NCT05430919

STATISTICAL ANALYSIS PLAN
VERSION: FINAL

Clinical Study Protocol Title:	A Two-Part Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy of the Anti-Bet v 1 Monoclonal Antibodies to Reduce Allergic Rhinitis and Conjunctivitis Symptoms and Skin Test Reactivity upon Exposure to Birch Allergen
Compound:	REGN5713, REGN5714, REGN5715
Protocol Number:	R5713-5714-5715-ALG-21111 Amendment 1
Clinical Phase:	Phase 2
Sponsor:	Regeneron Pharmaceuticals, Inc.
Versions/Dates:	Original Statistical Analysis Plan / 31 May, 2023

The approval signatures below indicate that these individuals have reviewed the Statistical Analysis Plan (SAP), and agreed on the planned analysis defined in this document for reporting.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
BOCF	Baseline observation carried forward
BPS	Birch pollen season
BUN	Blood urea nitrogen
CRF	Case report form (electronic or paper)
CSAC	Clinique Spécialisée en Allergie de la Capitale
CSMS	Combined Symptom and Medication Score
DMS	Daily Medication Score
ECG	Electrocardiogram
EEU	Environmental exposure unit
EOS	End-of-study
FAS	Full analysis set
FDA	United States Food and Drug Administration
ICF	Informed consent form
ISR	Injection Site Reaction
mAb(s)	Monoclonal antibody(ies)
MWD	Mean wheal diameter
MI	Multiple imputation

OPS	Oak pollen season
PFASQ	Pollen Food Allergy Symptom Questionnaire
PK	Pharmacokinetic
PI	Principal investigator
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
RQLQ(S)	Rhinoconjunctivitis Quality of Life Questionnaire
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SC	Subcutaneous
sIgE	Allergen-specific immunoglobulin E
SCIT	Subcutaneous immunotherapy
SLIT	Sublingual immunotherapy
SOC	System organ class
SPT	Skin prick test [tSPT = SPT using serial allergen titrations]
TEAE	Treatment-emergent adverse event
TNSS	Total Nasal Symptom Score
TOSS	Total Ocular Symptom Score
TSS	Total Symptom Score
WBC	White blood cell

1. OVERVIEW

The Statistical Analysis Plan (SAP) is intended to be a comprehensive and detailed description of the statistical methods, timing and presentation of analyses to be used for the study, as specified in protocol R5713-5714-5715-ALG-21111, amendment 1 dated Nov 11, 2022.

1.1. Study Description and Objectives

This two-part randomized, double-blind, placebo-controlled study is designed to assess the efficacy of the anti-Bet v 1 monoclonal antibodies to reduce allergic rhinitis and conjunctivitis symptoms and skin test reactivity upon exposure to birch allergen. The study will assess the efficacy of the anti-Bet v 1 monoclonal antibodies, in combination and as a single antibody.

1.1.1. Primary Objective(s)

The primary objective of this study is to assess the efficacy of a single dose of the anti-Bet v 1 monoclonal antibodies in the reduction of allergic nasal symptoms during an out-of-season birch allergen environmental exposure unit (EEU) challenge in participants receiving REGN5713-5714-5715 versus placebo (Part A).

1.1.2. Secondary Objective(s)

The secondary objectives are:

Out-of-season Birch EEU challenges (Part A):

- To assess the magnitude and duration of efficacy of a single dose of the anti-Bet v 1 monoclonal antibodies (dose #1) in the reduction of allergic symptoms during the out-of-season birch allergen EEU challenges in participants receiving REGN5713-5714-5715 versus placebo, REGN5713-5715 versus placebo, and REGN5715 versus placebo
- To compare differences in the degree of reduction of allergic symptoms during the out-of-season EEU challenges in participants receiving the different combinations of the anti-Bet v 1 antibodies in those receiving REGN5713-5714-5715, REGN5713-5715, or REGN5715

Out-of-season Oak EEU challenge (Part A):

- To assess the efficacy of a single dose of the anti-Bet v 1 monoclonal antibodies (dose #1) in the reduction of allergic symptoms during the out-of-season oak allergen EEU challenge in the subpopulation of oak allergic participants in those receiving REGN5713-5714-5715 versus placebo, REGN5713-5715 versus placebo, and REGN5715 versus placebo

Titrated skin prick test endpoints (parts A and B):

- To assess the efficacy of the anti-Bet v 1 monoclonal antibodies (dose #1) in the reduction of skin test reactivity from pre-treatment baseline by inhibiting a wheal response to a titrated skin prick test (SPT) with birch and related allergens (eg, alder, oak) during out-of-season assessments in participants who receive REGN5713-5714-5715 versus placebo, REGN5713-5715 versus placebo, and REGN5715 versus placebo
- To compare differences in the degree of reduction of skin test reactivity from pre-treatment baseline by inhibiting a wheal response to a titrated SPT with birch and related allergens (eg, alder, oak) during out-of-season assessments in participants receiving the different combinations of the anti-Bet v 1 antibodies in those receiving REGN5713-5714-5715, REGN5713-5715, or REGN5715
- To determine the efficacy of the anti-Bet v 1 monoclonal antibodies (dose #2) in the reduction of skin test reactivity from pre-treatment baseline by inhibiting a wheal response to a titrated SPT with birch and related allergens (eg, alder, oak) after the natural BPS in participants who receive REGN5713-5714-5715 versus placebo, REGN5713-5715 versus placebo, and REGN5715 versus placebo

Peak season EEU challenge (Part B):

- To assess the efficacy of the anti-Bet v 1 monoclonal antibodies (dose #2) in the reduction of allergic symptoms during the in-season birch allergen EEU challenge in participants receiving REGN5713-5714-5715 versus placebo, REGN5713-5715 versus placebo, and REGN5715 versus placebo

In-season field data during birch pollen season (BPS) and peak BPS (Part B):

- To determine the efficacy of the anti-Bet v 1 monoclonal antibodies (dose #2) in the reduction of allergic symptoms during the birch pollen season (BPS) and peak BPS in participants receiving REGN5713-5714-5715 versus placebo, REGN5713-5715 versus placebo, and REGN5715 versus placebo
- To assess health-related quality of life during the BPS and peak BPS in participants who receive REGN5713-5714-5715 versus placebo, REGN5713-5715 versus placebo, and REGN5715 versus placebo

Drug Concentration, Safety and Immunogenicity (Part A and Part B)

- To evaluate the safety and tolerability of the anti-Bet v 1 monoclonal antibodies as compared to placebo following single administration (dose #1) and after repeat dosing (dose #2)
- To determine systemic concentrations over time of total antibody (free + antigen-bound) for each of the individual monoclonal antibody (mAb): REGN5713, REGN5714, and REGN5715 at various time points following single administration (dose #1) and after repeat dosing (dose #2)

- To assess the immunogenicity of REGN5713, REGN5714, and REGN5715 in birch-allergic participants following single administration (dose #1) and after repeat dosing (dose #2). The study objectives must be copied verbatim from the corresponding protocol amendment.

1.1.3. Exploratory Objectives

The exploratory objectives are:

- To assess the efficacy of a dose of the anti-Bet v 1 monoclonal antibodies (dose #2), given ahead of the anticipated BPS, in the reduction of allergic symptoms during the birch allergen EEU challenge at the end of the BPS in participants receiving the REGN5713-5714-5715 versus placebo, REGN5713-5715 versus placebo, and REGN5715 versus placebo (Part B)
- To compare the within-participant magnitude of treatment effects as degree of responses in the reduction of allergic symptoms during the EEU challenges (out-of-season and in-season) with the field data during BPS and peak BPS in participants receiving the anti-Bet v 1 antibodies or placebo
- To compare the within-participant degree of responses in the reduction of allergic symptoms during the EEU challenges at different time points (out-of-season and in-season) in participants receiving the anti-Bet v 1 antibodies or placebo
- To compare the within-participant degree of responses in the reduction of skin test reactivity using titrated SPTs at different timepoints in participants receiving the anti-Bet v 1 antibodies versus placebo
- To determine the efficacy of the anti-Bet v 1 antibodies in the reduction of allergic symptoms during the natural oak pollen season (OPS) in the subpopulation of oak-allergic participants in those receiving REGN5713-5714-5715 versus placebo, REGN5713-5715 versus placebo, and REGN5715 versus placebo (Part B)
- To assess reduction in allergic reactions to foods associated with pollen food allergy syndrome in participants treated with anti-Bet v 1 antibodies versus placebo
- To assess allergen-specific IgE levels (Bet v 1 and birch pollen) at screening/baseline to assess sensitization status and to evaluate the relationship between clinical response to anti-Bet v 1 antibodies and poly/mono-sensitization during EEU challenges and field data assessments
- To assess allergen-specific IgE levels to other allergens (eg, Bet v 2, alder, grass) using blood samples collected at baseline to assess relationship between polysensitized status and response to anti-Bet v 1 antibodies during EEU challenges and field data assessments
- To assess the inhibitory effect of anti-Bet v 1 antibodies on basophil activation after ex-vivo stimulation with birch pollen extract

1.2. Statistical Hypothesis

The following hypotheses of the primary endpoint will be tested:

H_0: The mean of TNSS in a birch allergen EEU at day 29 in Part A is equal between REGN5713-5714-5715 versus placebo.

H_1: The mean of TNSS in a birch allergen EEU at day 29 in Part A is different between REGN5713-5714-5715 versus placebo.

1.3. Interim Analysis/Planned Analyses

No formal interim analysis is planned.

A primary analysis may be performed after all participants complete at least day 29 EEU challenges (visit 6) in Part A or discontinue from study. (Note: day 29 EEU challenge will be considered complete if visit 6 is not performed for any reason and participant is continuing into the subsequent part of the study). A select team will be unblinded at the database lock of Part A to review the results but to ensure study integrity, the team members directly involved in the continued conduct of the trial will remain blinded.

Final database lock and unblinded analyses of the study results for efficacy endpoints will be performed when all randomized participants have completed visit 15 (EOS). These will be considered the final analyses for the efficacy endpoints. Additional data between this database lock and last participant completing the last visit will be summarized in the CSR or an addendum.

1.4. Modifications from the Statistical Section in the Final Protocol

No significant changes have been made to the key endpoints or statistical methods outlined in the protocol. However, there are some minor modifications, which are listed below:

Table 1: Modifications from the Statistical Section in the Protocol Amendment 1

Section	Modification
Section 3.1	The abbreviation of "FAS – B" in Section 3.1 is different from "mFAS" in protocol section 10.3.1 in format but the definition is still the same.
Section 3.2 and Section 3.3	Modified Intent-to-Treat Set (mITT) and Part A Completers Set (CS-A) are added in the analysis sets for supplemental analyses and within-participant comparisons.
Section 7.1.2	The following endpoints listed in protocol will be analyzed based on both **pre-treatment** and **pre-season** baseline: • The change and percent change from baseline in the symptom and medication scores (CSMS, TSS, TNSS, TOSS, and DMS), averaged during the BPS and peak BPS • The change and percent change from baseline in the symptom and medication scores, averaged during the OPS • Change and percent change from baseline in the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ(S]) score during BPS and peak BPS

Section	Modification
Section 7.2.1.1	The pollen season occurring before Day 29 is identified as an intercurrent event of study primary objective and added in Section 7.2.1.1. As a result, associated estimands for efficacy endpoints at Day 29 are established.
Section 7.2.3	There are some additional exploratory analyses added. The combined active group is defined as participants who received any active treatment (REGN5713-5714-5715, REGN5713-5715, or REGN5715). For the oak allergen EEU challenge, the following endpoints will be analyzed by comparing the combined active group versus the placebo group. • The mean of symptom scores (TNSS [2-6 hours], TOSS [2-6 hours] and TSS [2-6 hours]) during out-of-season oak allergen EEU challenge at day 36 • The change and percent change from pre-treatment baseline in symptom scores (TNSS [2-6 hours], TOSS [2-6 hours] and TSS [2-6 hours]) during an oak allergen EEU at day 36 • The change and percent change from pre-treatment baseline in the red oak titrated SPT mean wheal diameter (MWD) AUC The rationale is specified in Section 7.2.3.

1.5. Revision History for SAP Amendments

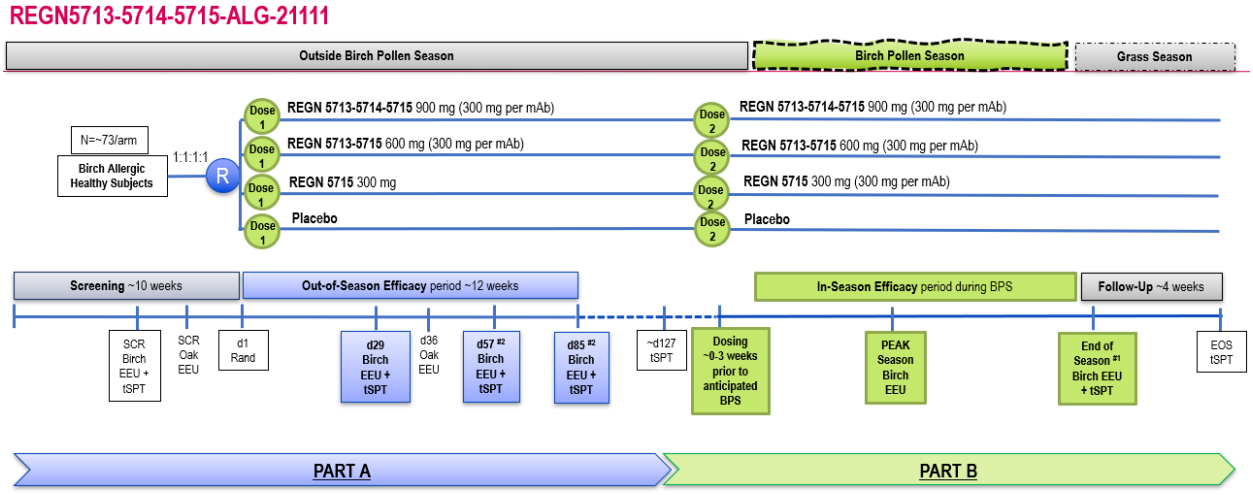
This is the original version of the SAP.

2. INVESTIGATION PLAN

2.1. Study Design

The study consists of 2 parts for a total study duration of up to approximately 46 weeks (including up to a 10-week screening period) (Figure 1). Part A of the study lasts up to approximately 28 weeks (including the screening period). Part B of the study starts after completion of Part A and lasts up to approximately 18 weeks (including an approximately 4-week follow-up period after end of BPS), dependent on the start and end times of the natural BPS. During the treatment period, there will be 2 visits during which study drug will be administered for a total of 6 injections. Participants will be randomized to receive placebo or 1 of 3 active treatment arms according to a central randomization scheme provided by an interactive voice response system (IVRS)/interactive web response system (IWRS). Stratification factors at randomization include oak allergy, grass sensitization status, and EEU site.

