STATISTICAL ANALYSIS PLAN
29 March 2019 FINAL

Anti-TSLP plus antigen-specific immunotherapy for induction of tolerance in individuals with cat allergy

PROTOCOL NUMBER ITN057AD

SPONSOR

This clinical study is supported and conducted by the Immune Tolerance Network, which is sponsored by the National Institute of Allergy and Infectious Diseases.

Immune Tolerance Network
185 Berry Street, Suite 3515
San Francisco, CA 94107

National Institute of Allergy and Infectious Diseases
5601 Fishers Lane
Rockville, MD, 20892-9828

PREPARED BY

Rho, Inc.
6330 Quadrangle Drive
Chapel Hill, NC 27517
Telephone: (919) 408-8000
Fax: (919) 408-0999

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Version: 2.0

DOCUMENT VERSION CONTROL

Version Number	Date	Comments/Changes
1.0	12 April 2017	Final
2.0	29 March 2019	Updated per protocol amendment v6.0

APPROVALS

Approved: _____ Date: _____

Jonathan Corren, MD
Protocol Chair

_____ Date: _____

Lisa M. Wheatley, MD, MPH
NIAID Medical Monitor

_____ Date: _____

Srinath Sanda, MD
ITN Clinical Trial Physician

_____ Date: _____

Michelle Sever, PhD
Rho Scientist

_____ Date: _____

Miguel Villarreal, MS
Rho Statistician

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1. PROTOCOL SYNOPSIS

Title	Anti-TSLP plus antigen-specific immunotherapy for induction of tolerance in individuals with cat allergy.
IND Sponsor	NIAID
Conducted by	Immune Tolerance Network
Protocol Chair	Jonathan Corren, MD
Accrual Objective	121 participants total enrollment
Study Design	This is a randomized, placebo-controlled trial in which four groups of cat-allergic subjects are treated until week 48 and then are followed without additional treatment until week 104. Allergy-related endpoints and exploratory endpoints related to mechanisms of immune modulation and tolerance will be assessed at 52, 78 and 104 weeks. Starting 1-3 days prior to immunotherapy or placebo for immunotherapy, AMG 157 or placebo will be administered intravenously using investigational product supplied by the manufacturer. AMG 157 will then be administered once every 4 weeks at a dose of 700 mg IV. Each AMG 157 dose will be administered at least 1 day before immunotherapy through week 24, then on the same day as immunotherapy thereafter. The treatment period for AMG 157 or placebo will be 48 weeks. Concurrently, immunotherapy using a standard cat allergen extract or placebo will be administered subcutaneously with a cluster dose and schedule currently in widespread use in the clinical practice of allergy in the United States. There will be an up-dosing period (approximately 12 weeks) during which small doses are gradually increased to a maintenance dose. Dosing levels may be individually tailored based on subject response. The combined up-dosing and maintenance periods will total 48 weeks.
Study Duration	Total study duration will be 154 weeks. Study enrollment to occur over 46 weeks Individual subject study participation will be 108 weeks.
Primary Objective	To determine if anti-TSLP in conjunction with antigen-specific immunotherapy can induce tolerance to cat allergen.
Primary Endpoint	Total nasal symptom score (TNSS) AUC from 0 to 1 hour after cat allergen challenge at 104 weeks. TNSS is calculated with a scale of 0 to 3 on the 4 parameters of sneezing, rhinorrhea, nasal congestion and blockade, and pruritus. Maximum score is 12.
Secondary	Skin prick test endpoint titration at baseline, 1, 4, 12, 26, 52, 78, 104 weeks.

Endpoints

Skin early phase response (EPR) to intradermal testing at baseline, 26, 52, 104 weeks. EPR is the skin response at 15 minutes.

Skin late phase response (LPR) to intradermal testing at baseline, 26, 52, 104 weeks. LPR is the skin response at 6 hours.

Peak TNSS EPR at baseline, 26, 52, 78, 104 weeks. Peak is the highest value recorded between 0 and 1 hour inclusive

TNSS EPR at baseline, 26, 52, 78, 104 weeks. EPR is the TNSS AUC from 0 to 1 hour.

TNSS LPR at baseline, 26, 52, and 104 weeks. LPR is the TNSS AUC from 5 to 6 hours.

Peak nasal inspiratory flow (PNIF) LPR AUC at baseline, 26, 52, 104 weeks. LPR is the PNIF AUC from5 to 6 hours.

PNIF EPR AUC at baseline, 26, 52, 78, 104 weeks. EPR is the PNIF AUC from 0 to 1 hour.

