Clinical Study Protocol

A PHASE 3 RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY ASSESSING THE EFFICACY OF ANTI-BET V 1 MONOCLONAL ANTIBODIES TO REDUCE SYMPTOMS OF SEASONAL ALLERGIC RHINITIS

Compound:	REGN5713-5714-5715
Clinical Phase:	3
Protocol Number:	R5713-5714-5715-ALG-2001
Protocol Version:	R5713-5714-5715-ALG-2001 Original
Date of Issue:	*See appended electronic signature page*
Medical/Study Director:	[redacted] Regeneron Pharmaceuticals, Inc. 777 Old Saw Mill River Road Tarrytown, NY 10591

[redacted]

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ACQ	Asthma Control Questionnaire
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AUC	Area under the curve
BAT	Basophil activation tests
BUN	Blood urea nitrogen
COVID-19	Coronavirus Disease 2019
CRF	Case report form (electronic or paper)
CRO	Contract research organization
CSMS	Combined symptom and medication score
CSR	Clinical study report
CTFG	Clinical Trial Facilitation Group
DMS	Daily medication score
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic data capture
EMA	European Medicines Agency
FAS	Full analysis set
FBR	Future biomedical research
FDA	Food and Drug Administration
FIH	First in human
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
ICF	Informed consent form
ICH	International Council for Harmonisation
Ig	Immunoglobulin
IRB	Institutional Review Board
IRT	Interactive response technology

VV-RIM-00121234-2.0 Approved - 28 Sep 2020 GMT-5:00

IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
IVRS	Interactive voice response system
IWRS	Interactive web response system
LAM	Lactational amenorrhea method
mAb	Monoclonal antibody
NAb	Neutralizing antibody
OAS	Oral allergy syndrome
PBMC	Peripheral blood mononuclear cells
PCA	Percutaneous anaphylaxis
PCSV	Potentially clinically significant value
PD	Pharmacodynamic
PFAS	Pollen food allergy syndrome
PFASQ	Pollen food allergy symptom questionnaire
PGI-S	Patient Global Impression of Severity
PK	Pharmacokinetic
POC	Proof of concept
RBC	Red blood cell
RBQM	Risk-Based Quality Monitoring
Regeneron	Regeneron Pharmaceuticals, Inc.
RQLQ (S)	Standardized Rhinoconjunctivitis Quality of Life Questionnaire
RSOC	Regeneron Safety Oversight Committee
RSV	Respiratory syncytial virus
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAS	Statistical Analysis System
SC	Subcutaneous
SCIT	Subcutaneous immunotherapy
sIgE	Allergen-specific IgE
SIT	Specific immunotherapy
SLIT	Sublingual immunotherapy

VV-RIM-00121234-2.0 Approved - 28 Sep 2020 GMT-5:00

SMS	Symptom and medical score
SMT	Safety Monitoring Team
SOC	System organ class
SPT	Skin prick test
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
WAO	World Allergy Organization
WBC	White blood cell
WOCBP	Women of childbearing potential

VV-RIM-00121234-2.0 Approved - 28 Sep 2020 GMT-5:00

TABLE OF CONTENTS

VV-RIM-00121234-2.0 Approved - 28 Sep 2020 GMT-5:00

VV-RIM-00121234-2.0 Approved - 28 Sep 2020 GMT-5:00

VV-RIM-00121234-2.0 Approved - 28 Sep 2020 GMT-5:00

VV-RIM-00121234-2.0 Approved - 28 Sep 2020 GMT-5:00

LIST OF TABLES

LIST OF FIGURES

VV-RIM-00121234-2.0 Approved - 28 Sep 2020 GMT-5:00

CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study Assessing the Efficacy of Anti-Bet v 1 Monoclonal Antibodies to Reduce Symptoms of Seasonal Allergic Rhinitis
Site Locations	Approximately 50 sites in North America and Europe
Principal Investigator	To be determined
Objectives	**Primary Objectives** The primary objective is to assess the reduction of allergic symptoms as measured by combined symptom and medication score (CSMS) during birch pollen season after a single dose of REGN5713-5714-5715 versus placebo. **Secondary Objectives** The secondary objectives are: • To assess the reduction of allergic symptoms and use of allergy-relieving medications after a single dose of REGN5713-5714-5715 versus placebo, as measured by the total symptom score (TSS), total nasal symptom score (TNSS), total ocular symptom score (TOSS), and daily medication score (DMS) • To evaluate the safety and tolerability of REGN5713-5714-5715, including the incidence of hypersensitivity reactions and local injection site reactions • To evaluate the reduction in early allergic response to birch allergen after a single dose of REGN5713-5714-5715 versus placebo, as measured by skin prick test (SPT) mean wheal diameter • To determine systemic exposure of total antibody (ie, free and antigen-bound) in the form of concentration of REGN5713, REGN5714, and REGN5715 in serum • To assess the immunogenicity to REGN5713, REGN5714, and REGN5715 in subjects after a single dose of REGN5713-5714-5715 • To evaluate "well days" *Note: "Well days" are defined as days when the TSS is ≤2 without the use of anti-allergy rescue medications.*

Exploratory Objectives

The exploratory objectives are:

- To assess asthma control as measured by the asthma control questionnaire (ACQ-5)
- To assess quality of life as measured by the rhinoconjunctivitis quality of life questionnaire (RQLQ [S])
- To evaluate the reduction in early allergic response to birch homologous allergens (alder and oak) as measured by SPT mean wheal diameter
- To assess the relationship between allergy sensitization status to Bet v 1 or birch pollen at screening (as measured by serum allergen specific-IgE [sIgE]) and clinical response to REGN5713-5714-5715 treatment
- To assess serum sIgE levels against Bet v 1 and birch pollen during birch pollen season to evaluate the relationship between the response to REGN5713-5714-5715 and change in sIgE levels in-season
- To assess the inhibitory effect of REGN5713-5714-5715 on the binding of endogenous serum IgE to birch allergen in an in vitro assay; to assess whether the degree of inhibition correlates with clinical improvement
- To assess sIgE levels against other allergens (eg, Bet v 2, alder and oak) at screening and to evaluate the relationship between response to REGN5713-5714-5715 and poly-allergic status
- To assess additional subclasses of serum antibodies (eg, total IgG and IgG4 against birch pollen and Bet v 1) to evaluate the relationship between endogenous anti-Bet v 1 antibodies and response to REGN5713-5714-5715
- To assess the reduction in pollen food allergy syndrome (PFAS) and related symptoms as measured by pollen food allergy symptom questionnaire (PFASQ)
- To assess patient rating of severity of seasonal allergy symptoms as measured by patient global impression of severity (PGI-S)

Study Design	This is a phase 3 multi-center, randomized, double-blind, placebo-controlled, parallel group study to assess the efficacy of anti-Bet v 1 monoclonal antibodies (mAbs; REGN5713-5714-5715) to reduce allergic rhinitis and conjunctivitis symptoms and the use of rescue medications during birch pollen season. Efficacy will be evaluated by assessing the reduction of allergic nose and eye symptoms and the reduction in the use of allergy rescue medications during birch pollen season, after a single SC dose of REGN5713-5714-5715 or placebo. The incidence and severity of treatment-emergent adverse events (TEAEs), including hypersensitivity reactions and local injection site reactions, will be assessed. Total concentration in serum and immunogenicity of REGN5713, REGN5714, and REGN5715 will also be measured.
Study Duration	The total study duration is approximately 28 weeks including screening, dependent on the start and end times of the local birch pollen season. The length of birch pollen season will vary based on geography.

End of Study Definition	The end of study is defined as the date the last subject completes the last study visit, withdraws from the study, or is lost to follow-up (ie, the study subject can no longer be contacted by the investigator).
Population	Approximately 300 generally healthy adult male and female subjects with birch allergy will be enrolled. Other inclusion and exclusion criteria apply.
Study Drug and Placebo **Dose/Route/Schedule:**	• REGN5713-5714-5715 900 mg (300 mg per mAb), single SC dose • Matching placebo that replaces REGN5713-5714-5715, single SC dose
Endpoints	**Primary Endpoint** The primary endpoint is the daily CSMS, averaged over the duration of the birch pollen season, in subjects who receive a single dose of REGN5713-5714-5715 versus placebo. **Secondary Endpoints** The secondary endpoints are: • TSS, TNSS, and TOSS, averaged over the duration of the birch pollen season, in subjects who receive a single dose of REGN5713-5714-5715 versus placebo • DMS, averaged over the duration of the birch pollen season, in subjects who receive a single dose of REGN5713-5714-5715 versus placebo • Incidence of TEAEs and serious TEAEs throughout the study • Change and percent change from baseline to the end of study in birch SPT mean wheal diameter in subjects who receive a single dose of REGN5713-5714-5715 versus placebo • Total REGN5713, REGN5714, and REGN5715 concentration in serum over the study duration • Incidence of treatment emergent anti-drug antibodies (ADAs) to REGN5713, REGN5714, or REGN 5715 throughout the study • The number of "well days" in each of the treatment groups, where the "well days" are defined as days when rescue medication is not utilized and the TSS is ≤2/18

	Exploratory Endpoints The exploratory endpoints are: • ACQ-5, averaged over the duration of the birch pollen season, for REGN5713-5714-5715 versus placebo • RQLQ (S), averaged over the duration of the birch pollen season, for REGN5713-5714-5715 versus placebo • Change and percent change from baseline to the end of study in SPT mean wheal diameter for birch homologous/cross-reactive allergens in REGN5713-5714-5715 versus placebo • Baseline allergen-specific IgE levels and correlation with average CSMS, TSS, TNSS, TOSS, DMS during birch pollen season • Change and percent change from baseline to the peak of birch pollen season in allergen-specific IgE • Change in inhibitory effect on serum IgE to birch allergen • Number of baseline sensitizations to other allergens (poly/mono-sensitization status, based on allergen-specific IgE levels) and correlation with CSMS, TSS, TNSS, TOSS, and DMS, averaged over the duration of the birch pollen season • Baseline serum antibody levels and correlation with CSMS, TSS, TNSS, TOSS, and DMS, averaged over the duration of the birch pollen season • To assess the reduction in PFAS and related symptoms, as measured by PFASQ, from baseline to end of study • To assess patient rating of severity of seasonal allergy symptoms, as measured by PGI-S, from baseline to end of study
Procedures and Assessments	The following procedures will be performed to determine study eligibility and characterize the baseline population: • Skin prick test (SPT) for birch and standard regional allergens • Serum allergen-specific IgE (sIgE) tests for birch tree pollen and Bet v 1 • Serum sIgE tests for concomitant and homologous allergens • Medical history, demographics, weight, height, vital signs, physical examination, electrocardiogram (ECG), spirometry, hematology, and blood chemistry Efficacy assessments will include TNSS, TOSS, DMS, ACQ-5, RQLQ (S), PFASQ, and PGI-S. Safety assessments will include monitoring laboratory tests (hematology, blood chemistry, pregnancy tests), weight, vital signs, physical examination, adverse events (AEs), concomitant medications, and spirometry. Samples will also be collected for PK, ADA, and exploratory research.

Statistical Plan

Justifications for Sample Size

This study is powered to detect differences between REGN5713-5714-5715 and placebo on the primary endpoint of the average CSMS during birch pollen season. A sample size of 150 enrolled subjects per arm gives 90% power to detect a mean difference in average CSMS of 1.9 (30% reduction from placebo) in REGN5713-5714-5715 (mean CSMS = 4.4) and placebo (mean CSMS = 6.3), assuming a common standard deviation in CSMS of 4.5. The minimum significant difference in CSMS is 1.14, or approximately an 18% reduction from placebo. This sample size calculation assumes a 20% drop out rate (30 subjects per arm) and a two-sample t-test with two-sided alpha of 0.05. Estimates of mean and variability of the CSMS are based on pooled estimates across several field studies for grass immunotherapy, 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.

Primary Efficacy Analysis

The primary analysis will focus on the comparison between the REGN5713-5714-5715 arm and placebo arm. The average CSMS during birch pollen season will be compared in subjects receiving REGN5713-5714-5715 and subjects receiving placebo using a linear mixed-effect model, with the treatment group and randomization stratification factors as fixed effects and pollen region as a random effect, to account for potential differences in birch pollen seasons based on the geographical location of each pollen region. Clinical sites will be pooled into different pollen regions which will be specified in the SAP. Subjects with at least one day of post-baseline diary record with symptom and medical score (SMS) will be included. The CSMS will be calculated on all available data during the birch pollen season. The primary analysis will be based on the available values of daily symptom score and daily medication score to calculate the average CSMS and no imputation will be needed for the primary endpoint during the birch pollen season.

The average CSMS will be calculated based on daily symptom score (TNSS and TOSS, max of 18/day) and daily medication score (max of 20/day) recorded over the duration of the birch pollen season. The start and end of the birch pollen season will be defined for each site based on the local birch pollen counts. Only days with observed data (including any available data of daily entries prior to subject discontinuation) will be included in the calculation of the average CSMS.