Figure 1: Study Flow Diagram



#1 End-of-Season EEU Challenge after the end of the birch season may not be performed in participants experiencing high symptom burden due to grass pollen allergy
#2 Day 57 and/or day 85 EEU challenges may not be performed in participants who have a high symptom burden assessed due to tree pollens
Note: Visit timeframes in Part B may vary based on the timing and duration of the anticipated local birch pollen season.

Randomization and Study Treatment

Part A:

Subcutaneous (SC) administration with a randomization ratio of 1:1:1:1 to 1 of 4 arms in a dose of study drug (dose #1)

- REGN5713-5714-5715 900 mg (300 mg per mAb) [3-mAb cocktail]
- REGN5713-5715 600 mg (300 mg per mAb) plus placebo that replaces REGN5714 [2-mAb cocktail]
- REGN5715 300 mg plus placebo that replaces REGN5713-5714
- Matching placebo that replaces active drug

Part B:

SC administration of a dose of study drug (dose #2)

- REGN5713-5714-5715 900 mg (300 mg per mAb) [3-mAb cocktail]
- REGN5713-5715 600 mg (300 mg per mAb) plus placebo that replaces REGN5714 [2-mAb cocktail]
- REGN5715 300 mg plus placebo that replaces REGN5713-5714
- Matching placebo that replaces active drug

Participants will receive the same treatment in Part B that they were originally randomized to receive in Part A.

Randomization will be stratified based on following factors:

- Oak allergy (yes or no) (oak allergy: TNSS ≥ 6 out of 12 on at least 2 timepoints during the oak EEU exposure challenge in screening period)
- Grass sensitization status (grass sensitized: grass SPT ≥3 mm or allergen-specific immunoglobulin E (sIgE) ≥0.35; not grass sensitized: grass SPT <3 mm and sIgE <0.35)
- EEU site

Part A (out-of-season) and Part B (in-season)

The efficacy will be tested out-of-season (Part A) as well as in-season (Part B) to fully evaluate treatment effects during experimental exposure to the allergen and also explore them during real-world exposure to birch and other related/ unrelated pollens during the BPS.

Out-of-season EEU challenges at visit 6, visit 8 and visit 9 with birch pollen and visit 7 with oak pollen (Part A) are expected to be completed outside of the local BPS.

- Some participants that are symptomatic due to tree pollens may not complete day 57 (visit 8) and/or day 85 (visit 9) birch EEU challenges.
- For some participants that were enrolled later, out-of-season EEU challenges may not be performed if there is not sufficient time to complete the visit (within the protocol specified visit window) before the start of the local birch season.

Timeframes for visits 10 to 15 (part B) are based upon the timing and duration of the anticipated local BPS. Therefore, the timing of these visits can vary and are dependent on the local pollen season and on timing of participant enrollment.

(*Note: Anticipated birch season timeframes are based on pollen projections, local climate predictions and historical pollen data (based on recommendations and data from local pollen expert in Canada [Aerobiology]. Current BPS and peak BPS are defined after local current pollen counts become available for the study year.*)

- The daily symptom and medication scores are collected starting at visit 10 (visit 10 is intended to occur prior to the start of the local birch season to obtain a pre-season baseline) to the end of the study (visit 15).
  - For some participants, visit 10 may occur prior to completion of Part A visits as visit 10 is expected to be conducted prior to anticipated birch season start to allow for the collection of nasal and ocular allergy symptoms and allergy medication use before the start of the BPS.
- At minimum, a 12-week interval between doses #1 and #2 is required. Dose #2 is intended to be given within 3 weeks prior to an anticipated birch season and a dosing stop date is defined within approximately 1 week after the concurrent birch pollen season start. Some participants may receive dose #2 after start of the birch pollen season. Some participants that are enrolled later in the study may not receive dose #2 if they do not meet the minimum 12-week interval prior to the defined dosing stop date.
- In-season peak EEU challenge at visit 13 is intended to be conducted in the birch season during the approximate anticipated peak season (after dose #2 for those expected to receive it)
- End-of-season EEU challenge (visit 14) is expected to be performed after the end of the local birch season. *(Note: Participants that are highly symptomatic to grass pollens or unable to wash out allergy rescue medications may not perform this EEU challenge.)*

2.2. Sample Size and Power Considerations

During the study design stage, a sample size of 65 participants per arm was calculated to obtain 90% power to detect a mean difference in average TNSS (2 to 6 hours) of 1.61 (30% reduction from placebo) between REGN5713-5714-5715 (mean TNSS = 3.74) and placebo (mean TNSS = 5.35), assuming a common standard deviation of 2.8. Assuming 10% dropout, approximately 73 participants per arm will be required to detect a difference of 1.61 in mean TNSS between REGN5713-5714-5715 (3-mAb) and placebo with a minimum detectable difference of 1.0 (~19% reduction from placebo in mean TNSS). Across all 4 treatment arms, the proposed sample size is approximately 300 participants.

This sample size is calculated at a 2-sided significance level of 5% using a 2-sample t-test. Estimates of mean in placebo and variability of the TNSS are based on birch tree SLIT-tablet data (Couroux P, 2019), and a 30% treatment effect relative to placebo is in line with what was observed in the phase 1b POC study for REGN5713-5714-5715.

Pollen related allergy trials are dependent on timing of the specific pollen seasons. As such, enrollment is affected by pollen season start dates. A sample size of 50 participants per arm gives approximately 80% power to detect a mean difference in average TNSS (2 to 6 hours) using the same assumptions. This study is powered to detect differences between REGN5713-5714-5715 900 mg and placebo on the primary endpoint of the mean of TNSS during a birch pollen EEU challenge (2 to 6 hours) at day 29 in Part A.

3. ANALYSIS SETS

The following defines the set(s) of subjects whose data will be used for statistical analyses.

3.1. The Full Analysis Set (FAS)

The efficacy endpoints in Part A will be analyzed using the Full Analysis Set (FAS), which consists of all randomized participants. The efficacy analysis set is based on the treatment allocated (as randomized).

The efficacy endpoints in Part B will be analyzed using the FAS - B, which consists of participants who receive study drug in Part B.

3.2. Modified Intent-to-Treat Set (mITT)

The mITT includes all randomized participants that were eligible to complete their day 29 EEU challenge (visit 6) prior to the start of local birch pollen season. This mITT analysis set excludes any participants that were unable to complete their day 29 EEU challenge prior to their local birch season start (due to earlier than expected birch season start).

3.3. Part A Completers Set (CS-A)

The CS-A includes all randomized participants who complete all out-of-season birch EEU challenges in Part A (visit 6, visit 8, and visit 9). CS-A will be used to assess the durability of response in part A and evaluate within-participant changes over time in Part A.

3.4. The Safety Analysis Set (SAF)

The safety analysis will be based on the safety analysis set (SAF), defined as all randomized participants who receive any study drug, regardless of the amount of treatment administered. The SAF is based on the treatment received (as treated). As-treated is defined as when a patient receives at least one dose of any amount of study drug, in case of interrupted dosing. The patient will be regarded as treated with 3-mAb cocktail study drug REGN5713-5714-5715 if the patient receives at least 1 dose of the 3-mAb cocktail. Similarly, if a patient receives at least one dose of the 2-mAb cocktail, but no doses of REGN5714, the patient will be considered treated with REGN5713-5715. If a patient receives at least one dose of the single mAb REGN5715 but no doses of REGN5713 or REGN5714, then the patient will be considered treated with REGN5715. If the patient receives no REGN5713, REGN5714, or REGN5715, the patient is considered as treated with placebo.

3.5. Immunogenicity Analysis Sets

3.5.1. ADA Analysis Set (AAS)

The ADA analysis sets (AAS) are defined for each study drug separately and include all treated participants who received any amount of study drug (active or placebo [SAF]) and had at least one non-missing ADA result following the first dose of the respective study drug or placebo. The ADA analysis set is based on the actual treatment received (as treated) rather than as randomized.

3.6. Pharmacokinetic Analysis Set (PKAS)

The PK analysis set (PKAS) includes all participants who received any active drug and who had a at least 1 non-missing serum drug concentration following a single dose of study drug. Participants will be analyzed according to the treatment actually received rather than as randomized.

4. GENERAL STATISTICAL ANALYSIS CONSIDERATIONS

Unless otherwise stated, the following conventions will be applied when presenting summary level statistics for data.

Continuous variables will be summarized within each treatment group, presenting the following summary statistics. The sample size (i.e. number of observations with an available value of the variable), average, sample standard deviation, median, minimum, maximum, 1st quartile and 3rd quartile.

Categorical data will be summarized within each treatment group by frequency (i.e., total number of observations within each level of the categorical variable in a given treatment group). All levels of the categorical variable will be included. If there are observations where the level of the categorical variable is missing, a separate category titled "Missing" will be created. For categorical variables that are ordinal in nature, the order in which the levels of the categories are displayed will be consistent with the natural ordering of the category levels. Percentages will also be calculated for each level of the categorical variables with respect to the total sample size for the respective treatment arm.

5. PATIENT DISPOSITION

5.1. Screening Dispositions

The number of enrolled participants (i.e. participants who signed the informed consent form (ICF)) who are randomized (i.e. assigned a randomization number in the IWRS system) and screen-fail will be presented. Participants who screen-fail will be broken out by screen-fail reason. If applicable, the number of participants who are improperly randomized (i.e. did not meet study eligibility criteria yet were assigned a randomization number in the IWRS system) will also be displayed. The corresponding percentages with respect to the total number of enrolled participants will also be presented.

5.2. Treatment Period Dispositions

A patient is considered to have completed the study treatment period if they make it to the End-of-Study Visit (visit 15/day 253). The disposition of all randomized participants during the study treatment period will be displayed by treatment group.

The following summaries will be provided for each treatment group and total (unless otherwise specified):

- Study drug administration
- The total number of participants in each analysis set
- The number of participants who complete the study treatment period
- Duration of study treatment period
- The number of participants completing each visit
- The number of participants who withdraw from the study treatment period. This number will be further broken out by reason for early withdrawal and whether the early termination/ withdrawal was prior to or after the start of the local BPS.

6. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

6.1. Demographics

The following demographic variables will be summarized by treatment group and overall:

- Age at screening (years) as a continuous variable
- Age categories (years, 18 to <50, >= 50)
- Sex (Male, Female)
- Race (American Indian or Alaskan Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Not Reported)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported)
- Weight (kg)
- Height (cm)
- Body mass index (BMI) (kg/m2)
- EEU location (Cliantha, Kingston)
- Site location (Cliantha, Kingston, CSAC)

6.2. Baseline Disease Characteristics

The following disease characteristics will be summarized by treatment group and overall:

- Birch EEU Mean TNSS (2 to 6 hours), Mean TOSS (2 to 6 hours), Mean TSS (2 to 6 hours) at Visit 2
- Oak EEU Mean TNSS (2 to 6 hours), Mean TOSS (2 to 6 hours), Mean TSS (2 to 6 hours) at Visit 3 [only for oak-allergic participants, i.e., those who developed a TNSS of at least 6 out of 12 at 2 or more timepoints during the screening oak EEU at visit 3]
- Screening and randomization FEV1 (L and percent predicted)
- Baseline history for allergic disease, including duration of disease [e.g., allergic rhinitis, allergic conjunctivitis, asthma and pollen food allergy, and prior SIT] (as recorded in CRF)
- SPT *mean wheal diameter* for birch allergens, birch-related allergens, and unrelated allergens (mm)
- Serum total IgE (kU/L)
- Serum allergen-specific IgE for birch allergens, birch-related allergens, and unrelated allergens (kU/L)
- Serum allergen-specific birch IgE (<17.5 kUa/L; ≥17.5 kUa/L)

- Sensitization to allergens by either sIgE or by SPT
- Sensitization status by sIgE or by SPT (sensitized to birch and related allergens only; sensitized to unrelated trees; sensitized to non-tree pollens; sensitized to indoor perennial allergens)
- Serum Bet v 1 sIgG, birch sIgG, and oak sIgG (if data are available)

Note: Refer to Section 14.5 for allergen definitions.

6.3. Medical History

Patient medical histories will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®). The frequency and percentage of each medical history will be summarized by SOC and PT for each treatment arm, and overall using the FAS.

7. EFFICACY/PHARMACODYNAMIC DATA

7.1. Description of Efficacy/Pharmacodynamic Data

EEU Data (symptom scores recorded during the 6 hour EEU challenges):

Nasal and ocular symptom data will be collected during EEU visits that occur during the screening period, out-of-season efficacy period, in-season efficacy period, and at end-of-season. The methodology for collecting and scoring the nasal and ocular symptom data in the EEU is consistent across all periods stated previously.

- TNSS (2 to 6 hours):

  Instantaneous TNSS measures nasal symptom severity at the time point of assessment. In the EEU, instantaneous TNSS is recorded using an e-diary prior to start of pollen exposure and then approximately every 20 min during the 6-hour EEU pollen exposure.

  The instantaneous TNSS score ranges from 0 to 12 and is based on assessment of 4 nasal symptoms graded on a Likert scale ranging from 0 (none) to 3 (severe) for nasal congestion, itching, and runny nose, and sneezing. Higher score indicates worse symptoms.

  The mean TNSS (2-6 hours) is calculated as an average of the observed instantaneous TNSS scores during the 12 timepoints from hour 2 to 6 during the EEU session (details in Section 11.4).

- TOSS (2 to 6 hours):

  Instantaneous TOSS measures ocular symptom severity at the time point of assessment. In the EEU, instantaneous TOSS is recorded using an e-diary prior to start of pollen exposure and then approximately every 20 min during the 6-hour EEU pollen exposure.

  The intantaenous TOSS score ranges from 0 to 6 and is based on 2 groups of eye symptoms: itching/redness/gritty feeling and tearing/watering. Each of the 2 symptom groups is graded on a Likert scale ranging from 0 (none) to 3 (severe). Higher score indicates worse symptoms.

  The mean TOSS (2-6 hours) is calculated as an average of the observed instantaneous TOSS scores during the 12 timepoints from hour 2 to 6 during the EEU session (details in Section 11.4).