Inclusion Criteria

Patients must meet all of the following criteria to be eligible for this study:

1. Age 18-65 years.
2. Removed in protocol version 4.0.
3. History of moderate-severe allergic rhinitis (AR) caused by cat exposure for at least 2 years.
4. Skin prick test wheal greater than or equal to 5 mm to standardized cat extract.
5. Removed in protocol version 3.0.
6. Screening nasal allergen challenge in which:
    - TNSS is less than or equal to 3 after the 0 concentration (vehicle control only) dose,
        - TNSS increase is less than or equal to 1 from the TNSS prior to allergen administration to the TNSS after the 0 concentration (vehicle control only) dose,
    - TNSS is greater than or equal to 8 after the highest dose,
    - Between the first non-zero dose and 10 minutes after the

highest dose, either:

- 3 or more sneezes are counted or
- Greater than 20% drop in PNIF is recorded.

7. Body mass index (BMI) is greater or equal to 18.0 and less than or equal to 35.0 kg/m^2, at screening.
8. Clinically acceptable physical examination and electrocardiogram (ECG) results (12-lead reporting RR, PR, QRS, QT and QTcF) prior to Day 0 based on the opinion of the investigator.
9. Adequate renal function defined as CrCl greater than 80 mL/min using the Cockcroft Gault equation.
10. For women of childbearing age, a willingness to use a highly effective form of contraception for four months after last dose of study medication. Highly effective methods of birth control include abstinence, vasectomy by the male partner, or a condom with spermicide in combination with either hormonal birth control, IUD or barrier methods used by the woman.
11. For men with female partners of childbearing potential, agreement not to donate sperm and to inform their female partner of their participation in this clinical study and use highly effective methods of birth control for four months after last dose of study medication. Highly effective methods of birth control include abstinence, vasectomy, or a condom with spermicide in combination with either hormonal birth control, IUD or barrier methods used by the woman.
12. The ability to give informed consent and comply with study procedures.
13. Not currently taking and, for the duration of the study, agreement not to take any form of immunotherapy, including sublingual, subcutaneous or investigational immunotherapy.

Exclusion Criteria

Patients who *meet any* of the following criteria will *not* be eligible for this study:

1. Removed in protocol version 4.0.
2. Prebronchodilator FEV1 less than 80% of predicted value at screening visit.
3. Removed in protocol version 3.0.
4. History of asthma meeting the NAEPP EPR3 classification of mild-persistent or worse in the past year,

other than with cat exposure, requiring regular inhaled corticosteroids for greater than 4 weeks per year.

5. History of serious chronic medical conditions which might interfere with treatment or assessments.
6. History of emergency visit or hospital admission for asthma in the previous 12 months.
7. History of chronic obstructive pulmonary disease (COPD).
8. History of significant recurrent acute sinusitis, defined as 2 episodes per year for the last 2 years, all of which required antibiotic treatment.
9. History of chronic sinusitis, defined as a sinus symptoms lasting greater than 12 weeks that includes 2 or more major factors or 1 major factor and 2 minor factors. Major factors are defined as facial pain or pressure, nasal obstruction or blockage, purulent or discolored postnasal discharge, purulence in nasal cavity, or impaired or loss of smell. Minor factors are defined as headache, fever, halitosis, fatigue, dental pain, cough, and ear pain, pressure, or fullness.
10. History of systemic disease affecting the immune system such as autoimmune diseases, immune complex disease, or immunodeficiency, where, in the opinion of the study physician, participation in the trial would pose a risk or significant effect on the immune system.
11. Type I or type II diabetes.
12. Evidence of any clinically significant active or suspected bacterial, viral, fungal or parasitic infections within 14 days prior to screening nasal allergen challenge. Participants may be re-evaluated for eligibility after an appropriate course of treatment has been completed and symptoms have resolved.
13. High risk of parasitic disease as judged by the investigator.
14. Positive QuantiFERON® tuberculin test unless the potential subject has been treated with appropriate chemoprophylaxis.
15. Exposure to an individual with active tuberculosis within

six months from randomization.

16. Subjects tested positive for HIV antibody, Hep B surface antigen, or Hep C antibody.
17. Removed in protocol version 3.0.
18. History of malignancy of any type, including basal cell and squamous cell cancers of the skin, within 5 years of enrollment
19. Any smoking within the last year or a history of greater than or equal to 10 pack years.
20. Previous immunotherapy treatment with cat allergen within the previous 10 years.
21. Any history of grade 4 anaphylaxis due to any cause as defined by the CTCAE grading criteria for immunotherapy.
22. History of bleeding disorders or treatment with anticoagulation therapy.
23. Treatment with omalizumab within 6 months prior to randomization.
24. Currently taking any of the following medications: beta blockers; tricyclic antidepressants; monoamine oxidase inhibitors; or anti-IgE monoclonal antibody treatment.
25. Ongoing systemic immunosuppressive treatment.
26. History of intolerance to the study therapy, rescue medications, or their excipients.
27. For women of childbearing age a positive serum or urine pregnancy test with sensitivity of less than 50 mIU/mL within 72 hours before the start of study therapy.
28. The use of any investigational drug or currently using an investigational device within 30 days or five half-lives (whichever is longer) prior to randomization.
29. The presence of any medical condition that the investigator deems incompatible with participation in the trial.