1. INTRODUCTION

1.1. Allergic Disease, Birch Allergy, and Allergen-Specific Immunotherapy

Allergic rhinitis with or without conjunctivitis is a common disease with a significant socioeconomic burden, due to direct costs (eg, medications and physician visits) and indirect costs (eg, loss of productivity/working day) (Vandenplas, 2018). The current prevalence of allergic rhinitis is 10% to 30% in adults worldwide, and up to 37% in children in some Western countries (Pawankar, 2011), affecting approximately 500 million people worldwide (Brozek, 2017). Allergic rhinitis is characterized by 1 or more symptoms including sneezing, itching, nasal congestion, and rhinorrhea on consecutive days. Allergic conjunctivitis is also commonly coexistent, occurring in approximately 65% of people with the nasal symptoms of allergic rhinitis (Navarro, 2009) (Rosario, 2011). Symptoms of fatigue, malaise, irritability, and neurocognitive deficits are prevalent (Wallace, 2008). Perennial allergic rhinitis is typically caused by sensitization to indoor allergens (eg, dust mites, mold, and animal dander), while seasonal allergic rhinitis is most often due to sensitization to pollen allergens (eg, trees, grass, and weeds). In addition, asthma prevalence is 10% to 40% in those with allergic rhinitis (Shaaban, 2008), and allergic rhinitis is a risk factor for the development of asthma (Guerra, 2002) (Leynaert, 2000).

In Europe and North America, clinically relevant sensitization to birch tree pollen affects approximately 8% to 16% of the overall population (Biedermann, 2019a) (Chan-Yeung, 2010) (Salo, 2014) and approximately 20% to 30% of the population with allergic rhinitis (Burbach, 2009) (Galant, 1998) (Lin, 2002) (Pablos, 2016) (Sierra-Heredia, 2018). Birch pollen contains a mix of allergenic and non-allergenic proteins, and Bet v 1 is the most abundant allergenic pollen protein (Erler, 2011) (Schenk, 2011). Sensitization rates to Bet v 1 among birch-allergic individuals reach >95% (Erler, 2011) (Jarolim, 1989) (Schenk, 2011). Birch pollen exposure is associated with an increase in asthma-related emergency department visits (Guilbert, 2018) (Ito, 2015). Up to 70% of people with pollen allergy also experience oral reactions to particular fresh fruits, vegetables, and nuts, a condition known as oral allergy syndrome (OAS), or pollen food allergy syndrome (PFAS). Pollen food allergy syndrome is not a separate food allergy but rather occurs because of cross-reactive epitopes present in pollen and associated foods (Ebner, 1995) (Vanek-Krebitz, 1995). Pollen food allergy syndrome symptoms typically manifest as itching of lips, mouth, and throat, but potentially involve lip and tongue swelling and angioedema (Bucher, 2004) (Eriksson, 1982), leading people to avoid these fresh fruits, vegetables, and nuts. Approximately 70% of people with birch allergy also have PFAS to foods with similar epitopes as Bet v 1, such as apple, carrot, stone fruits, and hazelnut (Biedermann, 2019b).

Antihistamines and intra-nasal corticosteroids are first line therapy for allergic rhinitis, but only provide poor or partial symptom control and short-term relief to over half of allergic rhinitis sufferers (Halken, 2017) (Wallace, 2017a) (Wallace, 2008) (Wallace, 2017b) (Wei, 2016). Second line therapy for allergic rhinitis is allergen-specific immunotherapy (SIT), taken as either subcutaneous immunotherapy (SCIT) or sublingual immunotherapy (SLIT) tablets or drops (Bousquet, 1998) (Calderon, 2007) (Durham, 1999) (Ewbank, 2003) (Nelson, 2004) (Walker, 2001). Birch pollen SIT is used to treat birch-sensitive allergic rhinitis, including allergies caused by pollen from the birch homologous group of trees (eg, alder and hazel) (Biedermann, 2019a) (Makela, 2018) (Mauro, 2007). Birch pollen SIT has been shown to reduce

asthma medication use and to reduce the risk of new-onset asthma (Wahn, 2019). Immunotherapy using natural or recombinant Bet v 1 is as effective as immunotherapy with birch pollen extract in reducing daily allergic rhinitis symptom scores compared to placebo groups, highlighting the immunodominance of Bet v 1 in birch pollen allergy (Pauli, 2008). Moreover, in vitro inhibition studies with birch pollen have shown a high degree of inhibition of human IgE binding to alder, hazel, and oak allergen extracts (Niederberger, 1998). Studies also demonstrate that birch pollen SIT may offer symptom amelioration of PFAS (Asero, 1998) (Asero, 2003) (Asero, 2004) (Bergmann, 2008) (Bolhaar, 2004) (Herrmann, 1995) (Kelso, 1995).

However, SIT has many limitations. For the treatment of allergic rhinitis, SCIT or SLIT must be administered for at least 2 to 6 months prior to the onset of efficacy, and the efficacy of SIT requires high adherence to prevent rhinitis symptoms upon allergen exposure (Biedermann, 2019a) (Demoly, 2016) (Didier, 2011) (Durham, 2010) (Durham, 2012) (Durham, 2016) (Durham, 1999) (Lemberg, 2017) (Nolte, 2016). Subcutaneous immunotherapy is administered weekly during initiation of therapy and then monthly, under direct supervision in the clinic. Sublingual immunotherapy is administered daily at home. Both SCIT and SLIT have a high incidence of adverse events (AEs), including anaphylaxis. Anaphylaxis does not typically occur with routine, environmental pollen exposure. When allergens are administered through immunotherapy, there is higher allergen exposure, and therefore, there is risk of more significant allergic reactions including anaphylaxis. Anaphylaxis occurs more frequently with SCIT (up to 0.4%, affecting 7% of treated patients) compared to SLIT (Epstein, 2017). Since SLIT is administered at home, even though the risk of anaphylaxis with SLIT is lower compared to SCIT, any risk of severe allergic reactions causes a significant safety concern. Reactions to SCIT occur in 40% to 50% of patients, ranging from mild (eg, swelling, injection site reaction, de novo allergic response, and urticaria) to life-threatening (eg, asthma exacerbation and anaphylaxis) (Frew, 2006a) (Frew, 2010) (Frew, 2006b). Reactions to SLIT occur in the majority of patients, commonly involving irritation or swelling in the mouth or throat, predominantly over the first few weeks of therapy (Biedermann, 2019a). Subcutaneous immunotherapy and SLIT are generally contraindicated in patients with moderate to severe asthma (Cox, 2011).

Adherence to SIT is poor, likely due to the slow time to onset of action, the significant risk of allergic reactions, and the requirement for strict adherence for efficacy, including frequent clinic visits and monitoring needs in the case of SCIT (Musa, 2017). Due to these limitations, there remains an unmet need for a more robust, safer, rapid, and more convenient therapeutic approach for the prevention and treatment of moderate to severe allergic rhinitis and comorbid asthma.

1.2. Monoclonal Antibodies for the Treatment of Allergic Diseases

It has been hypothesized that high-affinity monoclonal “blocking antibodies” could be developed and administered as a form of passive immunotherapy for the treatment of allergy. 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. During SIT, clinical symptom improvement correlates with the ability of blocking IgG4s to compete with IgE for allergen-binding (James, 2011) (Uermosi, 2010). To test the hypothesis that IgG4 blockade to an allergen can reduce allergic symptoms upon exposure to the allergen, a cocktail of 2 IgG4 monoclonal antibodies (mAbs; REGN1908-1909) that bind to

VV-RIM-00121234-2.0 Approved - 28 Sep 2020 GMT-5:00

Fel d 1, the major allergen in cat dander, was developed. In allergic rhinitis patients with cat allergy, when symptom reduction was evaluated in a nasal allergen challenge model following administration of REGN1908-1909, total nasal symptom score (TNSS) area under the curve (AUC; hour 0 to 1) was reduced in REGN1908-1909-treated patients compared to placebo at days 8, 29, and 85 ($p = 0.0005$, $p = 0.0004$, and $p = 0.0187$, respectively; by analysis of covariance [ANCOVA]) (Orengo, 2018).

1.3. REGN5713, REGN5714, and REGN5715: Fully Human Monoclonal Antibodies Against Bet v 1

Similar to REGN1908-1909 (Orengo, 2018), 3 IgG4 mAbs against Bet v 1 (REGN5713, REGN5714, and REGN5715) have been developed for the treatment of birch allergy. Preclinical studies demonstrate that the 3 mAbs bind independently and non-competitively to the Bet v 1 allergen. Data also indicate that all 3 mAbs are required to optimally inhibit binding of Bet v 1 to human polyclonal IgE, and thus reduce in vitro effector cell degranulation and subsequent Type 1 hypersensitivity reaction. A single ascending dose-escalation clinical trial of the 3 mAb cocktail (REGN5713-5714-5715; in 1:1:1 ratio) has been completed and demonstrated that a single 150 mg subcutaneous (SC), 450 mg SC, 900 mg SC, or 900 mg intravenous (IV) dose had a favorable safety profile and was well-tolerated for 3 months post-dose, which was the follow-up period for the study.

In a phase 1b proof-of-concept (POC) study conducted in subjects with birch allergy (N=64), 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 8, 29, and 57 days post-dose, resulting in a 32%, 27%, and 19% improvement in TNSS AUC (hour 0 to 1), respectively, relative to placebo. Subjects showed improvement 8 weeks post-dose, demonstrating 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) was also 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 hypersensitivity observed. Basophil activation tests (BAT) were also performed on a subset of subjects to characterize immune modulation during treatment. Significant suppression of basophil responsiveness to birch, alder, and hazel pollen extract was observed with treatment (n=13) versus placebo (n=13) as measured by percent change from baseline in EC_{50} (birch and alder on days 8, 57, 113, all $p < 0.001$; hazel on day 8, $p < 0.001$, on day 57, $p = 0.01$). Thus, clinical efficacy of anti-Bet v 1 mAbs in birch-allergic subjects may be achieved partly through the suppression of basophils and mast cell-mediated allergic responses and may also be extended to those allergic to birch homologous trees such as alder and hazel. Pharmacokinetic (PK) and pharmacodynamic (PD) data also support the use of a single 900 mg SC dose of REGN5713-5714-5715 (300 mg per mAb) to prevent allergy symptoms and reduce the need for rescue medication for the duration of birch pollen season.

VV-RIM-00121234-2.0 Approved - 28 Sep 2020 GMT-5:00

In summary, these data provide proof of principle evidence that direct administration of allergen-specific mAbs may offer a rapid and effective approach to reducing allergic symptoms. Utilizing human mAbs such as REGN5713-5714-5715 to treat birch allergy may overcome several limitations currently hampering SIT. As compared to SIT, blocking mAbs may:

- Be safer: As the allergic subject is not exposed to native allergen, there is less risk of hypersensitivity events related to treatment.
- Have a faster onset of action: For example, a single SC dose of 900 mg REGN5713-5714-5715 demonstrated clinical efficacy after 8 days (the earliest time point evaluated).
- Offer more predictable efficacy: SIT efficacy is variable depending on how well the patient tolerates up dosing.
- Offer more convenience: A single SC dose may treat allergic symptoms for the entire birch pollen season. The patient would not be constrained to a rigorous weekly or monthly schedule as is the case for SIT.
- Potentially broaden benefit to include allergic reactions induced by birch-tree homologous pollens and/or birch related foods.
- Offer an effective treatment option to patients with more persistent or uncontrolled asthma who may have previously been contraindicated to receive SIT.

This phase 3 randomized, double-blind, placebo-controlled study will assess the efficacy of REGN5713-5714-5715 to reduce allergic rhinitis and conjunctivitis symptoms and the use of rescue medications in the field during birch pollen season. Additional background information on the study drug and development program can be found in the Investigator's Brochure.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective is to assess the reduction of allergic symptoms as measured by combined symptom and medication score (CSMS) during birch pollen season after a single dose of REGN5713-5714-5715 versus placebo.

2.2. Secondary Objectives

The secondary objectives are:

- To assess the reduction of allergic symptoms and use of allergy-relieving medications after a single dose of REGN5713-5714-5715 versus placebo, as measured by the total symptom score (TSS), total nasal symptom score (TNSS), total ocular symptom score (TOSS), and daily medication score (DMS)
- To evaluate the safety and tolerability of REGN5713-5714-5715, including the incidence of hypersensitivity reactions and local injection site reactions
- To evaluate the reduction in early allergic response to birch allergen after a single dose of REGN5713-5714-5715 versus placebo, as measured by SPT mean wheal diameter
- To determine systemic exposure of total antibody (ie, free and antigen-bound) in the form of concentration of REGN5713, REGN5714, and REGN5715 in serum
- To assess the immunogenicity to REGN5713, REGN5714, and REGN5715 in subjects after a single dose of REGN5713-5714-5715
- To evaluate "well days"

  Note: "Well days" are defined as days when the TSS is ≤2 without the use of anti-allergy rescue medications.