- TSS (2 to 6 hours) (calculated):

  The mean TSS (2 to 6 hours) is calculated as an average of the sum of observed instantaneous TNSS and instantaneous TOSS scores during the 12 timepoints from hour 2 to 6 during the EEU session (details in Section 11.4). The mean TSS (2 to 6 hours) score ranges from 0 to 18 with higher scores indicating worse symptoms.

Note: Baseline data are obtained from the screening baseline EEU challenge for birch (visit 2) and oak (visit 3).

Daily scores:

Daily nasal, ocular, and medication data will be collected during pre-treatment baseline, pre-season baseline, and then starting at visit 10 until end of the study. The methodology for collecting and scoring the daily nasal, ocular, and medication data is consistent across all periods stated previously.

- TNSS (daily)

  Reflective TNSS measures nasal symptom severity over the past 24 hours and is recorded before the participant goes to bed for the night. It is recorded daily using an e-diary in the Part B. All daily TNSS scores during the season after the dose #2 will be used to calculate the average TNSS, except for the day of and one day following EEU challenge in Part B.

- TOSS (daily)

  Reflective TOSS is similar to the reflective TNSS defined above.

- TSS (calculated)

  The TSS is calculated by adding the TNSS and TOSS together, with scores ranging between 0 and 18. Higher score indicates worse symptoms.

- DMS (daily)

  To calculate the DMS, participants will be asked to record their daily rescue medication use using an e-diary before going to bed for the night, including which medications and the amount of these pre-specified medications. This information will be used to calculate the DMS for the following medications or the approved in-class equivalents, as follows:

  – Desloratadine 5 mg 6 points/dose; maximum daily score 6 points

  – Olopatadine 1 mg/mL each drop 1.5 points/drop; maximum daily score 6 points

  – Mometasone furoate 50 ug/dose 2.0 points/spray; maximum daily score 8 points

  The maximum DMS score is 20 (Calderon, 2014). DMS is recorded using an e-diary from visit 10 to visit 15, in addition to an approximately 2-week period during screening. After completion of the EEU challenges, use of allergy medicines will be recorded in the e-diary until approximately 24 hours after the start of the EEU challenges. All daily e-diary scores during the season after dose #2 will be used to calculate the average, except for the day of and one day following EEU challenge in Part B.

- Daily CSMS (calculated)

  The CSMS is calculated by adding the DMS and TSS together, with scores ranging between 0 and 38. For each participant, an average of the daily symptom and medication scores is calculated during their local BPS.

Note: Daily TNSS, TOSS, DMS, CSMS scores on the day of and the day after an EEU challenge will not be used as part of the field data calculations (to avoid any potential overlap of symptoms related to the EEU).

- Standardized RQLQ(S) for Ages 12+

  The RQLQ(S) is a self-administered questionnaire to measure health-related quality of life in those 12 years of age and above, as a result of perennial or seasonal allergic rhinitis.

  There are 28 items on the RQLQ(S) in 7 domains: activity limitation, sleep problems, nasal symptoms, eye symptoms, non-nasal/eye symptoms, practical problems, and emotional function. The RQLQ(S) responses are based on a 7-point Likert scale with responses ranging from 0 (not troubled) to 6 (extremely troubled). The overall RQLQ(S) score is the mean of all 28 responses and the individual domain scores are the means of the items in those domains. Higher scores indicated more health-related quality of life impairment (lower scores are better).

  Questionnaire is administered weekly (starting at visit 10 to the end of the study) and an average of the questionnaires during the BPS will be calculated.

Titrated Skin Prick Testing for European White Birch, White Alder, and Red Oak Allergens

The titrated SPT will be performed with 6 serial dilutions for three allergen extracts (European White Birch, White Alder, and Red Oak), a negative control, and a histamine positive control. Serial dilutions for each of the allergens will be created using diagnostic allergen extract (1:20 weight/volume concentration). The 6 dilutions for the titrated SPT will be created as sequential 50% dilutions to yield 1:40 w/v, 1:80 w/v, 1:160 w/v, 1:320 w/v, 1:640 w/v and 1:1280 w/v concentrations for each allergen. The *mean wheal diameter*s for the 6 serial dilutions for each allergen will be used in the calculation of the area under the curve of the titrated SPT.

The AUC of the titrated SPT *mean wheal diameter*s will be derived using the trapezoidal rule. For each patient, the AUC will be calculated for the *mean wheal diameter*calculated over the titrated concentrations of birch allergen on a log scale. For example, the AUC will be calculated using the formula (Orengo J, 2018):

$$AUC_{[\text{Titrated SPT MWD}]} = \left[\sum_{i=1}^{5}(l_{i+1} - l_i) * (D_{i+1} + D_i)/2\right] / (l_6 - l_1)$$

Where

- D_i is the *mean wheal diameter*(in mm) obtained at concentration c_i
- $l_i = \log(c_i)$, where c_i is the concentration (in w/v units) for which D_i is measured, such as c_1 =1:40, c_2 =1:80, c_3 =1:160, c_4 =1:320, c_5 =1:640, c_6 =1:1280.

Note: c_0 (1:20 w/v concentration of the diagnostic allergen extract) will not be used to calculated the AUC of the titrated SPT mean wheal diameters. Histamine phosphate 1 mg/ml for SPT will be used as the positive control. All normalized SPT values will be considered positive if >=3mm greater than the negative control

Definition Pollen Sites and Pollen Seasons

Pollen Sites

Pollen sites, based on local pollen counter locations, will be used to define the start and end of the local pollen season at the patient level.

Birch pollen season

Local pollen count data will be used to determine the start and end of the BPS for participants at each pollen site. The start of the BPS is defined as the first of 3 consecutive days with a pollen count of 10 grains/m3 or greater. The end of the BPS is defined as the last day of the last occurrence of 3 consecutive days with a pollen count of 10 grains/m3 or greater. Additionally, a threshold using 30 grains/m3 for defining the birch season may be used (higher threshold may be more consistent in predicting the onset of symptoms in birch allergic participants) (Caillaud, 2023; Taudorf, 1988; Biedermann, 2019).

Peak birch pollen season

Peak BPS is defined as the 15 consecutive days within the BPS with the highest 15-day moving average pollen count.

Oak Pollen season

The start of the OPS is defined as the first of 3 consecutive days with a pollen count of 10 grains/m3 or greater. The end of the OPS is defined as the last day of the last occurrence of 3 consecutive days with a pollen count of 10 grains/m3 or greater. The peak OPS is defined similarly to peak BPS, which is the 15 consecutive days within the OPS with the highest 15-day moving average pollen count.

7.1.1. Primary Efficacy Data

The primary efficacy endpoint in the study is the mean of Total Nasal Symptom Score [TNSS (2 to 6 hours)] during a birch allergen EEU challenge at day 29. The primary comparison will be in participants receiving REGN5713-5714-5715 versus placebo.

7.1.2. Secondary Efficacy Data

Secondary endpoints, specified without order, are:

Out-of-season Birch EEU challenges: Symptom endpoints (Part A)

- The mean of symptom scores during out-of-season birch allergen EEU challenges at days 29, 57, and 85
  - TNSS (2 to 6 hours)
  - TOSS (2 to 6 hours)
  - TSS (2 to 6 hours)
- The change and percent change from pre-treatment baseline in symptom scores (TNSS [2-6 hours], TOSS [2-6 hours] and TSS [2-6 hours]) during out-of-season birch allergen EEU challenges at days 29, 57, and 85

- The proportions of participants achieving different degrees of clinical responses will be compared across different symptom response thresholds (TNSS [2-6 hours], TOSS [2-6 hours] and TSS [2-6 hours]) at days 29, 57, and 85

Out-of-season Oak EEU challenge: Symptom endpoints (Part A)

(Note: Day 36 oak EEU challenges are performed only in the subgroup of oak allergic participants, [developed a TNSS of at least 6 out of 12 at 2 or more timepoints during the screening oak EEU at visit 3])

- The mean of symptom scores (TNSS [2-6 hours], TOSS [2-6 hours] and TSS [2-6 hours]) during out-of-season oak allergen EEU challenge at day 36
- The change and percent change from pre-treatment baseline in symptom scores (TNSS [2-6 hours], TOSS [2-6 hours] and TSS [2-6 hours]) during an oak allergen EEU at day 36

Titrated skin prick test endpoints (parts A and B)

- The change and percent change from pre-treatment baseline at days 29, 57, 85 and 127 in the birch, alder and red oak titrated SPT *mean wheal diameter* AUC
- The proportions of participants achieving different degrees of responses in the birch, alder and red oak titrated SPT *mean wheal diameter* AUC will be compared across different response thresholds at days 29, 57, and 85
- The change and percent change from pre-treatment baseline to end-of-season and end-of-study (EOS) visits in the birch (and related allergens) titrated SPT *mean wheal diameter* AUC

Peak season EEU challenge: Symptom endpoints (Part B)

(Note: Peak season EEU is an in-season challenge corresponding to approximate timing of the peak BPS)

- The mean of symptom scores (TNSS [2-6 hours], TOSS [2-6 hours] and TSS [2-6 hours]) during the peak-season birch allergen EEU challenge

In-season field data during birch pollen season (BPS) and peak BPS (Part B)

- The daily symptom and medication scores (CSMS, TSS, TNSS, TOSS, and DMS), averaged during the BPS and peak BPS
- The change and percent change from pre-treatment and pre-season baseline in the symptom and medication scores (CSMS, TSS, TNSS, TOSS, and DMS), averaged during the BPS and peak BPS
- The mean of the total RQLQ(S) score during BPS and peak BPS
- Change and percent change from pre-treatment and pre-season baseline in the RQLQ(S) score during BPS and peak BPS

Drug Concentration, Safety and Immunogenicity (Part A and Part B)

- Incidence rates of treatment-emergent adverse events (TEAEs) and serious TEAEs through EOS
- Total REGN5713, REGN5714, and REGN5715 concentration in serum over the duration of the study
- Incidences and titers of ADA to REGN5713, REGN5714, and REGN5715 over time

7.1.3. Exploratory Efficacy Data

Exploratory endpoints, specified without order, are:

- The mean of symptom scores (TNSS [2-6 hours], TOSS [2-6 hours] and TSS [2-6 hours]) during end-of-season birch allergen EEU challenge (visit 14)
- Within participant comparisons of the treatment effect of anti-Bet v 1 antibodies or placebo to reduce allergic symptoms between the EEU challenges (out-of-season and in-season) and the field, as estimated by the correlation coefficient, mean difference, and heteroscedasticity calculated on the following metrics:
  - Average symptom scores for TNSS (2-6 hours), TOSS (2-6 hours), TSS (2-6 hours) in a birch pollen EEU as compared to average symptom score for TNSS, TOSS, TSS during the BPS and peak BPS
  - Change and percent change from pre-treatment baseline for TNSS (2-6 hours), TOSS (2-6 hours), TSS (2-6 hours) in birch pollen EEU challenges
- Within participant comparisons of the treatment effect of the anti-Bet v 1 antibodies or placebo to inhibit the skin test reactivity (using birch and related allergen titrated SPTs), as estimated by the correlation coefficient, mean difference, and heteroscedasticity calculated on the following metrics:
  - Change and percent change from pre-treatment baseline for titrated SPT *mean wheal diameter*AUC
- The pooled estimate for symptom scores (TNSS, TOSS and TSS) during peak-season birch allergen EEU challenge and daily scores during the BPS
- The daily symptom and medication scores (CSMS, TSS, TNSS, TOSS, and DMS), averaged during the OPS
  - CSMS, TSS, TNSS, TOSS, and DMS, averaged during the OPS
  - The change and percent change from pre-treatment and pre-season baseline in the symptom and medication scores, averaged during the OPS
- The incidence and severity of allergic reactions upon consumption of a food associated with birch pollen food allergy syndrome in participants receiving anti-Bet v 1 antibodies

7.2. Analysis of Efficacy/Pharmacodynamic Data

Six comparisons between treatment groups will be made:

1. REGN5713-5714-5715 versus placebo
2. REGN5713-5715 versus placebo
3. REGN5715 vs placebo
4. REGN5713-5714-5715 versus REGN5715 (numerical comparison)
5. REGN5713-5714-5715 versus REGN5713-5715 (numerical comparison)
6. REGN5713-5715 versus REGN5715 (numerical comparison)

7.2.1. Analysis of the Primary Endpoint

The analysis of the primary efficacy variable will be performed using an analysis of covariance (ANCOVA) model, with the treatment group, randomization stratification factors (as stratified) as fixed-effects and TNSS baseline as a covariate.

7.2.1.1. Estimand Framework for the Primary Endpoint

The intercurrent events, strategies, and the corresponding missing data handling approaches for the primary estimands of interest for the primary endpoint are provided in detail in Table 2. Day 29 EEU data during out-of-birch pollen season are planned to assess in the protocol amendment #1 dated November 2022. However, some randomized participants are not eligible to complete EEU Day 29 challenges due to early start of the pollen season. The pollen season occurring before Day 29 is identified as an intercurrent event for the study primary objective. The corresponding estimand framework is used by hypothetical setting not to collect EEU data at Day 29 (all values during EEU Visit 6 are missing). In cases where EEU assessments at Day 29 are collected after the pollen season, these collected EEU data will be set to missing (hypothetical strategy).

Table 2: Summary of Estimand for Primary Endpoint

Endpoint Category	Estimand			
	Endpoint	**Population**	**Intercurrent event(s) handling strategy and missing data handling**	**Population-level summary**
Primary endpoint – Continuous	Mean Total Nasal Symptom Score (TNSS) (2 to 6 hours) in a birch allergen EEU at day 29 in Part A	FAS	The intercurrent events will be handled as follows: • Relevant prohibited medication[1] taken prior to the EEU challenge: all available data will be utilized (treatment policy). • Any severe or clinically concerning adverse event necessitating removal from the chamber and/or use of rescue treatment[2] taken during the EEU challenge: data after exiting the EEU or the use of the rescue medication will be set to mean TNSS from 2 to 6 hours in the baseline EEU (BOCF, composite strategy) In addition, if all values during the EEU visit are missing due to any other reason, e.g., early start of BPS, then the averaged value will be imputed using multiple imputation (MI).	ANCOVA model with treatment group and stratification factors as fixed effect and the baseline mean TNSS (2 to 6 hours) at visit 2 as a covariate.

[1] Relevant prohibited medications include allergy relieving medications (treatment policy); no participants used systemic steroids, biologics or immune therapeutics or allergen specific immunotherapy that are expected to impact type 2 allergic disease prior to completion of expected out-of-season EEU visits.

