NCT05430919

IND Number: 138377 Regeneron Pharmaceuticals, Inc.

Clinical Study Protocol

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

Compounds:	REGN5713; REGN5714; REGN5715
Clinical Phase:	2
Protocol Number:	R5713-5714-5715-ALG-21111
Protocol Version:	R5713-5714-5715-ALG-21111 Amendment 1
Date of Issue:	*See appended electronic signature page*
Original Date of Issue:	17 May 2022

Medical /Study Director: [redacted]

Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, NY 10591

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
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)
CRO	Contract research organization
CSMS	Combined Symptom and Medication Score
CSR	Clinical study report
DMS	Daily Medication Score
EC	Ethics Committee
ECG	Electrocardiogram
EC_{50}	Half maximal effective concentration
EDC	Electronic data capture
EEU	Environmental exposure unit
EOS	End-of-study
FAS	Full analysis set
FBR	Future biomedical research
FDA	United States Food and Drug Administration
FIH	First-in-human
GCP	Good Clinical Practice
ICF	Informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
INCS	Intranasal corticosteroids
IRB	Institutional Review Board
IV	Intravenous
mAb(s)	Monoclonal antibody(ies)
MI	Multiple imputation
OPS	Oak pollen season

Abbreviation	Definition
PFASQ	Pollen Food Allergy Symptom Questionnaire
PK	Pharmacokinetic
POC	Proof-of-concept
PI	Principal investigator
RBC	Red blood cell
RBQM	Risk-Based Quality Monitoring
Regeneron	Regeneron Pharmaceuticals, Inc.
RQLQ(S)	Rhinoconjunctivitis Quality of Life Questionnaire
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SC	Subcutaneous
SCIT	Subcutaneous immunotherapy
sIgE	Allergen-specific immunoglobulin E
SIT	Specific immunotherapy
SLIT	Sublingual immunotherapy
SOC	System organ class
SPT	Skin prick test [tSPT = SPT using serial allergen titrations]
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TNSS	Total Nasal Symptom Score
TOSS	Total Ocular Symptom Score
TSS	Total Symptom Score
WBC	White blood cell

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

AMENDMENT HISTORY

Amendment 1

The main purpose of this amendment is to decrease the minimum interval between study drug dose #1 and dose #2.

The following table outlines the changes made to the protocol and the rationale.

Description of Change	Brief Rationale	Sections Changed
The minimum interval between study drug dose #1 and dose #2 was reduced from 18 weeks to 12 weeks. - Time window for day 85 environmental exposure unit (EEU) challenges expanded from "±7d" to "-28 to +14" days to allow participants with a shorter interval to complete Part A assessments prior to the birch season. Therefore, the day 85 visit can be completed from as early as day 57 and up to day 99. - Minimum interval between EEU challenges clarified at approximately 1 week or longer for all EEU challenges. - Participants who experience a high symptom burden that is assessed as due to tree pollens may not complete the day 57 and/or day 85 EEU challenge(s). Therefore, the primary analysis may be performed after all participants complete at least the day 29, rather than the day 57, EEU challenges in Part A or discontinue. - Visit 10 may not be performed if participants 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)	A shorter interval between doses will allow participants to be enrolled over a longer duration within the seasonality constraints to complete both the out-of-season and in-season portions of the study and aid with enrollment timelines. Flexibility to decrease patient burden for visit assessments was added given the reduced timing between some visits that may apply.	Protocol Synopsis: Study Duration; Statistical Plan Section 3.2.2 Rationale for Dose Selection Section 5.1 Study Description and Duration Section 5.2 Planned Analyses Figure 1: Study Flow Diagram Section 8.1.1 Footnotes for the Schedule of Events Table, footnotes #6, #14, #40 and #41 Section 10.5 Timing of Statistical Analysis

Description of Change	Brief Rationale	Sections Changed
The sponsor will define the last possible date for dosing in Part B in each geographical area based on the anticipated timing and duration of the local birch pollen season in consultation with the local pollen expert. Participants who are unable to receive dose #2 prior to the defined dosing end date will discontinue study drug (Section 7.3.2) but should be encouraged to remain in the study.	This change prevents participants from receiving dose #2 when there may not be a reasonable opportunity for benefit during the season.	Protocol Synopsis: Study Design Section 5.1 Study Description and Duration
Text was added to clarify that screening and pre-season e-diary assessments should be obtained for a minimum of 1 week.	This clarifying text will ensure a minimum timeframe for baseline e-diary assessment collection.	Section 5.1 Study Description and Duration Section 8.1.1 Footnotes for the Schedule of Events Table, footnotes #25 and #26
Under the severity grading for injection site reactions (ISRs), the below text was removed: "Potentially Life Threatening: Pain that requires an emergency room visit or hospitalization; erythema characterized by necrosis or exfoliative dermatitis or induration characterized by necrosis"	The description for potentially life threatening and severe ISR categories overlapped in the prior protocol version. The sponsor recommends that all adverse events (AEs), including ISRs, be graded as mild, moderate, or severe per the protocol descriptions. Life-threatening AEs should be reported as a serious adverse event (SAE), as applicable.	Section 9.2.4 Severity
A duplicate medication (systemic steroid treatment) was removed from the list of prohibited medications preceding environmental exposure unit visits and Part B assessments.	This type of medication is already prohibited per the protocol with a 30 day washout during the entire study.	Section 7.9.1 Prohibited Medications and Procedures
Minor changes to language were made for consistency and accuracy. Minor typos were corrected.	Minor edits were made to improve clarity.	Protocol Synopsis: Objectives; Statistical Plan Section 2.2 Secondary Objectives and Endpoints Section 5.1 Study Description and Duration Section 5.2 Planned Analyses Section 7.2 Rescue Treatments Section 7.9.2 Permitted Medications and Procedures Table 1: Schedule of Events Section 8.1.1 Footnotes for the Schedule of Events Table, footnotes #21 and #27

Description of Change	Brief Rationale	Sections Changed
		Section 8.2.2.6 Skin Prick Testing Section 8.2.2.7 Titrated Skin Prick Testing and Birch-Related Allergens Section 8.2.6.1 Basophil Activation Test Typos: Throughout the protocol.

CLINICAL STUDY PROTOCOL SYNOPSIS

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
Site Locations	North America
Principal Investigator	[redacted]
Objectives	**Primary Objective:** 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) **Secondary Objectives:** • 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 (Part A) • 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 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 (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 (Part A) • 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 (Part A) • To compare differences in the degree of reduction of skin test reactivity from pre-treatment baseline by inhibiting a wheal response to a titrated skin prick test 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 (Part A) • 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 (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 and peak birch pollen season in participants receiving REGN5713-5714-5715 versus placebo, REGN5713-5715 versus placebo, and REGN5715 versus placebo (Part B) • 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 skin prick test with birch and related allergens (eg, alder, oak) after the natural birch pollen season in participants who receive REGN5713-5714-5715 versus placebo, REGN5713-5715 versus placebo, and REGN5715 versus placebo (Part B) • 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 • 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 antibodies (mAbs): 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)
Study Design	REGN5713-5714-5715-ALG-21111 is a 2-part randomized, double-blind, placebo-controlled study in birch-allergic participants to assess the efficacy of the anti-Bet v 1 monoclonal antibodies, in combination (the 3-mAb and the best 2-mAb) and as a single best antibody. Efficacy in the reduction of allergic rhinitis and conjunctivitis symptoms as well as birch skin test reactivity will be tested using assessments out-of-season (Part A: EEU challenges and titrated skin prick testing) and during the birch pollen season (Part B: EEU challenges, field assessments, and titrated skin prick testing). Participants will receive 2 doses of the study drug: a dose at randomization outside of the birch pollen season (dose #1; Part A) and a dose of the study drug in Part B ahead of the anticipated birch pollen season (dose #2; Part B). The sponsor will define the last possible date for dosing in Part B in each geographical area based on the anticipated timing and duration of the local birch pollen season; any participants who are unable to receive dose #2 prior to the defined dosing end date will discontinue study drug but should be encouraged to remain in the study. The efficacy will be tested out-of-season as well as in-season to fully evaluate treatment effects during experimental exposure to the allergen and during natural exposure to birch and other related/ unrelated pollens during the birch pollen season.
Study Duration	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). 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 a 4-week follow-up period after end of birch pollen season), dependent on the start and end times of the natural birch pollen season.

End of Study Definition	The end of study is defined as the date the last participant completes the last study visit, withdraws from the study, or is lost to follow-up (ie, the study participant can no longer be contacted by the investigator).
Population	
Sample Size:	The study will enroll approximately 300 participants.
Target Population:	Generally healthy male and female participants 18 years of age or older with birch pollen allergy will be enrolled in this study.
Treatments	
Study Drug	Part A:
Dose/Route/Schedule:	Subcutaneous administration of a dose of study drug (dose #1): • 3-mAb cocktail REGN5713-5714-5715 900 mg (300 mg per mAb) • 2-mAb cocktail REGN5713-5715 600 mg (300 mg per mAb) plus placebo that replaces REGN5714 • 1-mAb REGN5715 300 mg plus placebo that replaces REGN5713-5714 Part B: Subcutaneous administration of dose of study drug (dose #2) • 3-mAb cocktail REGN5713-5714-5715 900 mg (300 mg per mAb) • 2-mAb cocktail REGN5713-5715 600 mg (300 mg per mAb) plus placebo that replaces REGN5714 • 1-mAb REGN5715 300 mg plus placebo that replaces REGN5713-5714 Participants will receive the same treatment in Part B that they were originally randomized to receive in Part A.
Placebo	Parts A and B:
Route/Schedule:	• Subcutaneous administration of matching placebo that replaces active drug
Endpoints	
Primary:	**Primary endpoint:** The mean of Total Nasal Symptom Score [TNSS (2 to 6 hours)] during a birch allergen EEU challenge at day 29

Secondary:	**Secondary Endpoints:**
	• The mean of symptom scores during out-of-season birch allergen EEU challenges at days 29, 57, and 85
	  ○ TNSS (2 to 6 hours) (except day 29 for 3-mAb)
	  ○ Total Ocular Symptom Score (TOSS) (2 to 6 hours)
	  ○ Total Symptom Score (TSS) (2 to 6 hours)

- The change and percent change from pre-treatment baseline in 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 at days 29, 57, 85, and 127 in the birch (and related allergens) titrated skin prick test (SPT) mean wheal diameter AUC
- The mean of symptom scores during out-of-season oak allergen EEU challenge at day 36
  - 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 during an oak allergen EEU at day 36 in subpopulation of oak-allergic participants
  - TNSS (2 to 6 hours)
  - TOSS (2 to 6 hours)
  - TSS (2 to 6 hours)
- 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 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 proportions of participants achieving different degrees of clinical responses will be compared across different symptom response thresholds at days 29, 57, and 85
  - TNSS (2 to 6 hours)
  - TOSS (2 to 6 hours)
  - TSS (2 to 6 hours)
- The proportions of participants achieving different degrees of responses in the birch (and related allergens) titrated SPT mean wheal diameter AUC will be compared across different response thresholds at days 29, 57, and 85
- The mean of symptom scores during the peak-season birch allergen EEU challenge

	○ TNSS (2 to 6 hours) ○ TOSS (2 to 6 hours) ○ TSS (2 to 6 hours) • The daily symptom and medication scores, averaged during the BPS and peak BPS ○ Combined Symptom and Medication Score (CSMS), TSS, TNSS, TOSS, and Daily Medication Score (DMS), averaged during the BPS ○ CSMS, TSS, TNSS, TOSS, and DMS, averaged during the peak BPS • The change and percent change from baseline in the symptom and medication scores, averaged during the BPS and peak BPS ○ CSMS, TSS, TNSS, TOSS, and DMS, averaged during the BPS ○ CSMS, TSS, TNSS, TOSS, and DMS, averaged during the peak BPS • 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 • The mean of the total Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ[S]) score during BPS and peak BPS ○ RQLQ(S), averaged during the BPS and peak BPS ○ Change and percent change from baseline in the average RQLQ(S) during the BPS and peak BPS • Incidence rates of treatment-emergent adverse events (TEAEs) and serious TEAEs through end of study • Total REGN5713, REGN5714, REGN5715 concentration in serum over the duration of the study • Incidences and titers of anti-drug antibodies (ADA) to REGN5713, REGN5714, and REGN5715 over time
Procedures and Assessments	Procedures to determine study eligibility and/or baseline characteristics include SPT for birch, birch-related and unrelated common allergens, allergen-specific IgE, total IgE, electrocardiogram (ECG), laboratory testing, height measurement, weight measurement, pregnancy testing in women of childbearing potential, and follicle stimulating hormone determination (in postmenopausal women if postmenopausal status is in question). Procedures to assess measures of efficacy include the EEU chamber challenges (TNSS, TOSS), daily symptom and medication scores during the birch pollen season (TNSS, TOSS, TSS, DMS, CSMS), SPT to birch and related allergens, titrated SPT to birch and birch-related allergens, RQLQ(S), Pollen Food Allergy Symptom Questionnaire, and the Outdoor Time Questionnaire. Procedures to assess safety include measurement of vital signs, physical examination, spirometry, collection of adverse events, collection of concomitant medications, and laboratory testing. Blood draws will be performed to collect samples for analysis of drug concentration and immunogenicity measurements. Blood draws will also be performed to collect samples for pharmacodynamic and exploratory biomarker procedures, including for the basophil activation test.

	Whole blood samples for DNA extraction will be collected for pharmacogenomic analysis from participants who opt to participate in the optional pharmacogenomic sub-study. Additional serum and plasma samples, as well as nasal fluid samples, will be collected from participants who opt to participant in the optional future biomedical research sub-study.
Statistical Plan	**Justification of Sample Size** This study is powered to detect differences between REGN5713-5714-5715 900 mg and placebo on the primary endpoint of the mean TNSS during a birch pollen EEU challenge (2 to 6 hours) at day 29 in Part A. A sample size of 65 participants per arm gives 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. 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, and a 30% treatment effect relative to placebo is in line with what was observed in the phase 1b proof-of-concept (POC) study for REGN5713-5714-5715. **Efficacy Analysis Sets** 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 modified FAS (mFAS), which consists of participants who receive study drug in Part B. **Primary Efficacy Analysis Methods** The average of TNSS (2 to 6 hours) in a birch allergen EEU at day 29 in Part A will be analyzed by an analysis of covariance (ANCOVA) model, with the treatment group and randomization stratification factors (oak allergy, grass sensitization, EEU site) as fixed effects and the baseline TNSS as a covariate. If any rescue treatments are taken during the EEU challenge, the data from this EEU will be set as missing and day 29 will be imputed by baseline observation carried forward (BOCF). Otherwise, all observed data will be used. Missing data will be imputed by multiple imputation (MI). Additional details will be specified in the SAP. **Secondary Efficacy Analysis Methods** The secondary continuous efficacy endpoints will be analyzed in a manner similar to that described above for the primary efficacy endpoint analysis unless further specified below. The intercurrent events, strategies, and the corresponding missing data handling approaches for the estimand for the continuous secondary efficacy endpoint from EEU challenges may be the same as for the primary endpoint with details to be provided in the SAP.

For the secondary endpoints from titrated SPT, if the antihistamines are not withheld before the titrated SPT, the data from this titrated SPT will be assigned by worst observation from the participant, including baseline.

The proportions of participants achieving different degrees of clinical responses and change/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 graphically using the cumulative distribution function. The AUC of the responder curves may also be calculated as a descriptive summary to compare across different symptom thresholds at days 29, 57, and 85 after receiving a single dose of REGN5713-5714-5715, REGN5713-5715, or REGN5715. Titrated SPT endpoints will be analyzed in a similar manner.

Safety Analysis Set

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).

Safety Analysis Methods

The safety variables, including AEs, laboratory parameters, vital signs, and physical examinations, will be summarized using descriptive statistics.

Timing of Statistical Analyses

The primary analysis may be performed after all participants complete at least the day 29 EEU challenges (visit 6) in Part A or discontinue. A select team will be unblinded 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 unblinded analyses of the study results for efficacy endpoints may be performed when all randomized participants have completed visit 14 (after end of birch pollen season). 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 clinical study report (CSR).

1. INTRODUCTION

Birch-pollen-induced allergic rhinitis with or without conjunctivitis is common in Europe and North America, with clinically relevant sensitization to birch pollen affecting approximately 8% to 16% of the overall population (Chan-Yeung, 2010) (Salo, 2014) (Biedermann, 2019a) and approximately 20% to 30% of the population with allergic rhinitis (Burbach, 2009) (Galant, 1998) (Lin, 2002) (Pablos, 2016) (Sierra-Heredia, 2018). Regardless of the specific allergen, symptoms in allergic rhinoconjunctivitis include rhinorrhea, nasal congestion, nasal itching, sneezing, as well as ocular itching/redness/gritty feeling and eye tearing/watering. These symptoms can result in time away from work/school, medication usage, and overall reduced quality of life (Dykewicz, 2020) (Vandenplas, 2018) and similar is expected for patients with birch allergy. Birch pollen contains a mix of allergenic and non-allergenic proteins; Bet v 1 is the most abundant allergenic birch pollen protein (Erler, 2011) (Schenk, 2011). Sensitization rates to Bet v 1 among birch-allergic individuals reach >95% (Erler, 2011) (Jarolim, 1989) (Schenk, 2011).

Antihistamines and intranasal corticosteroids (INCS) are standard of care for the treatment of allergic rhinoconjunctivitis regardless of the specific allergen inducing the symptoms, including for patients with birch pollen allergic disease. While the antihistamines are only modestly effective, INCS are more effective at treating nasal symptoms; however, they are less effective for allergic eye symptoms (Ciprandi, 2011) (Durham, 2016) (Dykewicz, 2020). Patients with uncontrolled symptoms on standard of care pharmacotherapy, including those with birch pollen-induced allergic rhinitis, are recommended allergen specific immunotherapy (SIT) (Dykewicz, 2020). Although disease-modifying, SIT can have several practical limitations including safety with a risk of local and systemic allergic reactions (including potentially life-threatening anaphylaxis), variable response and tolerability, challenges with time commitment and potential issues with poor patient adherence (Walker, 2011) (Zuberbier, 2010) (Cox, 2011) (Roberts, 2018). There is a need for new medications due to limitations of the current standards of care, such as antihistamines, INCS, and allergen immunotherapy.