2.3. Exploratory Objectives

The exploratory objectives are:

- To assess asthma control as measured by the asthma control questionnaire (ACQ-5)
- To assess quality of life as measured by the rhinoconjunctivitis quality of life questionnaire (RQLQ [S])
- To evaluate the reduction in early allergic response to birch homologous allergens (alder and oak) as measured by SPT mean wheal diameter
- To assess the relationship between allergy sensitization status to Bet v 1 or birch pollen at screening (as measured by serum allergen specific-IgE [sIgE]) and clinical response to REGN5713-5714-5715 treatment
- To assess serum sIgE levels against Bet v 1 and birch pollen during birch pollen season to evaluate the relationship between the response to REGN5713-5714-5715 and change in sIgE levels in-season
- To assess the inhibitory effect of REGN5713-5714-5715 on the binding of endogenous serum IgE to birch allergen in an in vitro assay; to assess whether the degree of inhibition correlates with clinical improvement
- To assess sIgE levels against other allergens (eg, Bet v 2, alder and oak) at screening and to evaluate the relationship between response to REGN5713-5714-5715 and poly-allergic status

VV-RIM-00121234-2.0 Approved - 28 Sep 2020 GMT-5:00

- To assess additional subclasses of serum antibodies (eg, total IgG and IgG4 against birch pollen and Bet v 1) to evaluate the relationship between endogenous anti-Bet v 1 antibodies and response to REGN5713-5714-5715
- To assess the reduction in PFAS and related symptoms as measured by pollen food allergy symptom questionnaire (PFASQ)
- To assess patient rating of severity of seasonal allergy symptoms as measured by patient global impression of severity (PGI-S)

3. HYPOTHESIS AND RATIONALE

3.1. Hypothesis

A single SC dose of REGN5713-5714-5715 is more effective than placebo in the reduction of CSMS during birch pollen season.

Refer to Section 11.1 for the statistical hypothesis.

3.2. Rationale

3.2.1. Rationale for Study Design

Study design and duration

This is a phase 3 multi-center, randomized, double-blind, placebo-controlled, parallel group study to assess the efficacy of anti-Bet v 1 mAbs (REGN5713-5714-5715) to reduce allergic rhinitis and conjunctivitis during birch pollen season. The study will last approximately 28 weeks, including screening (refer to Table 1 for a schedule of events). The actual duration of the study will vary depending on the start, peak, and end dates of the local birch pollen season for each study site, which will be variable across different geographies (refer to Section 9.2.2):

- **Screening**: Generally healthy male and female subjects 18 years and older with a history of birch allergy for at least 2 years will undergo screening visits before the onset of the birch pollen season. Subjects will be asked to refrain from taking specific prohibited medications within the specified period preceding screening (refer to Section 8.9.1).
- **Randomization**: Candidate subjects who meet all inclusion and no exclusion criteria will be randomized and receive the study drug. Randomization will be stratified based on geographical regions and sIgE levels at screening (refer to Section 8.5).
- **In-season visits**: Approximately 1 month after randomization (timing will vary based on the local pollen season), a telephone contact will occur to collect any AEs and concomitant medication information. There will be an in-clinic visit at the anticipated local peak of birch pollen season. An additional telephone contact will occur at the end of the local birch pollen season. An in-clinic visit will occur at the end of the study. Subjects will be asked to stop using specific rescue medications within 5 days of the end of study visit (refer to Section 8.9.1).

VV-RIM-00121234-2.0 Approved - 28 Sep 2020 GMT-5:00

Efficacy measurements

Subjects will record symptom scores (TNSS, TOSS) daily. Subjects will be provided with rescue medications to treat allergic symptoms during the study (refer to Section 8.2) to treat their allergic rhinitis with or without conjunctivitis. Subjects will be asked to record their daily use of rescue medications using an e-diary throughout the birch pollen season to calculate the DMS. TNSS and TOSS are scored for a combined TSS. The TSS and DMS are combined for the CSMS.

ACQ-5 will be completed weekly to assess asthma control in asthmatic subjects. To assess subject quality of life, RQLQ (S) will be assessed weekly in all subjects. In addition, PFASQ and PGI-S will be administered throughout the study to assess treatment effects on PFAS symptoms and overall patient impression of severity. Refer to Section 9.2.4 for more details on these efficacy measures.

Primary objective

The primary objective of the study is to assess the reduction of allergic symptoms as measured by CSMS during birch pollen season after a single dose of REGN5713-5714-5715 versus placebo. The primary endpoint is CSMS, averaged over the duration of the birch pollen season, in subjects who receive a single dose of REGN5713-5714-5715 versus placebo. Based on recent reviews of SLIT products, for registration, the Food and Drug Administration (FDA) expects a treatment to reduce average CSMS by at least 15% compared to placebo. The European Medicines Agency (EMA) has a set a similar standard (approximately 20% compared to placebo) based on guidance from the World Allergy Organization (WAO) task force (Canonica, 2014). As CSMS is the recommended endpoint for in-field studies for allergic rhinitis treatments, this study will provide data on the treatment effect of REGN5713-5714-5715 on the CSMS.

Secondary objectives

A secondary objective of the study is to evaluate the average TSS, TNSS, TOSS, and DMS during birch pollen season comparing subjects who receive a single dose of REGN5713-5714-5715 versus placebo.

Incidence rates of treatment-emergent AEs (TEAEs) and serious TEAEs, as well as hypersensitivity reactions and local injection site reactions, will be collected to determine safety and tolerability of REGN5713-5714-5715.

Total concentration of REGN5713, REGN5714, and REGN5715 in serum will be assessed to determine systemic exposure of total antibody (ie, free and antigen-bound) throughout the study. In addition, immunogenicity to REGN5713, REGN5714, and REGN5715, as determined by the incidence, titer and clinical impact of treatment-emergent ADA responses will be assessed.

"Well days" will also be assessed. Well days are defined as days when rescue medication is not utilized and the TSS is $\leq$2/18. This exploratory objective will provide information about the number of days a patient is not affected by their allergic rhinitis symptoms.

Exploratory objectives

Sensitization to birch and birch homologous group (alder and oak) will be assessed by SPT at screening and after a single 900 mg SC dose of REGN5713-5714-5715 or placebo.

Because these anti-Bet v 1 mAbs target Bet v 1 specifically, exploratory objectives will assess whether their efficacy is related to baseline levels of specific IgE to birch and Bet v 1. As it is known that allergen-specific IgE (sIgE) levels increase during the natural pollen season, other exploratory objectives are to determine whether efficacy is related to changes in birch and Bet v 1 sIgE. In addition, allergen sensitization to a panel of allergens, including but not limited to alder and oak, will be determined by baseline serum sIgE (cutoff value 0.35 kUa). Also, of interest is whether the treatment response is associated with circulating levels of anti-birch or anti-Bet v 1 IgG and IgG4. The regional SPT panel and sIgE panel that is performed before dosing will be analyzed to understand whether allergen sensitization to non-birch allergens is associated with treatment effect during birch pollen season.

Local tree pollen counts will be obtained to assess whether the efficacy of the anti-Bet v 1 antibody cocktail is associated with non-birch trees or other plants that may be pollinating at similar times as birch.

3.2.2. Rationale for Dose Selection

The proposed doses for this study are based on the results of Part B of the phase 1b POC, first-in-human (FIH) study, which was conducted in healthy, birch-allergic subjects. In that study, a single dose of 900 mg SC REGN5713-5714-5715 (300 mg per mAb) resulted in a significant reduction in allergic rhinitis symptoms following a nasal allergen challenge for at least 2 months post-dose. Additionally, reduction in SPT-induced skin reaction was maintained for approximately up to 4 months post-dose in healthy subjects who were allergic to birch pollen. This dose was well-tolerated, with TEAEs generally of a mild to moderate severity, and occurred in similar rates in the placebo and REGN5713-5714-5715 treatment groups.

REGN5713-5714-5715 exhibited linear PK. Throughout the duration of the study, the concentration of total REGN5713-5714-5715 in serum was maintained above 10 mg/L, which had been identified from preclinical testing in the mouse percutaneous anaphylaxis (PCA) model as the concentration above which response to Bet v 1 was fully blocked.

Based on the above summary of safety, PK, and PD data, a single 900 mg SC dose of REGN 5713-5714-5715 (300 mg per mAb) is expected to prevent allergic symptoms and reduce the need for rescue medication for the duration of birch pollen season. Additional information on clinical and preclinical PK, PD, and safety can be found in the Investigator's Brochure.

3.2.3. Rationale for the Selected Anti-Bet v 1 Monoclonal Antibody Cocktail

Preclinical studies were conducted to determine the optimal combination of anti-Bet v 1 mAbs REGN5713, REGN5714, and REGN5715. In addition to binding assays showing simultaneous, non-competitive binding to Bet v 1, a BAT using peripheral blood mononuclear cells (PBMCs) from birch-allergic donors showed near complete blocking efficacy using the 3-mAb cocktail. Specifically, when REGN5713-5714-5715 were added as a cocktail, there was 97% median blocking of Bet v 1-induced basophil activation with ≥90% blockade observed in 9 of 10 donors tested. The single antibodies (REGN5713, REGN5714, and REGN5715) achieved a median of 50%, 55%, and 67% blocking, respectively, reaching ≥90% blockade in only ≤2 of 10 donors.

Regeneron has developed other mAbs against exogenous targets, including REGN1908 and REGN1909 (for Fed d 1); REGN10933 and REGN10987 (for SARS-CoV-2); atoltivimab, odesivimab, and maftivimab (for Ebola); REGN3048 and REGN3051 (for MERS-CoV), and suptavumab (for respiratory syncytial virus [RSV]). These mAbs demonstrated specificity to their exogenous targets with no significant safety findings and low incidence of hypersensitivity, injection site reactions, or immunogenicity. Similarly, REGN5713-5714-5715 was generally well-tolerated in the FIH study. In Part B of the FIH study, the overall frequency of treatment-related TEAEs was comparable between REGN5713-5714-5715 (21.9%) and placebo (25.0%), all of which were of mild or moderate intensity and resolved without sequalae. There were no SAEs or AEs leading to study discontinuation/death.

3.3. Risk-Benefit

REGN5713-5714-5715 has been administered as a single dose to 56 healthy adult subjects (24 without known birch allergy and 32 with known birch allergy) in a FIH study with no significant clinical safety findings observed. No important identified risks have been established with REGN5713-5714-5715. In birch-allergic subjects, 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. A potential benefit for subjects in this study and future patients may be to have an effective, rapid, and convenient therapeutic option with a favorable safety profile to prevent and treat birch-related allergic rhinitis. In a nonclinical toxicology study conducted in monkeys, REGN5713-5714-5715 was well tolerated at significantly higher doses than are planned for clinical evaluation.

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 (SMT) will monitor blinded safety data on an ongoing basis to assess the risk-benefit profile of REGN5713-5714-5715 (refer to Section 6.3.1). Additionally, an Independent Data Monitoring Committee (IDMC) will be involved in the review of unblinded data in an ongoing manner (refer to Section 6.3.2).

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 patients 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 patients 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.

4. ENDPOINTS

4.1. Primary Endpoint

The primary endpoint is the daily CSMS, averaged over the duration of the birch pollen season, in subjects who receive a single dose of REGN5713-5714-5715 versus placebo.

4.2. Secondary Endpoints

The secondary endpoints are:

- TSS, TNSS, and TOSS, averaged over the duration of the birch pollen season, in subjects who receive a single dose of REGN5713-5714-5715 versus placebo
- DMS, averaged over the duration of the birch pollen season, in subjects who receive a single dose of REGN5713-5714-5715 versus placebo
- Incidence of TEAEs and serious TEAEs throughout the study
- Change and percent change from baseline to the end of study in birch SPT mean wheal diameter in subjects who receive a single dose of REGN5713-5714-5715 versus placebo
- Total REGN5713, REGN5714, and REGN5715 concentration in serum over the study duration
- Incidence of treatment emergent anti-drug antibodies (ADAs) to REGN5713, REGN5714, or REGN 5715 throughout the study
- The number of “well days” in each of the treatment groups, where the “well days” are defined as days when rescue medication is not utilized and the TSS is ≤2/18

VV-RIM-00121234-2.0 Approved - 28 Sep 2020 GMT-5:00

4.3. Exploratory Endpoints

The exploratory endpoints are:

- ACQ-5, averaged over the duration of the birch pollen season, for REGN5713-5714-5715 versus placebo
- RQLQ (S), averaged over the duration of the birch pollen season, for REGN5713-5714-5715 versus placebo
- Change and percent change from baseline to the end of study in SPT mean wheal diameter for birch homologous/cross-reactive allergens in REGN5713-5714-5715 versus placebo
- Baseline allergen-specific IgE levels and correlation with average CSMS, TSS, TNSS, TOSS, DMS during birch pollen season
- Change and percent change from baseline to the peak of birch pollen season in allergen-specific IgE
- Change in inhibitory effect on serum IgE to birch allergen
- Number of baseline sensitizations to other allergens (poly/mono-sensitization status, based on allergen-specific IgE levels) and correlation with CSMS, TSS, TNSS, TOSS, and DMS, averaged over the duration of the birch pollen season
- Baseline serum antibody levels and correlation with CSMS, TSS, TNSS, TOSS, and DMS, averaged over the duration of the birch pollen season
- To assess the reduction in PFAS and related symptoms, as measured by PFASQ, from baseline to end of study
- To assess patient rating of severity of seasonal allergy symptoms, as measured by PGI-S, from baseline to end of study

5. STUDY VARIABLES

5.1. Demographic and Baseline Characteristics

Baseline characteristics will include standard demography (eg, age, race, weight, height, etc), medical history, medication history, asthma history, SPT mean wheal diameter, and serum sIgE levels for each subject.