[2] Per Section 7.2 in Protocol, rescue medication may be given during the EEU challenge if any severe or clinically concerning reactions (as judged by the principle investigator (PI)). These rescue medications used during the EEU may include but not limited to antihistamines, topical steroids, systemic steroids, bronchodilators, epinephrine (considered treatment failure and handled using composite strategy).

For the MI procedure, the average EEU TNSS (2 to 6 hours) will be imputed 50 times to generate 50 complete data sets utilizing the SAS procedure PROC MI. Note that any imputation by baseline EEU TNSS (2 to 6 hours) score as specified in Table 2 will occur prior to MI.

Missing values of average EEU TNSS (2 to 6 hours) at day 29 will be imputed using a monotone regression method. The imputation model will include the covariates in the ANCOVA model. Any score imputed outside the range of EEU TNSS (2 to 6 hours) (0 to 12) will be truncated to the nearest value of TNSS (2 to 6 hours) according to the following algorithm:

- If the imputed score > 12, then the final imputed score will be 12.
- If the imputed score < 0, then the final imputed score will be 0.

Sample SAS syntax code for MI:

```
proc mi data=mi3 out=mi4 nimpute=50 seed=571345;
class TRTP STRAT1 STRAT2 STRAT3;
monotone reg;
var TRTP STRAT1 STRAT2 STRAT3 BASELINE TNSS29;
run;
```

Each imputed data set will then be analyzed by ANCOVA as previously described. The SAS procedure PROC MIANALYZE will be used to generate valid statistical inferences by combining results from these 50 ANCOVA analyses using Rubin's formula. The least squares means (LS-means) estimates for the average EEU TNSS (2 to 6 hours) at day 29 of the treatment period for each treatment group, as well as the difference between the REGN5713-5714-5715 and placebo will be provided along with the corresponding 2-sided p-value and associated 95% confidence interval.

7.2.1.2. Sensitivity Analyses/Supplemental Analyses

Sensitivity analyses are planned to assess alternative missing data mechanisms. With respect to the missing data handling of EEU symptom score entries, sensitivity analyses will be performed to confirm robustness of the conclusion drawn based on the main model for primary analysis.

Two supplemental analyses will be performed. One with all intercurrent events handled via a treatment policy for primary endpoint and only using all observed data. The other one with the primary endpoint analyzed using the mITT population.

7.2.1.2.1. Tipping Point Analysis

Sensitivity analysis using a tipping point approach with MI will be performed to assess the robustness of the results due to data that may be missing not-at-random (MNAR). This approach will introduce a sensitivity parameter, delta. Estimations will be performed using MI methodology. The delta is 0%, 10%, 20%, 30%,…, 100% of the observed mean treatment difference between REGN5713-5714-5715 and placebo until conclusion from the primary analysis is overturned. When delta = 0, the missing data pattern is MAR; when delta>0, the missing data pattern is MNAR. The steps of performing tipping analysis are as below:

1. Using a standard MAR-based MI approach from PROC MI to impute the data. Missing data will be imputed 50 times to generate multiple data sets with complete data.
2. For participants in any of REGN5713-5714-5715 with a dropout from the corresponding scenario, a delta will be added after the dropout time.
3. Using ANCOVA model in the primary analysis to analyze the completed data using PROC MIXED on the multiple imputed data
4. Obtaining the overall results using PROC MIANALYZE

7.2.1.3. Subgroup Analyses

Subgroups are defined by key baseline factors recorded on the CRF (unless otherwise specified) and listed as follows. The analysis for the subgroups (except for Race and Ethnicity) may not be performed if the number of participants within the subgroup is small, e.g., 20% or 11 participants for participants receiving REGN5713-5714-5715 and participants receiving placebo.

Subgroups to be considered for primary efficacy endpoint:

- Age group (Years: 18 to <50, ≥50)
- Sex (Male, Female)
- Ethnicity: Hispanic or Latino (Yes, No)
- Race (White, Other)
- Serum specific birch pollen IgE level at screening (<17.5 kUa/L, ≥17.5 kUa/L)
- Oak allergy status (Based on the symptom scores collected at visit 3: Yes, No)
- Pollen food allergy syndrome (Yes, No)
- EEU site location (Cliantha, Kingston)
- Baseline sensitization status based on sIgE or SPT (Sensitized to indoor perennial allergens, Not sensitized to indoor perennial allergens)

Note: The stratification factor of grass sensitization status, is rather more related to field study in Part B, not to EEU. Thus, the stratification factor will not be used as the subgroup variable.

Subgroups defined above for the primary endpoint for the participants receiving REGN5713-5714-5715 versus placebo will be analyzed based on the FAS. If 2-mAb or 1-mAb arm demonstrates reasonable efficacy over placebo, then similarly, subgroup analyses may be performed on these arms.

To assess the consistency in treatment effects across different subgroup levels, subgroup analyses will be performed for the primary efficacy endpoint using analysis method described in Section 7.2.1.1. If the model-based inferential statistics cannot be computed, or are deemed inappropriate, e.g. small number of participants in a subgroup, only descriptive statistics will be provided.

Treatment difference and its 95% confidence interval in subgroups of subjects will be presented in forest plots.

7.2.2. Analyses of Secondary Endpoints

The secondary continuous efficacy endpoints will be analyzed in a manner similar to that described above (Section 7.2.1.1 Table 2) for the primary efficacy endpoint analysis unless further specified in Table 3. In addition, MI will only be applied for endpoints measured at Day 29.

The proportions of participants achieving different degrees of clinical responses and percent change from pre-treatment baseline in TNSS (2 to 6 hours), TOSS (2 to 6 hours), and TSS (2 to 6 hours) will be compared numerically and graphically using the cumulative distribution function. Participants receiving different combinations of the anti-Bet v 1 antibodies in those receiving

REGN5713-5714-5715, REGN5713-5715, or REGN5715 will be compared with placebo, as well as the comparison between any two active groups. The minimum percent improvement in relevant score will be plotted on the horizontal axis and proportion of participants will be plotted on the vertical axis for each treatment group separately. The AUC of the responder curves derived using the trapezoidal rule will also be calculated as a descriptive summary to compare across different symptom thresholds [as well as including response thresholds such as 30%, 50%, 60%, 75% and 90%], at days 29, 57, and 85 after receiving a single dose of REGN5713-5714-5715, REGN5713-5715, or REGN5715.

The proportions of participants achieving different degrees of change and percent change from pre-treatment baseline in the birch (and related allergens) titrated SPT *mean wheal diameter*AUC will be compared graphically using the cumulative distribution function. The AUC of the responder curves may also be calculated as a descriptive summary to compare across different thresholds [as well as including response threshold such as 30%, 50%, 60%, 75% and 90%] at days 29, 57, 85 in participants receiving REGN5713-5714-5715, REGN5713-5715, or REGN5715.

Subgroups listed in Section 7.2.1.3 might also be applied for secondary endpoints for exploratory analysis. Additional potential sub-group analyses for in-season data:

- Grass sensitization status
- Timing of receipt of dose #2 relative to the local BPS (prior to the season start or after season start), as applicable
- The interval between dose #1 and dose #2 (the cutoff will be decided by the distribution of data, e.g., the median may be used), as applicable

In addition, some in-season efficacy analyses in Part B may be performed including participants with available in-season data irrespective of whether they received dose 2.

More details concerning other secondary endpoints, see Section 14.1.

7.2.2.1. Estimand Framework for Secondary Endpoints

The intercurrent events, strategies, and the corresponding missing data handling approaches for the secondary estimands of interest for the secondary endpoints are provided in detail in Table 3:

Table 3: Summary of Estimands for Secondary Endpoints

Endpoint Category	Estimand			
	Endpoint	Population	Intercurrent event(s) handling strategy and missing data handling	Population-level summary
Secondary endpoint - Continuous	Titrated SPT MWD	FAS[1]	If the antihistamines are not withheld before the titrated SPT, the post-randomized data will be assigned by worst observation (including baseline) before the collection of the assessment from the same participant (composite strategy). If all dilutions are missing due to any reason, e.g., early start of BPS, then the averaged value will be imputed using multiple imputation (MI).	ANCOVA model with treatment group and stratification factors as fixed effect and the baseline tSPT as a covariate.
	EEU symptom scores[3] in Part B	FAS-B	Same manner as the primary endpoint with the following exception: If systemic steroids, biologics or immune therapeutics impacting type 2 allergic disease are used due to birch pollen related symptoms[6] prior to the EEU challenge, data will be set to mean score from 2 to 6 hours in the baseline EEU (BOCF, composite strategy).	Same manner as the primary endpoint
	Field symptom scores[4] in BPS[5] and peak BPS	FAS-B	The intercurrent events will be handled as follows: • If Systemic steroids, Biologics or immune therapeutics impacting type 2 allergic disease are used due to birch pollen related symptoms[6], data will be set to mean score from the other participants in the same treatment group (composite strategy). If due to any other reason, data after the use of medication will be set to missing (hypothetical strategy). • Study provided anti-allergy rescue treatment taken during the study: all available data will be utilized (treatment policy) • Data during travel periods with no exposure to birch pollen will be set to missing and other observed data during exposure to birch pollen will be used to calculate the mean scores (while on treatment policy)	ANCOVA model with treatment group, stratification factors as fixed effect, average pollen count during local BPS and the corresponding pre-treatment baseline symptom scores as covariate.

[1] Endpoints related to tSPT at day 127 will be analyzed in subgroup that had a visit 10 performed at least 12 weeks after Part A dose (not included if visit 10 combined with other visits or if visit 10 done prior to other out-of-season visits).
[2] Rescue medication may be given during the EEU challenge if any severe or clinically concerning reactions (as judged by the PI).
[3] EEU symptom scores include TNSS (2 to 6 hours), TOSS (2 to 6 hours), TSS (2 to 6 hours).
[4] Field symptom scores from e-diary include CSMS [TSS+DMS], TSS [TNSS+TOSS], daily TNSS, daily TOSS, and DMS.
[5] If there is no protocol defined BPS due to local climactic conditions at any pollen site, then those data will not be included in the calculation for field data.
[6] Whether the medication is used due to birch pollen related symptoms (considered treatment failure) or not will be adjudicated in a blinded manner.

7.2.3. Analysis of Exploratory Endpoints

Continuous exploratory efficacy variables, e.g., change and percent change from pre-treatment baseline for TNSS, TOSS, TSS in birch pollen EEU challenges, will be analyzed by using an ANCOVA model similar to the analyses of primary endpoint. For categorical exploratory variables, only descriptive summary will be provided. In addition, the duration of the BPS and the average pollen counts will be provided by pollen site for Part B analysis.

Within-participants comparisons will be conducted using FAS and CS-A.

The combined active group is defined as participants who received any active treatment (REGN5713-5714-5715, REGN5713-5715, or REGN5715). For the oak allergen EEU challenge, the following endpoints will be analyzed by comparing the combined active group versus the placebo group:

- The mean of symptom scores (TNSS [2-6 hours], TOSS [2-6 hours] and TSS [2-6 hours]) during out-of-season oak allergen EEU challenge at day 36
- The change and percent change from pre-treatment baseline in symptom scores (TNSS [2-6 hours], TOSS [2-6 hours] and TSS [2-6 hours]) during an oak allergen EEU at day 36
- The change and percent change from pre-treatment baseline in the red oak titrated SPT mean wheal diameter (MWD) AUC

Rationale: *REGN5715 is the only monoclonal antibody that has been demonstrated to exhibit binding to oak in pre-clinical ELISA experiments (REGN5713 and REGN5714 have not demonstrated binding). Therefore, symptom endpoints during day 36 oak EEU challenge and oak titrated SPT endpoints will be assessed in participants receiving active treatment (REGN5713-5714-5715, REGN5713-5715 or REGN5715) versus placebo (3:1) in subpopulation of oak allergic participants if the individual active arms versus placebo are reasonably comparable.*

8. HYPOTHESIS TESTING METHODS AND MULTIPLICITY CONTROL

8.1. Hypotheses Testing Methods

The statistical hypothesis specified in Section 1.2 will be tested on the selected secondary endpoints at a 2-sided 5% significance level. The study will be declared positive if at least the null hypothesis for the primary efficacy endpoint for REGN5713-5714-5715 versus placebo is rejected.

The hypothesis for other endpoints will be performed using the same procedure and testing method as above.

8.2. Multiplicity Control

The study is powered on the comparison of the primary endpoint between REGN5713-5714-5715 and placebo for Part A of the study with 2-sided alpha level of 0.05.

A hierarchical procedure will be used to control overall Type-1 error rate at 0.05 for the primary endpoint, TNSS (2-6 hours) in birch challenge EEU at day 29 and change from pre-treatment baseline in titrated SPT mean wheal diameter at day 29 in Part A, for testing multiple comparison groups. Each hypothesis will be formally tested only if the preceding one is significant at the 2-sided 0.05 significance level. The hierarchical testing order is shown as below:

1. The mean of Total Nasal Symptom Score [TNSS (2 to 6 hours)] during a birch allergen EEU challenge at day 29, in subjects who receive REGN5713-5714-5715 versus placebo
2. The percent change from pre-treatment baseline in birch allergen titrated SPT mean wheal diameter AUC at day 29 in subjects who receive REGN5713-5714-5715 versus placebo
3. The percent change from pre-treatment baseline in birch allergen titrated SPT mean wheal diameter AUC at day 29 in subjects who receive REGN5713-5715 versus placebo
4. The mean of Total Nasal Symptom Score [TNSS (2 to 6 hours)] during a birch allergen EEU challenge at day 29, in subjects who receive REGN5713-5715 versus placebo
5. The percent change from pre-treatment baseline in birch allergen titrated SPT mean wheal diameter AUC at day 29 in subjects who receive REGN5715 versus placebo
6. The mean of Total Nasal Symptom Score [TNSS (2 to 6 hours)] during a birch allergen EEU challenge at day 29, in subjects who receive REGN5715 versus placebo

9. SUMMARY OF EXPOSURE DATA

9.1. Investigation Study Drug Exposure and Compliance

Part A observation duration:

The number (%) of subjects with observation periods will be presented by specific time periods. The time periods of interest are specified as: ≥1 day, ≥29 days, ≥36 days, ≥57 days, ≥85 days in Part A and before the 2nd dose.

Part B observation duration:

The time periods of interest are specified as: days during BPS in Part B and after the 2nd dose.

The summary of exposure to study drug will include the duration of exposure in Part A and Part B and the number of study drug administered in each of the two doses, given as 3 injections sequentially on one day for each dose. Duration of exposure will be summarized for each treatment group using the number of participants, mean, SD, minimum, median, Q1, Q3, and maximum.