The Sponsor has demonstrated that high-affinity monoclonal “blocking antibodies” could be developed and administered as a form of “passive immunotherapy” for the treatment of allergy (Orengo, 2018) (Atanasio, 2022) (Gevaert, 2022). This concept grew out of the observation that allergen-specific polyclonal IgG4 titers increase during SIT and may inhibit effector cell activation by blocking allergen-binding to mast cell and basophil membrane-bound, high-affinity IgE receptors, effectively preventing early-phase allergic symptoms. Clinical symptom improvement has been shown to correlate with the ability of blocking IgG4s to compete with IgE for allergen-binding for some allergens during SIT (James, 2011) (Uermosi, 2010), and similarly expected for other allergens including birch.

The REGN5713-5714-5715 treatment includes a combination of 3 human monoclonal antibodies (mAbs) that specifically target Bet v 1, the major birch tree allergen. Preclinical data indicate that all 3 mAbs are required to maximally inhibit binding of Bet v 1 to human polyclonal IgE, reduce in vitro effector cell degranulation, and subsequent Type 1 hypersensitivity reaction (Atanasio, 2022). REGN5713-5714-5715 was most effective in blocking Bet v 1 binding to polyclonal human IgE and inhibiting Bet v 1- or birch pollen extract-induced basophil activation. REGN5713-5715 was the best dual antibody cocktail when compared to REGN5713-5714 or REGN5714-5715, but less efficient than REGN5713-5714-5715 across all assays. REGN5715 single mAb achieved the highest median percent blocking in-vitro as compared to REGN5713 or

REGN5714. In a humanized Passive Cutaneous Anaphylaxis mouse model, using human plasma containing polyclonal birch specific-IgE, REGN5713-5714-5715 achieves 90% blockade of mast cell degranulation in 4/5 donors evaluated while REGN5713-5715 achieves the same magnitude of blockade in only 1/5 donors evaluated. As compared with the single mAb or double mAb combination, these data suggest that greater blockade of Bet v 1-induced allergy may be achieved with REGN5713-5714-5715 triple antibody cocktail.

Structural data show that simultaneous binding of REGN5713 and REGN5715 leaves more than half of the surface area of Bet v 1 exposed (Atanasio, 2022). REGN5714 binds in one exposed region, but cannot cover all of it, suggesting that it is not necessary to mask 100% of the allergen surface with an antibody cocktail in order to achieve robust blocking potency. Rather, identification and blockade of immunodominant IgE binding epitopes can achieve maximal blockade of the birch allergic response across a diverse and polyclonal birch allergic population. Taken together, the combinations of REGN5713, REGN5714, and REGN5715 that were selected for clinical studies represent the combinations most likely to succeed clinically based on preclinical data.

The first-in-human study (R5713-5714-5715-HV-1857), a 2-part, phase 1, randomized, double-blind, placebo-controlled study of the 3-mAb cocktail (REGN5713-5714-5715), was conducted in 96 healthy subjects. Part A was an ascending dose-escalation study in 32 healthy subjects randomized to receive either a single dose of REGN5713-5714-5715 150 mg subcutaneous (SC), 450 mg SC, 900 mg SC, or 900 mg intravenous (IV) or placebo. REGN5713-5714-5715 had a favorable safety profile and was well-tolerated for 3 months post-dose in Part A, which was the follow-up period for Part A of the study (Gevaert, 2022). Part B was a proof-of-concept (POC) study, conducted in generally healthy subjects with birch allergy (N=64), randomized 1:1 to REGN5713-5714-5715 or placebo. A single 900 mg SC dose of REGN5713-5714-5715 (300 mg per mAb) prophylactically blocked early allergic response to nasal challenge with birch allergen at all time points assessed, days 8, 29, and 57, resulting in a 32%, 27%, and 19% improvement relative to placebo in percent change from baseline in Total Nasal Symptom Score (TNSS) area under the curve (AUC) (hour 0 to 1), respectively (achieved nominal statistical significance compared with placebo at every time point except day 57). These data demonstrate that a single 900 mg SC dose of REGN5713-5714-5715 could reduce allergic rhinitis symptoms upon birch allergen exposure for as long as 2 months.

The effect of REGN5713-5714-5715 on early phase skin responses following titration skin prick test (SPT) with serial dilutions of birch allergen was observed up to 4 months post-dose, as measured by a significant reduction in the AUC of the SPT mean wheal diameters relative to placebo (placebo-adjusted percent changes relative to the baseline SPT of -72.39%, -65.61%, -77.90%, and -73.56% on study days 8, 29, 57, and 113, respectively). Overall, REGN5713-5714-5715 was well tolerated, with no anaphylaxis or evidence of systemic hypersensitivity observed.

A phase 3, randomized, double-blind, placebo-controlled clinical study (R5713-5714-5715-ALG-2001) in 353 birch-allergic participants has been completed. The primary endpoint, daily Combined Symptom and Medication Score (CSMS [TSS+DMS]), averaged over the duration of birch pollen season, met statistical significance. Numerical improvements were observed in TNSS, Total Ocular Symptom Score (TOSS), Daily Medication Score (DMS), and Total Symptom Score (TSS [TNSS+TOSS]); these improvements were more

pronounced during peak season and for participants dosed ahead of the birch season. Robust suppression of skin prick test to birch (and birch-related allergens) was observed in the overall population. REGN5713-5714-5715 900 mg was well tolerated in this subject population. The majority of TEAEs were mild or moderate in intensity and resolved without sequelae. The incidence of SAEs was low and none were deemed related to REGN5713-5714-5715; there were no deaths or adverse events of special interest (AESIs; no severe or systemic hypersensitivity reactions or severe injection site reactions). No new safety signal was observed and overall, REGN5713-5714-5715 900 mg SC had a favorable safety profile.

Taken together, these clinical studies, during experimental and natural exposure to birch pollen, support the use of REGN5713-5714-5715 in the prevention of allergic symptoms in patients with birch pollen allergy upon exposure to birch pollen. The main purpose of this study is to confirm that a combination of all 3 antibodies is required for maximal treatment effect due to broader epitope coverage when 3 antibodies are utilized together.

Additional background information on the study drug and development program can be found in the Investigator's Brochure.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Primary Objective and Endpoint

The primary objective and endpoint of the study are outlined below:

Primary Objective	Primary Endpoint
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)**	The mean of Total Nasal Symptom Score [TNSS (2 to 6 hours)] during a birch allergen EEU challenge at day 29

2.2. Secondary Objectives and Endpoints

The secondary objectives and endpoints of the study are outlined below:

Secondary Objectives	Secondary Endpoints
• 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 **(Part A)**	• The mean of symptom scores during out-of-season birch allergen EEU challenges at days 29, 57, and 85 o TNSS (2 to 6 hours) (except day 29 for 3-mAb) o TOSS (2 to 6 hours) o TSS (2 to 6 hours) • The change and percent change from pre-treatment baseline in symptom scores during out-of-season birch allergen EEU challenges at days 29, 57, and 85 o TNSS (2 to 6 hours) o TOSS (2 to 6 hours) o TSS (2 to 6 hours)
• 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 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 **(Part A)**	• The change and percent change from pre-treatment baseline at days 29, 57, 85, and 127 in the birch (and related allergens) titrated SPT mean wheal diameter AUC

Secondary Objectives	Secondary Endpoints
• 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 **(Part A)**	• The mean of symptom scores during out-of-season oak allergen EEU challenge at day 36 o TNSS (2 to 6 hours) o TOSS (2 to 6 hours) o TSS (2 to 6 hours) • The change and percent change from pre-treatment baseline in symptom scores during an oak allergen EEU at day 36 in subpopulation of oak-allergic participants o TNSS (2 to 6 hours) o TOSS (2 to 6 hours) o TSS (2 to 6 hours)
• 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 (**Part A**)	• The mean of symptom scores during out-of-season birch allergen EEU challenges at days 29, 57, and 85 o TNSS (2 to 6 hours) o TOSS (2 to 6 hours) o TSS (2 to 6 hours) • The change and percent change from pre-treatment baseline in symptom scores during out-of-season birch allergen EEU challenges at days 29, 57, and 85 o TNSS (2 to 6 hours) o TOSS (2 to 6 hours) o TSS (2 to 6 hours) • The proportions of participants achieving different degrees of clinical responses will be compared across different symptom response thresholds at days 29, 57, and 85 o TNSS (2 to 6 hours) o TOSS (2 to 6 hours) o TSS (2 to 6 hours)

Secondary Objectives	Secondary Endpoints
• To compare differences in the degree of reduction of skin test reactivity from pre-treatment baseline by inhibiting a wheal response to a titrated skin prick test 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 (**Part A**)	• The proportions of participants achieving different degrees of responses in the birch (and related allergens) titrated SPT mean wheal diameter AUC will be compared across different response thresholds at days 29, 57, and 85
• 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 **(Part B)**	• The mean of symptom scores during the peak-season birch allergen EEU challenge o TNSS (2 to 6 hours) o TOSS (2 to 6 hours) o TSS (2 to 6 hours)
• 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 and peak birch pollen season in participants receiving REGN5713-5714-5715 versus placebo, REGN5713-5715 versus placebo, and REGN5715 versus placebo **(Part B)**	• The daily symptom and medication scores, averaged during the BPS and peak BPS o CSMS, TSS, TNSS, TOSS, and DMS, averaged during the BPS o CSMS, TSS, TNSS, TOSS, and DMS, averaged during the peak BPS
	• The change and percent change from baseline in the symptom and medication scores, averaged during the BPS and peak BPS o CSMS, TSS, TNSS, TOSS, and DMS, averaged during the BPS o CSMS, TSS, TNSS, TOSS, and DMS, averaged during the peak BPS
• 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 skin prick test with birch and related allergens (eg, alder, oak) after the natural birch pollen season in participants who receive REGN5713-5714-5715 versus placebo, REGN5713-5715 versus placebo, and REGN5715 versus placebo **(Part B)**	• 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

Secondary Objectives	Secondary Endpoints
• 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	• The mean of the total Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ[S]) score during BPS and peak BPS o RQLQ(S), averaged during the BPS and peak BPS o Change and percent change from baseline in the average RQLQ(S) during the BPS and peak BPS
• 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)	• Incidence rates of treatment-emergent adverse events (TEAEs) and serious TEAEs through end of study
• To determine systemic concentrations over time of total antibody (free + antigen-bound) for each of the individual mAbs: REGN5713, REGN5714, and REGN5715 at various time points following single administration (dose #1) and after repeat dosing (dose #2)	• Total REGN5713, REGN5714, REGN5715 concentration in serum over the duration of the study
• To assess the immunogenicity of REGN5713, REGN5714, and REGN5715 in birch-allergic participants following single administration (dose #1) and after repeat dosing (dose #2)	• Incidences and titers of ADA to REGN5713, REGN5714, and REGN5715 over time

2.3. Exploratory Objectives and Endpoints

The exploratory objectives and endpoints of the study are:

Exploratory Objectives	Exploratory Endpoints
• [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Exploratory Objectives	Exploratory Endpoints
• [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	
[redacted]	[redacted]
	[redacted]
[redacted]	[redacted]
[redacted]	

Exploratory Objectives	Exploratory Endpoints
• [redacted] [redacted] [redacted] [redacted]	

3. HYPOTHESIS AND RATIONALE

3.1. Hypotheses

Part A Hypotheses:

- A single dose of a cocktail of 3 anti-Bet v 1 monoclonal antibodies (REGN5713-5714-5715) is more effective than placebo in the reduction of allergic nasal symptoms in a birch allergen EEU and in the reduction of skin test reactivity.
- A single dose of a cocktail of 2 anti-Bet v 1 monoclonal antibodies (REGN5713-5715) is more effective than placebo in the reduction of allergic nasal symptoms in a birch allergen EEU and in the reduction of skin test reactivity.
- A single dose of a single monoclonal antibody (REGN5715) is more effective than placebo in the reduction of allergic nasal symptoms in a birch EEU and in the reduction of skin test reactivity.
- A single dose of the 3 anti-Bet v 1 monoclonal antibodies (REGN5713-5714-5715) is more effective than the cocktail of 2 anti-Bet v 1 monoclonal antibodies (REGN5713-5715) and single REGN5715 mAb in a birch EEU as indicated by a numerically greater treatment effect across different endpoints (including allergic nasal and ocular symptoms as well as skin test reactivity), in addition to a higher proportion of participants achieving greater responses across different thresholds for these endpoints.
- Similarly, a single dose of the cocktail of 2 anti-Bet v 1 monoclonal antibodies (REGN5713-5715) is more effective than the single monoclonal antibody (REGN5715) in a birch EEU as indicated by a numerically greater treatment effect across different endpoints, in addition to a higher proportion of participants achieving greater responses across different endpoint thresholds.

Part B Hypotheses:

- REGN5713-5714-5715 is more effective than placebo in the reduction of allergic symptoms during the natural birch pollen season and in the reduction of skin test reactivity to birch allergen.
- REGN5713-5715 is more effective than placebo in the reduction of allergic symptoms during the natural birch pollen season and in the reduction of skin test reactivity to birch allergen.
- REGN5715 is more effective than placebo in the reduction of allergic symptoms during the natural birch pollen season and in the reduction of skin test reactivity to birch allergen.
- REGN5713-5714-5715 is more effective than REGN5713-5715 and REGN5715 during the natural birch pollen season as indicated by a numerically greater treatment effect across different endpoints in-season as well as higher proportion of participants achieving greater responses across these endpoint thresholds (including nasal and ocular symptoms, allergy medication use, and skin test reactivity).

- Similarly, REGN5713-5715 is more effective than REGN5715 during the natural birch pollen season as indicated by a numerically greater treatment effect across different endpoints in-season as well as higher proportion of participants achieving greater responses across these endpoint thresholds.

3.2. Rationale

3.2.1. Rationale for Study Design

R5713-5714-5715-ALG-21111 is a 2-part randomized, double-blind, placebo-controlled study in birch-allergic participants to assess the efficacy of the anti-Bet v 1 monoclonal antibodies. The study will assess the efficacy of the anti-Bet v 1 monoclonal antibodies, in combination (the 3-mAb and the best 2-mAb) and as a single best antibody (REGN5713-5714-5715, REGN5713-5715, and REGN5715). 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 but also explore them during real-world exposure to birch and other related/ unrelated pollens during the birch pollen season.

Day 29 was chosen as the primary endpoint as a period of expected maximum efficacy, also anticipated to coincide with approximate timing for the peak pollen season. Treatment effects will be evaluated at different out-of-season time points to ensure adequate coverage during an expected natural season accounting for the potential variability between timing of dosing relative to the start of the natural birch pollen seasons and also the year-to-year variability in the length and timing of the birch pollen seasons (Biedermann, 2019c) (Lo, 2019).

Primary efficacy analyses may be performed after all participants complete at least the day 29 EEU challenges or discontinue (Section 10.4.3). Participants will receive the same treatment in Part B that they were originally randomized to receive in Part A (Section 7.5). Additionally, efficacy and safety of repeat dosing of the antibodies will be evaluated during the birch pollen season.

A combination of pre-specified endpoints in Part A (Section 10.4.3) will be used to delineate the contribution of components.

Rationale for the 2-Part "Hybrid" EEU and Field Study Design to Assess the Efficacy of the Anti-Bet v 1 Monoclonal Antibodies in the Reduction of Clinical Symptoms and Skin Test Reactivity

Part A of this study employs the classic, phase 2, out-of-season EEU design to assess the primary and secondary endpoints to compare the efficacy of the anti-Bet v 1 mAb(s) in combination and as a single mAb (REGN5713-5714-5715 versus placebo, REGN5713-5715 versus placebo, and REGN5715 versus placebo), to reduce allergic rhinitis and conjunctivitis symptoms in birch-allergic participants. Skin test reactivity to birch and related allergens will be tested by the inhibition of the SPT mean wheal diameter to serial titrations of birch and related allergens.

Part B of this study uses a hybrid design to incorporate both a "field study" and EEU challenges during the peak and end of natural birch season to examine the correlation between the treatment effect of the anti-Bet v 1 antibodies (REGN5713-5714-5715 and REGN5713-5715) on symptoms elicited in the EEU and the treatment effects on symptoms and medication use observed in the natural season. The in-season portion (Part B) allows for assessment of efficacy during continuous

and variable pollen exposures during the natural birch season (and overlapping other related and unrelated tree pollens) using a combination of chamber and field assessments. Similarly, the inhibition of skin test reactivity will be tested during the natural birch season and a within-participant comparison during out-of-season and in-season assessments.

The same anti-allergic therapies will be investigated in the EEU outside of birch pollen season, during a natural birch pollen season, as well as in the EEU during the peak and end of the birch pollen season, for direct comparability of the treatment effect of REGN5713-5714-5715 in different birch pollen exposures in the same subject population.

Traditionally, phase 2 EEU studies have been utilized to confirm dose selection and test efficacy of anti-allergic therapies (Biedermann, 2019b) (Couroux, 2009) (Didier, 2011) (Horak, 2009) (Nolte, 2016) (Nolte, 2015). Field studies can have large geographic variability in pollen exposures compounded by the limited ability to predict local seasonal and climate changes (Zhang, 2022) in addition to individual differences in exposures. Data indicate that the magnitude of treatment effect is impacted by degree of pollen exposures (Durham, 2014), which highlight the challenges in field studies. The current COVID-19 pandemic has also imposed several challenges and restrictions in activities, as well as mask mandates in recent times that have complicated field assessments of symptoms in the short term (Bergmann, 2021). Alternatively, field studies may be integrated into EEU studies as "hybrid" trials, to potentially demonstrate clinical efficacy for novel therapies with fewer participants with shorter timelines, but more importantly, allowing the interpretation of efficacy in both controlled allergen exposures, as well as real-world field-based assessments (Ellis, 2021a). To support a goal to use EEU studies as an adjunct to field studies, investigators have published data demonstrating that there is a high correlation between allergic symptoms elicited in the EEU and in the field (Jacobs, 2011) (Jacobs, 2014), that EEUs can be performed both in season and out-of-season (Badorrek, 2011) (Ellis, 2021b), and that 2 EEUs can be used together in dual-center clinical trials (Ellis, 2019), in addition to assessing different allergens sequentially in EEU trials (Couroux, 2019).

