

STATISTICAL ANALYSIS PLAN
06 April 2017

**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**

PROTOCOL ICAC-27

SPONSOR

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DOCUMENT VERSION CONTROL

Version Number	Date	Comments/Changes
Version 0.1	14 March 2017	Draft for external review
Version 0.2	28 March 2017	Draft after first round of external comments
Version 0.3	03 April 2017	Draft after second round of external comments
Version 1.0	06 April 2017	Collected signatures and versioned to 1.0

APPROVALS

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List of Abbreviations

ACT	Asthma Control Test
AE	Adverse Event
eCRF	Electronic Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DAIT	Division of Allergy, Immunology, and Transplantation
DSMB	Data Safety Monitoring Board
IB	Investigator Brochure
ICAC	Inner-City Asthma Consortium
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
PNIF	Peak Nasal Inspiratory Flow
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
TNSS	Total Nasal Symptom Score
VAS	Visual Analog Scale

1. 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	<p>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.</p> <p>Secondary objectives are:</p> <ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 1. Change in chemokines and other biomarkers in nasal secretions 2. Change in cockroach-specific T-cell epitopes in peripheral blood
Accrual Objective	<i>35 (Phase 1 - 10 adults, Phase 2 - 25 children)</i>
Study Duration	<i>1 year</i>
Treatment Description	Participants will receive escalating doses of glycerinated German cockroach allergenic extract administered via the intranasal route.
Inclusion Criteria	<p>Individuals who meet all of the following criteria are eligible for enrollment as study participants for Phase 1a and Phase 2:</p> <ol style="list-style-type: none"> 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).

	<ol style="list-style-type: none"> 3. Have a history of asthma for a minimum of 1 year before study entry. <ol style="list-style-type: none"> 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: <ol style="list-style-type: none"> 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. <p>Individuals who meet the following criteria are eligible for enrollment as study participants in Phase 1b after completion of Phase 1a:</p> <ol style="list-style-type: none"> 1. The participant's asthma must be well controlled as defined by: <ol style="list-style-type: none"> 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	<p>Individuals who meet any of these criteria are not eligible for enrollment as study participants in Phase 1a and Phase 2:</p> <ol style="list-style-type: none"> 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: <ol style="list-style-type: none"> 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

	<p>one course within the last 3 months.</p> <ul style="list-style-type: none"> 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. <ol style="list-style-type: none"> 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. <p>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:</p> <ol style="list-style-type: none"> 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: <ul style="list-style-type: none"> a. Require a dose of greater than 500 mcg of fluticasone
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	<p>per day or the equivalent of another inhaled corticosteroid.</p> <ul style="list-style-type: none"> 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. <ul style="list-style-type: none"> 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 <ul style="list-style-type: none"> 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
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	<p>immunosuppressive medications in the period between Phase 1a and Phase 1b</p> <ul style="list-style-type: none"> 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. <p>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.</p> <p>Participants who meet any of the following criteria are not eligible for enrollment and may not be reassessed. Participants are ineligible if they:</p> <ul style="list-style-type: none"> 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	<p>Study enrollment and treatment will be suspended pending expedited review of all pertinent data after the occurrence of:</p> <ul style="list-style-type: none"> 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, <u>in</u>

	<p><u>at least 2 participants:</u></p> <ul style="list-style-type: none">a. Anaphylactic reaction grade 2 or higherb. 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.
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2. Introduction

This statistical analysis plan includes pre-planned analyses related to the study objectives outlined in the protocol.

3. General Analysis and Reporting Conventions

The following analyses and reporting conventions will be used:

- Categorical variables will be summarized using counts (n) and percentages (%) and will be presented in the form “n (%)” Percentages will be rounded to one decimal place.
- Numeric variables will be summarized using n, mean, standard deviation (SD), median, minimum (min), maximum (max). The min/max will be reported at the same level of significance as original data. The mean and median will be reported at one more significant digit than the precision of the data, and SD will be reported at two more significant digits than the precision of the data.
- The median will be reported as the average of the two middle numbers if the dataset contains an even number of observations.
- Test statistics including t and z test statistics will be reported to two decimal places.
- P -values will be reported to three decimal places if greater than or equal to 0.001. If less than 0.001, the value will be reported as “<0.001.” A p -value can be reported as “1.000” only if it is exactly 1.000 without rounding. A p -value can be reported as “0.000” only if it is exactly 0.000 without rounding.

If departures from these general conventions are present in the specific evaluations section of this SAP, then those conventions will take precedence over these general conventions.

4. Analysis Samples

The safety population will include all study participants who received the initial dose during the Challenge Visit. This population breaks down further into the Phase 1 adult and Phase 2 child cohorts.