Treatment compliance is not applicable since the subject will only have two treatment administrations in the study.

9.2. Duration of Follow-up

There are two study follow-up periods. The first follow up period is after the last out-of-season EEU exposures until visit 10, where applicable, and the second one is after the end of the BPS until EOS.

9.3. Prior and Concomitant Medications

Medications will be recorded from the day of informed consent until the end-of-study (EOS) visit and will be coded using WHO Drug Dictionary (WHODD). The prior and concomitant medications are defined as below:

Prior medications: medications taken, prior to administration of the first dose of study drug.

Concomitant medications (CMs) for the whole study: medications taken following the first dose of study drug through the EOS visit. The number and proportion of subjects taking prior medications will be summarized by treatment group, as well as the number and proportion taking concomitant medications during the pretreatment period, on-treatment as defined in Section 10.1 based on the FAS.

Prohibited Medications

The prohibited medications will not be analyzed in an independent section but will be included in the prior and concomitant medications.

The number and proportion of subjects performing prior medication will be summarized by treatment group, as well as the number and proportion performing concomitant procedures during the pre-treatment period, on-treatment as defined in Section 10.1 based on the FAS. Similar tables will be provided for the number and proportion of subjects taking prohibited procedures. Each table will be sorted by decreasing frequency of Anatomical Therapeutic Chemical (ATC) level 2

and ATC level 4 based on the overall incidence. Subjects will be counted only once for each medication class (ATC levels 2 and 4) linked to the medication.

Rescue Medications

Participants will be provided with the following allergy-relieving rescue medications (or appropriate in-class equivalent, after agreement with sponsor) to treat allergic symptoms as needed during the study:

1. oral desloratadine 5 mg (second generation antihistamine)
2. topical olopatadine 1 mg/mL (antihistamine eye drops)
3. topical mometasone furoate 50 µg/dose (INCS)

During the screening baseline period and post visit 10 through the end of the study, participants will be asked to record their daily rescue medication use using an e-diary, including the name and amount of these pre-specified medications.

9.4. Prior and Concurrent Procedures

Procedures will be recorded from the day of informed consent until the end-of-study (EOS) visit and all procedures will be coded to a "Preferred Term (PT)" and associated primary "System Organ Class (SOC)" according to the Medical Dictionary for Regulatory Activities (MedDRA). The prior and concomitant procedures are defined as below:

Prior procedures: procedures performed, prior to administration of the first dose of study drug.

Concomitant procedures (CPs) for the whole study: procedures performed following the dose of study drug through the EOS visit.

Number and proportion of participants taking prior/concomitant procedures will be summarized for study total based on the SAF, sorted by decreasing frequency of SOC and PT based on the overall incidence. Participants will be counted only once for each SOC and PT linked to the procedure. Number of participants receiving prior immunotherapy (Subcutaneous Immunotherapy (SCIT), Sublingual Immunotherapy (SLIT)) will be summarized separately.

10. ANALYSIS OF SAFETY DATA

The analysis of safety will be performed on the SAF, as defined in Section Section 3.4 . The safety analysis will be based on the reported AEs and other safety information (vital signs, physical examination and clinical laboratory parameters).

Thresholds for treatment-emergent Potential Clinically Significant Values (PCSV) in laboratory variables are defined in Section 14.3. Treatment-emergent PCSV is any PCSV that developed or worsened in severity compared to the baseline during the on-treatment period which also includes the follow-up period. The baseline when determining treatment-emergent PCSV refers to the baseline value of the study.

The summary of safety results will be presented for each treatment group. The time interval to detect any event or abnormality is during on-treatment period as defined in Section 10.1.

In addition, the summary of safety results (including TEAEs, clinical laboratory, vital signs, and physical examination) will be performed for subjects who were impacted by COVID-19 pandemic and not impacted by COVID-19 pandemic in each study part, respectively if deemed appropriate. The summary will be performed for pre-, during, and post-COVID-19 periods for participants impacted by COVID-19, if deemed appropriate.

10.1. Adverse Events

Adverse events (AEs) and serious adverse events (SAEs) as defined in ther study protocol (Section 9.2.1 and Section 9.2.2) will be collected from the time of informed consent signature and then at each visit until the end of the study.

For safety variables, following observation periods are defined:

- The pre-treatment period is defined as the time from signing the ICF but before receiving the first administration of study drug.
- The on-treatment period in study is defined as the first dose date to the end of study (visit 15).

Treatment-emergent adverse events are defined as those that are not present prior to randomization or represent the exacerbation of a pre-existing condition during the on-treatment period (which includes the follow-up period after the end of the local BPS).

All new or worsening AEs occurring between signing of the ICF and the end of the study will be recorded and coded using the Medical Dictionary for Regulatory Activities (MedDRA).

AEs will be summarized with incidence tables for Part A and Part B separately. AE incidence tables will present the number (n) and percentage (%) of participants experiencing an AE within each treatment arm, sorted by decreasing frequency of SOC and PT in the 3-mAb (REGN-5713-5714-5715) treatment arm. Multiple occurrences of the same event in a patient will only be counted once in the summary. For tables showing AE severity, for instances where a patient has multiple occurrences of the same PT or SOC, only the worst severity will be counted in the summary.

The following AE summaries will be presented for TEAEs:

- Overview of TEAEs
- TEAEs by Primary SOC and PT
- TEAEs by PT
- TEAEs by Primary SOC, HLT and PT
- TEAEs by Primary SOC, PT, and Severity
- TEAEs Related to Study Drug by Primary SOC and PT
- Treatment-emergent AESIs by Primary SOC and PT
- Serious TEAEs by Primary SOC and PT
- Serious TEAEs Related to Study Drug by Primary SOC and PT
- Serious TEAEs Related to Study Drug by PT
- TEAEs by severity
- Injection Site Reactions (ISRs)
- ISRs by severity
- TEAEs leading to permanent treatment withdrawal by Primary SOC and PT
- TEAEs leading to study discontinuation by Primary SOC and PT
- Death due to TEAEs by Primary SOC and PT

10.1.1. Adverse Events of Special Interest

An adverse event of special interest (AESI; serious or non-serious) is one of scientific and medical interest specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the PI to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. AESI will be identified using both CRF flag and SMQ search criteria, and needs clinical adjudication.

List of below is AESI for this study:

- Systemic or severe hypersensitivity reactions

Detailed filter of AESI criteria is specified in Section 14.4.

10.2. Laboratory Parameters

The following laboratory tests will be collected and summarized according to the Schedule Events in Section 14.2:

Blood Chemistry

Sodium	Total protein, serum	Aspartate aminotransferase (AST)
Potassium	Creatinine	Alanine aminotransferase (ALT)
Chloride	Blood urea nitrogen (BUN)	Alkaline phosphatase
Carbon dioxide	Total bilirubin	Albumin
Calcium	Glucose	
Albumin		

Blood chemistry samples should be collected prior to the administration of study drug and prior to EEU challenges, when applicable.

Hematology

Hemoglobin	Differential:
Hematocrit	Neutrophils
Red blood cells (RBCs)	Lymphocytes
White blood cells (WBCs)	Monocytes
Red cell indices	Basophils
Platelet count	Eosinophils

Urinalysis

Color	Glucose	RBC
Clarity	Blood	WBC
pH	Bilirubin	Bacteria
Specific gravity	Leukocytes esterase	Epithelial cells
Ketones	Nitrite	Yeast
Protein		

Other Laboratory Tests

Participants will be tested for FSH levels (if postmenopausal status is in question) and will undergo serum and urine pregnancy testing (women of childbearing potential only); pregnancy testing is not required of women confirmed to be menopausal. Samples will be collected for quantitative assessment of allergen specific IgE.

Clinical laboratory analytes will be converted to standard international (SI) units and grouped by function in summary tables. Below statistic summaries will be provided:

- Descriptive statistics of clinical laboratory values and change from baseline in clinical laboratory values to all scheduled assessment times by visit and by treatment group
- Number (n) and percentage (%) of participants with a treatment-emergent potentially clinically significant value (PCSV) at any post-randomization time point

Patient laboratory parameter measurements will be evaluated by PCSV criteria, specifically identifying participants with at least one post-baseline measurement that meets the PCSV criteria (Section 14.3). Participants meeting the PCSV criteria will be summarized by patient count (and percent) for a post-baseline PCSV measurement by treatment group, regardless of baseline PCSV status. When the PCSV definition involves a change from baseline value, participants must have a baseline value to be included in the summaries. All measurements collected during the study including, values from unscheduled visits, will be used in the PCSV analyses.

10.3. Vital Signs

The following vital signs parameters will be recorded pre-dose and 2 hours post dose, and summarized according to the Schedule Events in Section Section 14.2:

- Temperature
- Systolic/diastolic blood pressure
- Heart rate
- Respiration rate

Summaries of vital sign variables will include:

- Descriptive statistics of vital sign variable and change from baseline by visit by treatment group
- The number (n) and percentage (%) of subjects with treatment-emergent PCSV

10.4. Other Safety Data

A standard 12-lead ECG will be performed at the screening visit/baseline only. Heart rate will be recorded from the ventricular rate and the PR, QRS, and QT (identify QTcB or QTcF) will be recorded. The ECG strips or reports will be retained with the source documentation.

10.5. Immunogenicity Data

Samples for ADA measurement will be collected at visits listed according to Schedule Events in Section 14.2. The samples are to be collected prior to the administration of study drug. In the event of suspected SAEs, such as anaphylaxis or systemic hypersensitivity, additional samples for the analysis of ADA may be collected as close to the event as practically possible.

10.5.1. Immunogenicity Variables

The immunogenicity variables include ADA status, titer at nominal sampling time/visit. Serum samples for ADA will be collected at the clinic visits specified in Section 14.2. For each study drug, samples positive in the ADA assay will be further characterized for ADA titers.

10.5.2. Analysis of Immunogenicity Data

The immunogenicity variables described in Section 10.5.1 will be summarized using descriptive statistics. Immunogenicity will be characterized per drug molecule by ADA status, ADA category and maximum titer observed in participants in the ADA analysis sets. For samples confirmed as drug specific ADA positive, but found negative at the lowest titer dilution, the lowest dilution in the titer assay is imputed.

The ADA status of each participant may be classified as one of the following:

- Positive
- Pre-existing - If the baseline sample is positive and all post baseline ADA titers are reported as less than 9-fold the baseline titer value
- Negative - If all samples are found to be negative in the ADA assay.

The ADA category of each positive participants is classified as:

- Treatment-boosted - A positive result at baseline in the ADA assay with at least one post baseline titer result ≥ 9-fold the baseline titer value
- Treatment-emergent - A negative result or missing result at baseline with at least one positive post baseline result in the ADA assay. Participants that are treatment-emergent will be further categorized as follows:

Treatment-emergent is further sub-categorized as:

- Persistent - A positive result in the ADA assay detected in at least 2 consecutive post baseline samples separated by at least a 16-week post baseline period [based on nominal sampling time], with no ADA-negative results in-between, regardless of any missing samples
- Transient - Not persistent or indeterminate, regardless of any missing samples
- Indeterminate - A positive result in the ADA assay at the last collection time point only, regardless of any missing samples

The maximum titer category of each participant is classified as:

- Low (titer <1,000)
- Moderate (1,000 ≤ titer ≤ 10,000)
- High (titer >10,000)

The following will be summarized by treatment group and ADA titer level:

- Number (n) and percent (%) of ADA-negative participants
- Number (n) and percent (%) of pre-existing participants

- Number (n) and percent (%) of treatment-emergent ADA positive participants
  - Number (n) and percent (%) of persistent treatment-emergent ADA positive participants
  - Number (n) and percent (%) of indeterminate treatment-emergent ADA positive participants
  - Number (n) and percent (%) of transient treatment-emergent ADA positive participants
- Number (n) and percent (%) of treatment-boosted ADA positive participants

Listing of all ADA titer levels will be provided for participants with pre-existing, treatment-emergent and treatment-boosted ADA response.

10.5.3. Association of Immunogenicity with Exposure, Safety and Efficacy

10.5.3.1. Immunogenicity and Exposure

Potential association between immunogenicity and systemic exposure to REGN5713, REGN5714, and REGN5715 will be explored by treatment groups. Plots of individual REGN5713 , REGN5714, and REGN5715 concentration time profiles by ADA status or titer may be provided to examine the potential impact of ADA on systemic exposure.

10.5.3.2. Immunogenicity and Safety and Efficacy

Potential association between immunogenicity variables and safety may be explored with a primary focus on the following safety events during the TEAE period:

- Injection site reaction (serious or severe)
- Hypersensitivity (SMQ: Hypersensitivity [Narrow])
- Anaphylaxis (SMQ: Anaphylactic Reaction [Narrow])

Potential association between immunogenicity variables and efficacy endpoints may be explored (e.g., scatter plot or spaghetti plot).

The safety and efficacy analyses mentioned above will be conducted using the following categories:

- ADA Positive
  - Treatment-emergent
  - Treatment-boosted
- Maximum post-baseline titer category in ADA positive participants

10.6. Pharmacokinetic Data

10.6.1. Pharmacokinetic Variables

Concentrations in serum of total (free + antigen bound) REGN5713, REGN5714, and/or REGN5715 will be measured at time points specified in the study schedule of events in Section 14.2 . Pharmacokinetic variables consist of concentrations of individual antibodies (REGN5713, REGN5714, and/or REGN5715) as well as total drug (REGN5713+REGN5714+REGN5715 or REGN5713+REGN5715) in serum, and time (both nominal and actual time).

10.6.2. Analysis of Pharmacokinetic Data

Descriptive statistics of total REGN5713, total REGN5714, total REGN5715, and/or total drug (REGN5713+REGN5714+REGN5715 or REGN5713+REGN5715) concentrations in serum at each sampling timepoint will be provided. Plots of mean concentration versus nominal time may be presented. Select PK parameters may be calculated.

Exposure Response analysis of biomarkers, efficacy, and safety endpoints may be conducted as necessary and presented in separate reports.

10.7. Biomarker Data

Exploratory biomarker data may be described in a separate exploratory analysis plan. Analyses may include (but are not limited to) evaluating relationships between biomarkers and clinical responses. Exploratory biomarker variables may include (but are not limited to) serum allergen-specific IgE levels (birch, Bet v 1, Bet v 2, and other common allergens) and basophil activation. Relevant biomarker data analyses may be included in the CSR and/or a separate biomarker report.