Furthermore, testing of REGN5713-5714-5715, REGN5713-5715, and REGN5715 out-of-season and in-season, both in chamber and field settings, provides a comprehensive approach to the evaluation of these anti-Bet v 1 antibodies.

Skin Prick Test Endpoints Support the Evaluation of the Anti-Bet v 1 Antibodies

Development of allergen-specific polyclonal IgE antibodies is considered a hallmark of allergen "sensitization" (Flicker, 2003) (Murphy, 2017). A larger wheal size showing a greater degree of sensitization significantly increases the risk of having symptoms. This has also been demonstrated specifically for birch allergen (Haahtela, 2014) suggesting the relevance of the SPT wheal size in predicting clinical allergy with the likelihood of developing symptoms.

The SPT assesses the immediate early phase IgE-mediated allergic response in the skin that is induced by mast cell degranulation after challenge with an allergen via skin prick in previously sensitized allergic subjects (Burks, 2019) (Friedman, 1988). As such, SPT is a highly sensitive, objective, easy-to-perform test to determine allergic sensitization, and in addition to its wide use diagnostically, it has been used to help understand the pathophysiology of the allergic response (Burks, 2019) and to evaluate the mechanisms of action of several anti-allergy therapeutics (Persi, 1999) (Frossard, 2008).

As expected, and in line with the mechanism of action of these anti-Bet v 1 antibodies, data from the first-in-human (FIH) study and phase 3 study show robust suppression of the SPT mean wheal diameter in participants treated with the anti- Bet v 1 antibodies (REGN5713-5714-5715). Corresponding to the reduction in TNSS seen in the FIH study at days 8, 29, and 57, REGN5713-5714-5715 inhibited a titrated SPT to birch allergen also as early as day 8 (earliest time point tested) and sustained on days 29, 57, and 113 (last time point tested). Similarly, there was robust SPT inhibition to alder, a birch related allergen. These data suggest that REGN5713-5714-5715 inhibits type I, immediate, IgE-mediated response compared to placebo. Similar to clinical endpoints, it is expected that the inhibition of SPT reactivity using a titrated SPT to serial dilutions of birch allergen will support the assessment the contribution of components. Therefore, the mechanism of action and clinical data support the use of the SPT test endpoints as an objective biomarker to test activity of the anti-allergen antibodies.

3.2.2. Rationale for Dose Selection

In Part A, a single SC dose of REGN5713-5714-5715 900 mg (300 mg per mAb), a single SC dose of REGN5713-5715 600 mg (300 mg per mAb), and a single SC dose of REGN5715 (300 mg), plus a matching placebo group are proposed. Participants will receive the same treatment in Part B that they were originally randomized to receive in Part A (Section 7.5).

Clinical Experience and Rationale to Support Proposed Dose

The proposed dose for this study is supported by the results of the phase 1b POC study, (Part B of the FIH study), which was conducted in healthy, birch-allergic participants, and the phase 3 field study conducted in birch allergic participants. In both studies, participants received 300 mg/mAb of REGN5713-5714-5715. In the FIH study, this dose was able to reduce allergic rhinitis symptoms for at least 2 months following periodic nasal allergen challenges with Bet v 1 pollen. In the phase 3 study, this dose was able to reduce (improve) CSMS during the birch pollen season.

In addition to demonstrating effects on allergic rhinitis symptoms, 300 mg/mAb (REGN5713-5714-5715) was well-tolerated in both studies, with TEAEs generally of mild to moderate severity, and occurring in similar rates in the placebo and REGN5713-5714-5715 treatment groups. Additionally, no participant developed treatment-emergent or treatment-boosted anti-drug antibodies (ADA) following administration of REGN5713-5714-5715 in either study.

The pharmacokinetics (PK) of REGN5713-5714-5715 are consistent in both clinical studies, exhibiting linear, dose-proportional PK with a half-life of 26.9, 34.0, and 35.1 days for REGN5713, REGN5714, and REGN5715, respectively. Dose #2 in Part B of this study is expected to be administered at least 12 weeks from dose #1 in Part A. The dosing interval in this study is primarily driven by timing of participant enrollment and the pollen season while ensuring accumulation of study drug is within exposure (C_{max} and AUC) observed in the FIH study following 300 mg/mAb IV dosing. With a minimum dosing interval of 12 weeks, accumulation of REGN5713-5714-5715 is expected to be approximately 15% between dose #1 and dose #2 and is predicted to be within the C_{max} and AUC that were measured in the FIH trial following administration of 300 mg/mAb IV, which showed a favorable safety profile. Additionally, analysis of the concentration-response relationship between concentrations of REGN5713-5714-5715 and various clinical endpoints has shown consistent responses across a range of concentrations.

Additional information on clinical and preclinical PK, PD, and safety can be found in the Investigator's Brochure.

Based on the above summary of safety, PK, and PD data, a dose of 300 mg/mAb mg SC is expected to provide efficacy in an EEU setting, as well as in the field setting.

3.3. Risk-Benefit

REGN5713, REGN5714, and REGN5715 are 3 human mAbs of the IgG4 isotype that specifically bind to Bet v 1, the major birch tree allergen, with high affinity and at distinct epitopes (Atanasio, 2022). Preclinical data indicate that all 3 mAbs are required to maximally inhibit binding of Bet v 1 to human polyclonal IgE, reduce in vitro effector cell degranulation and subsequent Type 1 hypersensitivity reaction.

The FIH study (R5713-5714-5715-HV-1857) was a 2-part phase 1, randomized, double-blind, placebo-controlled study of the 3-mAb cocktail (REGN5713-5714-5715) in 96 healthy participants (32 healthy subjects without birch allergy in part A and 64 subjects with birch pollen allergy in part B) (Gevaert, 2022). Part A demonstrated that doses up to 900 mg (300 mg/mAb) of REGN5713-5714-5715 administered via SC or IV were generally well tolerated. Part B was a nasal allergen challenge study in birch allergic healthy participants, which showed a significant reduction in TNSS following a nasal allergen challenge was demonstrated through day 57, and a durable reduction in SPT response to birch was demonstrated through day 113. These results suggest that a single 900 mg SC dose of REGN5713-5714-5715 reduced allergic rhinitis symptoms upon birch allergen exposure for as long as 2 months (last time point evaluated), the approximate duration of a typical birch pollen season.

The phase 3 field study (R5713-5714-5715-ALG-2001) in adults with birch pollen-induced allergic rhinitis with or without conjunctivitis demonstrated a reduction in the combined symptom and medication composite score in birch allergic participants during birch pollen season in participants treated with REGN5713-5714-5715 versus placebo. While the numerical reductions seen in TNSS, TOSS, DMS, and TSS did not meet statistical significance in the overall population, in post-hoc analyses, the efficacy improved and most of these endpoints showed nominally significant results during peak season as well for participants dosed ahead of the season. Similar to the FIH study, a robust suppression of SPT reactivity to birch (and birch related allergens) was observed in the overall population.

REGN5713-5714-5715 has been administered as a single dose to 229 healthy adult study participants in studies completed to date (24 healthy subjects without known birch allergy and 205 subjects with known birch allergy) with no significant clinical safety findings observed including no deaths, cases of systemic hypersensitivity, or anaphylaxis. No severe injection site reactions were noted. No important identified risks have been established with REGN5713-5714-5715 administration. The important potential risks with REGN5713-5714-5715 (based on preclinical evaluation, mechanism of action targeting an exogeneous antigen, and risks associated with mAbs in general) include systemic hypersensitivity reactions and immunogenicity. REGN5713-5714-5715 has been generally well tolerated and risks have been adequately managed. To date, no significant safety information with regard to the important potential risks of systemic hypersensitivity reactions or immunogenicity has been reported. Currently, the available safety data along with the risk minimization and monitoring activities support the continued development of REGN5713-5714-5715.

As with most other protein therapeutics that are administered SC, mild or moderate injection site reactions may occur and may be treated symptomatically. Allergy/hypersensitivity reactions may develop; the most concerning are those that may develop immediately or within a few hours of administration of REGN5713-5714-5715. Because REGN5713-5714-5715 is composed of antibodies whose sequence is fully human, the risk of these immediate reactions is considered to be extremely low. Emergency equipment and medication for the treatment of these potential adverse effects (including but not limited to antihistamines, corticosteroids, acetaminophen, and/or epinephrine) are available for immediate use in this study. Considering the safety data and the exogenous nature of the target antigen, the risk of other adverse reactions is considered to be extremely low. A risk-benefit statement with respect to the overall development program is provided in the Investigator's Brochure.

A safety monitoring team internal to the sponsor will monitor blinded safety data on an ongoing basis to assess the risk-benefit profile of REGN5713-5714-5715. Additionally, an Independent Data Monitoring Committee (IDMC) will be involved in the review of unblinded data in an ongoing manner (Section 5.3.1).

Recognizing that the "Coronavirus Disease 2019" (COVID-19) pandemic will have an impact on the conduct of clinical trials, the Sponsor does not intend to screen any participants in this study until the impact of the COVID-19 pandemic is deemed manageable and no longer interfering with the conduct of trials at individual sites, and participants can safely participate in this study. Until then, the Sponsor plans to obtain approvals from Health Authorities/Ethics Committees to enable initiation of study sites for this study, as allowed by local laws and regulations. For information regarding the permitted timing of COVID-19 vaccinations, see Section 7.9.2.

Taken together, these clinical studies during experimental and natural exposure to birch pollen and a favorable safety profile support a positive benefit-risk assessment of REGN5713-5714-5715 in subjects with birch pollen allergy. The treatment with anti-Bet v 1 antibodies may offer a rapid and potentially effective approach for the treatment of birch pollen allergy.

4. STUDY VARIABLES

4.1. Demographic and Baseline Characteristics

Baseline characteristics will include standard demography (eg, age, race, weight, height, etc), medical history (including characterization of allergy and asthma history), medication history, SPT for birch, birch-related and other common allergens, titrated SPT for birch and related allergens, allergen-specific IgE levels, and total IgE, for each participant. Baseline screening EEU challenges to birch will provide baseline nasal and ocular symptoms for determining eligibility and the baseline screening EEU challenge to oak will characterize oak allergy status. Screening baseline assessment will evaluate daily nasal and ocular symptom and medication scores during screening.

4.2. Efficacy Variables

Efficacy variables include TNSS, TOSS, TSS (which results from adding the TNSS and TOSS), DMS, CSMS (which results from adding the DMS and TSS). In addition, the mean wheal diameter of birch and related allergen titrated SPT, RQLQ(S) parameters, Pollen Food Allergy Symptom Questionnaire (PFASQ) parameters, and outdoor time questionnaire parameters will be evaluated.

4.3. Safety Variables

Safety variables include vital signs, physical examination findings, adverse events, spirometry, and laboratory safety tests.

4.4. Pharmacokinetic Variables

The PK variables are the concentrations of total REGN5713, REGN5714, and REGN5715 in serum at each time point as specified in Table 1.

4.5. Immunogenicity Variables

The immunogenicity variables are ADA status, titer, and time-point/visit. Samples in this study will be collected at the clinic visits specified in Table 1.

4.6. Pharmacodynamic and Other Biomarker Variables

Exploratory biomarker variables may include, but are not limited to, [redacted].

These results may be reported outside of the clinical study report (CSR) as a part of exploratory research analyses.

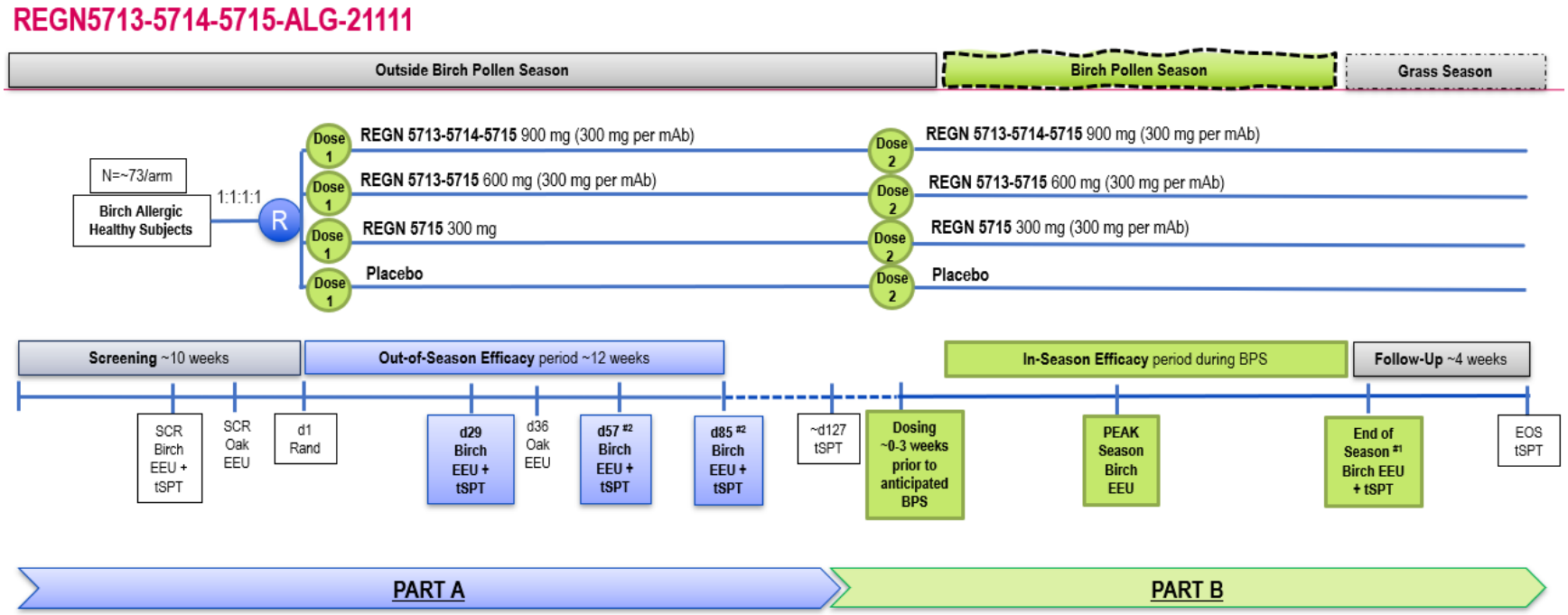
5. STUDY DESIGN

5.1. Study Description and Duration

REGN5713-5714-5715-ALG-21111 is a 2-part randomized, double-blind, placebo-controlled study in birch-allergic participants to assess the efficacy of the anti-Bet v 1 monoclonal antibodies. 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 birch pollen season), dependent on the start and end times of the natural BPS.

The study will assess the efficacy of the anti-Bet v 1 monoclonal antibodies, in combination and as a single antibody. Efficacy in the reduction of allergic rhinitis and conjunctivitis symptoms as well as birch skin test reactivity will be tested using assessments out-of-season (Part A: EEU challenges and titrated skin prick testing) and during the birch pollen season (Part B: EEU challenges, field assessments, and titrated skin prick testing). Participants will receive 2 doses of the study drug: a dose at randomization outside of the BPS (dose #1; Part A) and a dose of the study drug in Part B ahead of the anticipated BPS (dose #2; Part B). The efficacy will be tested out-of-season as well as in-season to fully evaluate treatment effects during experimental exposure to the allergen and during natural exposure to birch and other related/ unrelated pollens during the BPS.

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.

Part A Overview:

In Part A (out-of-season), participants will be randomized to 1 of 4 arms and receive a dose of either REGN5713-5714-5715 (3-mAb), REGN5713-5715 (2-mAb), REGN5715 (1-mAb), or matching placebo. Part A will assess whether a dose of either a monotherapy or a combination(s) of anti-Bet v 1 monoclonal antibodies (REGN5715, REGN5713-5715, REGN5713-5714-5715) demonstrates a greater reduction in TNSS than placebo in a birch EEU. Clinical efficacy in the EEU when exposed to oak allergen will also be tested for the anti-Bet v 1 monoclonal antibodies in the subpopulation of participants who are oak-allergic to determine if there is a treatment effect to another important North American pollen with similar epitopes as the birch pollen, given the shared homology. Additionally, the efficacy of the anti-Bet v 1 monoclonal antibodies in the reduction of skin test reactivity to birch and related allergens will be assessed using titrated skin prick testing and to determine the relationship of the symptom endpoints to the biomarker endpoints.

Primary efficacy will be assessed during the out-of-season birch allergen EEU challenge on day 29 after birch-allergic participants receive a dose of the study drug on day 1. Additionally, efficacy may be tested up to day 85 to ensure durability of the response through these time points. Primary analyses may be performed after all participants complete at least day 29 EEU challenges or discontinue.

Part B Overview:

In Part B (in-season), participants will receive a dose (dose #2) of the study drug (monoclonal antibody[ies] or placebo) administered ahead of the anticipated birch pollen season (determined using historical local pollen data), that is intended as a single dose for coverage of the entire birch season.

Pollen counts will be monitored during the study period. The start of the birch pollen season is defined as the first of 3 consecutive days with a pollen count of 10 grains/m^3 or greater. The end of the birch pollen season is defined as the last day of the last occurrence of 3 consecutive days with a pollen count of 10 grains/m^3 or greater. The peak birch pollen season is defined as the 15 consecutive days within the birch pollen season with the highest 15-day moving average pollen count. The OPS will be similarly defined.

After completion of all Part A assessments outside of the BPS, participants start Part B of the study prior to the start of the BPS. Dosing in Part B of the study will begin at least 12 weeks from study drug dosing in Part A (Section 3.2.2). Participants will receive study drug (dose #2) ahead of the anticipated BPS (dosing window 0 to 3 weeks prior to the anticipated start of the BPS), which is intended as a single dose for coverage of the entire birch season. Dosing is expected to occur at least 12 weeks after initial dose in Part A, depending on the projected start of the local birch pollen season.

To allow comparability of the within-subject treatment effect of the anti-Bet v 1 antibodies across different time points, the same anti-allergic therapies will be investigated in the same participant population during out-of-season and in-season exposures to birch allergen in the EEU as well as field settings. This will help reduce any potential impact of any potentially remaining active study drug from Part A on Part B on the placebo treatment effects in Part B. Participants will receive the same treatment in Part B that they were originally randomized to receive in Part A.