5.2. 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), RQLQ (S), PFASQ, ACQ-5 (in subjects with a history of asthma), and PGI-S.

5.3. Safety Variables

Safety variables include AEs, vital signs, physical examinations, electrocardiogram (ECG), and laboratory safety tests.

5.4. Pharmacokinetic Variables

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

5.5. Immunogenicity Variables

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

5.6. Pharmacodynamic and Other Biomarker Variables

Exploratory biomarker variables include, but not be limited to: serum total IgE, serum sIgE for birch and Bet v 1, serum sIgE for concomitant allergens and homologous allergens, SPT results for birch, birch homologous, and other common allergens.

These results may be reported outside of the clinical study report (CSR).

5.7. Other Variables

Outdoor pollen counts will be measured daily by the study site or by a vendor during the expected pollen season using a pollen sampler.

6. STUDY DESIGN

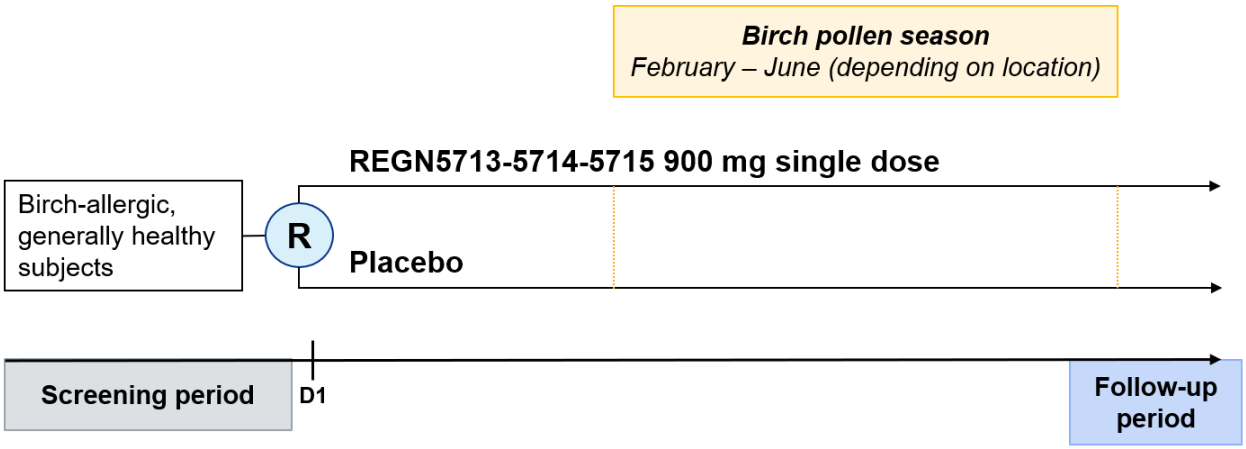
6.1. Study Description and Duration

This is a phase 3 multi-center, randomized, double-blind, placebo-controlled, parallel group study to assess the efficacy of REGN5713-5714-5715 to reduce allergic rhinitis and conjunctivitis symptoms and the use of rescue medications during birch pollen season.

The total study duration is approximately 28 weeks including screening, dependent on the start and end times of the local birch pollen season (Figure 1). The length of birch pollen season will vary based on geography. Approximately 300 birch-allergic subjects will be randomized 1:1 to REGN5713-5714-5715 or placebo (refer to Section 8.1 for more details).

Efficacy will be evaluated by assessing the reduction of allergic nose and eye symptoms and the reduction in the use of allergy rescue medications during birch pollen season, after a single SC dose of REGN5713-5714-5715 or placebo. The incidence and severity of TEAEs, including hypersensitivity reactions and local injection site reactions, will also be assessed. Total concentration in serum and immunogenicity of REGN5713, REGN5714, and REGN5715 will be measured at the sampling times specified in Table 1.

Figure 1: Study Flow Diagram



6.1.1. Study Stopping Rules

If there are significant safety concerns based on an ongoing assessment by the IDMC or a Regeneron SMT, a recommendation may be made to temporarily pause, alter, or terminate the study. Once SMT or IDMC recommendations have been received, further discussions and consultation with Regeneron Safety Oversight Committee (RSOC) may be conducted to determine if these or other actions should be taken. Refer to Section 6.3.1 and Section 6.3.2 for more information on the SMT and IDMC, respectively.

6.1.2. End of Study Definition

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

6.2. Planned Interim Analysis

No formal interim analysis will be conducted.

A description of the statistical methods to be employed is in Section 11.5, and blinding implications are discussed in Section 8.6.

6.3. Study Committees

6.3.1. Safety Monitoring Team

A Regeneron SMT will meet periodically to review blinded safety data as needed. The team may be comprised of the Medical/Study Director, a Global Patient Safety representative, representatives from Biostatistics and Data Management, as well as representatives from Clinical Operations and Regulatory Affairs. The data to be reviewed will include, but are not limited to:

- Treatment-emergent adverse events that result in an early study withdrawal
- Serious adverse events
- Severe AEs
- Selected laboratory tests, as deemed appropriate by the SMT
- Additional adverse events of special interest (AESIs), as defined in Section 10.1.3

Appropriate action, if needed, will be taken based upon this review and in consultation with the Medical Monitor. The SMT may make a recommendation to the RSOC to halt the study or make other changes in study conduct. 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.

6.3.2. Independent Data Monitoring Committee

An IDMC will actively review data throughout the study to monitor subject 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 subject 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 subjects enrolled in these studies. All activities and responsibilities of the IDMC are described in the IDMC charter.

7. SELECTION, WITHDRAWAL, AND REPLACEMENT OF SUBJECTS

7.1. Number of Subjects Planned

Approximately 300 adult subjects will be enrolled at multiple sites in Canada, United States, and Europe.

7.2. Study Population

Generally healthy adult male and female subjects with birch allergy will be enrolled.

7.2.1. Inclusion Criteria

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

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

7.2.2. 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 trial
2. Recurrent or chronic rhinitis or sinusitis not associated with birch pollen season, or due to daily contact with other allergens causing symptoms that are expected to coincide with birch pollen season, as assessed by the investigator
3. Subjects who anticipate major changes in allergen exposure in their home or work environments that are expected to coincide with study assessments, per investigator discretion
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. Participants may be re-evaluated for eligibility after symptoms resolve
5. Documentation of active SARS-CoV-2 infection

   Note: A subject with a documented, positive PCR or serology test for SARS-CoV-2 may be enrolled, provided that the subject has:

   - *Recovered from COVID-19 (all COVID-19-related symptoms and major clinical findings which can potentially affect the safety of the patient should be resolved to baseline),* ***and***
   - *Had 2 negative results from a health authority-authorized nucleic acid amplification (PCR) test for COVID-19 taken at least 48 hours apart*
6. Abnormal lung function as judged by the investigator with FEV_1 <70% of predicted at screening or randomization
7. A clinical history of moderate to severe asthma with 2 or more asthma exacerbations requiring hospitalizations or systemic corticosteroids in the previous year

8. History of significant, recurrent sinusitis, defined as at least 3 episodes requiring antibiotic treatment per year for the last 2 years prior to screening
9. History of nasal polyps
10. Active lung disease other than asthma
11. History of birch or related tree allergy immunotherapy (SCIT, SLIT, or oral immunotherapy) within 5 years prior to screening
12. Use of anti-IgE or other biological therapy that modifies Type 2 inflammation within 6 months prior to screening
13. Allergen-specific immunotherapy with any allergen other than birch within 6 months prior to screening
14. History of clinically significant cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematological, psychiatric, or neurological disease that, in the opinion of the study investigator, might confound the results of the study or pose an additional risk to the subject by study participation
15. Any physical examination findings and/or history of any illness that, in the opinion of the study investigator, might confound the results of the study or pose an additional risk to the subject by study participation
16. 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, including but not limited to:
    a. Clinically significant/active underlying hepatobiliary disease
    b. Abnormal laboratory values at screening, such as:
        - Neutrophils $<1.5 \times 10^3/\mu L$
        - Platelets <100,000 cells/mm^3
17. History of drug or alcohol abuse within a year prior to screening
18. 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
19. Clinically significant abnormal ECG in the screening period as assessed by the investigator
20. History of acute hypersensitivity and/or anaphylaxis to excipients in the study medication or allergies that could represent a substantial risk to the subject in the opinion of the investigator
21. Treatment with an investigational drug or therapy within 2 months or at least 5 half-lives (if known), whichever is longer
22. Unwilling or unable to comply with the permitted and prohibited medication specifications for this study

23. Member of the clinical site study team and/or his/her immediate family, unless prior approval granted by the Sponsor
24. Pregnant or breastfeeding women
25. Women of childbearing potential (WOCBP)* who are unwilling to practice highly effective contraception prior to study drug administration, during the study, and for at least 6 months after the dose of study medication. 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),
    e. and/or 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.

26. Sexually active men who are unwilling to use the following forms of medically acceptable birth control during the study drug follow-up period and for 6 months after the study drug administration: vasectomy with medical assessment of surgical success ***or*** consistent use of a condom. Sperm donation is prohibited during the study and for up to 9 months after the study drug administration.

7.3. Premature Withdrawal from the Study

A subject 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 subject from the study if it is no longer in the interest of the subject to continue in the study, or if the subject's continuation in the study places the scientific outcome of the study at risk (eg, if a subject does not or cannot follow study procedures). An excessive rate of withdrawals would render the study uninterpretable; therefore, unnecessary withdrawal of subjects should be avoided.

Subjects who are withdrawn prematurely from the study will be asked to complete the early termination visit, as described in Section 9.1.2.

7.4. Replacement of Subjects

Subjects who are randomized, receive study drug, and/or are prematurely discontinued from study will not be replaced.

8. STUDY TREATMENTS

8.1. Investigational and Reference Treatments

REGN5713, REGN5714, and REGN5715 are provided individually in open-label vials in carton. Each 20 mL vial contains 265 mg of lyophilized protein. Matching placebo is provided as a lyophilized powder in 20 mL open-label vials in carton.

Instructions are provided in the pharmacy manual to create the following treatments:

- Single SC dose of REGN5713-5714-5715 900 mg (300 mg per mAb)
- Single SC dose of matching placebo that replaces REGN5713-5714-5715

Randomization will be stratified as described in Section 8.5.

8.2. Rescue Treatments

Subjects will be provided with the following medications to treat allergic symptoms during the study:

- Desloratadine 5 mg (second generation antihistamine)
- Olopatadine 1 mg/mL (antihistamine eye drop)
- Mometasone furoate 50 ug/dose (intranasal steroid)

From the time of study drug dosing throughout the birch pollen season, subjects will be asked to record their daily medication use using an e-diary, including information regarding which medications was used and the amount of the pre-specified medications that was used. Utilization of rescue medications should be initiated when subjects reach a symptoms threshold of approximately TSS ≥4/18. Subjects will be provided with training to understand the severity of symptoms associated with a TSS ≥4/18.

Subjects should be instructed not to utilize rescue medications in the anticipation of the birch pollen season. Subjects should also be instructed not to utilize antihistamines (ie, desloratadine or olopatadine) for 5 days before the end of study visit.

For skin prick tests

Local allergen exposure through SPT typically only results in local allergic reactions that dissipate within a short time. Uncommonly, systemic immediate or late allergic reactions can occur. Such reactions should 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 should be given after study endpoint data collection is obtained (eg, after the skin wheals are measured after application of allergen).

8.3. Dose Modification and Study Treatment Discontinuation Rules

This is a single dose study. Dose modification for an individual subject is not allowed. Study treatment discontinuation is not applicable to this study.