11. DATA CONVENTIONS

11.1. Definition of Baseline for Efficacy/Safety Variables

Unless otherwise specified, the Baseline assessment for all measurements will be the latest available valid measurement taken prior to the administration of investigational product. The following rules specify the determination of baseline by both date/time information:

- The date and time of first injection will be used to determine the baseline for the AE, lab, PK and ADA data.
- Only the date of first injection will be used to determine the baseline for other data except the AE, lab, PK and ADA data.

For the efficacy endpoints, the baseline is defined as following:

- For all symptom scores (TNSS or TOSS) collected in EEU chambers, the baseline is defined as the mean of the corresponding measurements (2 to 6 hours) during the allergen EEU challenge in screening period. The baseline visit for Birch is Visit 2, and the baseline visit for Oak is Visit 3.
- For daily e-diary scores (daily TNSS, daily TOSS, DMS, daily TSS, daily CSMS, RQLQ(S), PFASQ, and outdoor questionnaire), there are two baselines defined, pre-treatment baseline and pre-season baseline.
  - The pre-treatment baseline is defined as the average of the daily score during the screening period before the first dose. All days with scores during the screening period will be used to calculate the average, except for the day of and one day following EEU challenge.
  - The pre-season baseline is defined as the average of the daily score start from the Visit 10 to the day before the local BPS, except for the day of and one day following EEU challenge.

  The number of non-missing daily records must be at least 3 after excluding the records happening on the same day and the next day of the EEU visit for pre-treatment and pre-season baseline (both pre-treatment baseline) calculation. If the baseline value is smaller than 1, the baseline will be set to 1.

For the rescreened participants, only data from the enrolled subject ID will be used.

11.2. Data Convention

For the laboratory safety variables and biomarker data, if the data are below the lower limit of quantification (LLOQ)/limit of linearity, half the lower limit value (i.e., LLOQ/2) will be used for quantitative analyses. For data above the upper limit of quantification (ULOQ)/ limit of linearity, the upper limit value (i.e., ULOQ) will be used for quantitative analyses.

Note that for total IgE, Birch sIgE, and Bet v 1 sIgE, samples whose data are above the ULOQ will be re-analyzed at 1:10 dilution and IgE/sIgE levels will be derived from the results of the dilution assay (i.e, calculated using a factor of 10).For mis-stratification, data from oak allergy status (yes or no) determined based on oak EEU challenge, grass sensitization status (grass

sensitized: grass SPT ≥3 mm or sIgE ≥0.35; not grass sensitized: grass SPT <3 mm and sIgE <0.35) and EEU site as collected from CRF will be used for analysis rather than as randomized.

11.3. Data for Non-Efficacy Endpoints

Missing data will not be imputed in listings.

Adverse event

If the intensity of a TEAE is missing, it will be classified as "severe" in the frequency tables by intensity of TEAEs. If the assessment of relationship of a TEAE to the investigational product is missing, it will be classified as related to the investigational product.

Adverse event start date

AE start date will be used for AE classification and analysis of AESIs. If AE start date is not complete, then the character variable will keep the original incomplete date, the numerical date variable will be imputed, and an imputation flag will be used to indicate which date component is missing.

If AE start day is missing, and AE start month and year are not missing: If AE start year is the same as first dose year and AE start month is the same as first dose month, then AE start day will be imputed using the day of first dose. If this leads to a date after the AE end date, AE end date will be used instead. If AE start month different from first dose month, AE start day will be imputed using the first day of the month. If this leads to a date before informed consent date, the informed consent date will be used. Imputation flag is 'D'.

If AE start month is missing, and AE start year is not missing: If AE start year is before the first dose year, the informed consent day and month will be used. If AE start year is the same as first dose year, the first dose day and month will be used. If this leads to a date after AE end date, AE end date will be used instead. If AE start year is after the first dose year, January 1st will be used. Imputation flag is 'M'.

If AE start year is missing: The date of first dose will be used. If this leads to a date after the AE end date, AE end date will be used instead. Imputation flag is 'Y'.

Adverse event end date

The general recommendation is not to impute AE end date. However, since AE end date will be used for AE start date imputation, to carry through the logic for programming, the following intermediate step will be used. Afterwards, only the original character/numeric date recorded in CRF will be kept in the final analysis dataset.

If AE end day is missing, and AE end month and year are not missing: AE end date will be imputed using the last day of the month. If this leads to a date after EOS follow up date, the end of follow up date will be used instead.

If AE end month is missing, and AE end year is not missing: AE end date will be imputed using December 31st as the day and month. If this leads to a date after EOS follow up date, the end of follow up date will be used instead.

If AE end year is missing: AE end date will be imputed using end of follow up date.

Medication start and end date missing

To determine whether a medication is prior medication or concomitant medication or both, the missing medication start date is estimated as early as possible, and the missing medication end date is estimated as late as possible. If the medication start date is missing, the onset day will not be calculated in medication listing.

Prior medication start date

If start day is missing, and start month and year are not missing: the start day will be imputed using the first day of the month. Imputation flag is 'D'.

If start month is missing, and start year is not missing: the day and month will be imputed using January 1st. Imputation flag is 'M'.

If start year is missing: the start date will be imputed using 2 years before informed consent date. Imputation flag is 'Y'.

A special note: for start date with year missing, the general principle is not to impute. However, to simplify the programming flow, the imputation is proposed to align with protocol which specifies to collect up to 2 years prior medication. Since the start date of prior medication will not be used in any analysis, the rule will not impact the analysis result.

Prior medication end date

If end day is missing, and end month and year are not missing: the end date will be imputed using the last day of the month. If this leads to a date on or after first dose intake date, the first dose intake date – 1 will be used. Imputation flag is 'D'.

If end month is missing, and end year is not missing: the end date will be imputed using December 31st as the day and month. If this leads to a date on or after first dose intake date, the first dose intake date – 1 will be used instead. Imputation flag is 'M'.

If end year is missing: the end date will be imputed using the first dose intake date – 1. Imputation flag is 'Y'.

Concomitant medication start date

The imputation rule for concomitant medication start date is the same as prior medication start date.

Concomitant medication end date

If end day is missing, and end month and year are not missing: the end date will be imputed using the last day of the month. If this leads to a date after EOS follow up date, the end of follow up date will be used. Imputation flag is 'D'.

If end month is missing, and end year is not missing: the end date will be imputed using December 31st as the day and month. If this leads to a date after EOS follow up date, the end of follow up date will be used instead. Imputation flag is 'M'.

If end year is missing: the end date will be imputed using the end of follow up date. Imputation flag is 'Y'.

Medication coding

Medications whose ATC level 4 cannot be coded will be summarized by setting ATC4=ATC2 in the table programs. However, these uncoded ATC level 4 records still need to be confirmed with study data manager and study medical director.

PCSV

Subjects who had post-baseline PCSV but missing baseline value will be regarded as having treatment-emergent PCSV.

11.4. Assignment of Data to Visit Windows and Unscheduled Assessments

Unscheduled Assessments

Data analyzed by-visit-analysis (including efficacy, laboratory data, vital sign, ADA) will be summarized by the study scheduled visits described in the "Schedule of Events" of study protocol and SAP.

The analysis visit windows are created per study Schedule of Events (SOE) table for each parameter and will be applied if the data from study scheduled visits are unavailable. The following general rules will be applied to unscheduled visit and/or early termination (ET) visit mapping for each parameter.

1. If ET visit falls in an analysis window which already has non-missing observed value of this parameter from the scheduled visit, ET will be mapped to the next scheduled visit in the same part.
2. If both ET visit and unscheduled visit of the same parameter are available in the same analysis visit window, only ET visit will be mapped.
3. If multiple unscheduled visits of the same parameter are available in the same analysis visit window, the unscheduled visits will be mapped using the following rules:
    a. The closest unscheduled visit from the target day will be selected.
    b. If the distance is a tie, the unscheduled visit after the target day of the scheduled visit will be used.
    c. If multiple unscheduled visits exist on the same day, the first unscheduled visit will be used.
4. If mapping distance is greater than 6 weeks, the unscheduled visit will not be mapped.

Unscheduled visits and ET visit will be mapped per the following analysis visit windows for Part A and Part B based on the study day/visit of each parameter, respectively.

1. Part A visit window: All data collected after the last out-of-season EEU visit and/or the Visit 10 (whichever is later) will not be used for Part A analysis.
2. Part B visit window: All data not in Part A visit window will be included in Part B visit window.

Table 4: Analysis Visit Window for Safety and Laboratory Testings

Part	Visit from SOE	Target Study Day[1]	Vital Sign, Physical examination		Hematology, Blood chemistry	Drug Concentration sample	ADA sample
			Allergic to Oak[2]	Not Allergic to Oak[2]			
	Baseline	<=1	<=1				<=1
Part A	Visit 6	29	[2, 33]	[2, 43]	[2, 43]	[2, 43]	-
	Visit 7	36	[34, 47]	-	-	-	-
	Visit 8	57	[48, 61]	[44, 61]	[44, 61]	[44, 61]	-
	Visit 9	85	>=62		>=62	>=62	>=2
Part B	Visit 10[3]	Before the dose in Part B	All data after the last out-of-season EEU visit and before the dose in Part B.				
	Visit 11	~0 to 3 weeks prior to start of BPS	-				
	Visit 13	During peak BPS	Assessment during the actual local BPS				-
	Visit 14	At the end of BPS	Assessment at the end of the actual local BPS				-
	Visit 15 (EOS)	After BPS	Assessment after the actual local BPS		-	Assessment after the actual local BPS	Assessment after the actual local BPS

[1] Study days in Part A are calculated from the day of 1st injection. Study day = (date of assessment – 1st injection date + 1) when date of assessment ≥1st injection date; otherwise, study day = (date of assessment – 1st injection date). If subject never received any dose of study drug, randomization date will be used in the place of 1st injection date. Visit timeframes in Part B (visits 10 to 15) may vary based on the timing and duration of the anticipated BPS.

[2] The visit mapping rule for participants who are allergic to oak is slightly different with participants who are not allergic to oak for vital sign and physical examination.

[3] If visit 10 is combined with visit 6, visit 8, or visit 9, there will be no assessment for visit 10 and no titrated SPT in unscheduled visit will be mapped to visit 10. If visit 10 is combined with visit 7, the unscheduled titrated SPT collected after the last out-of-season EEU visit and before the dose in Part B will be mapped to visit 10.

Mapping rule for EEU symptom scores

All symptom scores collected in EEU will be mapped to nominal time due to an allowed window to answer the questionnaire.

Table 5: Summary of EEU Nominal and Derived Times

EEU Time	Analysis Timepoint	Nominal Time	Window for Derived Time[1,2]
EEU Qualification	-1	-0:15	< -0:10
Pre-EEU	0	0:00	[-0:10, 0:10)
In EEU 0 to <2 hours	1	0:20	[0:10, 0:30)
	2	0:40	[0:30, 0:50)
	3	1:00	[0:50, 1:10)
	4	1:20	[1:10, 1:30)
	5	1:40	[1:30, 1:50)
	6	2:00	[1:50, 2:10)
In EEU 2-6 hours[3]	7	2:20	[2:10, 2:30)
	8	2:40	[2:30, 2:50)
	9	3:00	[2:50, 3:10)
	10	3:20	[3:10, 3:30)
	11	3:40	[3:30, 3:50)
	12	4:00	[3:50, 4:10)
	13	4:20	[4:10, 4:30)
	14	4:40	[4:30, 4:50)
	15	5:00	[4:50, 5:10)
	16	5:20	[5:10, 5:30)
	17	5:40	[5:30, 5:50)
	18	6:00	[5:50, 6:10)

[1] Derived time = actual assessment calendar time (hh:mm) – EEU entry calendar time (hh:mm) for Cliantha site, as well as the EEU qualification and pre-EEU measurement in Kingston site. Derived time = actual assessment calendar time (hh:mm) – EEU entry calendar time (hh:mm)-15 min for Kingston Site (15 mins for Kingston site to prepare the pollen exposure after participants enter the EEU).

[2] If a patient has 2 or more timepoints within the same window, the first non-missing value will be used for analysis.

[3] Records during this period will be used to calculate the average symptom scores in EEU from 2 to 6 hours.

11.5. Pooling of Categorical Variables for Statistical Analyses

No categorical variables will be pooled in the analyses.

12. TECHNICAL DETAILS PERTAINING TO INTERIM ANALYSIS/(ES)

Not applicable as no formal interim analysis is planned.

13. REFERENCES

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14. APPENDIX

14.1. Summary of Statistical Analyses

Efficacy/PD Analysis:

Endpoint	Analysis Populations	Primary Analysis	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Primary Endpoint						
EEU TNSS (2-6 hours)	FAS	Mean at day 29 for 3-mAb versus placebo	ANCOVA model with treatment group and stratification factors as fixed effect and the baseline mean TNSS (2 to 6 hours) at visit 2 as a covariate.	Yes, sensitivity and supplemental analysis described in Section 7.2.1.2	Yes, subgroups are listed in Section 7.2.1.3	Plots
Secondary Endpoints						
EEU (2-6 hours): TNSS, TOSS, TSS	FAS	Mean, change and percent change from pre-treatment baseline, at days 29*, 57, 85 for **each of** anti-bet v 1 monoclonal antibodies versus placebo	Same as above	No	No	Numerical comparison between three anti-bet v 1 monoclonal antibodies.
EEU (2-6 hours): TNSS, TOSS, TSS	FAS with subjects allergic to oak	Mean, change and percent change from pre-treatment baseline, at days 36 for **each of** anti-bet v 1 monoclonal antibodies versus placebo	Same as above	No	No	Comparison between combined active group versus placebo
EEU (2-6 hours): TNSS, TOSS , TSS	FAS - B	Mean for each of anti-bet v 1 monoclonal antibodies versus placebo	Same as above	No	No	No
CSMS, TSS, TNSS, TOSS, DMS	FAS - B	Mean, change and percent change from **pre-treatment** and **pre-season** baseline, in BPS, peak BPS for **each of** anti-bet v 1 monoclonal antibodies versus placebo	Same as above except for the average pollen count during local BPS will also be used as a covariate in the model.	No	No	Analyses using 30 grains/ m^3 as the cutoff for defining BPS start and end

Endpoint	Analysis Populations	Primary Analysis	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
RQLQ(S)	FAS - B	Mean , change and percent change from **pre-treatment** and **pre-season** baseline, in BPS, peak BPS for **each of** anti-bet v 1 monoclonal antibodies versus placebo	Same as above	No	No	No
Titrated SPT MWD AUC	FAS for Day 29, 57, and 85 FAS with visit 10 performed at least 12 weeks after dose #1 for Day 127	Change and percent change from pre-treatment baseline, at days 29, 57, 85 and 127 for **each of** anti-bet v 1 monoclonal antibodies versus placebo	Same as above	No	No	Plots; Numerical comparison between three anti-Bet v 1 monoclonal antibodies.
Titrated SPT MWD AUC	FAS - B	Change and percent change from pre-treatment baseline, end-of-season to EOS for **each of** anti-bet v 1 monoclonal antibodies versus placebo	Same as above	No	No	Plots; Analyses using FAS with available in-season data irrespective of whether they received dose 2

Note: *except day 29.