5. Study Subjects

5.1 Disposition of Subjects

The disposition of all enrolled subjects in the Phase 1 adult and Phase 2 child cohorts will be summarized in tables and listed. The numbers and percentages of subjects in each cohort, and completing each study visit, as well as reasons for early termination from the study will be presented. For subjects discontinuing study participation early, the reasons for discontinuing study participation early will also be presented.

5.2 Demographic and Other Baseline Characteristics

Summary descriptive statistics for baseline and demographic characteristics will be reported by cohort. Demographic characteristics to be summarized include site, age, race, ethnicity, sex, and cockroach allergen home exposure level. Baseline clinical characteristics to be summarized include cockroach allergen skin prick test wheal size, cockroach specific IgE, history of rhinitis (yes or no), ongoing rhinitis (yes or no), and asthma treatment step equivalency (1-4).

6. Study Operations

6.1 Protocol Deviations

Protocol deviations will be listed by site with information such as type of deviation, severity of the deviation (major or non-major), date of occurrence, and the reason for the deviation. Protocol deviations will be summarized in tabular format by phase and by type of deviation.

7. Endpoint Evaluation

7.1 Overview of Efficacy Analysis Methods

7.1.1 Multicenter Studies

Study subjects will be recruited from 5 study sites: Cincinnati, Dallas, Denver, New York, and Washington DC. Due to the small number of subjects in the study, study data within each cohort will be analyzed as a whole, and no formal accommodation for site-to-site variation will be made. Basic descriptive analyses of baseline demographics, medical history, and key study endpoints will be repeated for each site individually in order to allow qualitative exploration of site-to-site variability.

7.1.2 Assessment Time Windows

All data collected at scheduled visits will be included in analyses, regardless of time of assessment and whether data were collected within protocol visit windows. Assessments occurring outside of established visit windows will be noted as protocol deviations.

Unscheduled visits may occur throughout the study. Measurements from unscheduled visits will be included in listings, but will not be analyzed in tabular displays or graphs.

7.1.3 Primary Efficacy Outcomes

The primary objective is to estimate the prevalence of positive Nasal Allergen Challenge response at each cockroach allergen dose in each of the Phase 1a adult and Phase 2 child cohorts.

7.1.4 Computation of the Primary Efficacy Outcomes

In adults in the Phase 1a cohort, a positive response at each dose will be defined as TNSS ≥ 8 or a sneezing score of 3. In children in the Phase 2 cohort, a positive response at each dose will be defined as TNSS ≥ 6 or a sneezing score of 3.

The probability of reaching a positive response will be estimated by calculating the percentage of responses in subjects at each of the 9 doses. Although a participant will stop receiving doses once they have a positive response, it is assumed that they would continue to respond for the remaining doses. For example, if 7 of the 10 participants in Phase 1 respond prior to Dose 5, 3 will be challenged with Dose 5, and the proportion presented for Dose 5 would be $(7 + \# \text{ responders at Dose 5})/10$.

7.1.5 Primary Analysis of the Primary Efficacy Outcome

Associated exact 95% confidence intervals for the probability of reaching a positive response at each dose will be estimated for each dose using the Clopper-Pearson method for both the Phase 1a and Phase 2 cohorts.

TNSS, sneeze score, and other TNSS component scores will also be summarized over all participants at each dose with tables and boxplots. TNSS and sneeze score at each dose will additionally be listed and overlaid graphically for each subject. Attainment of the positive response thresholds for TNSS and sneeze score at each dose will additionally be analyzed with frequency tables.

7.2 Secondary Efficacy Outcomes

Participants stopped receiving doses once they reached a positive response, so all doses were not observed for each subject. This truncated nature of the data violates assumptions of standard statistical tests. In light of this issue, we will use descriptive statistics to assess secondary study hypotheses instead of formal hypothesis tests.

7.2.1 Secondary Efficacy Outcome 1 – Number of Sneezes

The number of sneezes will be summarized across participants in each of the Phase 1a and Phase 2 cohorts at each dose during the challenge. Frequency tables will be used to descriptively assess whether there is an association between dose and number of sneezes. Number of sneezes at each dose will additionally be listed and displayed graphically for each subject.

7.2.2 Secondary Efficacy Outcome 2 – Maximum TNSS Score Over All Doses

The maximum TNSS score over all doses received in each of the Phase 1a and Phase 2 cohorts will be summarized across participants and examined with 95% confidence intervals and boxplots. Maximum TNSS score will additionally be listed for each subject.

7.2.3 Secondary Efficacy Outcomes 3-8 – Change from Baseline in TNSS, PNIF, PEF, VAS, Tryptase in Nasal Secretions, and Albumin in Nasal Secretions.