8.4. Management of Acute Reactions

8.4.1. Acute Injection Reactions

8.4.1.1. Systemic Injection Reactions

Emergency equipment and medication for the treatment of systemic reactions must be available for immediate use if required for treatment. All injection reactions must be reported as AEs (as defined in Section 10.2.1) and graded using the grading scales as instructed in Section 10.2.4.

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.

8.4.1.2. Local Injection Site Reactions

Local injection site reactions must be reported as AEs and graded according to Section 10.2.4.

8.5. Method of Treatment Assignment

Subjects will be randomized according to a central randomization scheme provided by interactive response technology (IRT) to the designated study pharmacist (or qualified designee) as per Table 1.

Subjects will be randomized 1:1 as below (refer to Section 8.1 for more details):

- REGN5713-5714-5715
- Matching placebo

Randomization will be stratified based on the following:

- Serum specific birch pollen IgE levels at screening (<17.5 kUa/L versus ≥17.5 kUa/L)
- **In North America only:** Serum specific oak pollen IgE levels at screening (<0.7 kUa/L versus ≥0.7 kUa/L)
- Geographical region (North America versus Europe)

8.6. Blinding

Study subjects, the principal investigators, and study site personnel (excluding the unblinded pharmacy staff) will remain blinded to all randomization assignments 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 subject randomization assignments.

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.

8.7. Emergency Unblinding

Unblinding of treatment assignment for a subject 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 subject's treatment assignment.

- If unblinding is required:
  - Only the investigator will make the decision to unblind the treatment assignment
  - Only the affected subjects 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/unmask the subject. Unblinding is performed using the interactive voice/web response system (IVRS/IWRS) which will notify Regeneron
  - The investigator will notify Regeneron and/or designee as soon as possible after unblinding the subject

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 subject'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.

8.8. Treatment Logistics and Accountability

8.8.1. Packaging, Labeling, and Storage

A medication numbering system will be used to label blinded 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 subject.

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

8.8.2. 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 at site with approval by Regeneron or returned for destruction.

Rescue medications may be procured and distributed by the study site.

8.8.3. 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 subject
- Returned from each subject (if applicable)
- 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.

8.8.4. Treatment Compliance

As the investigational study drug will be administered in the clinic, treatment compliance is not applicable.

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

8.9. Concomitant Medications

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.

8.9.1. Prohibited Medications

Preceding screening

Use of the below concomitant medications is prohibited within the following time period preceding the screening and randomization visits:

- Topical or systemic first generation H1 antihistamines (eg, diphenhydramine and chlorpheniramine) (3 days)
- Second generation and long-acting H1 antihistamines (eg, cetirizine) (5 days)
- Cromoglycates (14 days)
- Leukotriene modifiers (30 days)
- Intranasal corticosteroids (14 days)
- Systemic steroid treatment (30 days)
- Topical steroids, with the exception of hydrocortisone (≤1%) (48 hours)
- Anticholinergics (eg, Ipratropium [Atrovent 40 μg]) (12 hours)
- Intramuscular corticosteroids (3 months prior to screening and during the study)
- Systemic or topical calcineurin inhibitors (14 days prior to screening and during the study)
- Topical or oral decongestants (72 hours)
- Tricyclic antidepressants/typical antipsychotics (14 days)
- Birch-specific allergen immunotherapy (5 years)
- Immune-directed biologic therapies that would interfere with Type 2 allergic disease or suppress the immune system (6 months)
- Long-acting anti-muscarinic agents (7 days)
- Ultra-long-acting β-agonists (eg, indacaterol, vilanterol, olodaterol) (14 days)
- Methylxanthines (eg, oral theophylline) (24 hours)

Preceding the end of study visit

Use of the below medications is prohibited within the following time period preceding the end of study visit. Refer to Section 8.2 for more information on rescue medications:

- Desloratadine (5 days)
- Olopatadine (5 days)
- Topical steroids, with the exception of hydrocortisone (≤1%) (48 hours)

Any time throughout the study

- Anticholinergics
- Leukotriene modifiers
- Cromoglycates
- Topical or oral decongestants
- Systemic steroid treatment
- Tricyclic antidepressants/typical antipsychotics
- Any allergen immunotherapy
- Immune-directed biologics therapies that would interfere with Type 2 allergic disease or suppress the immune system
- Methylxanthines (eg, oral theophylline)
- Anti-allergic medications (antihistamines, anti-allergic eye drops, anti-allergic nasal sprays) outside of study-related anti-allergic medications as they will be supplied as part of the study (refer to Section 8.2)

8.9.2. Permitted Medications

Use of standard-of-care medications not prohibited per Section 8.9.1 will be allowed. Treatment for acute reactions is allowed during the study (see Section 8.2).

9. STUDY SCHEDULE OF EVENTS AND PROCEDURES

9.1. 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

	SCREENING PERIOD	TREATMENT PERIOD		FOLLOW-UP PERIOD				
Study Procedure	**Screening Visit 1[1]**	**Randomization Visit 2[2-4]**	**Visit 3 Tel.**	**Visit 4 Tel.**	**Visit 5[3]**	**Visit 6 Tel.**	**EOS/ET Visit 7[3]**	**Unscheduled Visit**
Day	**-84 to -7**	**1[3]**	**2**	**28[3]**	**57[3]**	**85**	**113[3]**	
Window (Days)	**+7**	**±3**		**±7**	**±14**	**±14**	**±14**	
Inclusion/exclusion[2]	X	X						
Informed consent	X							
Medical history	X[4]							
Demographics	X							
SPT for birch and birch homologous allergens and select regional or relevant allergens[1]	X						X	
Standard regional SPT for birch and other common allergens[1]	X							
FSH (in postmenopausal women)	X							
Treatment								
Randomization[2]		X						
Study drug administration[2]		X						
Efficacy								
E-diary and rescue medications dispensation/return[5]		X					X	
TNSS[6]		Daily via e-diary						
TOSS[6]		Daily via e-diary						
DMS[6]		Daily via e-diary						
ACQ-5 (in subjects with asthma)[7]		Weekly via e-diary						X
RQLQ (S)[8]		Weekly via e-diary						X
PFASQ[9]		X					X	
PGI-S[10]		X			X		X	
Safety								
Vital signs[11]	X	X[11]			X			X
Physical examination[12]	X	X					X	X
ECG	X							
AEs	X	X	X	X	X	X	X	X
Height	X							
Weight	X							
Concomitant medications	X	X	X	X	X	X	X	X
Spirometry	X[4]	X						X

	SCREENING PERIOD	TREATMENT PERIOD		FOLLOW-UP PERIOD				
Study Procedure	**Screening Visit 1[1]**	**Randomization Visit 2[2-4]**	**Visit 3 Tel.**	**Visit 4 Tel.**	**Visit 5[3]**	**Visit 6 Tel.**	**EOS/ET Visit 7[3]**	**Unscheduled Visit**
Day	**-84 to -7**	**1[3]**	**2**	**28[3]**	**57[3]**	**85**	**113[3]**	
Window (Days)	**+7**	**±3**		**±7**	**±14**	**±14**	**±14**	
Laboratory Testing								
Hematology	X[4]				X		X	X
Blood chemistry	X[4]				X		X	X
Pregnancy test, urine (in WOCBP)[13]		X[13]		X[13]	X	X[13]	X	X
Pregnancy test, serum (in WOCBP)[13]	X							X
Urinalysis	X							X
Serum total IgE		X			X		X	
Serum sIgE for birch pollen and Bet v 1 and other regional or relevant allergens	X	X			X		X	X
Serum sIgE for concomitant and homologous allergens		X			X		X	
Interference assay, serum		X						
Pharmacokinetics and Immunogenicity								
PK[14]		X[14]			X		X	X
ADA[14]		X[14]					X	X
Biomarkers and Pharmacogenomics								
FBR samples, serum and plasma (optional)[15]		X			X		X	
Genomic DNA sample (optional)[16]		X[16]						

ACQ-5=asthma control questionnaire-5; ADA=anti-drug antibody; AE=adverse event; DMS=daily medication score; ECG=electrocardiogram; EOS=end of study; ET=early termination; FBR=future biomedical research; FSH=follicle stimulating hormone; PFASQ=pollen food allergy symptom questionnaire; PGI-S=patient global impression of severity; PK=pharmacokinetics; RQLQ (S)=standardized rhinoconjunctivitis quality of life questionnaire; sIgE=allergen-specific immunoglobulin E; SPT=skin prick test; Tel=telephone; TNSS=total nasal symptom score; TOSS=total ocular symptom score; WOCBP=women of childbearing potential.

9.1.1. Footnotes for the Schedule of Events Table

1. Screening SPT for birch, birch homologous trees, and other common allergens will be performed as described in the study manual. Skin prick test for birch should be performed prior to other screening assessments. If screening SPT for birch is negative (ie, mean wheal diameter <5 mm greater than a negative control), then other screening visit procedures do not need to be performed as the subject will have failed screening (refer to Section 7.2.1 Inclusion Criteria, #3).
2. Randomization may occur within 1 day prior to study drug administration. All safety assessments performed at screening must be normal and checked against the inclusion/exclusion criteria prior to study drug administration.
3. The timing of in-clinic visits may vary for each study site, depending on the start, peak, and end dates of the local birch pollen season (as determined by local pollen counts; refer to Section 9.2.2). The randomization visit will be scheduled approximately 2 weeks before the start of birch pollen season, and the end of study (EOS) visit approximately 16 weeks after the randomization visit (depending on the duration of the local birch pollen season). In addition, visit 5 will be scheduled to occur within 2 weeks of the anticipated local peak of the birch pollen season.
4. If randomization occurs >60 days after the screening visit, medical history, blood chemistry, hematology, and spirometry must be repeated prior to randomization.
5. E-diary and rescue medications will be dispensed at the randomization visit. E-diary and any unused rescue medications will be returned at the EOS visit. Refer to Section 8.2 for more information on rescue treatments.
6. TNSS, TOSS, and DMS will be recorded daily via e-diary, starting at the randomization visit until EOS. Refer to Section 9.2.4.1, Section 9.2.4.2, and Section 9.2.4.4 for procedural details.
7. In asthmatic subjects, ACQ-5 scores will be recorded weekly via e-diary, starting from the randomization visit until EOS. Refer to Section 9.2.4.6 for procedural details.
8. In all subjects, RQLQ (S) scores will be recorded weekly via e-diary starting from the randomization visit until EOS. Refer to Section 9.2.4.7 for procedural details. In asthmatic subjects, the weekly RQLQ (S) and ACQ-5 assessments may be performed on the same day.
9. Refer to for Section 9.2.4.8 procedural details.
10. Refer to for Section 9.2.4.9 procedural details.
11. Vital signs include systolic and diastolic blood pressure, respiratory rate and heart rate. Vital signs will be collected in a seated position. At the randomization visit, vital signs are taken prior to PK blood draw, prior to study drug administration, and at 2 hours (±10 min) after completion of the injection.
12. A full physical exam must be performed at screening, at baseline, and at EOS. A limited physical exam will be done at remaining visits depending on presentation of the subject.

13. If the urine pregnancy test is positive, the site must perform a serum pregnancy test for confirmation. At the randomization visit, if a serum pregnancy test must be performed, study drug cannot be administered unless the serum pregnancy test is negative. Urine pregnancy test can be performed on day -1 of the visit at the investigator's discretion.

    At-home pregnancy testing: WOCBP will be provided with urine pregnancy tests for at-home testing prior to visits 4 and 6. Study sites will collect the results by telephone at these visits. If the urine pregnancy test is positive, the site must perform a serum pregnancy test for confirmation.

14. PK and ADA samples are to be collected prior to study drug administration. In the event of suspected SAEs, such as anaphylaxis or hypersensitivity, additional samples for PK and ADA analyses may be collected as close to the event as practically possible.
15. Refer to Section 9.2.11.
16. Genomic analysis is optional for all subjects enrolling in the study. One DNA sample is to be collected at the randomization visit, but if this sample collection was omitted at baseline, it can be collected at any subsequent visit. Refer to Section 9.2.12.

9.1.2. Early Termination Visit

Subjects who are withdrawn from the study after randomization or at any time before the end of study visit will be asked to return to the study site for an early termination (ET) visit. Refer to Table 1 for assessments to be performed at an ET visit.

9.1.3. Unscheduled Visits

All attempts should be made to keep subjects 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. Refer to Table 1 for assessments to be performed at unscheduled visits.

9.2. Study Procedures

9.2.1. Procedures Performed Only at the Screening/Baseline Visit

The following procedures will be performed primarily for determining study eligibility or characterizing the baseline population: medical history, demographics, and standard regional SPT. However, these assessments may also be performed at any unscheduled visit at the investigator's discretion.

9.2.2. Pollen Counting

Local pollen levels will be monitored throughout the study by the study sites or by a vendor. The start and the end of birch pollen season will be determined for each site using current standards for defining pollen seasons, factoring in local pollen counts from each site due to regional variability in pollen seasons (Pfaar, 2017). 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.

