Attribution Definitions

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

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 12.3.4 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: there is insufficient evidence to suggest a causal relationship.
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

12.4.1 Collection Period

Adverse events (including SAEs) will be collected from the time of consent, until a subject completes study participation or until 10 days after he/she prematurely withdraws (without withdrawing consent) or is withdrawn from the study.

12.4.2 Collecting Adverse Events

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

- Observing the subject.
- Interviewing the subject [e.g., using a checklist, structured questioning, diary, etc.].
- Receiving an unsolicited complaint from the subject.
- In addition, an abnormal value or result from a clinical or laboratory evaluation can also indicate an adverse event, as defined in 12.3.3 Grading and Attribution of All Other Adverse Events

12.4.3 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 therapy regimen or 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 10 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 the IND Sponsor *DAIT/NIAID*

This section describes the responsibilities of the site investigator to report serious adverse events to the IND sponsor via the SAE eCRF. Timely reporting of adverse events is required by 21 CFR 312 and ICH E6 guidelines.

Site investigators will report to the SACCC (Rho Federal) and DAIT/NIAID Medical Monitor all serious adverse events (see Section 12.2.4, *Serious Adverse Event)*, 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

[redacted]

12.5.2 Reporting to Health Authority

After an adverse event requiring 24 hour reporting (per Section 12.5.1, *Reporting of Serious Adverse Events to the IND Sponsor*) is submitted by the site investigator and assessed by the IND sponsor (DAIT/NIAID). The IND sponsor must report an event to the appropriate health authorities using one of these two options:

12.5.2.1 Standard Reporting (report in the IND Annual Report)

This option applies if the AE is classified as one of the following:

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

Note that all adverse events (not just those requiring 24-hour reporting) will be reported in the IND Annual Report.

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 12.2.1.1, *Suspected Adverse Reaction* and Section 12.2, *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 sponsor (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., angioedema, hepatic injury, or Stevens-Johnson Syndrome);
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 shall 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.

The sponsor (DAIT/NIAID) must notify the FDA, 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.

Study investigators are responsible for SAE reporting to the respective IRB as mandated by the IRB.

12.5.3 Reporting of Adverse Events to Central IRB

All adverse events, including expedited reports, will be reported in a timely fashion to the central IRB in accordance with applicable regulations and guidelines. All Safety Reports to the FDA shall be distributed by the sponsor (DAIT/NIAID) or designee to all participating investigators for central IRB submission.

12.6 Pregnancy Reporting

The investigator shall be informed immediately of any pregnancy in a study subject. A pregnant subject will not undergo the NAC. If pregnancy occurs after the NAC procedure has occurred, 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. If pregnancy is detected during the study screen and prior to any study procedures, no pregnancy monitoring will be required.

The investigator shall report to the Statistical and Clinical Coordinating Center (SACCC) and the sponsor (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 except as specified above. The Pregnancy eCRF shall be updated and submitted to the SACCC when details about the outcome are available.

Information requested about the fetal outcome 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 SACCC and the sponsor (DAIT/NIAID) using the SAE reporting procedures described above.

12.7 Reporting of Other Safety Information

An investigator shall promptly notify 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 eCRFs.

In addition, the DAIT/NIAID 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 the IND Sponsor DAIT/NIAID and 12.6, Pregnancy Reporting.

12.8.2 DSMB Review

The DAIT NIAID and 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 and Safety Monitoring Board (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.

12.8.2.2.1 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 establish a range of German cockroach doses that, when delivered intranasally, can induce a positive response to NAC in adults (TNSS ≥8 out of 12 or a sneezing score of 3) and children (TNSS ≥6 out of 12 or a sneezing score of 3). Other secondary objectives are to determine whether these doses are safe, to test the validity of objective outcomes of nasal challenge, and to assess the reproducibility of the nasal challenge.

13.2 Outcomes

13.2.1 Primary Outcomes

The primary outcomes are:

1. The prevalence of positive NAC, defined as a sneezing score of 3 or a TNSS ≥8 out of 12 in Phase 1 or a TNSS ≥6 out of 12 in Phase 2.
2. The number of reported adverse events and serious adverse events, including their severity, seriousness, and treatment relatedness.

13.2.2 Secondary Outcomes

1. Number of sneezes.
2. Maximum TNSS recoded out of all doses received.
3. Change in TNSS.
4. Change in PNIF.
5. Change in PEF.
6. Visual Analog Scale (VAS).
7. Change in tryptase in nasal secretions
8. Change in albumin in nasal secretions

13.2.3 Exploratory Outcomes

1. Change in chemokines in nasal secretions
2. Change in cockroach-specific T-cell epitopes in peripheral blood

13.3 Measures to Minimize Bias

This is a one arm open label study without randomization. All laboratory assays for tryptase and albumin will be performed in a central laboratory.

