STATISTICAL ANALYSIS PLAN
VERSION: AMENDMENT 1

Clinical Study Protocol 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

Compound: REGN5713-5714-5715

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

Clinical Phase: Phase 3

Sponsor: Regeneron Pharmaceuticals, Inc.

Study Biostatistician: [redacted]

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Study Medical Director: [redacted]

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

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
BAT	Basophil activation test
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
HRQoL	Health-related quality of life
ICF	Informed consent form
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INCS	Intranasal Corticosteroids

IRB	Institutional Review Board
IRT	Interactive response technology
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
SAS	Statistical Analysis System
SC	Subcutaneous
SCIT	Subcutaneous immunotherapy
sIgE	Allergen-specific IgE
SIT	Specific immunotherapy

SLIT	Sublingual immunotherapy
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

1. OVERVIEW

The purpose of the statistical analysis plan (SAP) is to ensure the credibility of the study results by pre-specifying the statistical approaches for the analysis of study data prior to database lock. The SAP is intended to be a comprehensive and detailed description of the strategy and statistical methods to be used in the analysis of data for R5713-5714-5715-ALG-2001 study.

This plan may be revised during the study to accommodate protocol amendments and/or to make changes to adapt to unexpected issues in study execution and/or data that affect planned analyses. A final plan will be issued prior to data lock and before treatment code breaking.

1.1. Background/Rationale

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 (INCS) 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). The best reported treatment effects for antihistamines and INCs are 5% to 22% relative reduction of total nasal symptoms compared to placebo (Durham, 2016b), and INCS are considered to have limited efficacy for allergic eye symptoms (Bielory, 2011). 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).

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, 2016a) (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 occurs more frequently with SCIT compared to SLIT (Epstein, 2017). 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 or uncontrolled 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.

Three 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 in healthy adults (FIH: Part A) 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. Part B of this FIH study demonstrated efficacy in healthy individuals with birch pollen allergy in reducing nasal symptoms assessed by TNSS AUC during nasal allergen challenges at

days 8, 29 and 57 after a single dose of 900 mg of REGN5713-5714-5715. There were no serious adverse events, no deaths and no TEAEs resulting in discontinuation for both parts A and B.

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.

1.2. Study Objectives

1.2.1. 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.

1.2.2. 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 antiallergy rescue medications.

1.2.3. Modifications from the Statistical Section in the Final Protocol

- The per protocol analysis set (PPS) was removed since estimands are constructed with aligned method of analysis that better address the objective, and analysis of PPS might not provide additional insights.

1.2.4. Revision History for SAP Amendments

The purpose of this amendment is to update the intercurrent events strategy for use of prohibited medications per FDA's suggestion. A composite strategy will be applied only for the use of

systemic steroids and Type 2 biologics. For the other prohibited medications, a treatment policy will be applied.

Section	Description of Additions/Updates
Section 5.6 Table 1	• Update the intercurrent events strategy for use of relevant prohibited medications
Section 5.6.1 Table 2	• Update the list of relavant prohibited medications that will affect efficacy

2. INVESTIGATION PLAN

2.1. Study Design and Randomization

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 (nose) and conjunctivitis (eye) 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 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 throughout the study.

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

- 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 (NA) versus Europe (EU))

2.2. 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.

2.3. Sample Size and Power Considerations

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 120 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 with a two-sample t-test at 2-sided significance level of 0.05. Assuming 20% drop out rate during the birch pollen season, the target is to randomize 150 subjects per arm.

Estimates of mean and variability of the CSMS are based on pooled estimates across several field studies for grass sublingual 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.

This planned sample size (150 subjects per arm) also gives 93% power to detect a mean difference in TNSS of 0.6 (26% reduction from placebo) in REGN5713-5714-5715 (mean TNSS=1.7) and placebo (mean TNSS=2.3), assuming a common standard deviation in TNSS of 1.5 at 2-sided alpha of 0.05 using a two-sample t-test. The assumptions of TNSS endpoint are based on effects observed in the GT-08 trial of timothy grass sublingual tablet (Dahl, 2006). With the same mean for placebo and common standard deviation from GT-08 but a 30% reduction from placebo for REGN5713-5714-5715 as observed in the phase 1b POC study, the study will have a greater power.