9.2.3. Birch Allergen and Standard Regional Skin Prick Tests

An SPT with birch allergen extract and a regional SPT (such as with dust mites, grasses, other trees, including other birch homologous trees [such as alder and oak], cat, and dog) will be performed to assess sensitization status. Skin prick test data may be used to determine the relationship between birch and regional allergen sensitization at baseline and pharmacodynamic effects of REGN5713-5714-5715 to reduce allergic symptoms upon birch pollen allergen challenges. Mean wheal diameter is measured approximately 15 minutes after placement. Aside from the birch skin test requirement for enrollment, a positive response is defined by a mean wheal diameter at least 3 mm greater than a negative control.

For patients who enroll in the study, SPT will be performed as noted in Table 1 and the mean wheal diameters will be used to assess clinical responses to treatment. The allergens used for SPT will include birch pollen and 1 or 2 additional related homologous tree allergens.

9.2.4. Efficacy Procedures

Efficacy measures will be assessed at time points indicated on Table 1.

9.2.4.1. Total Nasal Symptom Score

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 congestion, itching, and rhinorrhea, and for sneezing. The TNSS will be recorded using an e-diary.

9.2.4.2. Total Ocular Symptom Score

The TOSS ranges from 0 to 6 and is based on 2 symptoms: itching/redness/gritty feeling and tearing/watering. Each of the 2 symptoms is graded 0 (absent), 1 (mild), 2 (moderate), or 3 (severe). The TOSS will be recorded using an e-diary.

9.2.4.3. Total Symptom Score

The TSS is calculated by adding the TNSS and TOSS together, for a combined TSS of 0 to 18.

9.2.4.4. Daily Medication Score

Subjects 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 as follows: desloratadine 5 mg 6 points/dose; maximum daily score 6 points, olopatadine 1 mg/mL each drop 1.5 points/drop; maximum daily score 6 points, mometasone furoate 50 ug/dose 2.0 points/spray; maximum daily score 8 points). The maximum DMS score is 20 (Calderon, 2014).

9.2.4.5. Combined Symptom and Medication Score

The CSMS is calculated by adding the DMS and TSS together, with scores ranging between 0 and 38.

9.2.4.6. Asthma Control Questionnaire

The ACQ measures the adequacy of asthma control and change in asthma control that occurs spontaneously or as a result of treatment. The ACQ-5 is comprised of 5, patient-reported items that were rated by clinicians as the most important to evaluate control: (1) awakening at night due to symptoms, (2) morning symptoms, (3) limitation of daily activities, (4) shortness of breath, and (5) wheezing. The total score ranges from 0 to 6 with higher scores denoting less asthma control. A score of ≥1.5 is considered as uncontrolled asthma. The ACQ-5 will be recorded using an e-diary.

9.2.4.7. Standardized Rhinoconjunctivitis Quality of Life Questionnaire

The RQLQ (S) has 28 questions in 7 domains: activity limitation, sleep problems, nose symptoms, eye symptoms, non-nose/eye symptoms, practical problems, and emotional function. There are 3 subject-specific questions in the activity domain that allow subjects to select 3 activities in which they are most limited by their rhinoconjunctivitis. Subjects recall how bothered they have been by their rhinoconjunctivitis during the previous week and respond to each question on a 7-point scale (0 [not impaired at all] to 6 [severely impaired]). 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 (Juniper, 1991). The RQLQ (S) will be recorded using an e-diary.

9.2.4.8. Pollen Food Allergy Symptom Questionnaire

The PFASQ will be performed at time points according to Table 1 to determine the types of food that produce an allergic reaction, the type of reaction, and how soon the reactions occur [adapted from (Geroldinger-Simic, 2011)].

9.2.4.9. Patient Global Impression of Severity

The PGI-S assesses the severity of seasonal allergy symptoms over the past 1 week. Symptom severity ranges from 0 (no symptoms), 1 (mild), 2 (moderate), and 3 (severe) symptoms.

9.2.5. Safety Procedures

Safety measures will be assessed at time points indicated on Table 1.

9.2.5.1. Vital Signs

Vital signs include systolic and diastolic blood pressure, respiratory rate and heart rate. Vital signs will be collected in a seated position. On the day of study drug administration, vital signs are taken prior to PK blood draw, prior to study drug administration, and at 2 hours (±10 min) after completion of the injection.

9.2.5.2. Physical Examination

A complete physical examination will be performed according to Table 1.

9.2.5.3. Body Weight

Body weight will be assessed using calibrated scales. Subjects should remove shoes during weight assessments. Body weight will be recorded to the nearest 0.1 kg.

9.2.5.4. Spirometry

Spirometry (American Thoracic Society [ATS]/European Respiratory Society [ERS]-compliant) as adjudicated by the site investigator, including measurements of forced vital capacity (FVC [L]), forced expiratory volume (FEV_1 [L]), FEV_1/FVC (%), peak expiratory flow (L/s), forced expiratory flow 25 to 75 (L/s), will be performed during screening and randomization to exclude any subjects with abnormal lung function and/or poorly controlled asthma.

9.2.6. Electrocardiogram

A standard 12-lead ECG will be performed at time points according to according to Table 1. Heart rate will be recorded from the ventricular rate and the PR, QRS, and QT intervals will be recorded. The ECG strips or reports will be retained with the source documentation.

To minimize variability, it is important that the patient be in a resting position for ≥10 minutes prior to the ECG evaluation. Body position should be consistently maintained for each ECG to prevent changes in heart rate.

9.2.7. Laboratory Testing

9.2.7.1. Hematology, Blood Chemistry, Pregnancy Test, and Urinalysis

Hematology, chemistry, pregnancy test, and urinalysis will be analyzed by a central laboratory. 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
- Potassium
- Chloride
- Carbon dioxide
- Calcium
- Glucose
- Albumin
- Total protein, serum
- Creatinine
- Blood urea nitrogen (BUN)
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Alkaline phosphatase
- Total bilirubin
- Triglycerides
- Uric acid

Hematology

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

Urinalysis

Color	Glucose	RBC
Clarity	Blood	Hyaline and other casts
pH	Bilirubin	Bacteria
Specific gravity	Leukocyte esterase	Epithelial cells
Ketones	Nitrite	Crystals
Protein	WBC	Yeast

Other laboratory tests

Subjects will be tested for FSH levels (postmenopausal women only) and will undergo serum and urine pregnancy testing (WOCBP only); pregnancy testing is not required of women confirmed postmenopausal. If any urine pregnancy test is positive, the site must perform a serum pregnancy test for confirmation. If a serum pregnancy test must be performed, study drug cannot be administered unless the serum pregnancy test is negative.

Samples will be collected for quantitative assessment of total and allergen-specific IgE and will be analyzed by a central laboratory.

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 10.1.1.

9.2.7.2. Serum Antibodies

Levels of anti-birch pollen sIgE and anti-Bet v 1 sIgE will be measured according to Table 1 to evaluate the relationship between clinical response to REGN5713-5714-5715 and sensitization to birch pollen and Bet v 1. After the randomization visit, the detection of anti-Bet v 1 sIgE will be inhibited by study drug REGN5713-5714-5715, therefore the data will be used to assess effective competition between endogenous sIgE and study drug.

Serum total IgE will be measured according to Table 1 to assess the overall allergic disease burden in study subjects. The results will be used to evaluate the relationship between response to REGN5713-5714-5715 and overall allergic status.

Allergen-specific IgE levels against regional allergens and common perennial allergens will be measured according to Table 1 to assess sensitization status to other common allergens and to evaluate the relationship between response to REGN5713-5714-5715 and poly/mono-sensitization (Van Ree, 1999).

Additional subclasses of serum antibodies (eg, IgG and IgG4 against birch pollen and Bet v 1) will be measured at screening. These results will be part of exploratory research analysis and will be included in an exploratory biomarker report.

9.2.8. Drug Concentration and Measurements

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

Any unused samples may be used for exploratory research.

9.2.9. Immunogenicity Measurements and Samples

Samples for ADA assessment for REGN5713, REGN5714 and REGN5715 will be collected at time points listed in Table 1. Anti-REGN5713, REGN5714, and REGN5715 neutralizing antibodies (NAb) analysis may be performed on ADA-positive serum samples. The overall immunogenicity risk will be taken into consideration to assess the need for NAb analysis. Serum samples will be banked, if NAb analysis is to be conducted at a later time.

Any unused samples may be used for exploratory research.

9.2.10. Pharmacodynamic and Exploratory Biomarker Procedures

Blood samples will be obtained for additional exploratory research to better understand the effects of various anti-Bet v 1 antibodies on birch allergy. This will include the assessment of effective competition between REGN5713, REGN5714, and REGN5715 (either alone or in combination) and endogenous sIgE in serum for allergen binding in an in vitro interference/ inhibition assay.

These results will be part of exploratory research analysis and will be included in an exploratory biomarker report, which will not be described in the clinical study report.

9.2.10.1. Exploratory Biomarker Research

Blood samples will be obtained for additional exploratory research to better understand the effects of various anti-Bet v 1 antibodies on birch allergy. This will include the assessment of effective competition between REGN5713, REGN5714, REGN5715 (either alone or in combination), and endogenous serum IgE for allergen binding in an in-vitro interference/ inhibition assay.

Additional blood samples will be collected for measuring subclasses of serum antibodies (eg, IgG and IgG4 against birch pollen and Bet v 1) at screening.

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

9.2.11. Future Biomedical Research (Optional)

Subjects 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 will be collected for FBR. Residual biomarker 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.

9.2.12. Pharmacogenomic Analysis (Optional)

Subjects 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 (predose) but can be collected at a later study visit. DNA sample 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.

10. SAFETY EVALUATION AND REPORTING

10.1. Recording and Reporting Adverse Events

10.1.1. General Guidelines

The investigator must promptly record all clinical events occurring during the study data collection, from the time of signing the ICF to the end of on-treatment period (see Section 11.4.5.1). 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 subject. Adverse events may be directly observed, reported spontaneously by the subject, or by questioning the subject at each study visit. Subjects 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 10.2. 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.

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 serious adverse event (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 informed consent form) 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 10.2 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 10.1.2 and Section 10.1.3.

10.1.2. 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 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 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.

10.1.3. 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 systemic or severe hypersensitivity reactions and severe injection site reactions.
- **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 or female partner of a male, during the study or within 6 months of the last dose of study drug. Any complication of pregnancy affecting a female study subject or female partner of a male study subject, 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.

10.2. Definitions

10.2.1. Adverse Event

An AE is any untoward medical occurrence in a subject 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 which 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).

10.2.2. 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 subject is a passenger).
- Is **life-threatening** – in the view of the investigator, the subject 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 subject 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.

10.2.3. 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.

10.2.4. Severity

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

- **Mild:** Does not interfere in a significant manner with the subject 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 subject
- **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 subject's health. Treatment for symptom may be given and/or subject hospitalized

VV-RIM-00121234-2.0 Approved - 28 Sep 2020 GMT-5:00

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 ER visit or hospitalization; necrosis or exfoliative dermatitis

10.2.5. Causality

The investigator must provide causality assessment as whether or not there is a reasonable possibility that the drug caused the adverse event, 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.

The following factors should be considered when assessing causality:

- Temporal relationship: time to onset vs time drug was administered
- Nature of the reactions: immediate versus long term
- Clinical and pathological features of the events
- Existing information about the drug & same class of drugs
- Concomitant medications
- Underlying and concurrent illnesses
- Response to dechallenge (drug discontinuation) or dose reduction
- Subject'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, subject's clinical (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, subject'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, subject's clinical (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, subject's clinical state (eg, disease under study, concurrent diseases, and concomitant medications) or other external factors.

10.3. Safety Monitoring

The investigator will monitor the safety of study subject 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.

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

During the study, the Sponsor and/or the contract research organization (CRO) will inform health authorities, IECs/IRBs, and the participating investigators of any SUSARs (Suspected Unexpected Serious Adverse Reactions) occurring in other study centers or other studies of the active study drug (REGN5713-5714-5715), 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 Institutional Review Board (IRB)/Ethics Committee (EC) unless delegated to the Sponsor.

Event expectedness for study drug (REGN5713-5714-5715) 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 Clinical Study Report to health authorities and IECs/IRB as appropriate.

11. STATISTICAL PLAN

This section provides the basis for the statistical analysis plan (SAP) for the study. The SAP will be revised prior to the end of the study to accommodate amendments to the clinical study protocol and to make changes to adapt to unexpected issues in study execution and data that may affect the planned analyses. The final SAP will be issued before the first database lock.

Endpoints are listed in Section 4. Analysis variables are listed in Section 5.

11.1. Statistical Hypothesis

For comparison of a single dose of REGN5713-5714-5715 to placebo, the following hypothesis of the primary endpoint (average CSMS over birch pollen season) will be tested:

- **H0**: There is no difference in CSMS, averaged over the duration of the birch pollen season, in subjects receiving REGN5713-5714-5715 and placebo.
- **H1**: The CSMS, averaged over the duration of the birch pollen season, is statistically significant different in subjects receiving REGN5713-5714-5715 and placebo.