13.4 Analysis Plan

13.4.1 Analysis Populations

The study population consists of adults aged 18 through 55 years (phase 1) and children ages 8 through 14 years (phase 2) who have a history of asthma and are German cockroach sensitive. The study will examine the safety of the administration of non-standardized German cockroach extract delivered intranasally. This is a phase I safety pilot study 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 dose during the Challenge Visit. All statistical analyses will be performed on the Safety Population.

13.4.2 Primary Analysis of Primary Outcomes

The first primary objective of this analysis is to estimate a probability of positive response at each dose, defined as reaching a sneezing score of 3 or a TNSS of ≥8 in Phase 1 or a TNSS of ≥6 in Phase 2. The probability of reaching a positive response will be estimated using the percentage of responses in subjects at each of the 9 doses. Although a participant will stop receiving doses once they have reached a sneezing score of 3 or a TNSS of ≥8 in Phase 1 or a TNSS of ≥6 in Phase 2, it is assumed that they would continue to respond for the remaining doses. Therefore, if 7 people respond prior to Dose 5, 3 will be tested at Dose 5, and the proportion presented for Dose 5 would be (7 + # responders at Dose 5)/10. Associated exact 95% confidence intervals will be estimated using the Clopper-Pearson method.

The second primary objective of this analysis is to assess if intranasal delivery of cockroach allergen via a nasal allergen challenge 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 and Other Outcomes

The secondary statistical analyses will include summary statistics for the secondary endpoints and correlation analyses. Changes from baseline levels of TNSS, PNIF, and PEF will be estimated in absolute and relative terms.

To assess reproducibility of the adult nasal challenge, the first dose at which a positive response occurs for an individual will be compared between study visits. A weighted Kappa statistic and associated 95% confidence interval will be estimated for each dose category to quantify agreement between study visits.

13.5 Interim Analyses

Not Applicable.

13.6 Sample Size Considerations

This pilot study is powered based on the first primary outcome, the prevalence of positive response to NAC at each dose, defined as a sneezing score of 3 or TNSS ≥8 out of 12 in Phase 1 or TNSS ≥6 out of 12 in Phase 2. Because no preliminary data exists for this pilot study, the first primary objective of the analysis will be to estimate the probability of response at each of the 9 doses in the 10 subjects in Phase 1.

The table below summarizes the probabilities of observing a given number of responses for a given dose, along with exact 95% confidence intervals.

Number of observed responses at given dose (out of 10 subjects)	Probability of Response (95% CI)
0	0 (0.00, 0.31)
1	0.1 (0.003, 0.45)
2	0.2 (0.03, 0.56)
3	0.3 (0.07, 0.65)
4	0.4 (0.12, 0.74)
5	0.5 (0.19, 0.81)
6	0.6 (0.26, 0.88)
7	0.7 (0.35, 0.93)
8	0.8 (0.44, 0.97)
9	0.9 (0.55, 1.00)
10	1 (0.69, 1.00)

The proposed sample size for phase 2 of this protocol is 25 cockroach-sensitive children. Each participant will receive the optimal range of doses found in phase 1. The sample size of 25 children was chosen to provide further information about appropriate dosing levels.

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 IND sponsor (DAIT/NIAID), 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

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.

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.

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 NIAID Medical Monitor and Project Manager, c) notify the SACCC, and d) complete the Protocol Deviation form. The Protocol Deviation (PD) 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, and documentation of a corrective action plan. The SACCC and the IND sponsor (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 appropriate review bodies (SACCC, DAIT/NIAID, and the central IRB, per IRB regulations). Protocol deviations will be reported to the DSMB and the central IRB.

16. Ethical Considerations and Compliance with Good Clinical Practice

16.1. Quality Control and Quality Assurance

The investigator is required to keep accurate records to ensure that the conduct of the study is fully documented. The investigator is required to ensure that all CRFs are completed for every participant entered in the trial.

The sponsor is responsible for regular inspection of the conduct of the trial, for verifying adherence to the protocol, and for confirming the completeness, consistency, and accuracy of all documented data.

The CRFs will be completed online via a web-based electronic data capture (EDC) system that has been validated and is compliant with Part 11 Title 21 of the Code of Federal Regulations. Study staff at the site will enter information into the electronic CRFs, and the data will be stored remotely at a central database. Data quality will be ensured through the EDC system's continuous monitoring of data and real-time detection and correction of errors. All elements of data entry (i.e., time, date, verbatim text, and the name of the person performing the data entry) will be recorded in an electronic audit trail to allow all changes in the database to be monitored and maintained in accordance with federal regulations.

16.2. Statement of Compliance

This clinical study will be conducted using current good clinical practice (GCP) guidelines and all applicable regulatory requirements, 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 central IRB. Any amendments to the protocol or to the consent materials will also be approved by the IND Sponsor, the IRB, and submitted to the FDA before they are implemented.

16.3. 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 have 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 (or their legally acceptable representative) 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 process will be ongoing. 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.

16.4. 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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