Part B will assess whether the anti-Bet v 1 antibodies, administered just prior to the start of the BPS, reduces allergic rhinitis and conjunctivitis symptoms during the birch pollen season as compared to placebo. Given the variable nature of exposure to birch and related pollens during the natural season, in-season birch allergen EEU challenges will be conducted at the peak and end of the birch season to evaluate and compare the treatment effects seen during the birch season. Field assessments with daily records of nasal and ocular symptom scores, allergy-relieving rescue medication scores as well as weekly rhinoconjunctivitis quality of life scores will be evaluated during the entire BPS. Similar to Part A, the efficacy of the anti-Bet v 1 mAbs in the reduction of skin test reactivity to birch and related allergens will be tested in-season using titrated skin prick testing. Part B allows for assessment of efficacy during continuous natural pollen exposures (exposure to birch allergen as well as other overlapping related and unrelated tree pollens) using a combination of chamber and field assessments.

Within-participant differences will be evaluated at the different time points during the out-of-season and in-season challenges and also correlated with the field assessments. A correlation of the peak in-season EEU efficacy with the daily symptoms recorded during the peak BPS and entire BPS will also be informative.

Part A Study Periods:

As outlined above in Figure 1, study Part A consists of a screening period, randomization, an on-treatment efficacy assessment period, and a primary data analysis. These study periods are described below.

- Screening period: Up to 10 weeks with screening birch and oak challenges. Daily symptom and medication scores will be obtained during the screening baseline assessment for approximately 2 weeks or longer (at minimum 1 week) until randomization in eligible participants starting after the screening birch EEU challenge
- Randomization: 1:1:1:1 to 1 of 4 arms

Screening: Healthy male and female participants, age 18 years of age and older, with a history of birch pollen allergy for at least 2 years will undergo screening visits outside of BPS. There is an up to 14-week screening period, including an out-of-season screening EEU exposure to birch allergen, to determine eligibility. In eligible participants, oak allergen EEU challenge will be performed during screening to identify a subpopulation of oak-allergic participants.

- During the first screening visit, participants will review and sign the informed consent, undergo a medical history, allergy history, medication history, physical examination, ECG, vital signs, birch allergen extract SPT, and blood will be drawn for serum for birch and Bet v 1-specific IgE, spirometry, standard SPT (such as dust mites, grass, other related and unrelated trees, cat, dog, etc), laboratory testing, complete baseline assessments, and be evaluated for the remainder of the study eligibility criteria.
- Participants who meet all other inclusion and do not meet any exclusion criteria assessed at visit 1, will proceed to visit 2 for the screening birch EEU challenge. Using an e-diary, participants will record symptom scores (TNSS and TOSS) at baseline, and then at frequent time points while in the screening EEU. Participants must attain at least a TNSS ≥6 at 2 time points during the screening EEU exposure to be included in the study. Achieving the symptom threshold in the screening EEU challenge is required to

demonstrate that the participant has moderate to severe rhinitis symptoms during a birch pollen exposure. Participants will be asked to refrain from taking specific prohibited medications (Section 7.9.1) within the specified period preceding screening and EEU visits.

- Screening baseline assessment: Eligible participants who meet eligibility criteria for the study (including screening birch EEU challenge requirement) will record daily symptom and medication scores for approximately 2 weeks or longer (at minimum 1 week) until randomization
- Screening EEU challenges and baseline symptom and medication assessment are recommended to be done outside of relevant pollen seasons for pollen-allergic participants.
- Participants who are sensitized to oak and meet eligibility criteria for the study (including screening birch EEU challenge requirement) will also undergo an EEU challenge with oak allergen (visit 3) to determine clinical allergy to oak during screening.
- **Re-screening**: Participants may be re-screened up to one time; however, rescreening is not permitted if a participant screen failed on birch sensitization criteria (birch SPT or sIgE to birch or sIgE to Bet v 1) or screening birch EEU challenge eligibility criteria.

Randomization and study drug dosing (dose #1): Participants who meet all inclusion but no exclusion criteria will undergo randomization at visit 4. Stratification factors at randomization include oak allergy, grass sensitization status, and EEU site. Randomization and treatment assignment for Part A is discussed in Section 7.5. Participants will be observed for 2 hours after receiving the SC dose of study drug.

A primary analysis will be performed after all participants complete at least day 29 EEU challenges or discontinue.

Follow-up period after EEU exposures until visit 10.

Part B Study Periods:

As outlined above in Figure 1, study Part B consists of an on-treatment efficacy assessment period, an off-treatment safety follow-up period, and the end-of-study visit. These study periods are described below.

- Study drug dosing (dose #2): Participants will be administered a SC dose of the study drug (dose #2 at visit 11) within approximately 3 weeks prior to the anticipated start of the natural BPS, intended as a single dose for coverage of the birch season. The goal dosing window is within 3 weeks prior to the anticipated start of the birch pollen season, at least 12 weeks after initial dose in Part A. The sponsor will define the last possible date for dosing in Part B in each geographical area based on the anticipated timing and duration of the local birch pollen season in consultation with the local pollen expert (eg, if season is expected to be ending soon based on consistently low birch pollen counts noted without any explanatory transient climactic condition such as rain/ cold weather, etc, then those participants may not receive dose #2). Participants who are

unable to receive dose #2 prior to the defined dosing end date will discontinue study drug (Section 7.3.2) but should be encouraged to remain in the study.

- Randomization and treatment assignment for Part B is discussed in Section 7.5.
  - Participants will be observed for 2 hours after study drug dosing and will be called by telephone (visit 12) approximately 1 day after dosing to assess for any potential adverse events.
- **Follow-up period:** after the end of the birch pollen season for approximately 4 weeks.

Part B will be an approximately 18-week period based on timing and length of the natural BPS including an approximate 4-week safety follow up after the end of the season.

5.1.1. Study Stopping Rules

5.1.1.1. Study Stopping Criteria

There are no pre-specified study stopping rules; however, appropriate action, if needed, will be taken based upon ongoing data reviews, in consultation with the Regeneron Safety Oversight Committee and the IDMC. Applicable regulatory procedures will be adhered to as required by local laws in relation to any decisions related to a change in study conduct, temporary halt, study termination, or study restart.

5.1.2. End of Study Definition

The end of study is defined as the date the last participant completes the last study visit, withdraws from the study, or is lost to follow-up (ie, the study participant can no longer be contacted by the investigator).

5.2. 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. A select team will be unblinded to review the results but to ensure study integrity, the team members directly involved in the continued conduct of the trial will remain blinded. A description of the statistical methods to be employed is in Section 10.4.3, and blinding implications are discussed in Section 7.6.

Final unblinded analyses of the study results for efficacy endpoints may be performed when all randomized participants have completed visit 14 (after end of BPS). 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.

5.3. Study Committees

5.3.1. Independent Data Monitoring Committee

An IDMC will actively review data throughout the study to monitor participant safety and efficacy data. The IDMC is composed of members who are independent from the sponsor and the study investigators. The IDMC will provide oversight of participant safety by conducting formal reviews of accumulated safety data that will be blinded by treatment group; if requested, the IDMC may have access to the treatment allocation code or any other requested data for the purposes of a risk-benefit assessment. The IDMC will provide the sponsor with appropriate recommendations on the conduct of the clinical study to ensure the protection and safety of the participants enrolled in these studies. All activities and responsibilities of the IDMC will be described in the IDMC charter.

6. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PARTICIPANTS

6.1. Number of Participants Planned

Approximately 300 healthy male and female participants 18 years of age or older with birch pollen allergy will be enrolled in this study. All participants will be asked to complete both Part A and Part B of the study.

6.2. Study Population

6.2.1. Inclusion Criteria

A subject must meet the following criteria to be eligible for inclusion in the study:

1. Generally healthy males and females, age 18 years or older at the time of screening.
2. Documented or subject-reported history of birch tree pollen-triggered allergic rhinitis symptoms with or without conjunctivitis (for at least 2 seasons)
3. Positive SPT with birch tree pollen extract (mean wheal diameter at least 5 mm greater than the negative control) in screening period
4. Positive sIgE tests for birch tree pollen and Bet v 1 (≥0.7 kUa/L) in screening period
5. Demonstrated TNSS ≥6 out of 12 on at least 2 time points during the birch EEU exposure challenge in screening period
6. Willing and able to comply with clinic visits and study-related procedures
7. Provide informed consent signed by study participant or legally acceptable representative
8. Able to understand and complete study-related questionnaires

6.2.2. Exclusion Criteria

A subject who meets any of the following criteria will be excluded from the study:

1. Participation in a prior REGN5713-5714-5715 clinical study and received REGN5713-5714-5715 antibodies (receipt of placebo in a previous study is allowed)
2. Significant rhinitis, sinusitis, significant and/or severe allergies not associated with the birch pollen season, or due to daily contact with other non-birch related allergens causing symptoms that are expected to coincide or potentially interfere with the study EEU assessments or with the birch pollen season, as assessed by the investigator
3. Subjects who anticipate major changes in allergen exposure during the birch pollen season that are expected to coincide with study assessments or planned travel that is expected to interfere with the study assessments, as assessed by the investigator (eg, anticipated travel during planned EEU sessions or birch pollen season)

4. Persistent chronic or recurring acute infection requiring treatment with antibiotics, antivirals, or antifungals, or any untreated respiratory infections within 4 weeks prior to screening visit 1. Subjects may be re-evaluated for eligibility after resolution of symptoms and specified duration.
5. History of significant, recurrent sinusitis, defined as at least 3 episodes requiring antibiotic treatment per year for the last 2 years
6. Abnormal lung function as judged by the investigator with FEV1<75% of predicted at screening or randomization
7. A clinical history of moderate to severe asthma, uncontrolled asthma, global initiative for asthma [GINA] steps 3 to 5 (Bateman, 2008) (an isolated diagnosis of exercise-induced bronchospasm would be considered acceptable; eg, asthmatics requiring only intermittent use of a short-acting bronchodilator would be considered acceptable; per principal investigator [PI] judgement)
8. Clinical history of asthma exacerbations or wheezing episodes during 2 prior tree pollen seasons or a prior history or asthma exacerbations due to tree pollen allergy, per PI judgement
9. Asthma symptoms developed in the screening EEU challenge requiring intervention or inability to tolerate screening EEU session due to symptoms, per PI judgement
10. A clinical history of asthma with treatment of asthma requiring systemic (oral or parenteral) corticosteroid treatment more than twice within prior 12 months or once within 3 months prior to screening or has been hospitalized or has attended the Emergency Room/Urgent Care facility for asthma in prior 12 months before screening.
11. History of life-threatening asthma, defined as an asthma episode that required intubation and/or was associated with hypercapnia, respiratory arrest, and/or hypoxic seizures
12. Active lung disease other than asthma
13. History of nasal polyps
14. History of birch or other tree allergen immunotherapy (eg, subcutaneous immunotherapy [SCIT], sublingual immunotherapy [SLIT], or oral immunotherapy) in the 3 years prior to screening.
15. Use of anti-IgE or other biological therapy (including but not limited to anti IL-5, anti IL-4) that interferes with type 2 disease within 6 months prior to screening visit 1.
16. Allergen-specific immunotherapy with any allergen other than birch or other trees at screening.
17. History of clinically significant cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematological, psychiatric, or neurological disease, as assessed by the investigator, that may confound the results of the study or pose an additional risk to the subject by study participation
18. Any physical examination findings and/or history of any illness/ disease and/or the use of any medication that, in the opinion of the investigator, might confound the results of the study or pose an additional risk to the subject by study participation.

19. Subjects with any laboratory findings showing evidence of organ dysfunction or any clinically significant deviation from the normal range, as decided by the investigator at the screening visit(s), including but not limited to:

    Clinically significant/active underlying hepatobiliary disease.

    OR,

    Alanine aminotransferase (ALT) >3 upper limit of normal (ULN).

    Abnormal laboratory values at screening:

    - Platelets $<100 \times 10^3/\mu L$
    - Neutrophils $<1.5 \times 10^3/\mu L$
    - Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2

    NOTE: If an abnormal value is detected at screening, a repeat test can be performed to confirm the abnormality to categorize the subject as a screen failure.

20. Hospitalization (>24 hours) for any reason within 30 days of the screening visit 1
21. History of drug or alcohol abuse judged to be significant by the investigator within a year prior to screening visit 1
22. Any malignancy within the past 5 years, except for basal cell or squamous epithelial cell carcinomas of the skin or carcinoma in situ of the cervix or anus that have been resected, with no evidence of local recurrence or metastatic disease for 3 years
23. Clinically significant abnormal electrocardiogram (ECG) in the screening period as assessed by the investigator
24. History of acute hypersensitivity and/or anaphylaxis to protein therapeutics or components of formulation, or severe or significant allergies that in the opinion of the investigator could represent a substantial risk to the subject
25. Treatment with an investigational drug or therapy within 2 months or at least 5 half-lives (if known), whichever is longer.
26. Unwilling or unable to comply with the permitted and prohibited medication specifications for this study.
27. Is committed to an institution by virtue of an order issued either by the judicial or the administrative authorities
28. Members of the clinical site study team and/or his/her immediate family, unless prior approval granted by the sponsor.
29. Pregnant or breastfeeding women.

30. Women of childbearing potential (WOCBP)* who are unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least 6 months after the last dose (whichever is longer). Highly effective contraceptive measures include:

    a. stable use of combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening;
    b. intrauterine device (IUD); intrauterine hormone-releasing system (IUS);
    c. bilateral tubal ligation;
    d. vasectomized partner (provided that the male vasectomized partner is the sole sexual partner of the WOCBP study participant and that the vasectomized partner has obtained medical assessment of surgical success for the procedure); and/or
    e. sexual abstinence†, ‡.

    *WOCBP are defined as women who are fertile following menarche until becoming postmenopausal, unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

    A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient to determine the occurrence of a postmenopausal state. The above definitions are according to the Clinical Trial Facilitation Group (CTFG) guidance. Pregnancy testing and contraception are not required for women with documented hysterectomy or tubal ligation.

    †Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drugs. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

    ‡Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together.

6.3. Premature Withdrawal from the Study

A participant has the right to withdraw from the study at any time, for any reason, and without repercussion.

The investigator and/or sponsor have the right to withdraw a participant from the study if it is no longer in the interest of the participant to continue in the study, or if the participant's continuation in the study places the scientific outcome of the study at risk (eg, if a participant does not or cannot follow study procedures). An excessive rate of withdrawals would render the study uninterpretable; therefore, unnecessary withdrawal of participants should be avoided.

Participants who are withdrawn prematurely from the study will be asked to complete the early termination visit, as described in Section 8.1.2.

Rules for discontinuation of study treatment (permanent or temporary) are discussed in Section 7.3.2.

6.4. Replacement of Participants

Participants prematurely discontinued from the study or from study drug will not be replaced.

7. STUDY TREATMENTS

7.1. Investigational and Reference Treatments

Part A:

Subcutaneous administration of a dose of study drug (dose #1)

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

Part B:

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

- 3-mAb cocktail REGN5713-5714-5715 900 mg (300 mg per mAb)
- 2-mAb cocktail REGN5713-5715 600 mg (300 mg per mAb) plus placebo that replaces REGN5714
- 1-mAb 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.

Parts A and B:

Study drug will be provided as follows:

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]. It is recommended that for each dose, the 3 SC injections be given in separate locations, either the abdomen, thighs, or upper arms. 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. In order to maintain blinding, all participants will receive three 2-mL SC injections.

- For REGN5713-5714-5715 (300 mg/mAb); [redacted] injections will be administered for 900 mg total.
- For REGN5713-5715 (300 mg/mAb), [redacted] injections will be administered for 600 mg total. [redacted] placebo injection will be used to match volume.
- For REGN5715 (300 mg/mAb); at 150 mg/mL REGN5715; One 2.0 mL SC injection will be administered for 300 mg total. Two 2.0 mL placebo injections will be used to match volume.

Instructions on dose preparation are provided in the pharmacy manual.

7.2. Rescue Treatments

For all EEU challenges and in study **Part B**, 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 specified periods, including Part B of the study, participants will be asked to record their daily medication use using an e-diary, including the name and amount of these pre-specified medications.

For EEU Exposure(s) and Skin Prick Testing

Allergen exposure can induce immediate or late allergic reactions, such as allergic conjunctivitis, allergic rhinitis, asthma symptoms, or rarely anaphylaxis, in sensitized participants, which will be treated appropriately at the discretion of the investigator. With the exception of severe or clinically concerning reactions (as judged by the investigator), rescue treatments, as needed, can be dispensed after study endpoint data collection is obtained (eg, after EEU challenge data are collected, after the skin wheals are measured after application of allergen during skin prick testing).

During the study, participants will be asked to refrain from taking specific prohibited medications, including as specified within the time period preceding screening and EEU visits (Section 7.9.1).

7.3. Dose Modification and Study Treatment Discontinuation Rules

7.3.1. Dose Modification

Dose modification for an individual participant is not allowed.

7.3.2. Study Drug Discontinuation

Participants who permanently discontinue from study drug should be encouraged to remain in the study. Those who agree and do not withdraw from the study will be asked to return to the clinic for all remaining study visits per the visit schedule.

Participants who permanently discontinue from study drug and who opt to withdraw from the study will be asked to complete study assessments, per Section 8.1.2.

7.3.2.1. Reasons for Permanent Discontinuation of Study Drug

Study drug dosing will be permanently stopped in the event of:

- Evidence of pregnancy
- Serious or severe allergic reactions considered related to study drug
- Specific types of liver dysfunction (eg, Hy's law is met; (FDA, 2009))
- Participant withdraws consent
- If, in the investigator's opinion or at the specific request of the sponsor, continuation of study drug would be detrimental to the participant's well-being, or there is no longer any potential for benefit, or if continuation would undermine the scientific integrity of the study
- In the event of an important protocol deviation, at the discretion of the investigator or the sponsor

7.3.2.2. Reasons for Temporary Discontinuation of Study Drug

Study drug dosing will be temporarily discontinued in the event of:

- Sustained ALT/AST values greater than 3x the ULN plus total bilirubin >2x ULN or isolated AST/ALT >5x ULN (except if criteria for permanent study drug discontinuation are met as noted in Section 7.3.2.1)
- Hospitalization
- Other intercurrent illness or adverse event or use of prohibited medication or major surgery that could, in the opinion of the investigator, present an unreasonable risk to the participant as a result of his/her continued use of the study drug

After the condition leading to temporary discontinuation of study drug resolves, study drug dosing may resume if participant is within the appropriate dosing window. A decision to temporarily discontinue study drug and/or resume study drug dosing should be discussed with the Regeneron medical monitor.