Stopping Rules

Enrollment in the study will be stopped and administration of the investigational medication AMG 157 will be halted pending review by

DSMB, DAIT and the ITN if any of the following criteria are met:

1. Death of any participant at least possibly related to study participation.

2. Grade 4 anaphylaxis at least possibly related to study participation.

3. Two participants have a grade 3 or higher adverse event at least possibly related to AMG 157.

4. Five participants discontinue study treatment by experiencing two occurrences of grade 3 systemic reactions after administration of study therapy or nasal challenge.

5. Two participants have a systemic infection which in the judgment of the NIAID medical monitor is unusual or unusually severe.

6. Grade 3 serum sickness at least possibly related to study participation.

2. INTRODUCTION

This statistical analysis plan (SAP) only includes analyses related to the clinical endpoints. Mechanistic analyses will be performed at the Immune Tolerance Network (ITN), and a separate analysis plan will be created to detail the planned analyses. Relevant clinical data from the study will be submitted to the ITN Biomarker and Discovery Research (BDR) and ITN Bioinformatics Groups (BiG) to augment the mechanistic analyses.

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."

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

Intent to treat (ITT) sample: All randomized participants. ITT participants will be analyzed with the group to which they were randomized, regardless of the study therapy actually received. If participants discontinue treatment post-randomization, they will be invited to complete study assessments throughout the duration of the trial.

Per protocol (PP) samples: All ITT sample participants who remained in the study for at least 2 years and who had the primary endpoint assessed. Participants in the PP sample must be compliant with study medication and study assessments, defined as 1) The primary TNSS AUC endpoint at 104 weeks is collected and 2) Taking 75% of their study medication for the duration for the study. Compliance with study medication will be as assessed by meeting one or both of these conditions:

- 48 weeks of both SIT and AMG 157 treatments are taken regardless of dosage
- At least 12 of 16 (>=75%) prescribed SIT doses of 3000+ BAU and 10 of 13(75%) AMG 157 infusions are taken.

Safety sample (SS): All randomized participants who received at least one dose of study therapy, whether by IT injection or infusion. Participants in the safety sample will be analyzed with the group according to the study therapy they actually received, regardless of their randomized assignment.

5. STUDY SUBJECTS

5.1 Disposition of Subjects

The disposition of all enrolled participants will be summarized in a table and listed.

The numbers and percentages of participants randomized and in each analysis sample will be displayed by randomized group. Reasons for early treatment discontinuation and early termination from the study will be presented.

The listing of disposition data will also include dates of the first dose, randomization, last visit date, treatment discontinuation, and termination from protocol. The listing will be sorted by treatment group and subject ID.

5.2 Demographic and Other Baseline Characteristics

Summary descriptive statistics for baseline and demographic characteristics will be reported for the ITT and PP samples. Characteristics to be summarized include age, race, ethnicity, sex, body weight, height, and BMI.

Demographic and baseline characteristic data will be listed by treatment group and subject ID.

6. STUDY OPERATIONS

6.1 Protocol Deviations

Only major protocol deviations will be collected for this study. Protocol deviations will be listed with information such as type of deviation, date of occurrence, the reason for the deviation, and steps taken to address the deviation.

6.2 Treatment Compliance

Cat immunotherapy or placebo will be administered weekly during the updosing phase. Additional visits at the discretion of the investigator may be required for adjustment of allergen doses for individual participants during the updosing or maintenance phases of immunotherapy. If participants develop side effects during the updosing phase of subcutaneous immunotherapy, the site principle investigator, in consultation with the protocol chair and NIAID medical monitor, may decide to limit the planned maintenance dose of immunotherapy injections to less than 5,000 BAU. Efforts should be made to reach a dose of at least 3000 BAU to maximize potential for effectiveness.

Immunotherapy dose (BAU) will be presented graphically in a participant-level dot plot by site and day of injection relative to first treatment. The percent of cumulative received dose relative to expected total cumulative dose will be summarized by treatment group. A participant-level listing will also be produced.

Intravenous infusions will be administered every four weeks as specified in the schedule of events. Both AMG 157 and placebo will be delivered by an infusion of 100ml of sterile diluent over a 1-hour period. A participant-level dot plot by site and day of infusion will be produced graphically. Each participant is expected to receive a total of 13 AMG 157 infusions. The percent of received total doses relative to number of expected doses will be summarized by treatment group and displayed in a participant-level listing.