For each of the six variables TNSS, PNIF, PEF, VAS, tryptase, and albumin, the baseline score will be defined as the value obtained at the post-rinse baseline assessment in the challenge. The post-baseline score will be the one associated with the highest dose received in the challenge. Change from baseline will then be computed as post-baseline minus baseline. Whether change is different from zero will be assessed for each of these variables for each of the Phase 1a and Phase 2 cohorts using 95% confidence intervals and boxplots. Values for each of the six variables at each dose will be listed and displayed graphically for each subject. TNSS, sneeze score, and PNIF as well as TNSS, sneeze score, and VAS will be overlaid together graphically for each subject.

Tryptase and albumin will be transformed using a natural logarithm prior to analysis, as necessary. The lowest and highest detectable values will be substituted for values below and above the measureable thresholds, respectively. The number and percent of values that are above or below detectable thresholds will be tabulated for each variable and phase using frequency tables.

7.2.4 Secondary Efficacy Outcomes 9 – Reproducibility of the Primary Efficacy Outcome

The first dose at which a positive response occurs for an individual will be summarized for Phase 1b data in the same manner as in sections 7.2.1 and 7.2.2. The difference in the probability of reaching a positive response between Phase 1a and Phase 1b will be computed for each dose and summarized with 95% confidence intervals and boxplots. Frequency tables will be used to assess agreement between Phase 1a and Phase 1b in attainment of the positive response threshold.

8. Safety Evaluation

8.1 Overview of Safety Analysis Methods

All safety analyses will be carried out using the safety sample defined in Section 4 unless otherwise noted. Missing safety information will not be imputed. Safety will be analyzed separately in Phase 1a, Phase 1b, and Phase 2 through the reporting of adverse events (AEs).

Listings will be prepared for all safety measurements. All listings will be sorted in order of subject identifier and time of assessment.

8.2 Primary Adverse Events Endpoints

All AEs will be classified by system organ class (SOC) and preferred term, according to a standardized thesaurus (Medical Dictionary for Regulatory Activities [MedDRA] version 18.1). The severity of AEs will be classified, as applicable, using the following grading scales:

- The National Cancer Institute's Common Toxicity Criteria for Adverse Events version 4.03.
- Grading scale of local reactions related to the Nasal Allergen Challenge or skin testing.
- Declines in PEF during the Nasal Allergen Challenge visit
- Grading system of severity of anaphylaxis

Each AE is entered on the electronic case report form (eCRF) once at the highest severity.

An overall summary table will be developed to report the number of events and the number and percentage of subjects having at least one event in the following categories:

- AEs
- AEs indicated as serious
- AEs that lead to study drug discontinuation
- AEs with an outcome of death
- AEs that were reported as being related to a study drug, including instances where PEF declined by more than 20% from baseline
- AEs reported by maximum severity on each applicable grading scale.

Summary tables will present the total number of events as well as the number and percentage of subjects experiencing the events. If a subject experiences the same AE on multiple occasions, the event will be counted once for each occurrence when reporting the number of AEs. When reporting the number of subjects experiencing the events, a subject will only be counted once if they experience an event within the particular SOC or preferred term. Percentages will be based on the number of subjects in the safety population.

8.3 Deaths and Serious Adverse Events

Serious adverse events (SAEs) will be listed and summarized in the same manner described in Section 8.2. Separate displays listing and summarizing death, including time to death and cause of death, will also be created.

9. Other Analyses

9.1 Use of Medications

Medications will be coded according to the World Health Organization Drug Dictionary (WHODDE Version 2016.03). Medications reported on the CRF will be categorized for analysis as prior, concomitant, or after study treatment by comparing the medication start and stop dates with the first and last dose of study medication dates. Prior medications will have both the medication start and stop dates prior to the first dose of study medication date. After medications will have both the medication start and stop dates after the last dose of study medication date. All other medications will be classified as concomitant, indicating that use of the medication overlapped with use of the study medication by at least one day.

Displays of concomitant medication data will be limited to asthma and allergy medications for children and adults as well as anti-hypertensives, antipsychotics, antidepressants, and heartburn/GERD medications.

The number and percentage of subjects receiving prior, concomitant, and after medications will be presented overall, by cohort, and by medication class. When reporting the number of subjects receiving the medication, a subject will only be counted once if they ever received the medication within the medication class. Percentages will be based on the number of subjects in the analysis population.

10. Interim Analyses and Data Monitoring

The progress of the study will be monitored by the Data and Safety Monitoring Board (DSMB). The DSMB will be chartered to review safety data and to make recommendations regarding continuation, termination, or modification of the study. The DSMB will formally review the safety data at least yearly. The discontinuation of study treatment will also be periodically reported to the DSMB.

In addition, safety data will be reviewed by the DSMB when an event occurs that is of sufficient concern to the National Institute of Allergy and Infectious Diseases (NIAID) medical monitor or protocol chair to warrant review, or when an event occurs that could contribute to a predefined stopping rule specified in the protocol.

Findings will be reported to Institutional Review Boards (IRBs) and health authorities.