The investigator may temporarily discontinue study drug dosing at any time, even without consultation with the medical monitor if the urgency of the situation requires immediate action and if this is determined to be in the participant's best interest. However, the Regeneron medical monitor should be contacted as soon as possible. Resumption of study drug dosing requires consultation and agreement between the investigator and the Regeneron medical monitor.

If a participant requires a prohibited medication at any time during the study, the PI should contact the Regeneron medical monitor (except for illness requiring prompt treatment). Based on the discussions, study drug may be continued or temporarily or permanently discontinued.

7.4. Management of Acute Reactions

7.4.1. Acute Injection Reactions

7.4.1.1. Systemic Injection Reactions

Emergency equipment and medication for the treatment of systemic reactions must be available for immediate use. All injection reactions must be reported as AEs (as defined in Section 9.2.1) and graded using the grading scales as instructed in Section 9.2.4.

Acute systemic reactions following injection of study drug (SC) should be treated using clinical judgment to determine the appropriate response according to typical clinical practice.

7.4.1.2. Local Injection Site Reactions

Local injection site reactions must be reported as AEs and graded according to Section 9.2.4.

7.5. Method of Treatment Assignment

In Part A, at visit 4 (Table 1), approximately 300 participants will be randomized to 1 of 4 treatment arms (1:1:1:1) (described in Section 7.1) according to a central randomization scheme provided by an in interactive voice response system (IVRS)/interactive web response system (IWRS) to the designated study pharmacist (or qualified designee). Randomization will be stratified according to oak allergy status (yes or no) determined based on oak EEU challenge and 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.

All participants will be asked to complete both Part A and Part B of the study. Participants will receive the same treatment in Part B that they were originally randomized to receive in Part A.

7.6. Blinding

Study participants, the PIs, and study site personnel will remain blinded to all randomization assignments and blinded procedures throughout the study. The Regeneron Medical/Study Director, Study Monitor, and any other Regeneron and contract research organization (CRO) personnel who are in regular contact with the study site will remain blinded to all participant randomization assignments.

[redacted]

Selected individuals not involved in the conduct of the study may have access to unblinded data as needed for safety review or other data review.

One primary analysis may be performed. The team performing the primary analysis will be separate from the ongoing study team. Each study site will be required to have blinded and unblinded study teams. No study personnel involved in the day-to-day conduct of the study will have access to any unblinded data before the final database is locked for this study.

7.7. Emergency Unblinding

Unblinding of treatment assignment for a participant may be necessary due to a medical emergency or any other significant medical event (eg, pregnancy) and when a treatment decision is contingent on knowing the participant's treatment assignment. Study drug will be discontinued for participants whose treatment has been unblinded (Section 7.3.2).

- If unblinding is required:
  - Only the investigator will make the decision to unblind the treatment assignment.
  - Only the affected participants will be unblinded.
  - The designated study pharmacist(s)/designee at the study site will provide the treatment assignment to the investigator. If there is no study pharmacist, the investigator for the site will unblind the participant. Unblinding is performed using the IVRS/IWRS which will notify Regeneron.
  - The investigator will notify Regeneron and/or designee as soon as possible after unblinding the participant

Treatment assignment is not to be provided to site personnel, other than the unblinded study pharmacist (when applicable), at any time during the conduct of the study, except in the case of a true emergency and when a treatment decision is contingent on knowing the participant's treatment assignment. In the event that there is no study pharmacist, the individual at the site fulfilling that role will be the only unblinded member of the site personnel.

7.8. Treatment Logistics and Accountability

7.8.1. Packaging, Labeling, and Storage

A medication numbering system will be used to label open-label investigational study drug. Lists linking medication numbers with product lot numbers will be maintained by the groups (or companies) responsible for study drug packaging. In order to maintain the blind, these lists will not be accessible to individuals involved in study conduct.

The unblinded pharmacist will prepare the unblinded investigational product and dispense it in a blinded manner to the blinded study staff for administration to the participant.

Study drug will be stored at the site at a temperature of 2ºC to 8ºC; storage instructions will be provided in the pharmacy manual.

7.8.2. Supply and Disposition of Treatments

Study drug will be shipped at a temperature of 2ºC to 8ºC to the investigator or designee at regular intervals or as needed during the study. At specified time points during the study (eg, interim site monitoring visits), at the site close-out visit, and following drug reconciliation and documentation by the site monitor, all opened and unopened study drug will be destroyed/returned to the sponsor or designee.

7.8.3. Treatment Accountability

All drug accountability records must be kept current.

The investigator must be able to account for all opened and unopened study drug. These records should contain the dates, quantity, and study medication

- dispensed to each participant
- returned from each participant (if applicable), and
- disposed of at the site or returned to the sponsor or designee.

All accountability records must be made available for inspection by the sponsor and regulatory agency inspectors; photocopies must be provided to the sponsor at the conclusion of the study.

7.8.4. Treatment Compliance

All drug compliance records must be kept current and made available for inspection by the sponsor and regulatory agency inspectors.

7.9. Concomitant Medications and Procedures

Any treatment administered from the time of informed consent to the final study visit will be considered concomitant medication. This includes medications that were started before the study and are ongoing during the study.

7.9.1. Prohibited Medications and Procedures

Prohibited at Screening (Washout) and Any Time Throughout the Study

- Birch-specific or any tree allergen specific immunotherapy (3 years prior to screening and during the study)
- Allergen specific immunotherapy (SIT) to any allergen excluding birch or trees (during the study)
- Systemic steroid treatment (30 days prior to screening and during the study)
- Intramuscular corticosteroids or extended duration corticosteroids (eg, intra-articular, intra-vitreal) (3 months prior to screening and during the study)
- Systemic calcineurin inhibitors (14 days prior to screening and during the study)
- Biologic therapies or immune therapeutics impacting type 2 allergic disease (6 months prior to screening and during the study)

- Methylxanthines (eg, oral theophylline) (24 hours prior to screening and during the study)
- Tricyclic antidepressants/typical antipsychotics (14 days prior to screening and during the study)
- Ultra-long-acting β-agonists (eg, indacaterol, vilanterol, olodaterol) (during the study)
- Long-acting anti-muscarinic agents (eg, tiotropium) (during the study)
- Beta blockers (during the study)

Prohibited Preceding Environmental Exposure Unit Visits and Part B Assessments

Use of these concomitant medications are prohibited preceding and during an EEU visit. These medications are also prohibited in Part B from visit 10 to visit 15 (end of study) for field efficacy assessments.

- Topical (intranasal or ocular) or systemic first generation H1 antihistamines (eg, diphenhydramine and chlorpheniramine) (3 days) [except study provided rescue medication as specified for part B]
- Second generation and long-acting H1 antihistamines (eg, cetirizine) (5 days) [except study provided rescue medication as specified for part B]
- Intranasal or ocular corticosteroids (14 days) [except study provided rescue medication as specified for part B]
- Topical or oral decongestants (72 hours)
- Leukotriene modifiers (30 days)
- Cromoglycates (14 days)
- Anticholinergics (eg, Ipratropium [Atrovent 40 μg]) (12 hours)
- Inhaled corticosteroids (14 days)
- Long-acting β-agonists (eg, salmeterol) (7 days)
- Inhaled corticosteroids/long-acting β-agonists (14 days)
- Beta blockers (14 days)

Anti-allergic medications (eg, antihistamines, anti-allergic eye drops, anti-allergic nasal sprays, intranasal or ocular steroids, herbal anti-allergic preparations) outside of study-related anti-allergic medications as they will be supplied as part of the study (eg, desloratadine, olopatadine, mometasone furoate).

For EEU visits, rescue medications, as needed, will be dispensed at the end of symptom score collection when subjects leave the site for participants to use as needed after symptom data are collected. For Part B field assessments, all participants are provided allergy-relieving study rescue medications (including desloratadine, olopatadine eye drops, and mometasone intranasal spray or appropriate class equivalent) to use as needed during the birch season. This washout for study provided allergy rescue medications is not required for the peak in-season EEU challenge but

participants are recommended to use these allergy rescue medications after completion of the peak season EEU challenge and not in anticipation prior to the challenge.

Any additional medication(s) that, in the opinion of the investigator, may confound the results of the study or pose an additional risk to the participant may be prohibited during the study or specific periods in the study.

Skin prick testing: Antihistamines should be withheld for prior to all SPT assessments including titrated SPT: First generation antihistamines for 3 days (eg, diphenhydramine); second generation antihistamines for 5 days (eg, cetirizine, desloratadine) (longer acting antihistamines such as hydroxyzine, cyproheptadine are recommended to be withheld for longer [eg, 10 days]).

7.9.2. Permitted Medications and Procedures

Study-provided rescue medications (desloratadine, olopatadine, and mometasone furoate [or in-class equivalent in consultation with the Sponsor]) can be used, as needed, during the study (except during pre-specified washouts as required for EEU challenges and/or SPT testing). With the exception of severe or clinically concerning reactions (as judged by the investigator), rescue treatments should be dispensed to participants for use, if needed, after study endpoint data collection is obtained for EEU challenges. Treatment for acute reactions is allowed during the study.

COVID-19 Vaccination

A participant may receive a COVID-19 vaccine (initial series or booster) during the study as long as it is not administered within 72 hours (but ideally not within at least 1 week) of study drug dosing or the EEU chamber session(s). Administration of a COVID-19 vaccination should be separated from the time of administration of the investigational product or EEU session in order to avoid confounding the effects (eg, adverse effects) of the vaccine/booster with the effects of study drug or the allergen exposure via the chamber session.

Consistent with the receipt of any vaccination during the study, the COVID-19 vaccine will be recorded a concomitant medication.

8. STUDY SCHEDULE OF EVENTS AND PROCEDURES

8.1. Schedule of Events

In light of the public health emergency related to COVID-19, the continuity of clinical study conduct and oversight may require implementation of temporary or alternative mechanisms. Examples of such mechanisms may include, but are not limited to, any of the following: phone contact, virtual visits, telemedicine visits, online meetings, non-invasive remote monitoring devices, use of local clinic or laboratory locations, and home visits by skilled staff. Additionally, no waivers to deviate from protocol enrollment criteria due to COVID-19 will be granted. All temporary mechanisms utilized, and deviations from planned study procedures are to be documented as being related to COVID-19 and will remain in effect only for the duration of the public health emergency.

Study assessments and procedures are presented by study period and visit in Table 1.

Table 1: 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												

8.1.1. 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 ≤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 (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)

8.1.2. Early Termination Visit

Participants who are withdrawn from the study before the primary endpoint visit (day 29, week 4, visit 6) will be asked to return to the clinic: once for an early termination visit consisting of the end of study assessments described in Table 1 and again at select visits (eg, the primary endpoint visit and key secondary endpoint visit(s), as applicable).

8.1.3. Unscheduled Visits

All attempts should be made to keep participants on the study schedule. Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, or for any other reason, as warranted.

8.2. Study Procedures

8.2.1. Procedures Performed Only at the Screening/Baseline Visit

The following procedures will be performed only at screening/baseline to determine study eligibility or to characterize the baseline population: demographics, medical and allergy history, serum total IgE sample collection, ECG*, height measurement**, weight measurement***, urinalysis, and FSH determination (in postmenopausal women if postmenopausal status is in question).

* A standard 12-lead ECG will be performed. Heart rate will be recorded from the ventricular rate and the PR, QRS, and QT (identify QTcB or QTcF) intervals will be recorded. The ECG strips or reports will be retained with the source.

** Height will be recorded to the nearest 1 cm.

*** Body weight will be assessed using calibrated scales and will be recorded to the nearest 0.1 kg.

8.2.2. Efficacy Procedures

8.2.2.1. Total Nasal Symptom Score

TNSS will be recorded at the time points according to Table 1. Instantaneous TNSS measures (ie, an evaluation of symptom severity at the time point of assessment) are used in the EEU. Reflective TNSS measures (ie, an evaluation of symptom severity over the past 24 hours, before going to bed for the night) are implemented in the field study portion. A TNSS assessment is performed prior to the start of EEU exposure at visits 2, 3, 6, 7, 8, and 9. If TNSS $\leq$2 then the EEU visit activities can proceed. If TNSS is >2, then the visit can be rescheduled within the window. TNSS is 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). There is no TNSS threshold for the peak season EEU challenge. TNSS is recorded daily during the field portion of the study using an e-diary from visit 10 to visit 15, in addition to an approximately 2-week period during screening.

The TNSS 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.

8.2.2.2. Total Ocular Symptom Score

TOSS will be recorded at the time points according to Table 1. Instantaneous TOSS measures (ie, an evaluation of symptom severity at the time point of assessment) are used in the EEU. Reflective TOSS measures (ie, an evaluation of symptom severity over the past 24 hours, before going to bed for the night) are implemented in the field study portion. TOSS is 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). TOSS is recorded once daily during the field portion of the study using an e-diary from visit 10 to visit 15, in addition to a ~2-week period during screening.

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

8.2.2.3. Total Symptom Score

The TSS is calculated by adding the TNSS (see Section 8.2.2.1) and TOSS (see Section 8.2.2.2) together, for a combined TSS of 0 to 18.

8.2.2.4. Daily Medication Score

DMS will be recorded at the time points according to Table 1. For the DMS, before going to bed for the night, participants will be asked to record their daily rescue medication use using an e-diary, 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 µg/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 a ~2-week period during screening. 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.

8.2.2.5. Combined Symptom and Medication Score

The CSMS is defined as TSS (see Section 8.2.2.3) plus DMS (see Section 8.2.2.4).

8.2.2.6. Skin Prick Testing

SPT to birch, related and unrelated allergens will be performed according to the time points at Table 1 to determine sensitization status. A negative control (such as saline/ diluent), and a histamine positive control will also be performed. Eligibility criteria for birch allergen SPT is defined by a mean wheal diameter at least 5 mm greater than the negative control, in which SPT mean wheal diameter is defined as ([longest diameter + longest perpendicular]/2). For other allergens, a positive sensitization is defined as a mean wheal diameter of at least 3 mm greater than a negative control.

Allergen exposure can induce immediate or late allergic reactions, such as allergic conjunctivitis, allergic rhinitis, asthma symptoms, or rarely anaphylaxis, in sensitized participants, which will be treated appropriately at the discretion of the investigator. With the exception of severe or clinically concerning reactions (as judged by the investigator), rescue treatments, as needed, should be dispensed after study endpoint data collection is obtained (eg, after the skin wheals are measured after application of allergen).

Specific medications to be withheld prior to SPT are described in Prohibited Medications (Section 7.9.1). Details will be provided in a study reference manual for the sites.

8.2.2.7. Titrated Skin Prick Testing to Birch and Birch-Related Allergens

Titrated SPT to birch and birch-related or cross-reactive allergens (eg, alder, oak) will be performed according to the time points at Table 1. The titrated SPT will be performed with serial dilutions of the allergen extracts, a negative control (sch as saline/ diluent), and a histamine positive control. SPT mean wheal diameter is defined as ([longest diameter + longest perpendicular]/2).

Allergen exposure can induce immediate or late allergic reactions, such as allergic conjunctivitis, allergic rhinitis, asthma symptoms, or rarely anaphylaxis, in sensitized participants, which will be treated appropriately at the discretion of the investigator. With the exception of severe or clinically concerning reactions (as judged by the investigator), rescue treatments, as needed, should be dispensed after study endpoint data collection is obtained (eg, after the skin wheals are measured after application of allergen).

Specific medications to be withheld prior to SPT are described in Prohibited Medications (Section 7.9.1). Details will be provided in a study reference manual for the sites.

8.2.2.8. Standardized Rhinoconjunctivitis Quality of Life Questionnaire for Ages 12+

RQLQ(S) will be recorded at the time points according to Table 1. 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 with 1-week recall 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 were better).

8.2.2.9. Pollen Food Allergy Syndrome Questionnaire

The PFASQ will be administered at the time points according to Table 1 to assess patient-reported symptom burden associated with pollen-food allergy (before going to bed for the night).

8.2.2.10. Outdoor Time Questionnaire

The Outdoor Time Questionnaire will be administered via e-diary at the time points according to Table 1 to assess patient-reported average daily time spent outdoors (before going to bed for the night).

8.2.3. Safety Procedures

8.2.3.1. Vital Signs

Vital signs, including temperature, sitting blood pressure, pulse, and respiration, will be collected pre-dose at time points according to Table 1.

8.2.3.2. Physical Examination

A full physical examination or a limited relevant physical examination will be performed, as indicated, at time points according to Table 1. Care should be taken to examine and assess any abnormalities that may be present, as indicated by the participant's medical history.

8.2.3.3. Spirometry

Spirometry measurements include FVC (L), FEV1 (L), FEV1/FVC (%), PEF (L/s), FEF 25-75 (L/s). Spirometry, as adjudicated by the site investigator, will be performed locally during the study at specified time points (Table 1) (American Thoracic Society [ATS]/European Respiratory Society [ERS]-compliant) (Graham, 2019).

Spirometry will be performed in-clinic at screening and randomization for all participants to exclude any participants with abnormal lung function and/or poorly controlled asthma. FEV1 eligibility criteria are specified in exclusion criteria (Section 6.2.2).

Spirometry will be performed after a washout period of bronchodilators according to their action duration to avoid interference with spirometry assessments and the investigator will discuss this with the participants. Examples of washout periods that investigators can discuss with the participant include withholding the last dose of short acting bronchodilator (SABA, such as salbutamol/albuterol or levosalbutamol/levalbuterol) for at least 6 hours, long acting bronchodilator (LABA, such as formoterol or salmeterol) for at least 12 hours, ultra-long-acting LABA (such as vilanterol, indacaterol) for at least 24 hours, short acting muscarinic antagonist (SAMA, such as ipratropium) for at least 8 hours, and long acting muscarinic antagonist (LAMA, such as tiotropium, umeclidinium) for at least 24 hours. Withholding times will be verified before performing the measurements.

Details will be provided in a study reference manual for the sites.

8.2.3.4. Laboratory Testing

Hematology, chemistry, urinalysis, and pregnancy testing samples will be analyzed. Detailed instructions for blood sample collection are in the laboratory manual provided to study sites.