7. ENDPOINT EVALUATION

7.1 Overview of Efficacy Analysis Methods

7.1.1 Multicenter Studies

Study subjects will be recruited from 9 study sites. Due to the small number of subjects in the study relative to the number of sites in the study, study data will be summarized as a whole, and no formal analysis stratified by site will be made.

7.1.2 Assessment Time Windows

TNSS assessments at Weeks 52 and 104 will be assessed regardless if visit was performed out of window.

Other clinical endpoints including but not limited to Skin Prick Tests and Intradermal Skin Tests will be evaluated regardless if visit was performed out of window.

Allowable visit windows for all scheduled visits are provided in Table 7-1.

Table 7-1 Visit Windows

Windows for visits -1 and visit 0 are defined with respect to visit -2. Windows for the remainder of the visits are defined with respect to visit 0. All scheduled study visits should occur within the time limits specified below:

Visit -2:	no window
Visit -1:	+14 days
Visit 0:	+7 days
Visits 1 through 25:	±3 days
Visits 26 – 31:	AMG 157/placebo and cat immunotherapy/placebo may be given on separate days, ±3 days
Visit 32:	±7 days
Visits 33 through 38:	±30 days

Unscheduled visits may be performed to investigate poorly controlled allergic symptoms or symptoms that may be related to study therapy.

All data will be included in analyses, regardless of time of assessment. A listing of visits and timing of visits (in window vs. out of window) will be produced by site and subject ID.

7.2 Primary Endpoint

The primary endpoint is the response to Nasal Allergen Challenge (NAC) at 104 weeks measured by Total Nasal Symptom Score (TNSS) area under the curve (AUC) 0-1 hour.

7.2.1 Computation of the Primary Endpoint

The trapezoidal rule will be used to estimate the AUC of the TNSS measured at 0 to 1 hours of the Nasal Allergen Challenge (NAC).

7.2.2 Primary Analysis of the Primary Endpoint

The primary analysis will compare the mean TNSS AUC from 0 to 1 hour after cat Nasal Allergen Challenge at 104 weeks by treatment group, using a longitudinal repeated measures model in the ITT sample. The model will include fixed effects for treatment, time, and treatment by time interaction and will include covariates for site and baseline TNSS AUC. Other covariates such as cat exposure (high vs. low) and IT lot will be considered in the model. Since a nonlinear relationship between the TNSS AUC outcome and time is expected, time will be treated as a categorical variable. An unstructured covariance structure will be used to model the correlation among time points within a subject. If the model assuming an unstructured covariance matrix does not converge, a spatial power covariance structure will be used instead. The primary endpoint will be assessed at week 104 using a contrast in least squares means between the following groups: cat immunotherapy plus AMG 157 and cat immunotherapy plus placebo.

A supplementary analysis of the primary endpoint will also be performed using the PP sample.

7.2.3 Multiple Imputation for Missing Data

The dropout rate in this study is unknown but is assumed to be equally distributed among the randomized groups. The primary analysis does not require that missing data be imputed. However, any supportive cross-sectional analyses may require missing data to be imputed.

For analyses that require imputation, an iterative form of stochastic imputation will be used from the observed data to estimate multiple values for any data that are missing. The Markov Chain Monte Carlo method will be used assuming that all variables used in the model for the imputation procedure follow a joint multivariate normal distribution. A data augmentation algorithm will be used to impute values drawing from a multivariate normal distribution. A minimum of 10 imputation datasets will be generated using variables applicable to the analysis. Auxiliary variables will also be considered when specifying the imputation model if applicable.

Each imputed dataset will be analyzed separately and will compare the LS Means of TNSS AUC from 0 to 1 hour at 104 weeks by treatment group, using ANCOVA to adjust for site, baseline TNSS AUC (0-1hr) at the 0.05 level of significance between the following groups: cat immunotherapy plus AMG 157 and cat immunotherapy plus placebo. Estimated coefficients from each iteration will be pooled using the arithmetic mean to generate a single set of coefficients.

7.2.4 Sensitivity Analyses of the Primary Endpoint

A sensitivity analysis will be performed to address the effect of missing data on the primary analysis. A complete case analysis of the ITT sample will be performed on participants with baseline and week 104 NAC assessments as specified in section 7.2.3. Additionally, participants in the ITT sample who discontinued study therapy or terminated the study prior to week 104 will have their primary endpoint imputed under the assumptions of Missing At Random (MAR) and Missing Not At Random (MNAR).