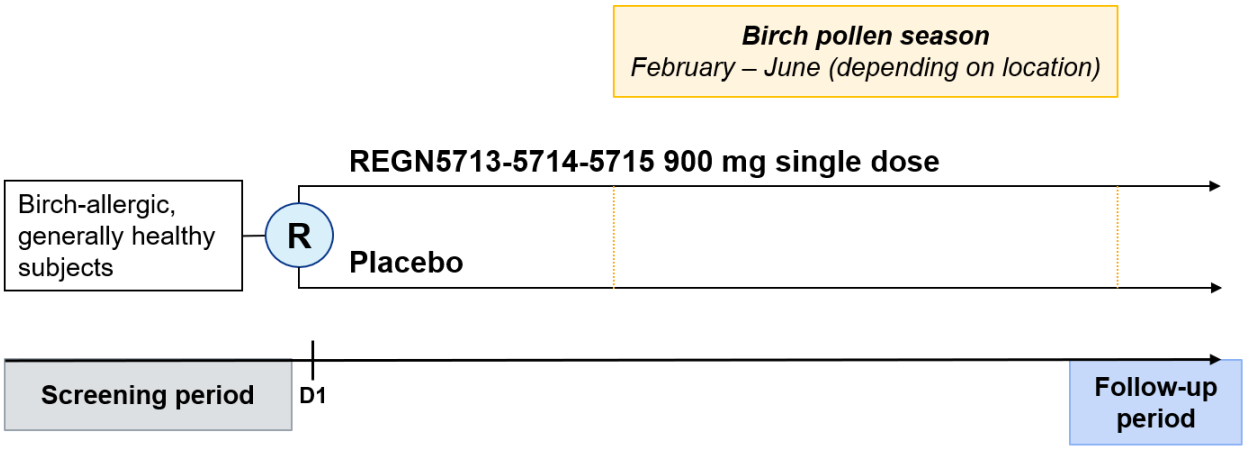
The sample size and power calculations were performed using nQuery Advisor 7.0

2.4. Study Plan

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.

The Schedule of Event table is presented in Section 10.2.

Figure 1: Study Flow Diagram



3. ANALYSIS POPULATIONS

In accordance with guidance from the International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline ICH E9 Statistical Principles for Clinical Trials (ICH, 1998), the following population of analysis will be used for all statistical analysis.

3.1. The Full Analysis Set (FAS)

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). Since the TNSS, TOSS and DMS will be completed sequentially, all randomized subjects with at lease 1 TNSS e-diary entry will be included in FAS. Efficacy endpoints will be analyzed using the FAS.

3.2. The Safety Analysis Set (SAF)

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

3.3. The Pharmacokinetic Analysis Set (PKAS)

The PK analysis set 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.

3.4. The Immunogenicity Analysis Set

The anti-drug antibody (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.

The neutralizing antibody (NAb) analysis set (NAS) includes all subjects who received any study drug and who tested negative at all ADA sampling times or tested positive with at least 1 non-missing result in the NAb assay after the first dose of the study drug. Subjects who are ADA-negative are set to negative in the NAb analysis set. Subjects will be analyzed according to the treatment actually received.

3.5. Subgroups

Subgroups are defined by key baseline factors recorded on the eCRF (unless otherwise specified) and listed as follows.

Subgroups to be considered for both efficacy and safety analyses:

- Age group (years; 18 to <50; ≥50)
- Sex (Male, Female)
- Ethnicity: Hispanic or Latino (Yes, No)

- Race (White, Other)

Subgroups to be considered for efficacy analysis only:

- Serum specific birch pollen IgE level at screening(<17.5 kUa/L; ≥17.5 kUa/L)
- Serum specific oak pollen IgE level at screening (<0.7 kUa/L; ≥0.7 kUa/L) (North America)
- History of asthma (Yes, No)
- Region (North America (NA), Europe (EU))
- Baseline sensitization status based on sIgE or SPT (only sensitized to birch and birch related allergens, sensitized to birch, birch related allergens and any of other allergens)

Note: birch and birch related allergens are listed as below based on sIgE and SPT:

	Birch	**Birch-related**
SPT	Birch	Alder
sIgE	Birch Silver	Alder Grey
	rBet v1	Hazelnut
	rBet v2	Hornbeam

4. ANALYSIS VARIABLES

4.1. Demographic and Baseline Characteristics

The following demographic and baseline characteristics variables will be summarized:

- Demographic variables:
  - Age at screening as a continuous variable
  - Age group (years; 18 to <50, ≥50)
  - Sex (Male, Female)
  - Race (White, Black or African American, Asian, American indian or Alaska native, Native Hawaiian or other pacific islander)
  - Ethnicity (Hispanic/Latino: Yes or No)
  - Baseline Weight (kg)
  - Baseline Height (cm)
  - Region (NA, EU)
- Baseline characteristics:
  - Standard regional skin prick test (SPT) for birch (mm)
  - Serum birch pollen sIgE at screening
  - Serum oak pollen sIgE at screening (North America)
  - Serum Bet v1 sIgE at screening
  - Baseline FEV1
  - Baseline sensitization status based on sIgE or SPT (e.g. sensitization to birch and birch related allergens only, sensitization to birch, birch related allergens and any of other allergens)

4.2. Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA®).