Samples for laboratory testing will be collected at visits according to Table 1. Tests will include:

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	

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	Leukocyte 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.

Abnormal Laboratory Values and Laboratory Adverse Events

All laboratory values must be reviewed by the investigator or authorized designee.

Significantly abnormal test results that occur after start of treatment must be repeated to confirm the nature and degree of the abnormality. When necessary, appropriate ancillary investigations should be initiated. If the abnormality fails to resolve or cannot be explained by events or conditions unrelated to the study medication or its administration, the Medical/Study Director must be consulted.

The clinical significance of an abnormal test value, within the context of the disease under study, must be determined by the investigator.

Criteria for reporting laboratory values as an AE are provided in Section 9.1.1.

8.2.4. Drug Concentration and Measurements

Samples for drug concentration measurement will be collected at visits listed in Table 1. 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 REGN5713, REGN5714, and REGN5715 drug concentration may be collected as close to the event as practically possible.

8.2.5. Immunogenicity Measurements and Samples

Samples for ADA measurement will be collected at visits listed in Table 1. 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.

8.2.6. Pharmacodynamic and Exploratory Biomarker Procedures

This section describes planned exploratory PD/biomarker analyses, some of which may be reported in the CSR. Samples will be collected at time points according to Table 1. The biomarkers studied will be those known or hypothesized to be relevant to the pathophysiology of birch allergy, mechanism of action and/or safety of REGN5713-5714-5715, REGN5713-5715, and REGN5715.

Detailed instructions for blood sample collection are included in the laboratory manual.

Any biological samples (eg, blood, serum, plasma) collected during the study, which are not used for their planned purpose, or for which material remains after their planned analysis, may be kept for up to 15 years after study completion (or for a shorter time period if required per regional laws and regulations) for use in exploratory research related to REGN5713-5714-5715, REGN5713-5715, and REGN5715 safety and/or efficacy, birch allergy and related allergies, the biology of Bet v 1 and/or for related assay development and/or validation.

8.2.6.1. Basophil Activation Test

In this study, exploratory biomarker assessments will be performed to better understand the effects of REGN5713-5714-5715, REGN5713-5715, and REGN5715 administration on biomarkers of birch allergy or relevant physiological and pathogenic processes. This will include the assessment of allergen-specific IgE levels in serum samples during the study. Additionally, whole blood may be collected and processed as per the laboratory manual for basophil responsiveness testing in the basophil activation test (BAT). If an indirect basophil activation assay is available, frozen serum samples may be tested.

Basophils are an effector cell type involved in acute allergic reactions. A BAT assay is an in vitro cellular functional test that measures basophil activation by the flow cytometric assessment of the degree of degranulation following stimulation of the sample with allergens or controls, providing an objective method to quantify the allergen-specific reactivity and sensitivity of basophils.

In a previous randomized, double-blind, placebo-controlled, 2-part phase 1 study, where in Part B, patients were administered a single dose of REGN5713-5714-5715 at 900 mg SC, it was demonstrated that treatment with REGN5713-5714-5715 significantly lowered basophil responsiveness to birch pollen extract as compared to placebo (Gevaert, 2022). A correlation between the basophil response as measured by BAT assay and the clinical symptom improvements

in TNSS and SPT was observed, indicating that the less sensitive the basophils are to birch pollen in a BAT assay, the greater the clinical benefit the patients may achieve. As such, it is possible that the inhibition of basophil/mast cell degranulation may be a key mechanism by which REGN5713-5714-5715 ameliorates the allergic symptoms downstream of birch pollen exposure. Therefore, in this study a BAT assay may be used to assess the inhibitory effect of anti-Bet v 1 antibodies (which may include but not be limited to assessments such as EC_{50} and/or % change in EC_{50} from baseline/pre-dose/EEU exposure) on basophil activation after ex-vivo stimulation with birch pollen and/or Bet v 1 in REGN5713-5714-5715, REGN5713-5715, and REGN5715 treated participants vs placebo. Correlations to clinical symptom measurements may also be made. A BAT assay may be performed for approximately 100 of the randomized participants (subset of the total enrolled population at one or both EEU sites; additional samples may be required at the screening visit since participants may screen fail after the EEU challenge). Assessments will be done in each of the active treatment arms versus placebo.

8.2.6.2. Nasal Fluid Collection

Nasal fluid may be collected from a subset of participants. It is recommended to collect these samples in the same participants from whom BAT samples were collected. Samples will be collected in approximately 100 randomized participants at specified visits in Table 1. 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.

Exploratory biomarker results not required for protocol-defined endpoint analyses will not be reported in the CSR. These results may be in a separate exploratory biomarker report.

8.2.7. Future Biomedical Research (Optional)

Participants who agree to participate in the future biomedical research (FBR) sub-study will be required to consent to this optional sub-study before samples are banked for FBR. Additional samples (plasma and serum) will be collected for FBR. Residual biomarker/biological samples for study-related research, as well as unused PK and ADA samples, will be stored for up to 15 years after the final date of the database lock (or for a shorter time period if required per regional laws and regulations). The samples may be utilized for FBR that may or may not be directly related to the study, including being used as reference samples and assay development or validation.

The results of these future biomedical research analyses will not be presented in the CSR.

8.2.8. Pharmacogenomic Analysis (Optional)

Participants who agree to participate in the genomics sub-study will be required to consent to this optional sub-study before collection of the samples. Whole blood samples for DNA extraction should be collected on day 1/baseline (pre-dose) but can be collected at a later study visit (Table 1). DNA samples will be collected for pharmacogenomics analyses to understand the genetic determinants of efficacy and safety associated with the treatments in this study and the molecular basis of birch allergy and related diseases. These samples will be single-coded as defined by the International Council for Harmonisation (ICH) guideline E15. Samples will be stored for up to 15 years after the final date of the database lock (or for a shorter time period if required per regional laws and regulations). If there are specific site or country requirements involving the

pharmacogenomic analyses which the sponsor is unable to comply with, samples will not be collected at those sites.

The purpose of the pharmacogenomic analyses is to identify genomic associations with clinical or biomarker response to REGN5713-5714-5715, other birch allergy clinical outcome measures and possible AEs. In addition, associations between genomic variants and prognosis or progression of birch allergy as well as related allergic diseases may also be studied. These data may be used or combined with data collected from other studies to identify and validate genomic markers related to the study drug, target pathway, or birch allergy and related diseases.

Analyses may include sequence determination or single nucleotide polymorphism studies of candidate genes and surrounding genomic regions. Other methods, including whole-exome sequencing, whole-genome sequencing, and DNA copy number variation may also be performed. The list of methods may be expanded to include novel methodology that may be developed during the course of this study or sample storage period. Results from the genomic analyses will not be reported in the CSR.

9. SAFETY EVALUATION AND REPORTING

9.1. Recording and Reporting Adverse Events

9.1.1. General Guidelines

The investigator must promptly record all clinical events occurring during the study data collection, from the time of signing the informed consent form (ICF) to the end of on-treatment period (see Section 10.4.5.1). Medical conditions that existed or were diagnosed prior to the signing of the informed consent will be recorded as part of medical history. Abnormal laboratory values and vital signs observed at the time of informed consent should also be recorded as medical history. Any subsequent worsening (ie, any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug should also be recorded as an AE.

At each visit, the investigator will determine whether any AEs have occurred by evaluating the participant. Adverse events may be directly observed, reported spontaneously by the participant, or by questioning the participant at each study visit. Participants should be questioned in a general way, without asking about the occurrence of any specific symptoms. The Investigator must assess all AEs to determine seriousness, severity, and causality, in accordance with the definitions in Section 9.2. The Investigator's assessment must be clearly documented in the site's source documentation with the Investigator's signature. The Investigator should follow up on SAEs (and AESIs) until they have resolved or are considered clinically stable; AEs should be followed until they are resolved or last study visit, whichever comes first.

Although not considered an adverse event, if a pregnancy occurs during the study, information about the progress and outcome of the pregnancy will be collected. This should include the date that the participant became pregnant, information about the health of the participant, any medication treatments received during the pregnancy, any medical problems affecting or related to the pregnancy and/or the baby, whether the pregnancy came to term, the date of the child's birth, and the health of the child after birth. To collect this information, the study staff should contact the participant every trimester for updates on the pregnancy. The participant should also be asked to contact the site as soon as possible in the event of any medical problem affecting or related to the pregnancy and/or baby. Once the baby is born, the study staff will ask for a final update after one well-baby visit with the pediatrician.

Always report the diagnosis as the AE or SAE term. When a diagnosis is unavailable, report the primary sign or symptom as the AE or SAE term with additional details included in the narrative until the diagnosis becomes available. If the signs and symptoms are distinct and do not suggest a common diagnosis, report them as individual entries of AE or SAE.

Laboratory results, vital signs, and other diagnostic results or findings should be appraised by the Investigator to determine their clinical significance. Isolated abnormal laboratory results, vital sign findings, or other diagnostic findings (ie, not part of a reported diagnosis) should be reported as AEs if they are symptomatic, lead to study drug discontinuation, dose reduction, require corrective treatment, or constitute an AE in the investigator's clinical judgment.

For events that are serious due to hospitalization, the reason for hospitalization must be reported as the SAE (diagnosis or symptom requiring hospitalization). A procedure is not an AE or SAE, but the reason for the procedure may be an AE or SAE. Pre-planned (prior to signing the ICF) procedures, treatments requiring hospitalization for pre-existing conditions that do not worsen in severity, and admission for palliative or social care should not be reported as SAEs (see Section 9.2 for Definitions).

For deaths, the underlying or immediate cause of death should always be reported as an SAE.

Any SAE that may occur subsequent to the reporting period (end of the on-treatment period) that the Investigator assesses as related to study drug should also be reported.

All AEs, SAEs, AESIs, and pregnancy reports are to be reported according to the procedures in Section 9.1.3.

9.1.2. Reporting Procedure

All events (serious and non-serious) must be reported with investigator's assessment of the event's seriousness, severity, and causality to the (when applicable: blinded) study drug. For SAEs and AESIs, a detailed narrative summarizing the course of the event, including its evaluation, treatment, and outcome should be provided on the AE case report form (CRF). Specific or estimated dates of event onset, treatment, and resolution should be included, when available. Medical history, concomitant medications, and laboratory data that are relevant to the event should also be summarized in the narrative. For fatal events, the narrative should state whether an autopsy was or will be performed, and include the results if available. Information not available at the time of the initial report must be documented in a follow-up report. Source documents (including hospital or medical records, diagnostic reports, etc) will be summarized in the narrative on the AE CRF, and retained at the study center and available upon request.

Urgent safety queries must be followed up and addressed promptly. Follow-up information and response to non-urgent safety queries should be combined for reporting to provide the most complete data possible within each follow-up.

The investigator (or designee) will record all AEs that occur from the time the informed consent is signed until the end of study with the exception of allergic symptoms that occur in response to the EEU challenge within 24 hours following the EEU. Allergic symptoms that occur in response to the EEU are not to be reported as AEs, as they will be recorded as outcome measures. However, AEs that occur in response to allergen exposure in the EEU that are outside of expected symptoms, including events which qualify as SAEs, up to 24 hours after EEU session, should be reported as AEs and SAEs, as applicable.

9.1.3. Events that Require Expedited Reporting to Sponsor

The following events also require reporting to the sponsor (or designee) within 24 hours of learning of the event:

- **SAEs**.
- **Selected Adverse Events of Special Interest** (AESI; serious and nonserious)**:** Adverse events of special interest for this study include the following:
  - Systemic or severe hypersensitivity reactions
  - 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)
- **Pregnancy:** Although pregnancy is not considered an AE, it is the responsibility of the investigator to report to the sponsor (or designee), within 24 hours of identification, any pregnancy occurring in a female participant during the study or within 6 months of the last dose of study drug, whichever is longer. Any complication of pregnancy affecting a female study participant and/or fetus and/or newborn that meets the SAE criteria must be reported as an SAE. Outcome for all pregnancies should be reported to the sponsor.

9.1.4. Other Adverse Events of Special Interest that do not Require Expedited Reporting to Sponsor

Although these AESIs do not require expedited reporting to Sponsor, the following events are of interest and will involve specific data collection to characterize better:

- Systemic or severe hypersensitivity reactions

9.2. Definitions

9.2.1. Adverse Event

An AE is any untoward medical occurrence in a participant administered a study drug which may or may not have a causal relationship with the study drug. Therefore, an AE is any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease that is temporally associated with the use of a study drug, whether or not considered related to the study drug (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).

For studies with patient reported outcomes (PRO), the PRO data are generally not reportable as individual AEs and thus will not be reported or reconciled as such.

9.2.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in **death** – includes all deaths, even those that appear to be completely unrelated to study drug (eg, a car accident in which a participant is a passenger).
- Is **life-threatening** – in the view of the investigator, the participant is at immediate risk of death at the time of the event. This does not include an AE that had it occurred in a more severe form, might have caused death.
- Requires in-patient **hospitalization** or **prolongation of existing hospitalization**. In-patient hospitalization is defined as a hospital admission (any duration) or an emergency room visit for longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay that is longer than was originally anticipated for the event, or is prolonged due to the development of a new AE as determined by the investigator or treating physician.
- Results in persistent or significant **disability/incapacity** (substantial disruption of one's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**
- Is an **important medical event** - Important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the participant or may require intervention to prevent one of the other serious outcomes listed above (eg, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse).

Criteria for reporting SAEs must be followed for these events.

9.2.3. 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 investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it.

9.2.4. Severity

The severity of AEs will be graded according to the following scale:

Mild: Does not interfere in a significant manner with the participant's normal functioning level. It may be an annoyance. Prescription drugs are not ordinarily needed for relief of symptoms, but may be given because of personality of the participant.

Moderate: Produces some impairment of functioning but is not hazardous to health. It is uncomfortable or an embarrassment. Treatment for symptom may be needed.

Severe: Produces significant impairment of functioning or incapacitation and is a definite hazard to the participant's health. Treatment for symptom may be given and/or participant hospitalized.

If a laboratory value is considered an AE, its severity should be based on the degree of physiological impairment the value indicates.

Injection Site Reactions

The severity of injection site reactions will be graded according to the following scale (semi-colon indicates "or" within description of grade:

Mild: Pain that does not interfere with activity; mild discomfort to touch; <5 cm of erythema or induration that does not interfere with activity

Moderate: Pain that requires repeated use of non-narcotic pain reliever >24 hours or interferes with activity; discomfort with movement; 5.1 cm to 10 cm erythema or induration or induration that interferes with activity

Severe: Pain that requires any use of narcotic pain reliever or that prevents daily activity; significant discomfort at rest; >10 cm erythema or induration; prevents daily activity; requires emergency room visit or hospitalization; necrosis or exfoliative dermatitis

9.2.5. Causality

The investigator must provide causality assessment as to whether or not there is a reasonable possibility that the drug caused the AE, based on evidence or facts, his/her clinical judgment, and the following definitions. The causality assessment must be made based on the available information and can be updated as new information becomes available.

For double blinded studies using an active comparator, the investigator should consider all study drugs in determining event causality.

The following factors should be considered when assessing causality:

- Temporal relationship: time to onset versus time drug was administered
- Nature of the reactions: immediate versus long term
- Clinical and pathological features of the events
- Existing information about the drug and same class of drugs
- Concomitant medications
- Underlying and concurrent illnesses
- Response to dechallenge (drug discontinuation) or dose reduction
- Response to rechallenge (re-introduction of the drug) or dose increase, when applicable
- Participant's medical and social history

Causality to the study drug (including study drug administration):

- Related:
  - The AE follows a reasonable temporal sequence from study drug administration, and cannot be reasonably explained by the nature of the reaction, participant's clinical state (eg, disease under study, concurrent diseases, concomitant medications), or other external factors.

  or

  - The AE follows a reasonable temporal sequence from study drug administration, and is a known reaction to the drug under study or its class of drugs, or is predicted by known pharmacology.
- Not Related:
  - The AE does not follow a reasonable sequence from study drug administration, or can be reasonably explained by the nature of the reaction, participant's clinical state (eg, disease under study, concurrent diseases, and concomitant medications) or other external factors.

Causality to the study conduct (protocol specified procedure):

- Related:
  - The AE follows a reasonable temporal sequence from a protocol specified procedure, and cannot be reasonably explained by the nature of the reaction, participant's clinical state (eg, disease under study, concurrent diseases, concomitant medications), or other external factors.
- Not Related:
  - The AE does not follow a reasonable sequence from a protocol specified procedure, or can be reasonably explained by the nature of the reaction, participant's clinical state (eg, disease under study, concurrent diseases, and concomitant medications) or other external factors.

9.3. Safety Monitoring

The investigator will monitor the safety of study participant at his/her site(s) as per the requirements of this protocol and consistent with current Good Clinical Practice (GCP). Any questions or concerns should be discussed with the sponsor in a timely fashion. The sponsor will monitor the safety data from across all study sites. The Medical/Study Director will have primary responsibility for the emerging safety profile of the compound, but will be supported by other departments (eg, Global Patient Safety; Biostatistics and Data Management). Safety monitoring will be performed on an ongoing basis (eg, individual review of SAEs) and on a periodic cumulative aggregate basis.

9.4. Notifying Health Authorities, Institutional Review Board/Ethics Committee, and Investigators

During the study, the sponsor and/or the CRO will inform health authorities, Institutional Review Boards (IRBs)/Ethics Committees (ECs), and the participating investigators of any Suspected Unexpected Serious Adverse Reactions (SUSARs) occurring in other study centers or other studies of the active study drug (REGN5713-5714-5715, REGN5713-5715, or REGN5715), as appropriate per local reporting requirements. In addition, the sponsor and/or CRO will comply with any additional local safety reporting requirements. All notifications to investigators will contain only blinded information.

Upon receipt of the sponsor's notification of a SUSAR that occurred with the study drug, the investigator will inform the IRB/EC unless delegated to the sponsor.

Event expectedness for study drug (REGN5713-5714-5715, REGN5713-5715, or REGN5715) is assessed against the Reference Safety Information section of the Investigator's Brochure that is effective for expedited safety reporting.

At the completion of the study, the sponsor will report all safety observations made during the conduct of the trial in the CSR to health authorities and IRB/EC as appropriate.

10. STATISTICAL PLAN

10.1. Statistical Hypothesis

The following hypotheses of the primary endpoint will be tested for each active treatment group versus placebo:

H_0: The mean of TNSS in a birch allergen EEU at day 29 in Part A is equal between active treatment group and placebo.