In addition to Multiple Imputation as described in section 7.2.3, a sensitivity analysis with a "tipping-point" approach will be implemented under the MNAR assumption to determine a delta, i.e., a shift parameter for the cat immunotherapy plus AMG 157 group, that reverses the study's conclusion from favorable to non-significant. Under this framework, it will be assumed that subjects who terminated early from the study in the cat immunotherapy plus AMG 157 group would have a worse unobserved treatment effect as compared to the observed efficacy in the subjects who completed the week 104 NAC assessment. Also, it is assumed that subjects who terminated early in the cat immunotherapy plus placebo group would have behaved similarly in terms of their immunotherapy and tolerance to the subjects who completed the study. A range of delta values will be considered. A table comparing the primary analysis results from the longitudinal repeated measures model, the complete case analysis results, and the results under the different assumptions, imputation methods, and deltas will be presented.

7.2.5 Supplemental Analysis of Primary Endpoint

Mean TNSS AUC 0-1hr at 104 weeks will be estimated by treatment group using a two-way analysis of variance technique for the ITT and PP samples. Covariates considered will be site, baseline TNSS AUC. Immunotherapy (active vs. placebo) and AMG 157 (active vs. placebo) will be included as main effects with an Immunotherapy-by-AMG 157 interaction term. All pair-wise comparisons will be reported; no correction for multiple testing will be done.

7.3 Secondary Endpoints

This study is not designed or powered to perform hypothesis testing on secondary endpoints. All secondary analyses will be treated as supportive. P-values will be presented for the secondary endpoints but will not be adjusted for multiplicity and should be interpreted with caution. The secondary endpoints will be analyzed using the ITT and PP samples, separately, and will include all pairwise comparisons among the four study groups.

1. Skin prick test endpoint titration at baseline, 1, 4, 12, 26, 52, 78, 104 weeks.
2. Skin early phase response (EPR) to intradermal testing at baseline, 26, 52, 104 weeks. EPR is the skin response at 15 minutes.

3. Skin late phase response (LPR) to intradermal testing at baseline, 26, 52, 104 weeks. LPR is the skin response at 6 hours.
4. Peak TNSS EPR at baseline, 26, 52, 78, 104 weeks. Peak is the highest value recorded between 0 and 1 hour inclusive.
5. TNSS EPR at baseline, 26, 52, 78, 104 weeks. EPR is the TNSS AUC from 0 to 1 hour.
6. TNSS LPR at baseline, 26, 52, 104 weeks. LPR is the TNSS AUC from 5 to 6 hours.
7. Peak nasal inspiratory flow (PNIF) LPR AUC at baseline, 26, 52, 104 weeks. LPR is the PNIF AUC from 5 to 6 hours.
8. PNIF EPR AUC at baseline, 26, 52, 78, 104 weeks. EPR is the PNIF AUC from 0 to 1 hour.

Parametric and nonparametric statistical methods will be considered when evaluating secondary endpoints depending on the distribution of the resulting data. The data will first be investigated to determine whether an assumption of normality is valid. If the data are grossly non-normal, then nonparametric methods will be considered.

7.3.1 Skin Prick Test Titration

Wheal size for skin prick test serial titration at baseline, 1, 4, 12, 26, 52, 78, and 104 weeks will be summarized by concentration and treatment group, separately, and presented as a series of figures. The mean of the left and right columns at each concentration and timepoint for each subject will be computed prior to any descriptive presentations and used for all analyses.

The estimated Least Squares Means (LS Means) wheal size and 95% CI will be plotted by treatment group over time for each concentration. Pairwise comparisons among the four groups at each timepoint that are significant at an alpha-level of 0.05 will be indicated in the figures. A similar longitudinal repeated measures model as described in section 7.2.2 will be used to estimate all parameters and compute pairwise comparisons.

Additionally, the AUC will be calculated for each subject's serial titration and summarized by treatment group and timepoint. AUC will be calculated using the trapezoidal rule over the course of concentration values. The analysis of AUC will compare the mean AUC by treatment group at each visit using a longitudinal repeated measures model as described above.

Cross-sectional analyses will also be considered at each timepoint. The comparison of LS Means among the four groups, adjusting for site and baseline AUC, will be computed using ANCOVA at the 0.05 level of significance.

Additionally, skin prick test serial titration mean diameter wheal results will be expressed as the concentration of allergen that caused a 5 mm wheal, or a wheal size as determined by interpolation of the dose-response curve, at each post-baseline visit.

7.3.2 Skin LPR and Skin EPR

The frequency of the concentration which resulted in a 15mm or greater wheal for intradermal skin testing will be tabulated at baseline by treatment group.

The LPR and EPR wheal size will be summarized by treatment group at each assessed visit (weeks 26, 52, and 104). The analyses of each endpoint will compare the LS Means wheal size for each visit, separately, using a longitudinal repeated measures model as described in section 7.2.2, adjusting for site, provocative dose, and other covariates. The estimated LS Means and 95% CI will be plotted over time by treatment group; any significant (at an alpha-level of 0.05) pairwise comparisons will be indicated in the figure.