The statistical hypothesis above is to test in a hierarchical procedure for primary efficacy and secondary endpoints at 2-sided 5% significance level.

11.2. Justification of Sample Size

This study is powered to detect differences between REGN5713-5714-5715 and placebo on the primary endpoint of the average CSMS during birch pollen season. A sample size of 150 enrolled subjects per arm gives 90% power to detect a mean difference in average CSMS of 1.9 (30% reduction from placebo) in REGN5713-5714-5715 (mean CSMS = 4.4) and placebo (mean CSMS = 6.3), assuming a common standard deviation in CSMS of 4.5. The minimum significant difference in CSMS is 1.14, or approximately an 18% reduction from placebo. This sample size calculation assumes a 20% drop out rate (30 subjects per arm) and a two-sample t-test with two-sided alpha of 0.05. Estimates of mean and variability of the CSMS are based on pooled estimates across several field studies for grass immunotherapy, 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.

11.3. Analysis Sets

11.3.1. Efficacy Analysis Sets

The full analysis set (FAS) includes all randomized subjects who had at least 1 e-diary entry with symptoms or medication score recorded during the birch pollen season; it is based on the treatment allocated (as randomized). Efficacy endpoints will be analyzed using the FAS.

The per protocol set (PPS) includes all subjects in the FAS except for those who are excluded due to specified important protocol violations. Final determination of the PPS will be made prior to the database lock and will be outlined in the SAP.

11.3.2. Safety Analysis Set

The safety analysis set (SAF) includes all randomized subjects who received any study drug; it is based on the treatment received (as treated). Treatment compliance/administration and all clinical safety variables will be analyzed using the SAF.

11.3.3. Pharmacokinetic Analysis Set

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

11.3.4. Immunogenicity Analysis Set

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

11.4. Statistical Methods

For continuous variables, descriptive statistics will include the following information: the number of subjects 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.

11.4.1. Subject Disposition

The following will be provided:

- The total number of screened subjects: met the inclusion criteria regarding the target indication and signed the ICF
- The total number of randomized subjects: received a randomization number
- The total number of subjects who discontinued the study, and the reasons for discontinuation
- The total number of subjects who discontinued from study treatment, and the reasons for discontinuation
- A listing of subjects treated but not randomized, subjects randomized but not treated, and subjects randomized but not treated as randomized
- A listing of subjects prematurely discontinued from treatment, along with reasons for discontinuation

11.4.2. Demography and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group, and by all subjects combined.

11.4.3. Efficacy Analyses

11.4.3.1. Primary Efficacy Analysis

The efficacy endpoints will be analyzed using the FAS defined in Section 11.3.1.

The primary analysis will focus on the comparison between the REGN5713-5714-5715 arm and placebo arm. The average CSMS during birch pollen season will be compared in subjects receiving REGN5713-5714-5715 and subjects receiving placebo using a linear mixed-effect model, with the treatment group and randomization stratification factors (as described in Section 8.5) as fixed effects and pollen region as a random effect, to account for potential differences in birch pollen seasons based on the geographical location of each pollen region. Clinical sites will be pooled into different pollen regions which will be specified in the SAP. Subjects with at least 1 day of post-baseline diary record with symptom and medical score (SMS) will be included. The CSMS will be calculated on all available data during the birch pollen season. The primary analysis will be based on the available values of daily symptom score and daily medication score to calculate the average CSMS and no imputation will be needed for the primary endpoint during the birch pollen season.

The average CSMS will be calculated based on daily symptom score (TNSS and TOSS, max of 18/day) and daily medication score (max of 20/day) recorded over the duration of the birch pollen season. The start and end of the birch pollen season will be defined for each site based on the local birch pollen counts. Only days with observed data (including any available data of daily entries prior to subject discontinuation) will be included in the calculation of the average CSMS.

Any rescue medication use will not be set to missing for the CSMS, but relevant prohibited medications (as listed in Section 8.9.1) that may have a long-term impact on symptom measurements will result in subsequent symptoms and medication scores to not be utilized in the CSMS for that subject for a specified period of time (determined by medication type). Relevant prohibited medications and corresponding time frames for censoring will be specified in the SAP.

In addition, as a supportive analysis, a non-parametric analysis using the Wilcoxon rank-sum test will be compared 2 group median in term of risk reduction from placebo for the primary endpoint of the average CSMS during the birch pollen season between REGN5713-5714-5715 and placebo. The Hodges-Lehmann estimator of median treatment difference for 95% confidence interval will be provided. With respect to the missing data handling of daily entries, sensitivity analyses may be performed to evaluate the robustness of the conclusion drawn based on the main model for primary analysis considering a minimum number of daily entries during the birch pollen season. Details of the sensitivity analyses will be provided in the SAP.

Subgroup analysis (eg, by baseline anti-birch pollen IgE level <17.5 kUa/L versus ≥17.5 kUa/L) may also be performed.

11.4.3.2. Secondary Efficacy Analysis

The average daily TNSS, TSS, TOSS, and DMS during the birch pollen season will be analyzed in the same fashion as the primary analysis for the subjects receiving REGN5713-5714-5715 versus placebo. Subjects with at least 1 day of post-baseline diary record will be included in the analysis, and only days with observed data (including any available data of daily entries prior to subject discontinuation) will be included in the calculation of average score.

11.4.3.3. Exploratory Efficacy Analysis

Exploratory efficacy endpoints, including the average ACQ-5, RQLQ (S), and PGI-S scores during the birch pollen season will be analyzed in the same fashion as the primary analysis for the subjects receiving REGN5713-5714-5715 versus placebo. Subjects with at least 1 day of data will be included in the analysis.

11.4.4. Control of Multiplicity

Type I error rate will be controlled using a hierarchical testing strategy for the primary and key secondary endpoints at the 2-sided significant level of 0.05. The hierarchical order of the primary and key secondary endpoints will be specified in the SAP.

11.4.5. Safety Analysis

11.4.5.1. Adverse Events

Definitions

For safety variables, 2 observation periods are defined:

- The pre-treatment 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 study visit.

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.

Analysis

All AEs reported in this study will be coded using the currently available version of the Medical Dictionary for Regulatory Activities (MedDRA®). Coding will be to lowest level terms. The preferred term (PT), and the primary system organ class (SOC) will be listed.

Summaries of all TEAEs by treatment group will include:

- The number (n) and percentage (%) of subjects with at least 1 TEAE by SOC and PT
- TEAEs by severity (according to the grading scale outlined in Section 10.2.4), presented by SOC and PT
- TEAEs by relationship to treatment (related, not related), presented by SOC and PT
- Treatment-emergent AESIs (defined with a PT or a prespecified grouping)

Deaths and other SAEs will be listed and summarized by treatment group.

Treatment-emergent adverse events leading to permanent treatment discontinuation will be listed and summarized by treatment group.

11.4.5.2. Other Safety

Vital signs

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

Laboratory tests

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

Number and percentage of subjects with a potentially clinically significant value (PCSV) at any post-randomization time point will be summarized for each clinical laboratory test for all subjects and separately for subjects in whom the PCSV criterion was normal or missing at baseline.

Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for laboratory tests of interest.

Listings will be provided with flags indicating the out of laboratory range values.

11.4.5.3. Treatment Exposure

This is a single dose study.

11.4.5.4. Treatment Compliance

Treatment compliance will be assessed via the summary of treatment exposure as described in Section 11.4.5.3.

11.4.6. Pharmacokinetics

11.4.6.1. Analysis of Drug Concentration Data

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

No formal statistical hypothesis testing will be performed.

11.4.7. Analysis of Immunogenicity Data

Immunogenicity will be characterized by the ADA response and titer 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, and ADA titers presented by subject, time point, and treatment group will be provided separately for REGN5713, REGN5714, and REGN5715. Incidence of treatment-emergent ADA will be assessed as absolute occurrence (N) and percent of subjects (%), grouped by treatment group and ADA titer level.

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

11.4.8. Analysis of Pharmacodynamic and Exploratory Biomarker Data

The change and percent change from baseline in the birch skin prick test mean wheal diameters will be analyzed using an analysis of covariance (ANCOVA) model, with treatment, randomization stratification factors, visit and the treatment by visit interaction as factors in the model and the baseline mean wheal diameter as a covariate. Between group estimates comparing REGN5713-5714-5715 versus placebo will be presented for the end of study.

The prevalence of poly-allergy for tree homologue allergens and others being tested in this study will be assessed based on SPT and sIgE test results. The relationship between baseline SPT and sIgE of birch and homologue tree allergens will also be evaluated, as well as the correlation between SPT and sIgE and symptom scores. The within-subject variability in sIgE in and out of birch pollen season will also be evaluated.

11.5. Additional Statistical Data Handling Conventions

The following analysis and data conventions will be followed:

Definition of baseline

The last assessment before the administration of study drug on day 1 will be considered as the baseline evaluation.

Handling data in case of grass pollen season overlap with birch pollen season

Grass pollen season may start as birch pollen season is ending, thus potentially confounding allergic symptoms evaluated during the overlap of birch and grass pollen seasons. If birch pollen season overlaps with grass pollen season during this study, symptom and medication data collected from days after the start of the grass pollen season will be excluded from analyses.

General rules for handling missing data

If the start date of an AE or concomitant medication is incomplete or missing, it will be assumed to have occurred on or after the intake of study medication, except if an incomplete date (eg, month and year) clearly indicates that the event started prior to treatment. If the partial date indicates the same month or year of the intake of study medication date, then the start date by the study medication intake date will be imputed; otherwise, the missing day or month by the first day or the first month will be imputed.

No imputations for missing laboratory data, ECG data, vital sign data, or physical examination data will be made.

Visit windows

Assessments taken outside of protocol-allowable windows will be displayed according to the case report form (CRF) assessment recorded by the investigator.

Unscheduled assessments

Extra assessments (laboratory data or vital signs associated with non-protocol clinical visits or obtained in the course of investigating or managing AEs) will be included in listings, but not summaries. If more than 1 laboratory value is available for a given visit, the first observation will be used in summaries and all observations will be presented in listings.

11.6. Interim Analysis

No formal interim analysis will be conducted.

11.7. 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 15.1.

12. 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.

12.1. Data Management and Electronic Systems

12.1.1. 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.

12.1.2. 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
- Electronic diary and tablet for collection of patient-reported outcomes data

12.2. Study Monitoring

12.2.1. 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 subjects 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.

12.2.2. Source Document Requirements

Investigators are required to prepare and maintain adequate and accurate subject 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.

12.2.3. Case Report Form Requirements

Study data obtained in the course of the clinical study will be recorded on electronic Case Report Forms (CRFs) within the EDC system by trained site personnel. All required CRFs must be completed for each and every subject 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 subject, the investigator must provide an electronic signature. A copy of each subject 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.

12.3. 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.

12.4. Study Documentation

12.4.1. Certification of Accuracy of Data

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

12.4.2. 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.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. 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.

13.2. 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 subject 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 subject in language that he/she can understand. The ICF should be signed and dated by the subject and by the investigator or authorized designee who reviewed the ICF with the subject.

- Subjects who can write but cannot read will have the ICF read to them before signing and dating the ICF.
- Subjects 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 subject's study record, and a copy of the signed ICF must be given to the subject.

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 subjects 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 subject’s study record and a copy must be given to the subject.

13.3. Subjects Confidentiality and Data Protection

The investigator must take all appropriate measures to ensure that the anonymity of each study subject will be maintained. Subjects should be identified by a subject 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 subject '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.

13.4. Institutional Review Board and 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 subjects (eg, advertising) before any subject 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 subject, 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 subjects 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.

13.5. 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.

14. 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.

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

15.1. 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.

15.2. 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 subject 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 subjects 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 subjects' interests.

16. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

17. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

18. PUBLICATION POLICY

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

19. REFERENCES

Asero R. Effects of birch pollen-specific immunotherapy on apple allergy in birch pollen-hypersensitive patients. Clin Exp Allergy 1998; 28(11):1368-73.

Asero R. Effects of birch pollen SIT on apple allergy: a matter of dosage? Allergy 2004; 59(12):1269-71.

Asero R. How long does the effect of birch pollen injection SIT on apple allergy last? Allergy 2003; 58(5):435-8.

Bergmann KC, Wolf H, Schnitker J. Effect of pollen-specific sublingual immunotherapy on oral allergy syndrome: an observational study. World Allergy Organ J 2008; 1(5):79-84.

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):1058-66.e6.

Biedermann T, Winther L, Till SJ, Panzner P, Knulst A, Valovirta E. Birch pollen allergy in Europe. Allergy 2019b; 74(7):1237-48.