H_1: The mean of TNSS in a birch allergen EEU at day 29 in Part A is different between active treatment group and placebo.

The statistical hypothesis specified above can 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.

10.2. Justification of Sample Size

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. A sample size of 65 participants per arm gives 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, 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.

10.3. Analysis Sets

10.3.1. Efficacy Analysis Sets

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 modified FAS (mFAS), which consists of participants who receive study drug in Part B.

10.3.2. Safety Analysis Set

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).

10.3.3. Pharmacokinetic Analysis Set

The PK analysis population includes all participants who received any study drug (safety population) and who had a at least 1 non-missing serum drug concentration following a single dose of REGN5713-5714-5715, REGN5713-5715, and/or REGN5715. Participants will be analyzed according to the treatment actually received.

10.3.4. Immunogenicity Analysis Set

The ADA analysis set will consist of all participants who received any study drug and had at least 1 non-missing ADA result after a single dose of study drug. Participants will be analyzed according to the treatment actually received.

10.4. Statistical Methods

For continuous variables, descriptive statistics will include the following information: the number of participants reflected in the calculation (n), mean, standard deviation, Q1, median, Q3, minimum, and maximum.

For categorical or ordinal data, frequencies and percentages will be displayed for each category.

10.4.1. Participant Disposition

The following will be provided:

- The total number of screened participants who have signed the ICF
- The total number of randomized participants: received a randomization number
- The total number of participants in each analysis set (eg, FAS, provided in Section 10.3.1)
- The total number of participants who discontinued the study, and the reasons for discontinuation

10.4.2. Demography and Baseline Characteristics

Demographic variables (eg, age, race, and gender), baseline characteristics, medical history, and prior and concomitant mediations and therapies will be summarized by treatment group. See Section 4.1 for a full list of demographic and baseline variables. No statistical hypothesis tests will be performed on these characteristics.

10.4.3. Efficacy Analyses

Part A data (as described below) will be used to evaluate the efficacy of the anti-Bet v 1 antibody(ies) and delineate the contribution of components using comparisons with placebo and between active treatment arms:

a. Assess the efficacy in the reduction of allergic symptoms during birch EEU challenges and birch skin test reactivity (TNSS [2 to 6 hours], TOSS [2 to 6 hours], TSS [2 to 6 hours]) and titrated SPT AUC] to determine treatment effects and durability of response.
b. Compare the proportions of birch-allergic participants achieving different degrees of clinical responses (TNSS [2 to 6 hours], TOSS [2 to 6 hours], TSS [2 to 6 hours] and titrated birch SPT AUC) across different response thresholds to evaluate the benefit of added epitope coverage.
c. In the subpopulation of oak-allergic participants, assess the treatment effect in the reduction of allergic symptoms during the oak EEU challenge and oak skin test reactivity (TNSS [2 to 6 hours], TOSS [2 to 6 hours], TSS [2 to 6 hours] and titrated oak SPT AUC) at day 36 to evaluate clinical efficacy against oak

Other relevant differences identified between the antibody combinations may also be considered in the decision-making process.

Six comparisons between treatment groups can be made:

1. REGN5713-5714-5715 versus placebo
2. REGN5713-5715 versus placebo
3. REGN5715 vs placebo
4. REGN5713-5714-5715 versus REGN5715
5. REGN5713-5714-5715 versus REGN5713-5715
6. REGN5713-5715 versus REGN5715

These 6 comparisons may be applied for efficacy endpoints. Additional details will be provided in the statistical analysis plan (SAP).

10.4.3.1. Primary Efficacy Analysis

The average of TNSS (2 to 6 hours) in a birch allergen EEU at day 29 in Part A will be analyzed by an analysis of covariance (ANCOVA) model, with the treatment group and randomization stratification factors (oak allergy, grass sensitization, EEU site) as fixed effects and the baseline TNSS (average TNSS [2 to 6 hours] during birch allergen EEU at screening) as a covariate.

If any rescue treatments are taken during the EEU challenge, the data from this EEU will be set as missing and day 29 will be imputed by baseline observation carried forward (BOCF). Otherwise, all observed data will be used.

Missing data will be imputed by multiple imputation (MI). Additional details will be specified in the SAP.

The intercurrent events, strategies, and the corresponding missing data handling approaches for the estimand for the primary endpoint are summarized in Table 2.

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 of 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) • Rescue treatment taken during the EEU challenge[2] : the data from this EEU after the use of the rescue medication will be set to missing and assigned by baseline observation carried forward (composite strategy) In addition, missing data due to any reason will be imputed using multiple imputation (MI).	ANCOVA model with treatment group and stratification factors as fixed effect and baseline as a covariate.

[1] Relevant prohibited medication will be defined in the SAP
[2] Per Section 7.2, rescue medication may be given during the EEU challenge if any severe or clinically concerning reactions (as judged by the investigator)

To assess the consistency in treatment effects across different subgroup levels, subgroup analyses will be performed for the primary efficacy endpoint with respect to age group, gender, and other factors that will be specified in the SAP.

10.4.3.2. Secondary Efficacy Analysis

The secondary continuous efficacy endpoints will be analyzed in a manner similar to that described above (Section 10.4.3.1) for the primary efficacy endpoint analysis unless further specified below. The intercurrent events, strategies, and the corresponding missing data handling approaches for the estimand for the continuous secondary efficacy endpoint from out-of-season EEU challenges may be the same as in Table 2, with details to be specified in the SAP. Descriptive analyses may be applied for efficacy endpoints unless specified in the SAP.

Additional details will be specified in the SAP.

The proportions of participants achieving different degrees of clinical responses and change/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 graphically using the cumulative distribution function. The AUC of the responder curves may also be calculated as a descriptive summary to compare across different symptom thresholds at days 29, 57, and 85 after receiving a single dose of REGN5713-5714-5715, REGN5713-5715, or REGN5715.

For the secondary endpoints from titrated SPT, if the antihistamines are not withheld before the titrated SPT, the data from this titrated SPT will be assigned by worst observation from the participant, including baseline.

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 at days 29, 57, 85 in participants receiving REGN5713-5714-5715, REGN5713-5715, or REGN5715. Additional details will be specified in the SAP.

10.4.3.3. Exploratory Efficacy Analysis

The exploratory efficacy endpoints, including mean of symptom scores (ie, TNSS [2 to 6 hours], TOSS [2 to 6 hours], and TSS [2 to 6 hours]) during end-of-season birch allergen EEU challenges, daily CSMS, TSS, TNSS, TOSS, and DMS averaged during the OPS, change and percent change from baseline in CSMS, TSS, TNSS, TOSS, and DMS averaged during the OPS, will be analyzed in the same fashion as the primary analysis.

Within-participant comparisons of the treatment effect of anti-Bet v 1 antibodies or placebo to reduce allergic symptoms between the EEU challenges and the field may be explored via the correlation coefficient, mean difference, and heteroscedasticity calculated on the following metrics:

- Average symptom score (2 to 6 hours) for TNSS, TOSS, TSS in a birch pollen EEU as compared to average symptom score for TNSS, TOSS, TSS during the birch pollen season and peak birch pollen season

Similar analysis will be performed for the within-participant comparisons of the treatment effect of the anti-Bet v 1 antibodies or placebo to reduce allergic symptoms between out-of-season and in-season during the EEU challenges based on the following metrics:

- Change and percent change from pre-treatment baseline for TNSS, TOSS, TSS 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 skin prick tests) will be explored similarly based on the following metrics:

- Change and percent change from pre-treatment baseline for titrated SPT mean wheal diameter AUC

10.4.4. Control of Multiplicity

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.

Multiplicity controlled testing procedures will be used to control the overall type I error rate in Part A, for testing multiple comparison groups. Additional details will be specified in the SAP.

10.4.5. Safety Analysis

The safety analysis will be based on the SAF.

The safety variables, including AEs, laboratory parameters, vital signs, and physical examinations, will be summarized using descriptive statistics.

10.4.5.1. Adverse Events

Definitions

For safety variables, 2 observation periods are defined:

- The pretreatment period is defined as the time from signing the ICF to before the first dose of study drug.
- The on-treatment period is defined as the day from first dose of study drug to the end of the study.

Treatment-emergent adverse events are defined as those that are not present at baseline or represent the exacerbation of a pre-existing condition during the on-treatment period and follow-up period.

Analysis

All adverse events reported in this study will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®).

Summaries of all TEAEs by treatment group will include:

- The number (n) and percentage (%) of participants with at least 1 TEAE by system organic class (SOC) and preferred term (PT)
- TEAEs by severity (according to the grading scale outlined in Section 9.2.4), presented by SOC and PT
- Treatment-related TEAEs, presented by SOC and PT
- Treatment-emergent AESIs (which are defined in Section 9.1.4)
- Deaths, SAEs, and TEAE leading to permanent treatment discontinuation will be summarized by SOC and PT.

10.4.5.2. Other Safety

Vital Signs

Vital signs (pulse, blood pressure, respiration rate, and temperature) will be summarized by baseline and change from baseline to each scheduled assessment time point with descriptive statistics.

Laboratory Tests

Laboratory test results will be summarized by baseline and change from baseline to each scheduled assessment time point with descriptive statistics.

Number and percentage participants with a potentially clinically significant value (PCSV) at any post-randomization time point will be summarized for each clinical laboratory test.

10.4.5.3. Treatment Exposure

Treatment exposure is defined as the number of study treatment administrations for each participant in each study part. Since each part only has a single-dose, participants will have 1 study treatment administration, given as 3 injections sequentially on one day. Summary of the number of injections will be provided. Treatment compliance is not applicable.
For each study part, the duration of observation period is calculated as:

(Date of the last visit in the corresponding part – date of the investigational product administration) +1.
Duration of observation period will be summarized for each treatment group using the number of participants, means, SD, minimums, medians, and maximums.

10.4.6. Pharmacokinetics

10.4.6.1. Analysis of Drug Concentration Data

The concentrations of total REGN5713, total REGN5714, and total REGN5715 over time will be summarized by descriptive statistics for each of the treatment groups.

No formal statistical hypothesis testing will be performed.

10.4.7. Analysis of Immunogenicity Data

Immunogenicity will be characterized by the ADA response observed:

- Pre-existing immunoreactivity, defined as a positive ADA assay response at baseline, with all post-dose ADA results negative, or a positive assay response at baseline, with all post-dose ADA assay responses less than 9-fold over baseline titer levels
- Treatment-emergent ADA response, defined as any post-dose positive ADA assay response when the baseline results are negative
- Treatment boosted ADA response, defined as any post-dose positive ADA assay response that is 9-fold over baseline titer levels when baseline is positive in the ADA assay
- Maximum ADA titer values
  - Low (titer <1,000)
  - Moderate (1,000≤ titer ≤10,000)
  - High (titer >10,000)

Listings of pre-existing, treatment-boosted, and treatment-emergent ADA responses, ADA titers positivity presented by participant, time point, and treatment arm will be provided separately for REGN5713, REGN5714, and REGN5715. Incidence of treatment-emergent ADA will be assessed as absolute occurrence (N) and percent of participants (%), grouped by study cohorts and ADA titer level.

Plots of drug concentrations will be examined and the influence of ADAs on individual PK profiles evaluated separately for REGN5713, REGN5714, and REGN5715. Assessment of impact of ADA on safety and efficacy may be provided.

10.4.8. Analysis of Pharmacodynamic and Exploratory Biomarker Data

Biomarker results will be summarized by baseline, measured values, change from baseline, and percent change from baseline to each scheduled assessment time point with descriptive statistics.

The correlation between clinical response to anti-Bet v 1 antibodies and poly/mono-sensitization during EEU challenges and field data assessments will be explored. Subgroup analyses in participants polysensitized (to unrelated allergens) and those with comorbid pollen food allergy syndrome will be conducted.

10.5. Timing of Statistical Analysis

The primary analysis may be performed after all participants complete at least the day 29 EEU challenges (visit 6) in Part A or discontinue. A select team will be unblinded to review the results but to ensure study integrity, the team members directly involved in the continued conduct of the trial will remain blinded. Further study blinding implications are discussed in Section 7.6.

Final unblinded analyses of the study results for efficacy endpoints may be performed when all randomized participants have completed visit 14 (after end of BPS). 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.

10.6. Statistical Considerations Surrounding the Premature Termination of a Study

If the study is terminated prematurely, only those parameters required for the development program and/or reporting to regulatory authorities will be summarized. Investigator and sponsor responsibilities surrounding the premature termination of a study are presented in Section 14.1.

11. QUALITY CONTROL AND QUALITY ASSURANCE

In accordance with ICH E6, the sponsor is responsible for quality assurance to ensure that the study is conducted and the data generated, recorded, and reported in compliance with the protocol, GCP, and any applicable regulatory requirement(s). The planned quality assurance and quality control procedures for the study are described in this section.

11.1. Data Management and Electronic Systems

11.1.1. Data Management

A data management plan specifying all relevant aspects of data processing for the study (including data validation [quality-checking], cleaning, correcting, releasing) will be maintained and stored at Regeneron (Sponsor).

A medical coding plan will specify the processes and the dictionary used for coding. All data coding (eg, AEs, baseline findings, medication, medical history) will be done using internationally recognized and accepted dictionaries.

The CRF data for this study will be collected with an electronic data capture (EDC) system: Medidata Rave.

11.1.2. Electronic Systems

Electronic systems that may be used to process and/or collect data in this study will include the following:

- IVRS/IWRS system – randomization, study drug supply
- EDC system – data capture – Medidata Rave
- Statistical Analysis System (SAS) – statistical review and analysis
- Pharmacovigilance safety database – Argus
- e-diary

11.2. Study Monitoring

11.2.1. Monitoring of Study Sites

Regeneron uses a study-specific risk based approach to study monitoring and oversight, aligned with risk based quality principles, outlined in ICH E6 (R2) Guideline for Good Clinical Practice. Risk-Based Quality Monitoring (RBQM) methodology focuses on employing a fit-for-purpose monitoring strategy, supported either directly by Regeneron as sponsor, or via our CRO partners. RBQM strategies include: reduced source data verification (SDV), targeted source data review (SDR), the use of off-site/remote and triggered on-site monitoring visits, and Centralized Monitoring to identify site level risks and study level trends. The investigator must allow study-related monitoring activities to occur.

The study monitors will perform ongoing source data review to verify that data recorded in the CRF by authorized site personnel are accurate, complete, and verifiable from source documents, that the safety and rights of participants are being protected, and that the study is being conducted

in accordance with the current approved protocol version and any other study agreements, ICH GCP, and all applicable regulatory requirements.

11.2.2. Source Document Requirements

Investigators are required to prepare and maintain adequate and accurate participants records (source documents). The site is responsible to ensure quality within their records and systems and are accountable for ensuring that all source data and CRF data are timely, accurate and complete.

The investigator must keep all source documents on file with the CRF (throughout this protocol, CRF refers to either a paper CRF or an electronic CRF). Case report forms and source documents must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

11.2.3. Case Report Form Requirements

Study data obtained in the course of the clinical study will be recorded on electronic CRFs within the EDC system by trained site personnel. All required CRFs must be completed for each and every participants enrolled in the study. The investigator must ensure the accuracy, completeness, and timeliness of the data reported to the sponsor in the CRFs. After review of the clinical data for each participant, the investigator must provide an electronic signature. A copy of each participant CRF casebook is to be retained by the investigator as part of the study record and must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

Corrections to the CRF will be entered in the CRF by the investigator or an authorized designee. All changes, including date and person performing corrections, will be available via the audit trail, which is part of the EDC system. For corrections made via data queries, a reason for any alteration must be provided.

11.3. Audits and Inspections

This study may be subject to a quality assurance audit or inspection by the sponsor or regulatory authorities. Should this occur, the investigator is responsible for:

- Informing the sponsor of a planned inspection by the authorities as soon as notification is received, and authorizing the sponsor’s participation in the inspection
- Providing access to all necessary facilities, study data, and documents for the inspection or audit
- Communicating any information arising from inspection by the regulatory authorities to the sponsor immediately
- Taking all appropriate measures requested by the sponsor to resolve the problems found during the audit or inspection

Documents subject to audit or inspection include but are not limited to all source documents, CRFs, medical records, correspondence, ICFs, IRB/EC files, documentation of certification and quality control of supporting laboratories, and records relevant to the study maintained in any supporting pharmacy facilities. Conditions of study material storage are also subject to inspection. In addition, representatives of the sponsor may observe the conduct of any aspect of the clinical study or its supporting activities both within and outside of the investigator's institution.

In all instances, the confidentiality of the data must be respected.

11.4. Study Documentation

11.4.1. Certification of Accuracy of Data

A declaration assuring the accuracy and content of the data recorded on the CRF/eCRF must be signed electronically by the investigator. This signed declaration accompanies each set of participant final CRF/eCRF that will be provided to the sponsor.

11.4.2. Retention of Records

The investigator must retain all essential study documents, including ICFs, source documents, investigator copies of CRFs, and drug accountability records for at least 15 years following the completion or discontinuation of the study, or longer, if a longer period is required by relevant regulatory authorities. The investigator must obtain written approval from the sponsor before discarding or destroying any essential study documents during the retention period following study completion or discontinuation. Records must be destroyed in a manner that ensures confidentiality.

If the investigator's personal situation is such that archiving can no longer be ensured, the investigator must inform the sponsor (written notification) and the relevant records will be transferred to a mutually agreed-upon destination.

12. ETHICAL AND REGULATORY CONSIDERATIONS

12.1. Good Clinical Practice Statement

It is the responsibility of both the sponsor and the investigator(s) to ensure that this clinical study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the ICH guidelines for GCP and applicable regulatory requirements.

12.2. Informed Consent

The principles of informed consent are described in ICH guidelines for GCP.

The ICF used by the investigator must be reviewed and approved by the sponsor prior to submission to the appropriate IRB/EC. A copy of the IRB/EC -approved ICF and documentation of approval must be provided to the sponsor before study drug will be shipped to the study site.

It is the responsibility of the investigator or designee (if acceptable by local regulations) to obtain written informed consent from each participant prior to his/her participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the participant in language that he/she can understand. The ICF should be signed and dated by the participant and by the investigator or authorized designee who reviewed the ICF with the participant.