Additionally, cross-sectional analyses will be performed at each timepoint using ANCOVA at the 0.05 level of significance adjusting for site, provocative dose, and other covariates. All results will be plotted in a figure as specified above.

7.3.3 TNSS Peak, TNSS AUC EPR, and TNSS AUC LPR

Nasal LPR and nasal EPR will be defined as the TNSS AUC over the specified time periods after allergen challenge at 26, 52, 78 (EPR only), and 104 weeks. The analysis of LPR and EPR will compare the LS Means of TNSS AUC by treatment group at each timepoint, separately, using a longitudinal repeated measures model as described in section 7.2.2.

Additionally, a cross-sectional analysis of LPR and EPR will compare the LS Means of TNSS AUC by treatment group adjusting for site, baseline LPR and EPR using ANCOVA at the 0.05 level of significance.

Additionally, AUC as measured from 0-6 hours and from 1-6 hours will be analyzed longitudinally and cross-sectionally.

Peak TNSS will be analyzed similarly.

7.3.4 PNIF, PNIF EPR, PNIF LPR

PNIF, PNIF LPR, and PNIF EPR will be defined as PNIF AUC over the specified time periods after allergen challenge at Weeks 26, 52, 78 (EPR only), and 104. PNIF AUC is defined as the AUC over the entire NAC (0-6hr) time. The analyses for these three endpoints will compare the LS Means of the PNIF AUC at Weeks 26, 52, 78 (EPR only)

and 104 using a longitudinal repeated measures model (as specified in Section 7.2.2), adjusting for baseline PNIF AUC and site. Other covariates will be considered. Additional cross-sectional analyses will compare the LS Means of PNIF at each timepoint by treatment group, adjusting for site and baseline PNIF using ANCOVA and the 0.05 level of significance.

Additionally, AUC as measured from 1-6 hours will be analyzed similarly.

7.4 Mechanistic Assessments

TBD

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. These analyses will not be stratified by site.

8.2 Adverse Events

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 17.0 or higher).

The severity of AEs will be classified using several different grading scales:

Local reactions to cat immunotherapy not associated with systemic signs or symptoms will be graded according to the table in Section 8.2.2 of the protocol.

Systemic reactions to cat immunotherapy will be graded according to the WAO Subcutaneous Immunotherapy Systemic Reaction Grading System (see appendix 4 of the protocol).

All other adverse events related to cat immunotherapy or to AMG 157 will be graded according to the criteria set forth in the NCI-CTCAE (v4.03 published June 14, 2010).

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

Treatment-emergent AEs will be identified as those with an onset date on or after the first dose of study medication as well as those with onset before first dose but that continued and worsened in severity after first dose. If the start of the AE in relation to the start of study medication cannot be established (e.g., the start date for the AE is missing), then the AE will be considered treatment-emergent. All data tabulations will be of only treatment-emergent events while non-treatment-emergent AEs will be listed separately.

8.2.1 Collection Period for AEs and SAEs:

All systemic reactions and all grade 2 or greater local reactions occurring within 72 hours after cat immunotherapy and/or study procedures will be collected from visit -2 (week -4) until the participant completes the study (visit 40/week 104) or prematurely withdraws from the study. All other AEs will be collected from visit 0 (week 0) until the participant completes the study (visit 40/week 104) or prematurely withdraws from the study.

Serious AEs will be collected from visit -2 (week -4) until 30 days after the participant completes the study (visit 40/week 104) or prematurely withdraws from the study.

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

- AEs
- AEs indicated as serious
- AEs that were reported as related to either Immunotherapy/Placebo or AMG 157/Placebo that lead to discontinuation to study therapy
- AEs with an outcome of death
- AEs that were reported as being related to a study therapy or study procedure
- AEs reported by maximum severity for local reactions, systemic reactions, and CTCAE-graded events

In addition, AEs classified by MedDRA SOC and preferred term will be summarized for each treatment group and overall for each of the following:

- All AEs
- AEs by maximum severity for local reactions, systemic reactions, and CTCAE-graded events
- AEs by relationship to study therapy or study procedure

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.

Separate data listings will be provided for treatment-related AEs and AEs leading to study drug discontinuation.

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.

8.4 Clinical Laboratory Evaluation

Pertinent clinical laboratory measurements will be plotted for data presentations. Results will be converted to standardized units where possible. For numeric laboratory results, descriptive statistics of laboratory values and the change from baseline of laboratory values will be presented for each treatment group and overall. For categorical laboratory results, the number and percentage of subjects reporting each result will be presented for each treatment group and overall. Data listings sorted by treatment group, subject ID,

laboratory parameter, and time of assessment will also be provided for clinical laboratory measurements.