Bolhaar ST, Tiemessen MM, Zuidmeer L, van Leeuwen A, Hoffmann-Sommergruber K, Bruijnzeel-Koomen CA, et al. Efficacy of birch-pollen immunotherapy on cross-reactive food allergy confirmed by skin tests and double-blind food challenges. Clin Exp Allergy 2004; 34(5):761-9.

Bousquet J, Lockey R, Malling HJ, Alvarez-Cuesta E, Canonica GW, Chapman MD, et al. Allergen immunotherapy: therapeutic vaccines for allergic diseases. World Health Organization. American academy of Allergy, Asthma and Immunology. Ann Allergy Asthma Immunol 1998; 81(5):401-5.

Brozek JL, Bousquet J, Agache I, Agarwal A, Bachert C, Bosnic-Anticevich S, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines-2016 revision. J Allergy Clin Immunol 2017; 140(4):950-8.

Bucher X, Pichler WJ, Dahinden CA, Helbling A. Effect of tree pollen specific, subcutaneous immunotherapy on the oral allergy syndrome to apple and hazelnut. Allergy 2004; 59(12):1272-6.

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):1507-15.

Calderon MA, Alves B, Jacobson M, Hurwitz B, Sheikh A, Durham S. Allergen injection immunotherapy for seasonal allergic rhinitis. Cochrane Database Syst Rev 2007; 1:Cd001936.

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):1228-39.

Canonica GW, Cox L, Pawankar R, Baena-Cagnani CE, Blaiss M, Bonini S, et al. Sublingual immunotherapy: World Allergy Organization position paper 2013 update. World Allergy Organ J 2014; 7(1):6.

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):1404-13.

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.

Demoly P, Emminger W, Rehm D, Backer V, Tommerup L, Kleine-Tebbe J. Effective treatment of house dust mite-induced allergic rhinitis with 2 doses of the SQ HDM SLIT-tablet: Results from a randomized, double-blind, placebo-controlled phase III trial. J Allergy Clin Immunol 2016; 137(2):444-51.e8.

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):559-66.

Durham SR, Emminger W, Kapp A, Colombo G, de Monchy JG, Rak S, et al. Long-term clinical efficacy in grass pollen-induced rhinoconjunctivitis after treatment with SQ-standardized grass allergy immunotherapy tablet. J Allergy Clin Immunol 2010; 125(1):131-8.e1-7.

Durham SR, Emminger W, Kapp A, de Monchy JG, Rak S, Scadding GK, et al. SQ-standardized sublingual grass immunotherapy: confirmation of disease modification 2 years after 3 years of treatment in a randomized trial. J Allergy Clin Immunol 2012; 129(3):717-25.e5.

Durham SR, Penagos M. Sublingual or subcutaneous immunotherapy for allergic rhinitis? J Allergy Clin Immunol 2016; 137(2):339-49.e10.

Durham SR, Walker SM, Varga EM, Jacobson MR, O'Brien F, Noble W, et al. Long-term clinical efficacy of grass-pollen immunotherapy. N Engl J Med 1999; 341(7):468-75.

Ebner C, Hirschwehr R, Bauer L, Breiteneder H, Valenta R, Ebner H, et al. Identification of allergens in fruits and vegetables: IgE cross-reactivities with the important birch pollen allergens Bet v 1 and Bet v 2 (birch profilin). J Allergy Clin Immunol 1995; 95(5 Pt 1):962-9.

Epstein TG, Calabria C, Cox LS, Dreborg S. Current Evidence on Safety and Practical Considerations for Administration of Sublingual Allergen Immunotherapy (SLIT) in the United States. J Allergy Clin Immunol Pract 2017; 5(1):34-40.e2.

Eriksson NE, Formgren H, Svenonius E. Food hypersensitivity in patients with pollen allergy. Allergy 1982; 37(6):437-43.

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):1486-98.

Ewbank PA, Murray J, Sanders K, Curran-Everett D, Dreskin S, Nelson HS. A double-blind, placebo-controlled immunotherapy dose-response study with standardized cat extract. J Allergy Clin Immunol 2003; 111(1):155-61.

Frew AJ. Allergen immunotherapy. J Allergy Clin Immunol 2010; 125(2 Suppl 2):S306-13.

Frew AJ. Immunotherapy: how safe is safe? Clin Exp Allergy 2006a; 36(3):251-3.

Frew AJ, Powell RJ, Corrigan CJ, Durham SR, Group UKIS. Efficacy and safety of specific immunotherapy with SQ allergen extract in treatment-resistant seasonal allergic rhinoconjunctivitis. J Allergy Clin Immunol 2006b; 117(2):319-25.

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):203-10.

Geroldinger-Simic M, Zelniker T, Aberer W, Ebner C, Egger C, Greiderer A, et al. Birch pollen-related food allergy: clinical aspects and the role of allergen-specific IgE and IgG4 antibodies. J Allergy Clin Immunol 2011; 127(3):616-22.e1.

Guerra S, Sherrill DL, Martinez FD, Barbee RA. Rhinitis as an independent risk factor for adult-onset asthma. J Allergy Clin Immunol 2002; 109(3):419-25.

Guilbert A, Cox B, Bruffaerts N, Hoebeke L, Packeu A, Hendrickx M, et al. Relationships between aeroallergen levels and hospital admissions for asthma in the Brussels-Capital Region: a daily time series analysis. Environ Health 2018; 17(1):35.

Halken S, Larenas-Linnemann D, Roberts G, Calderon MA, Angier E, Pfaar O, et al. EAACI guidelines on allergen immunotherapy: Prevention of allergy. Pediatr Allergy Immunol 2017; 28(8):728-45.

Herrmann D, Henzgen M, Frank E, Rudeschko O, Jager L. Effect of hyposensitization for tree pollinosis on associated apple allergy. J Investig Allergol Clin Immunol 1995; 5(5):259-67.

Ito K, Weinberger KR, Robinson GS, Sheffield PE, Lall R, Mathes R, et al. The associations between daily spring pollen counts, over-the-counter allergy medication sales, and asthma syndrome emergency department visits in New York City, 2002-2012. Environ Health 2015; 14(71).

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. J Allergy Clin Immunol 2011; 127(2):509-16 e1-5.

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):385-95.

Juniper EF, Guyatt GH. Development and testing of a new measure of health status for clinical trials in rhinoconjunctivitis. Clin Exp Allergy 1991; 21(1):77-83.

Kelso JM, Jones RT, Tellez R, Yunginger JW. Oral allergy syndrome successfully treated with pollen immunotherapy. Ann Allergy Asthma Immunol 1995; 74(5):391-6.

Lemberg ML, Berk T, Shah-Hosseini K, Kasche EM, Mosges R. Sublingual versus subcutaneous immunotherapy: patient adherence at a large German allergy center. Patient Prefer Adherence 2017; 11(63-70).

Leynaert B, Neukirch F, Demoly P, Bousquet J. Epidemiologic evidence for asthma and rhinitis comorbidity. J Allergy Clin Immunol 2000; 106(5 Suppl):S201-5.

Lin RY, Clauss AE, Bennett ES. Hypersensitivity to common tree pollens in New York City patients. Allergy Asthma Proc 2002; 23(4):253-8.

Makela MJ, Gyllfors P, Valovirta E, Steffensen MA, Gronager PM, Savolainen J, et al. Immunotherapy With the SQ Tree SLIT-tablet in Adults and Adolescents With Allergic Rhinoconjunctivitis. Clin Ther 2018; 40(4):574-86.e4.

Mauro M, Russello M, Incorvaia C, Gazzola GB, Di Cara G, Frati F. Comparison of efficacy, safety and immunologic effects of subcutaneous and sublingual immunotherapy in birch pollinosis: a randomized study. Eur Ann Allergy Clin Immunol 2007; 39(4):119-22.

Musa F, Al-Ahmad M, Arifhodzic N, Al-Herz W. Compliance with allergen immunotherapy and factors affecting compliance among patients with respiratory allergies. Hum Vaccin Immunother 2017; 13(3):514-7.

Navarro A, Colas C, Anton E, Conde J, Davila I, Dordal MT, et al. Epidemiology of allergic rhinitis in allergy consultations in Spain: Alergologica-2005. J Investig Allergol Clin Immunol 2009; 19 Suppl 2(7-13).

Nelson HS. Advances in upper airway diseases and allergen immunotherapy. J Allergy Clin Immunol 2004; 113(4):635-42.

Niederberger V, Pauli G, Gronlund H, Froschl R, Rumpold H, Kraft D, et al. Recombinant birch pollen allergens (rBet v 1 and rBet v 2) contain most of the IgE epitopes present in birch, alder, hornbeam, hazel, and oak pollen: a quantitative IgE inhibition study with sera from different populations. J Allergy Clin Immunol 1998; 102(4 Pt 1):579-91.

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):1631-8.

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. Nat Commun 2018; 9(1):1421.

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

Pauli G, Larsen TH, Rak S, Horak F, Pastorello E, Valenta R, et al. Efficacy of recombinant birch pollen vaccine for the treatment of birch-allergic rhinoconjunctivitis. J Allergy Clin Immunol 2008; 122(5):951-60.

Pawankar R, Canonica GW, Casale T, RF L. The World Allergy Organization white book on allergy. In. Milwaukee: World Allergy Organization; 2011.

Pfaar O, Calderon MA, Andrews CP, Angjeli E, Bergmann KC, Bønløkke JH, et al. Allergen exposure chambers: harmonizing current concepts and projecting the needs for the future - an EAACI Position Paper. Allergy 2017; 72(7):1035-42.

Rosario N, Bielory L. Epidemiology of allergic conjunctivitis. Curr Opin Allergy Clin Immunol 2011; 11(5):471-6.

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):350-9.

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):1290-300.

Shaaban R, Zureik M, Soussan D, Neukirch C, Heinrich J, Sunyer J, et al. Rhinitis and onset of asthma: a longitudinal population-based study. Lancet 2008; 372(9643):1049-57.

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):375-83.

Van Ree R, Van Leeuwen WA, Akkerdaas JH, Aalberse RC. How far can we simplify in vitro diagnostics for Fagales tree pollen allergy? A study with three whole pollen extracts and purified natural and recombinant allergens. Clin Exp Allergy 1999; 29(6):848-55.

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):1274-86.e9.

Vanek-Krebitz M, Hoffmann-Sommergruber K, Laimer da Camara Machado M, Susani M, Ebner C, Kraft D, et al. Cloning and sequencing of Mal d 1, the major allergen from apple (Malus domestica), and its immunological relationship to Bet v 1, the major birch pollen allergen. Biochem Biophys Res Commun 1995; 214(2):538-51.

Wahn U, Bachert C, Heinrich J, Richter H, Zielen S. Real-world benefits of allergen immunotherapy for birch pollen-associated allergic rhinitis and asthma. Allergy 2019; 74(3):594-604.

Walker SM, Pajno GB, Lima MT, Wilson DR, Durham SR. Grass pollen immunotherapy for seasonal rhinitis and asthma: a randomized, controlled trial. J Allergy Clin Immunol 2001; 107(1):87-93.

Wallace DV, Dykewicz MS. Seasonal Allergic Rhinitis: A focused systematic review and practice parameter update. Curr Opin Allergy Clin Immunol 2017a; 17(4):286-94.

Wallace DV, Dykewicz MS, Bernstein DI, Blessing-Moore J, Cox L, Khan DA, et al. The diagnosis and management of rhinitis: an updated practice parameter. J Allergy Clin Immunol 2008; 122(2 Suppl):S1-84.

Wallace DV, Dykewicz MS, Oppenheimer J, Portnoy JM, Lang DM. Pharmacologic Treatment of Seasonal Allergic Rhinitis: Synopsis of Guidance From the 2017 Joint Task Force on Practice Parameters. Ann Intern Med 2017b; 167(12):876-81.

Wei C. The efficacy and safety of H1-antihistamine versus Montelukast for allergic rhinitis: A systematic review and meta-analysis. Biomed Pharmacother 2016; 83(989-97).

20. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: A PHASE 3 RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY ASSESSING THE EFFICACY OF ANTI-BET V 1 MONOCLONAL ANTIBODIES TO REDUCE SYMPTOMS OF SEASONAL ALLERGIC RHINITIS 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 Phase 3 Randomized, Double-Blind, Placebo-Controlled Study Assessing the Efficacy of Anti-Bet v 1 Monoclonal Antibodies to Reduce Symptoms of Seasonal Allergic Rhinitis

Protocol Number: R5713-5714-5715-ALG-2001

Protocol Version: R5713-5714-5715-ALG-2001 Original

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-00121234 v2.0

ESig Approval	[redacted]-2020 15:12:39 GMT+0000
ESig Approval	[redacted]20 15:13:57 GMT+0000
ESig Approval	[redacted]-2020 15:17:57 GMT+0000
ESig Approval	[redacted]00

Signature Page for VV-RIM-00121234 v2.0 Approved