- Participants who can write but cannot read will have the ICF read to them before signing and dating the ICF.
- Participants who can understand but who can neither write nor read will have the ICF read to them in presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was given.

The original ICF must be retained by the investigator as part of the participant's study record, and a copy of the signed ICF must be given to the participant.

If new safety information results in significant changes in the risk/benefit assessment, or if there are significant changes to the study procedures, the ICF must be reviewed and updated appropriately. All study participants must be informed of the new information and provide their written consent if they wish to continue in the study. The original signed revised ICF must be maintained in the participant's study record and a copy must be given to the participant.

12.3. Participants Confidentiality and Data Protection

The investigator must take all appropriate measures to ensure that the anonymity of each study participant will be maintained. Participants should be identified by a participant identification number only, on CRFs or other documents submitted to the sponsor. Documents that will not be submitted to the sponsor (eg, signed ICF) must be kept in strict confidence.

The participant's and investigator's personal data, which may be included in the sponsor database, will be treated in compliance with all applicable laws and regulations. The sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

12.4. Institutional Review Board/Ethics Committee

An appropriately constituted IRB/EC, as described in ICH guidelines for GCP, must review and approve:

- The protocol, ICF, and any other materials to be provided to the participants (eg, advertising) before any participant may be enrolled in the study
- Any amendment or modification to the study protocol or ICF before implementation, unless the change is necessary to eliminate an immediate hazard to the participant, in which case the IRB/EC should be informed as soon as possible
- Ongoing studies on an annual basis or at intervals appropriate to the degree of risk

In addition, the IRB/EC should be informed of any event likely to affect the safety of participants or the continued conduct of the clinical study.

A copy of the IRB/EC approval letter with a current list of the IRB/EC members and their functions must be received by the sponsor prior to shipment of drug supplies to the investigator. The approval letter should include the study number and title, the documents reviewed, and the date of the review.

Records of the IRB/EC review and approval of all study documents (including approval of ongoing studies) must be kept on file by the investigator.

12.5. Clinical Study Data Transparency

Final study results will be published on a public clinical trial website according to applicable local guidelines and regulations. Treatment codes will be disseminated to each investigation site thereafter.

13. PROTOCOL AMENDMENTS

The sponsor may not implement a change in the design of the protocol or ICF without an IRB/EC-approved amendment. Where required per local legislation, regulatory authority approval will also be sought.

14. PREMATURE TERMINATION OF THE STUDY OR CLOSE-OUT OF A SITE

14.1. Premature Termination of the Study

The sponsor has the right to terminate the study prematurely. Reasons may include efficacy, safety, or futility, among others. Should the sponsor decide to terminate the study, the investigator(s) will be notified in writing.

14.2. Close-out of a Site

The sponsor and the investigator have the right to close-out a site prematurely.

Investigator's Decision

The investigator must notify the sponsor of a desire to close-out a site in writing, providing at least 30 days' notice. The final decision should be made through mutual agreement with the sponsor. Both parties will arrange the close-out procedures after review and consultation.

Sponsor's Decision

The sponsor will notify the investigator(s) of a decision to close-out a study site in writing. Reasons may include the following, among others:

- The investigator has received all items and information necessary to perform the study, but has not enrolled any participant within a reasonable period of time
- The investigator has violated any fundamental obligation in the study agreement, including but not limited to, breach of this protocol (and any applicable amendments), breach of the applicable laws and regulations, or breach of any applicable ICH guidelines
- The total number of participants required for the study are enrolled earlier than expected

In all cases, the appropriate IRB/EC and Health Authorities must be informed according to applicable regulatory requirements, and adequate consideration must be given to the protection of the participants' interests.

15. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

16. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

17. PUBLICATION POLICY

Publication rights and procedures will be outlined in a separate clinical study agreement.

18. REFERENCES

Atanasio A, Franklin MC, Kamat V, Hernandez AR, Badithe A, Ben LH, et al. Targeting immunodominant Bet v 1 epitopes with monoclonal antibodies prevents the birch allergic response. J Allergy Clin Immunol 2022; 149(1):200-211.

Badorrek P, Dick M, Hecker H, Schaumann F, Sousa AR, Murdoch R, et al. Anti-allergic drug testing in an environmental challenge chamber is suitable both in and out of the relevant pollen season. Ann Allergy Asthma Immunol 2011; 106(4):336-341.

Bateman ED, Hurd SS, Barnes PJ, Bousquet J, Drazen JM, FitzGerald JM, et al. Global strategy for asthma management and prevention: GINA executive summary. Eur Respir J 2008; 31(1):143-178.

Bergmann KC, Kugler S, Zuberbier T,Becker S. Face masks suitable for preventing COVID-19 and pollen allergy. A study in the exposure chamber. Allergo J Int 2021:1-7.

Biedermann T, Kuna P, Panzner P, Valovirta E, Andersson M, de Blay F, et al. The SQ tree SLIT-tablet is highly effective and well tolerated: Results from a randomized, double-blind, placebo-controlled phase III trial. J Allergy Clin Immunol 2019a; 143(3):1058-1066.e1056.

Biedermann T, Kuna P, Panzner P, Valovirta E, Andersson M, de Blay F, et al. The SQ tree SLIT-tablet is highly effective and well tolerated: Results from a randomized, double-blind, placebo-controlled phase III trial. J Allergy Clin Immunol 2019b; 143(3):1058-1066 e1056.

Biedermann T, Winther L, Till SJ, Panzner P, Knulst A,Valovirta E. Birch pollen allergy in Europe. Allergy 2019c; 74(7):1237-1248.

Burbach GJ, Heinzerling LM, Edenharter G, Bachert C, Bindslev-Jensen C, Bonini S, et al. GA(2)LEN skin test study II: clinical relevance of inhalant allergen sensitizations in Europe. Allergy 2009; 64(10):1507-1515.

Burks A, Holgate S, O'Hehir R,al. e. *Middleton's Allergy: Principles and Practice.* Netherlands: Elsevier Health Sciences; 2019.

Calderon MA, Bernstein DI, Blaiss M, Andersen JS,Nolte H. A comparative analysis of symptom and medication scoring methods used in clinical trials of sublingual immunotherapy for seasonal allergic rhinitis. Clin Exp Allergy 2014; 44(10):1228-1239.

Chan-Yeung M, Anthonisen NR, Becklake MR, Bowie D, Sonia Buist A, Dimich-Ward H, et al. Geographical variations in the prevalence of atopic sensitization in six study sites across Canada. Allergy 2010; 65(11):1404-1413.

Ciprandi G, Incorvaia C, Scurati S, Puccinelli P, Soffia S, Frati F, et al. Patient-related factors in rhinitis and asthma: the satisfaction with allergy treatment survey. Current Medical Research and Opinion 2011; 27(5):1005-1011.

Couroux P, Ipsen H, Stage BS, Damkjaer JT, Steffensen MA, Salapatek AM, et al. A birch sublingual allergy immunotherapy tablet reduces rhinoconjunctivitis symptoms when exposed to birch and oak and induces IgG4 to allergens from all trees in the birch homologous group. Allergy 2019; 74(2):361-369.

Couroux P, Kunjibettu S, Hall N,Wingertzahn MA. Onset of action of ciclesonide once daily in the treatment of seasonal allergic rhinitis. Ann Allergy Asthma Immunol 2009; 102(1):62-68.

Cox L, Nelson H, Lockey R, Calabria C, Chacko T, Finegold I, et al. Allergen immunotherapy: a practice parameter third update. J Allergy Clin Immunol 2011; 127(1 Suppl):S1-55.

Didier A, Worm M, Horak F, Sussman G, de Beaumont O, Le Gall M, et al. Sustained 3-year efficacy of pre- and coseasonal 5-grass-pollen sublingual immunotherapy tablets in patients with grass pollen-induced rhinoconjunctivitis. J Allergy Clin Immunol 2011; 128(3):559-566.

Durham SR, Nelson HS, Nolte H, Bernstein DI, Creticos PS, Li Z, et al. Magnitude of efficacy measurements in grass allergy immunotherapy trials is highly dependent on pollen exposure. Allergy 2014; 69(5):617-623.

Durham SR,Penagos M. Sublingual or subcutaneous immunotherapy for allergic rhinitis? J Allergy Clin Immunol 2016; 137(2):339-349.e310.

Dykewicz MS, Wallace DV, Amrol DJ, Baroody FM, Bernstein JA, Craig TJ, et al. Rhinitis 2020: A practice parameter update. J Allergy Clin Immunol 2020; 146(4):721-767.

Ellis AK, DeVeaux M, Steacy L, Ramesh D, Suprun M, Langdon S, et al. Environmental exposure unit simulates natural seasonal birch pollen exposures while maximizing change in allergic symptoms. Ann Allergy Asthma Immunol 2021a; 127(4):488-495 e485.

Ellis AK, DeVeaux M, Steacy L, Ramesh D, Suprun M, Langdon S, et al. Environmental exposure unit simulates natural seasonal birch pollen exposures while maximizing change in allergic symptoms. Ann Allergy Asthma Immunol 2021b; 127(4):488-495.e485.

Ellis AK, Jacobs RL, Tenn MW, Steacy LM, Adams DE, Walker TJ, et al. Clinical standardization of two controlled allergen challenge facilities: The Environmental Exposure Unit and the Biogenics Research Chamber. Ann Allergy Asthma Immunol 2019; 122(6):639-646.e632.

Erler A, Hawranek T, Kruckemeier L, Asam C, Egger M, Ferreira F, et al. Proteomic profiling of birch (Betula verrucosa) pollen extracts from different origins. Proteomics 2011; 11(8):1486-1498.

FDA. Guidance for Industry Drug Induced Liver Injury: Premarketing Clinical Evaluation FDA. 2009; US Department of Health and Human Services Food and Drug Administration.

Flicker S,Valenta R. Renaissance of the blocking antibody concept in type I allergy. Int Arch Allergy Immunol 2003; 132(1):13-24.

Friedman MM,Kaliner M. Ultrastructural changes in human skin mast cells during antigen-induced degranulation in vivo. J Allergy Clin Immunol 1988; 82(6):998-1005.

Frossard N, Strolin-Benedetti M, Purohit A,Pauli G. Inhibition of allergen-induced wheal and flare reactions by levocetirizine and desloratadine. Br J Clin Pharmacol 2008; 65(2):172-179.

Galant S, Berger W, Gillman S, Goldsobel A, Incaudo G, Kanter L, et al. Prevalence of sensitization to aeroallergens in California patients with respiratory allergy. Allergy Skin Test Project Team. Ann Allergy Asthma Immunol 1998; 81(3):203-210.

Gevaert P, De Craemer J, De Ruyck N, Rottey S, de Hoon J, Hellings PW, et al. Novel antibody cocktail targeting Bet v 1 rapidly and sustainably treats birch allergy symptoms in a phase 1 study. J Allergy Clin Immunol 2022; 149(1):189-199.

Graham BL, Steenbruggen I, Miller MR, Barjaktarevic IZ, Cooper BG, Hall GL, et al. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. Am J Respir Crit Care Med 2019; 200(8):e70-e88.

Haahtela T, Burbach GJ, Bachert C, Bindslev-Jensen C, Bonini S, Bousquet J, et al. Clinical relevance is associated with allergen-specific wheal size in skin prick testing. Clin Exp Allergy 2014; 44(3):407-416.

Horak F, Zieglmayer P, Zieglmayer R, Lemell P, Devillier P, Montagut A, et al. Early onset of action of a 5-grass-pollen 300-IR sublingual immunotherapy tablet evaluated in an allergen challenge chamber. J Allergy Clin Immunol 2009; 124(3):471-477, 477 e471.

Jacobs RL, Harper N, He W, Andrews CP, Rather CG, Ramirez DA, et al. Effect of confounding cofactors on responses to pollens during natural season versus pollen challenge chamber exposure. J Allergy Clin Immunol 2014; 133(5):1340-1346, 1346.e1341-1347.

Jacobs RL, Ramirez DA,Andrews CP. Validation of the biogenics research chamber for Juniperus ashei (mountain cedar) pollen. Ann Allergy Asthma Immunol 2011; 107(2):133-138.

James LK, Shamji MH, Walker SM, Wilson DR, Wachholz PA, Francis JN, et al. Long-term tolerance after allergen immunotherapy is accompanied by selective persistence of blocking antibodies. Journal of Allergy and Clinical Immunology 2011; 127(2):509-516.e505.

Jarolim E, Rumpold H, Endler AT, Ebner H, Breitenbach M, Scheiner O, et al. IgE and IgG antibodies of patients with allergy to birch pollen as tools to define the allergen profile of Betula verrucosa. Allergy 1989; 44(6):385-395.

Lin RY, Clauss AE,Bennett ES. Hypersensitivity to common tree pollens in New York City patients. Allergy Asthma Proc 2002; 23(4):253-258.

Lo F, Bitz CM, Battisti DS,Hess JJ. Pollen calendars and maps of allergenic pollen in North America. Aerobiologia (Bologna) 2019; 35(4):613-633.

Murphy K, Travers P, Walport M,Janeway C. *Janeway's immunobiology.* New York: Garland Science; 2017.

Nolte H, Bernstein DI, Nelson HS, Kleine-Tebbe J, Sussman GL, Seitzberg D, et al. Efficacy of house dust mite sublingual immunotherapy tablet in North American adolescents and adults in a randomized, placebo-controlled trial. J Allergy Clin Immunol 2016; 138(6):1631-1638.

Nolte H, Maloney J, Nelson HS, Bernstein DI, Lu S, Li Z, et al. Onset and dose-related efficacy of house dust mite sublingual immunotherapy tablets in an environmental exposure chamber. J Allergy Clin Immunol 2015; 135(6):1494-1501 e1496.

Orengo JM, Radin AR, Kamat V, Badithe A, Ben LH, Bennett BL, et al. Treating cat allergy with monoclonal IgG antibodies that bind allergen and prevent IgE engagement. Nature Communications 2018; 9(1).

Pablos I, Wildner S, Asam C, Wallner M,Gadermaier G. Pollen Allergens for Molecular Diagnosis. Curr Allergy Asthma Rep 2016; 16(4):31.

Persi L, Demoly P, Harris AG, Tisserand B, Michel FB,Bousquet J. Comparison between nasal provocation tests and skin tests in patients treated with loratadine and cetirizine. J Allergy Clin Immunol 1999; 103(4):591-594.

Roberts G, Pfaar O, Akdis CA, Ansotegui IJ, Durham SR, Gerth van Wijk R, et al. EAACI Guidelines on Allergen Immunotherapy: Allergic rhinoconjunctivitis. Allergy 2018; 73(4):765-798.

Salo PM, Arbes SJ, Jr., Jaramillo R, Calatroni A, Weir CH, Sever ML, et al. Prevalence of allergic sensitization in the United States: results from the National Health and Nutrition Examination Survey (NHANES) 2005-2006. J Allergy Clin Immunol 2014; 134(2):350-359.

Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF, Jr., Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006; 117(2):391-397.

Schenk MF, Cordewener JH, America AH, Peters J, Smulders MJ,Gilissen LJ. Proteomic analysis of the major birch allergen Bet v 1 predicts allergenicity for 15 birch species. J Proteomics 2011; 74(8):1290-1300.

Sierra-Heredia C, North M, Brook J, Daly C, Ellis AK, Henderson D, et al. Aeroallergens in Canada: Distribution, Public Health Impacts, and Opportunities for Prevention. Int J Environ Res Public Health 2018; 15(8).

Uermosi C, Beerli RR, Bauer M, Manolova V, Dietmeier K, Buser RB, et al. Mechanisms of allergen-specific desensitization. J Allergy Clin Immunol 2010; 126(2):375-383.

Vandenplas O, Vinnikov D, Blanc PD, Agache I, Bachert C, Bewick M, et al. Impact of Rhinitis on Work Productivity: A Systematic Review. J Allergy Clin Immunol Pract 2018; 6(4):1274-1286.e1279.

Walker SM, Durham SR, Till SJ, Roberts G, Corrigan CJ, Leech SC, et al. Immunotherapy for allergic rhinitis. Clinical & Experimental Allergy 2011; 41(9):1177-1200.

Zhang Y,Steiner AL. Projected climate-driven changes in pollen emission season length and magnitude over the continental United States. Nature Communications 2022; 13(1):1234.

Zuberbier T, Bachert C, Bousquet PJ, Passalacqua G, Walter Canonica G, Merk H, et al. GA2LEN/EAACI pocket guide for allergen-specific immunotherapy for allergic rhinitis and asthma. Allergy 2010; 65(12):1525-1530.

19. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: 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 and agree to abide by all provisions set forth therein.

I agree to comply with the current International Council for Harmonisation Guideline for Good Clinical Practice and the laws, rules, regulations, and guidelines of the community, country, state, or locality relating to the conduct of the clinical study.

I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on studies for the sponsor or a partnership in which the sponsor is involved. I will immediately disclose it in writing to the sponsor if any person who is involved in the study is debarred, or if any proceeding for debarment is pending, or, to the best of my knowledge, threatened.

This document contains confidential information of the sponsor, which must not be disclosed to anyone other than the recipient study staff and members of the IRB/EC. I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the sponsor.

_____ _____

(Signature of Investigator) (Date)

_____

(Printed Name)

SIGNATURE OF SPONSOR'S RESPONSIBLE OFFICERS

(Medical/Study Director, Regulatory Representative, Clinical Study Lead, and Biostatistician)

To the best of my knowledge, this report accurately describes the planned conduct of the study.

Study 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

Protocol Number: R5713-5714-5715-ALG-21111

Protocol Version: Amendment 1

See appended electronic signature page

Sponsor's Responsible Medical/Study Director

See appended electronic signature page

Sponsor's Responsible Regulatory Liaison

See appended electronic signature page

Sponsor's Responsible Clinical Study Lead

See appended electronic signature page

Sponsor's Responsible Biostatistician

Signature Page for VV-RIM-00184270 v2.0

Approval/eSignature	[redacted] 11-Nov-2022 16:21:00 GMT+0000
Approval/eSignature	[redacted] 11-Nov-2022 17:01:50 GMT+0000
Approval/eSignature	[redacted] 11-Nov-2022 17:31:44 GMT+0000
Approval/eSignature	[redacted] 11-Nov-2022 17:31:56 GMT+0000

Signature Page for VV-RIM-00184270 v2.0 Approved