8.4.1 Vital Signs

Data listings sorted by treatment group, subject, vital sign parameter, and time of assessment will be provided for vital signs measurements.

8.4.2 Physical Examinations

Data listings will be provided for physical examination results and sorted by treatment group, subject, body system, and time of assessment.

9. OTHER ANALYSES

9.1 Use of Medications

Medications will be coded according to the World Health Organization (WHO) Drug Dictionary (version 2014.01). 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.

Separate data listings will be provided for prior, concomitant, and after medications.

10. INTERIM ANALYSIS

The interim analysis will be performed by an unblinded statistician who is not the primary study statistician. All data presentations will be prepared by the study statistician using partially blinded treatment codes that do not correspond to true treatment codes. The unblinded statistician will re-run all data presentations on the true treatment codes and produce a closed report for the DSMB to review. The closed report will not be made available to the study team.

The interim analysis will be performed on an initial cohort consisting of the first 10 participants enrolled into each treatment group who have either completed 48 weeks of both immunotherapy and AMG 157 treatment, regardless of dosing or have taken at least 12 of 16 prescribed immunotherapy injection doses of 3000 BAU or greater and 10 of 13 AMG 157 infusion without completing 48 weeks of treatment. The first 10 participants in each treatment group must also have evaluable baseline and Week 52 TNSS NAC data.

If the interim analysis does not coincide with a regularly planned DSMB review, an ad-hoc meeting will convene to review the data presentation.

An interim analysis for futility based on conditional power will be calculated assuming that there will be an observed difference in TNSS AUC 0-1 hr at week 52 of 32% comparing:

- cat immunotherapy plus AMG 157 to placebo-placebo
- cat immunotherapy plus placebo to placebo-placebo
- the combination of cat immunotherapy plus AMG 157 and cat immunotherapy plus placebo to placebo-placebo

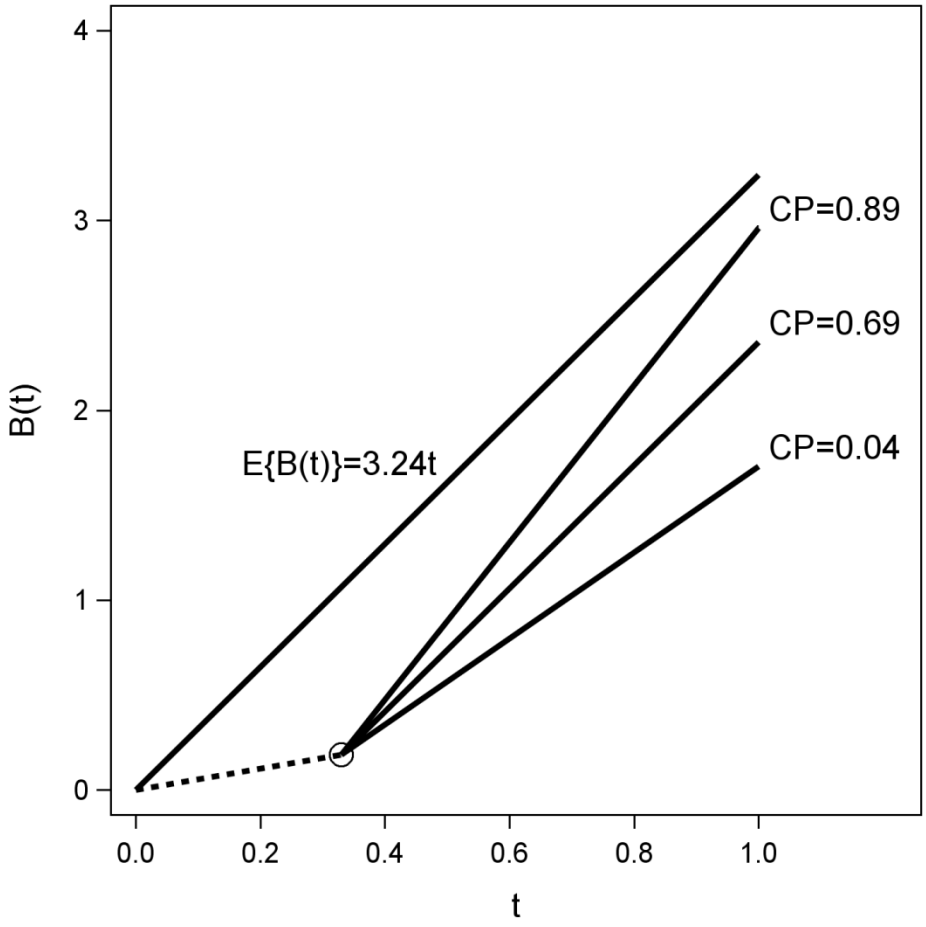
First, conditional power will be calculated using the originally assumed treatment effect and standard deviation. Secondly, conditional power will be calculated using the currently observed treatment effect, and the currently observed standard deviation. Lastly, conditional power will be calculated using the originally assumed treatment effect and the observed standard deviation. Conditional power will be computed using the least squares means estimates for each treatment group, adjusting for site and baseline AUC (0-1hr). The root mean square error from the model will be used as the estimate for the observed standard deviation.