Safety Analysis:

Endpoint	Analysis Populations	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
AEs	SAF	Descriptive statistics	No	No	No
Laboratory Measures	SAF	Descriptive statistics	No	No	No
Vital sign	SAF	Descriptive statistics	No	No	No
Physical examination	SAF	Descriptive statistics	No	No	No

14.2. Schedule of Events

	PART A									PART B						
	SCREENING			RAND	Out-of-Season										FOLLOW-UP	
Study Procedure	**Screening**	**Birch EEU**	**Oak EEU**	**Rand/ Dosing**	**Tel**	**Birch EEU**	**Oak EEU**	**Birch EEU**	**Birch EEU**	**In-Clinic**	**Dosing**	**Tel[15]**	**Birch EEU**	**Birch EEU**	**EOS/ ET**	Unsc. Visit[38]
Visit (V) Number	V1[1]	V2[5]	V3[6]	V4	V5	V6	V7[6]	V8[40]	V9[41]	V10[13,41]	V11[12,13]	V12[13]	V13[13]	V14[13]	V15[13]	
Appx. Week (wk)					wk1	wk4	wk5	wk8	wk12	~wk18	~wk22		~wk27	~wk32	~wk36	
Visit Day (d)	-d70 to -d1			d1	d8	d29	d36	d57	d85	d127	d155	d156	d190	d225	d253	
Visit Window (days)					±3d	±7d	-7d to +14d	±7d	-28d to +14d	±7d	±7d	+1d	±7d	±7d	±7d	
Screening:																
Inclusion/exclusion	X	X	X	X		X[19]	X[19]	X[19]	X[19]	X[19]	X[19]		X[19]	X[19]		
Informed consents	X															
Medical and allergy history[34]	X															
Demographics	X															
FSH (postmenopausal women only)	X															
Electrocardiogram[22]	X															X
Height	X															
Weight	X															
Urinalysis	X															X

	PART A									PART B						
	SCREENING			RAND	Out-of-Season										FOLLOW-UP	
Study Procedure	**Screening**	**Birch EEU**	**Oak EEU**	**Rand/ Dosing**	**Tel**	**Birch EEU**	**Oak EEU**	**Birch EEU**	**Birch EEU**	**In-Clinic**	**Dosing**	**Tel[15]**	**Birch EEU**	**Birch EEU**	**EOS/ ET**	Unsc. Visit[38]
Visit (V) Number	V1[1]	V2[5]	V3[6]	V4	V5	V6	V7[6]	V8[40]	V9[41]	V10[13,41]	V11[12,13]	V12[13]	V13[13]	V14[13]	V15[13]	
Appx. Week (wk)					wk1	wk4	wk5	wk8	wk12	~wk18	~wk22		~wk27	~wk32	~wk36	
Visit Day (d)	-d70 to -d1			d1	d8	d29	d36	d57	d85	d127	d155	d156	d190	d225	d253	
Visit Window (days)					±3d	±7d	-7d to +14d	±7d	-28d to +14d	±7d	±7d	+1d	±7d	±7d	±7d	
Sensitization/ Specialty Labs:																
SPT birch, birch-related and unrelated common allergens[2]	X[2*,35]					X[4]		X[4]	X[4]	X[4]				X[4]	X[4]	X[4]
Titrated SPT to birch and birch-related allergens[3]		X				X[4]		X[4]	X[4]	X[4]				X[4]	X[4]	
Serum allergen-specific IgE (eg, birch and Bet v 1 sIgE, other related/ unrelated allergens)	X			X[39]		X		X	X	X			X	X	X	X
Serum total IgE				X												
Whole blood for basophil activation test [31]		X				X							X			
Nasal fluid collection[33]		X				X		X					X	X		

	PART A									PART B						
	SCREENING			RAND	Out-of-Season										FOLLOW-UP	
Study Procedure	**Screening**	**Birch EEU**	**Oak EEU**	**Rand/ Dosing**	**Tel**	**Birch EEU**	**Oak EEU**	**Birch EEU**	**Birch EEU**	**In-Clinic**	**Dosing**	**Tel[15]**	**Birch EEU**	**Birch EEU**	**EOS/ ET**	Unsc. Visit[38]
Visit (V) Number	V1[1]	V2[5]	V3[6]	V4	V5	V6	V7[6]	V8[40]	V9[41]	V10[13,41]	V11[12,13]	V12[13]	V13[13]	V14[13]	V15[13]	
Appx. Week (wk)					wk1	wk4	wk5	wk8	wk12	~wk18	~wk22		~wk27	~wk32	~wk36	
Visit Day (d)	-d70 to -d1			d1	d8	d29	d36	d57	d85	d127	d155	d156	d190	d225	d253	
Visit Window (days)					±3d	±7d	-7d to +14d	±7d	-28d to +14d	±7d	±7d	+1d	±7d	±7d	±7d	
Exploratory research serum and plasma[32]		X		X		X		X	X		X		X	X	X	
Treatment:																
Randomization				X[10]												
Administer study drug[16]				X							X[11,14]					
Dispense rescue medications[27]		X	X			X	X	X	X	X	X		X	X		
Efficacy:																
EEU visits: TNSS, TOSS[7,8,9]		X[5]	X			X[7]	X[7]	X[7]	X[7]				X[8]	X[8]		
e-Diary: TNSS, TOSS, and DMS[24]		X[25]								X[26]						
RQLQ(S)[28]		X								X						
PFASQ[29]		X								X						
Outdoor time questionnaire[30]		X								X						

	PART A									PART B						
	SCREENING			RAND	Out-of-Season										FOLLOW-UP	
Study Procedure	**Screening**	**Birch EEU**	**Oak EEU**	**Rand/ Dosing**	**Tel**	**Birch EEU**	**Oak EEU**	**Birch EEU**	**Birch EEU**	**In-Clinic**	**Dosing**	**Tel[15]**	**Birch EEU**	**Birch EEU**	**EOS/ ET**	Unsc. Visit[38]
Visit (V) Number	V1[1]	V2[5]	V3[6]	V4	V5	V6	V7[6]	V8[40]	V9[41]	V10[13,41]	V11[12,13]	V12[13]	V13[13]	V14[13]	V15[13]	
Appx. Week (wk)					wk1	wk4	wk5	wk8	wk12	~wk18	~wk22		~wk27	~wk32	~wk36	
Visit Day (d)	-d70 to -d1			d1	d8	d29	d36	d57	d85	d127	d155	d156	d190	d225	d253	
Visit Window (days)					±3d	±7d	-7d to +14d	±7d	-28d to +14d	±7d	±7d	+1d	±7d	±7d	±7d	
Safety:																
Vital signs[18]	X	X	X	X		X	X	X	X	X	X		X	X	X	X
Physical examination[17]	X	X	X	X		X	X	X	X	X	X		X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Spirometry/PEF[23]	X[23*]	X	X	X[23*]		X	X	X	X		X		X	X		X
Laboratory Testing[20]:																
Hematology[32]	X			X		X		X	X	X			X	X		X
Blood chemistry[32]	X			X		X		X	X	X			X	X		X
Pregnancy test (urine) (WOCBP)[21]		X	X	X		X	X	X	X		X		X	X	X	X
Pregnancy test (serum) (WOCBP)[21]	X									X						X
Pharmacokinetics and Immunogenicity Sampling:																
Drug concentration sample[36]				X[36]		X		X	X	X	X[36]		X	X	X	X
ADA sample[36]				X[36]					X		X[36]				X	X

	PART A									**PART B**						
	SCREENING			RAND	Out-of-Season										FOLLOW-UP	
Study Procedure	**Screening**	**Birch EEU**	**Oak EEU**	**Rand/ Dosing**	**Tel**	**Birch EEU**	**Oak EEU**	**Birch EEU**	**Birch EEU**	**In-Clinic**	**Dosing**	**Tel**[15]	**Birch EEU**	**Birch EEU**	**EOS/ ET**	Unsc. Visit[38]
Visit (V) Number	V1[1]	V2[5]	V3[6]	V4	V5	V6	V7[6]	V8[40]	V9[41]	V10[13,41]	V11[12,13]	V12[13]	V13[13]	V14[13]	V15[13]	
Appx. Week (wk)					wk1	wk4	wk5	wk8	wk12	~wk18	~wk22		~wk27	~wk32	~wk36	
Visit Day (d)	-d70 to -d1			d1	d8	d29	d36	d57	d85	d127	d155	d156	d190	d225	d253	
Visit Window (days)					±3d	±7d	-7d to +14d	±7d	-28d to +14d	±7d	±7d	+1d	±7d	±7d	±7d	
Future Biomedical Research (optional sub-study):																
Serum sample collection for future biomedical research (optional)[32]		X		X		X		X	X		X		X	X	X	
Plasma sample collection for future biomedical research (optional)[32]		X		X		X		X	X		X		X	X	X	
Pharmacogenomics (optional sub-study):																
Blood for DNA (optional)[37]				X												

Footnotes for the Schedule of Events Table

1. Screening visit 1 can be split into additional visits, if required, to ensure medication washouts prior to any assessments being performed (per PI discretion).
2. Screening skin prick test (SPT) for birch and for other birch-related (eg, alder, oak) and unrelated common allergens (eg, grass, dust mites, etc) is performed as described in the study reference manual. SPT source documentation is required (eg, tape transfer method).

   ** If screening SPT for birch does not meet eligibility at screening visit 1 (mean wheal diameter less than at least 5 mm greater than the negative control), then other screening visit 1 procedures may not be performed, as the subject will have failed screening based upon birch skin prick testing (eg, recommend performing birch skin prick testing prior to blood draw, spirometry, etc).*
3. Titrated SPT with serial allergen titration for birch and related allergens is performed as described in the study reference manual. The titrated SPT should be performed prior to the EEU challenge during visits when both are scheduled.
4. Post-randomization SPT and titrated SPT will be performed in a blinded fashion (as described in the study reference manual).
5. All other eligibility criteria need to be met prior to the screening birch allergen EEU challenge (visit 2). It is recommended that the screening birch challenge is scheduled outside of relevant pollen seasons when pollen-allergic subjects are not significantly symptomatic due to other pollens.
6. It is recommended that EEU challenges (including birch and oak EEU sessions) be separated by approximately 1 week or longer between the challenges for a subject to avoid potential impact of any residual symptoms on the assessments, per PI judgement. Similarly, approximately 1 week or longer is recommended between EEU challenges and dosing to avoid any overlap of symptoms, per PI judgement. Eligible subjects who are oak-sensitized will also complete the oak EEU challenge at screening. Oak allergy status for stratification and day 36 challenges will be determined similar to birch EEU criteria during the screening oak challenges.
7. Part A EEU challenges: TNSS and TOSS are recorded using an e-diary at baseline and then every ~20 minutes while in the EEU, then continued ~ every 2 hours until ~24 hours after the start of the EEU exposure (except during sleep). After completion of the EEU challenges, use of allergy medicines will be recorded in the e-diary until ~24 hours after the start of the EEU challenges. An assessment of TNSS is performed once prior to the start of the EEU exposure at visits 2, 3, 6, 7, 8, 9. If TNSS $\leq$2, then the visit activities can proceed. If TNSS is >2, then the visit can be rescheduled within the window. Washouts for medications prior to EEU visits are specified in prohibited medications (Protocol Section 7.9.1).
8. Part B EEU challenges: There are no TNSS thresholds for the peak birch pollen season EEU visit (visit 13). The birch EEU challenge at the end of the season (visit 14) may not be performed in grass-allergic participants who are highly symptomatic or unable to wash out allergy relieving rescue medications due to grass pollen allergy symptoms, per PI discretion.

9. On a case-by-case basis, an EEU challenge visit window post-randomization may be extended up to +14 days for any illnesses (eg, respiratory illness, common cold, etc) that may potentially confound the assessments and/or potentially impact participant safety, per PI discretion in consultation with the sponsor.
10. Randomization may occur within 1 day prior to study drug administration.
11. In Part B, participants who received either 3-mAb, 2-mAb, 1-mAb, or placebo in Part A will continue the same treatment in Part B.
12. Dosing window for visit 11 is within approximately 0 to 3 weeks prior to start of the anticipated BPS.
13. Visit timeframes in Part B (visits 10 to 15) may vary based on the timing and duration of the anticipated BPS. End-of-season EEU challenge (visit 14) should occur after the end of the protocol-defined end of the BPS.
14. Dose #2 should be administered at minimum 12 weeks after dose #1.
15. Participants will be contacted within 1 day (visit 12) after dose 2 (visit 11) via telephone to monitor safety trends.
16. All safety assessments performed at screening must be normal and checked against the inclusion/exclusion criteria prior to study drug administration at visit 4. Similarly, it is recommended to review relevant safety assessments prior to dosing at visit 11. Participants will be observed for 2 hours after receiving the SC dose of study drug. Safety labs may be repeated if any concerns, per PI discretion.
17. A full physical exam must be done at screening, visits 4, 11, and 15. A limited relevant physical exam will be done at the remaining visits, per PI judgement, depending on presentation of the participant. Additional relevant physical exams may be conducted during and after completion of the EEU challenges, per PI discretion.
18. Vital signs include systolic and diastolic blood pressure, respiratory rate, heart rate, and temperature. Vital signs will be collected in a seated position.

    *On visit 4 (day 1) and visit 11, vital signs are taken prior to study drug administration and at 2 hours (approximately ±15 min) after completion of study drug administration.

    Additional vital signs may be recorded during and after completion of the EEU challenges, per PI discretion.
19. Inclusion/ exclusion criteria will be verified only to document any changes, not to determine study eligibility.
20. Testing for COVID-19 or other respiratory infections may be performed at visits, per site local protocols.