If the conditional power is ≥33% for any of the group comparisons, that will be taken as evidence against futility and as an indication that the trial should proceed.

If the conditional power is <33% for all the group comparisons, that will be taken as evidence of futility and consideration will be given to terminating the study based upon the recommendation of the DSMB and at the discretion of the ITN and NIH.

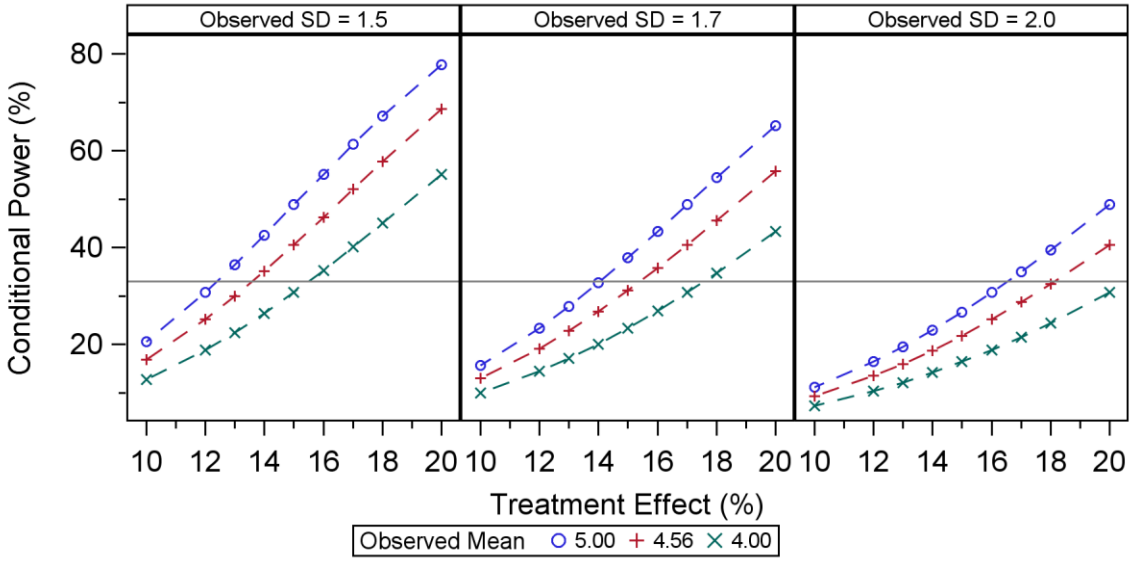
Since the main outcome of the study, tolerance, cannot be measured at week 52, and the main group comparison for the primary endpoint is not used in the interim analysis, no alpha adjustment will be made for the final analysis.

For each of the group comparisons, a figure similar to the one below will be generated. The solid line joining the origin and (1, 3.24) represents the expected value under the original assumptions for treatment effect and standard deviation. The x-axis represents the trial fraction and the y-axis, the Brownian motion (B-values), whose mean is a linear function of t. The circle represents the B-value at the time of the interim analysis using the current trend of data. A circle that lies below the line indicates that the trend at the interim analysis is poorer than expected. Each line joining the circle and B(t) when t=1 is the conditional power (CP) under the following assumptions: 1) Originally assumed treatment effect and standard deviation, 2) the originally assumed treatment effect and the observed standard deviation, and 3) the observed treatment effect and observed standard deviation.



The operating characteristics of the conditional power analysis are shown below for various values of the observed treatment effect (x-axis) ranging from a 10% difference between groups to 20% difference between groups (n=10 per group) for various mean

values (dashed lines) of TNSS AUC 0-1hr for the placebo-placebo group. Each of the three panels represents possible values for the observed standard deviation ranging from 1.5 to 2.0 and the horizontal reference line shows 33% conditional power. If the observed mean AUC 0-1hr in the placebo-placebo group is 4.56 and the pooled empirical standard deviation is 1.5, an immunotherapy treatment effect of at least 14% would yield a conditional power of more than 33%, giving evidence against futility.



11. CHANGES TO THE ANALYSES PLANNED IN THE PROTOCOL

12. REFERENCES

13. ATTACHMENTS