21. If the urine pregnancy test is positive, the site must perform a serum pregnancy test for confirmation. For visit 4 (randomization) if a serum pregnancy test must be performed, study drug cannot be administered unless the serum pregnancy test is negative. For all EEU visits (visits 2, 3, 6, 7, 8, 9, 13, and 14) and early termination, if a pregnancy test must be performed, EEU and associated procedures cannot be performed unless the pregnancy test is negative. Urine pregnancy test can be performed on day -1 of EEU visits and early termination, at the investigator's discretion.
22. Electrocardiogram will be performed locally by the site.
23. Spirometry will be performed locally by the site. *Spirometry at screening and randomization is required for all participants for eligibility. At other visits, spirometry and/or peak expiratory flow (PEF) may be performed for participants, per PI judgement.
24. Daily TNSS, TOSS, and DMS assessments will being collected by e-diary during screening and in Part B from visit 10 to visit 15. The e-diary is returned at visit 15.
25. Screening baseline assessment: e-diary assessments for symptoms and allergy rescue medication use should be obtained for an approximate 2-week period or longer (at minimum 1 week) starting after the screening birch EEU challenge until randomization (visit 4) in eligible subjects. It is recommended that it is performed outside of relevant pollen seasons when pollen-allergic subjects are not significantly symptomatic due to other pollens.
26. Pre-season baseline assessment: e-diary assessments for symptoms and allergy rescue medication use should be obtained approximately 2 weeks or longer up (at minimum 1 week) to receipt of dose 2 given ahead of the anticipated BPS (starting at visit 10 [Part B]) and prior to receiving dose 2 at visit 11 ahead of the BPS).
27. Allergy relieving rescue medications, as needed, should be dispensed at the end of symptom score collection on visits 2, 3, 6, 7, 8, and 9. Rescue medications are dispensed starting at visit 10 for management of symptoms during the pollen season up to visit 15.
28. RQLQ(S) is administered weekly starting at visit 2 (during screening baseline assessment period) and then weekly using an e-diary in Part B starting at visit 10 until visit 15.
29. Pollen food allergy questionnaire (PFASQ) is administered every 2 weeks at baseline starting at visit 2 (during screening baseline assessment period) and then every 2 weeks in Part B starting at visit 10 until visit 15.
30. Outdoor time questionnaire is administered daily at baseline starting at visit 2 (during screening baseline assessment period) and then daily using an e-diary in Part B starting at visit 10 until visit 15.
31. Basophil activation test (BAT) samples may be collected from approximately 100 randomized participants (subset of the total enrolled population at one or both EEU sites; additional samples may be collected at the screening EEU visit to account for potential screen failures). The initial samples for a BAT assay are to be collected prior to the administration of study drug and subsequent BAT assay samples are to be collected prior to the respective EEU challenges.
32. Samples are to be collected prior to the administration of study drug and prior to EEU challenges, when applicable.

33. Nasal fluid samples may be collected from a subset of participants. It is recommended to collect these samples in the same participants from whom BAT assay samples were collected. It will be collected in approximately 100 randomized participants at visits 2, 6, 8, 13, and 14 (subset of the total enrolled population at one or both EEU sites; additional samples may be collected at the screening EEU visit to account for potential screen failures). At each visit, the nasal fluid samples will be collected at 2 time points, prior to the start of the EEU challenge and then at 6 hours after completion of the challenge.
34. Medical, surgical, allergy and medication history, demographic and social history may be obtained from historical data for participants who have available source documentation of these within 6 months prior to screening. At screening, all historical data should be reviewed/ confirmed for accuracy and completeness with addition of any other relevant missing and/or interval changes since that last historical assessment. Eligibility criteria must be reviewed during screening to ensure that all inclusion criteria are met, and no exclusion criteria are met.
35. Skin prick testing data for allergens using standard diagnostic concentrations of allergen extracts [except birch, other trees (birch-related or unrelated), or grasses] may be obtained from historical data for participants who have source documentation of prior SPT performed within 6 months prior to screening.

    Note: Appropriate source documentation (eg, tape transfer method) must be available to calculate and verify the mean wheal diameter as per study requirements. Participants who do not have historical data for any of the other SPTs as specified in the study reference manual within 6 months prior to screening will need to perform them during the screening period. All participants are required to have an SPT for birch, other trees (birch-related or unrelated), and grasses during the study screening period regardless of the availability of historical data.
36. Pharmacokinetic (drug concentration) and immunogenicity (ADA) samples are to be collected prior to the administration of study drug. In the event of suspected serious adverse events (SAEs), such as anaphylaxis or systemic hypersensitivity, additional samples for the analysis of ADA as well as REGN5713, REGN5714, and REGN5715 drug concentration may be collected as close to the event as practically possible.
37. Pharmacogenomics sub-study is optional for all participants enrolling in the main study. One DNA sample is to be collected on day 1/randomization prior to receiving the study drug, but if this sample collection was omitted at baseline, it can be collected at any subsequent visit.
38. Unscheduled visit procedures may be performed per PI discretion based on the reason for the visit.
39. Allergen-specific IgE should be drawn prior to administration of study drug at the randomization visit (visit 4).
40. Day 57 and/or day 85 EEU challenges may not be performed in participants who have a high symptom burden assessed due to tree pollens.
41. Visit 10 may not be performed in participants if they are expected to be dosed within 3 weeks after the prior EEU visit. If visit 10 is not performed, then all visit 10 assessments (without any duplication) should be performed at the last prior EEU visit (including serum pregnancy test, e-diary, dispensing rescue medications, etc)

14.3. Criteria for Potentially Clinically Significant Values (PCSV)

Parameter	PCSV	Comments
Clinical Chemistry		
ALT*	>3 and ≤ 5 ULN and baseline ≤ 3 ULN* >5 and ≤ 10 ULN and baseline ≤ 5 ULN >10 and ≤ 20 ULN and baseline ≤ 10 ULN >20 ULN and baseline ≤ 20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – United States Food and Drug Administration (FDA) draft Guidance Oct 2007. Each category is calculated independently. * At least one level is required; multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution across the different PCSV levels, additional shift table on ≤3, >3 to ≤5, > 5 to ≤10, >10 to ≤20, and > 20 category for baseline vs. post baseline may be provided
AST*	>3 and ≤ 5 ULN and baseline ≤ 3 ULN* >5 and ≤ 10 ULN and baseline ≤ 5 ULN >10 and ≤ 20 ULN and baseline ≤ 10 ULN >20 ULN and baseline ≤ 20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Each category is calculated independently. * At least one level is required, multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution across the different PCSV levels, additional shift table on ≤3, >3 to ≤5, > 5 to ≤10, >10 to ≤20, and > 20 category for baseline vs. post baseline may be provided
Alkaline Phosphatase	>1.5 ULN and baseline ≤ 1.5 ULN	Enzyme activity must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007.
Total Bilirubin*	>1.5 and ≤ 2 ULN and baseline ≤ 1.5 ULN* >2 ULN and baseline ≤ 2.0 ULN	Must be expressed in ULN, not in µmol/L or mg/L. Categories are cumulative. Concept paper on DILI – FDA draft Guidance Oct 2007. * At least one level is required, multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution of significant level, additional shift table on ≤1.5, >1.5 to ≤2.0 and > 2.0 category for baseline vs. post baseline may be provided
(ALT or AST) and Total Bilirubin	((ALT >3 ULN or AST>3 ULN) and TBILI>2 ULN) and baseline ((ALT ≤3 ULN and AST ≤3 ULN) or TBILI ≤2 ULN))	Concept paper on DILI – FDA draft Guidance Oct 2007.
Creatinine	≥150 µmol/L (Adults) and baseline < 150 µmol/L ≥30% change from baseline and <100% change from baseline ≥100% change from baseline	Benichou C., 1994. 3 independent criteria
Blood Urea Nitrogen (BUN)	≥17 mmol/L and <17 mmol/L at baseline	Two independent criteria
Chloride	<80 mmol/L and baseline ≥ 80 mmol/L >115 mmol/L and baseline ≤115 mmol/L	Two independent criteria

Parameter	PCSV	Comments
Sodium	≤129 mmol/L and baseline > 129 mmol/L ≥160 mmol/L and baseline < 160 mmol/L	Two independent criteria
Potassium	<3 mmol/L and baseline ≥ 3 mmol/L ≥5.5 mmol/L and baseline < 5.5 mmol/L	FDA Feb 2005. Two independent criteria
Glucose Hypoglycaemia Hyperglycaemia	≤3.9 mmol/L and <LLN and baseline >3.9 mmol/L or ≥ LLN ≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted) and baseline < 11.1 mmol/L (unfasted); <7 mmol/L (fasted)	ADA Jan 2008.
Albumin	≤25 g/L and >25 g/L at baseline	
Hematology		
WBC	<3.0 Giga/L and ≥3.0 Giga/L at baseline (Non-Black); <2.0 Giga/L and ≥2.0 Giga/L at baseline (Black) ≥16.0 Giga/L and < 16 Giga/L at baseline	Increase in WBC: not relevant. *The default criteria. Summary by race (black and Non-black) are optional. To be interpreted only if no differential count available.
Lymphocytes (ALC)	>4.0 Giga/L and ≤4.0 Giga/L at baseline	
Neutrophils	<1.5 Giga/L and ≥1.5 Giga/L at baseline (Non-Black); <1.0 Giga/L and ≥1.0 Giga/L at baseline (Black)	International Consensus meeting on drug-induced blood cytopenias, 1991. *The default criteria. By race (black and Non-black) are optional.
Monocytes	>0.7 Giga/L and ≤ 0.7 Giga/L at baseline	
Basophils	>0.1 Giga/L and ≤ 0.1 Giga/L at baseline	
Eosinophils	(>0.5 Giga/L and >ULN) and (≤0.5 Giga/L or ≤ ULN at baseline)	Harrison- Principles of Internal Medicine 17th Ed., 2008.
Hemoglobin	≤115 g/L and > 115 g/L at baseline for male; ≤95 g/L and> 95 g/L at baseline for Female. ≥185 g/L and <185 g/L at baseline for Male; ≥165 g/L and < 165 g/L at baseline for Female Decrease from Baseline ≥20 g/L	Three criteria are independent. *The default criteria. By gender (male and female) are optional. Criteria based upon decrease from baseline are more relevant than based on absolute value. Other categories for decrease from baseline can be used (≥30 g/L, ≥40 g/L, ≥50 g/L).
Hematocrit	≤0.37 v/v and > 0.37 v/v at baseline for Male ; ≤0.32 v/v and > 0.32 v/v at baseline for Female ≥0.55 v/v and < 0.55 v/v at baseline for Male ; ≥0.5 v/v and < 0.5 v/v at baseline for Female	Two Criteria are independent *The default criteria. By gender (male and female) are optional.

Parameter	PCSV	Comments
RBC	<4 Tera/L and ≥ 4 Tera/L at baseline for Male ; <3 Tera/L and ≥ 3 Tera/L at baseline for Female ≥7 Tera/L and <7 Tera/L at baseline for Male ; ≥6 Tera/L and <6 Tera/L at baseline for Female	Unless specifically required for particular drug development, the analysis is redundant with that of Hb.
Platelets	<100 Giga/L and ≥100 Giga/L at baseline ≥700 Giga/L and < 700 Giga/L at baseline	International Consensus meeting on drug-induced blood cytopenias, 1991. Two independent criteria
Vital signs		
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm	
SBP	≤95 mmHg and decrease from baseline ≥20mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	
Respiratory rate	< 12 per minutes and ≥12 per minute at baseline >20 per minute and ≤20 per minute at baseline	
Temperature	>= 100.4 °F/38.0 °C	

14.4. Search Criteria for TEAE of Special Interest

AESI	Search Criteria
Systemic or severe hypersensitivity reactions	Narrow SMQ for hypersensitivity *Note: Anaphylaxis will be prospectively analyzed using the criteria discussed in the statement paper from the Second Symposium on the definition and Management of Anaphylaxis (Sampson, 2006).* This would include manual adjudication of relevant PTs performed by the study medical monitor, before database lock

14.5. Sensitization Status by SPT or sIgE

Sensitization status will be determined by SPT and sIgE testing. For SPT, a negative control (such as saline/diluent), and positive control (histamine) will be included. The SPT and sIgE tests used to evaluate sensitization status (including definitions of birch, birch-related, and unrelated allergens) are provided in the table below.

Summary of SPT and sIgE Tests Used to Evaluate Sensitization Status

Type	Group	Allergen	Tests
Birch Allergens	Tree pollens	European White Birch	SPT, sIgE
		Bet v 1	sIgE
		Bet v 2	sIgE
Birch-Related Allergens	Tree pollens	White Alder	SPT
		Grey Alder	sIgE
		American Hazel	SPT
		Red Oak	SPT, sIgE
Unrelated Allergens	Tree pollens	Sugar Maple	SPT
		White Poplar	SPT
		American Elm	SPT
		Mountain Cedar	SPT
		White Ash	SPT
	Grass pollens	Grass mix[1]	SPT
		Timothy grass	sIgE
	Weed pollens	Short Ragweed	SPT, sIgE
	Animal	Cat	SPT, sIgE
		Dog	SPT, sIgE
	House dust mite	House Dust Mite Mix[2]	SPT
		Dermatophagoides farinae	sIgE
		Dermatophagoides pteronyssinus	sIgE
	Mold	Mold mix[3]	SPT
		Alternaria	sIgE

[1] Grass Mix: Kentucky Bluegrass, Meadow Fescue, Orchard Grass, Perennial Ryegrass, Redtop, Sweet Vernal Grass, Timothy Grass.

[2] House Dust Mite Mix: *D. farinae*, *D. pteronyssinus*.

[3] Mold Mix: *Alternaria alternata*, *Aspergillus niger*, *Bipolaris sorokiniana*; *Cladosporium sphaerospermum*, *Penicillium chrysogenum var. chrysogenum*

Several distinct definitions of sensitization status (by either SPT or sIgE) will be used and are defined below.

- Mono-sensitization: defined as sensitization to birch and birch-related allergens only.
- Poly-sensitization: defined as sensitization to birch and birch-related allergens *and* sensitization to any unrelated allergen and specifically the following groups will be described based on sensitizations
  - Sensitization to non-tree pollens: defined as sensitization to either grass or weed pollens.
  - Sensitization to unrelated tree pollens: defined as sensitization to any unrelated tree pollen
  - Indoor perennial allergen sensitization: defined as sensitization to any of house dust mite, cat or dog.

Note:

- *Sensitization by SPT: defined as a mean wheal diameter of at least 3 mm or greater versus negative control. The eligibility criterion for birch sensitization by SPT requires a mean wheal diameter at least 5 mm greater versus negative control. SPT mean wheal diameter is defined as ([longest diameter + longest perpendicular]/2).*
- *Sensitization by sIgE: defined as serum sIgE of 0.35 kUa/L or greater.*

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