4.3. Pre-treatment / Concomitant Medication and Procedures

Medications/Procedures will be recorded from the day of informed consent until the end-of-study (EOS) visit. Medications will be coded using WHO Drug Dictionary (WHODD). Subjects will be counted once in each medication class linked to the medication.

Pre-treatment medications/procedures: medications taken or procedures performed prior to administration of the study drug.

Concomitant medications/procedures (CMs/CPs): medications taken or procedures performed following the dose of study drug through the EOS visit.

4.4. Prohibited or Rescue Medication/Procedure

4.4.1. 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.

- 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

Blinded adjudication of prohibited medications will be implemented before the database lock by the study medical director, considering the type of medication, indication, timing, frequency and the potential impact of the use of the prohibited medication. The adjudication procedure will be documented.

4.4.2. Rescue medication

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.

4.5. Efficacy Variable

4.5.1. Primary Efficacy Variable

The primary efficacy endpoint in the study 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. Details of duration of birch pollen season are described in section 4.10.

Total Nasal Symptom Score (TNSS)

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

The average TNSS will be calculated using all observed daily scores during birch pollen season.

Total Ocular Symptom Score (TOSS)

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 daily using an e-diary.

If a patient has at least 1 TOSS during the birch pollen season, average TOSS will be calculated using all observed daily scores during birch pollen season.

If a patient has no TOSS during the birch pollen season, the mean of average TOSS during birch pollen season in the treatment group that the patient is randomized to will be used for the missing.

Total Symptom Score (TSS)

The daily TSS is calculated by adding the TNSS and TOSS together, for a combined TSS of 0 to 18 if both of them are not missing.

The average TSS will be calculated by adding average TNSS and average TOSS during birch pollen season. Imputed TOSS will be used if all TOSS data were missing (described above).

Daily Medication Score (DMS)

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.

The average DMS will be calculated using the same method as described for TOSS.

Combined Symptom and Medication Score (CSMS)

The daily CSMS is calculated by adding the DMS and TSS together, with scores ranging between 0 and 38 if both of them are not missing.

The average CSMS will be calculated by adding average TNSS, average TOSS and average DMS during birch pollen season. Imputed TOSS and/or DMS will be used if missing is occurred.

4.5.2. Secondary Efficacy Variables

The secondary efficacy 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
- 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
- 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

Birch Allergen and Standard Regional Skin Prick Tests

An SPT with birch allergen extract and a regional SPT (such as with dust mites, grasses, ragweed, other trees, including other birch homologous trees [such as alder and oak], mold, 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 (which is >=5mm compared to the negative control), a positive response is defined by a mean wheal diameter at least 3 mm greater than a negative control.

4.5.3. Exploratory Efficacy Variables

Exploratory efficacy endpoints include:

- RQLQ (S), averaged over the duration of the birch pollen season, for REGN5713-5714- 5715 versus placebo
- ACQ-5, averaged over the duration of the birch pollen season, for REGN5713-5714-5715 versus placebo (only for patients with asthma)
- 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
- 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

Standardized Rhinoconjunctivitis Quality of Life Questionnaire [RQLQ (S)]

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.

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 for patients with asthma.

Pollen Food Allergy Symptom Questionnaire (PFASQ)

The PFASQ will be performed to determine the types of food that produce an allergic reaction, the type of reaction, and how soon the reactions occur.

Patient Global Impression of Severity (PGI-S)

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.

4.6. Safety Variables

4.6.1. Adverse Events and Serious Adverse Events

Adverse events (AEs) and serious adverse events (SAEs) defined in study protocol 10.2.1 and 10.2.2 will be collected from the time of informed consent signature and then at each visit until the end of the study. All adverse events are to be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

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

4.6.2. Adverse Events of Special Interest

Adverse events of special interest (AESI) for this study include systemic or severe hypersensitivity reactions and severe injection site reactions.

4.6.3. Laboratory Safety Variables

Hematology, chemistry, pregnancy test, and urinalysis will be analyzed by a central laboratory. Samples for laboratory testing will be collected at visits according to Table 3. Tests will include:

Blood chemistry

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

Hematology

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

Urinalysis

Color	Glucose	RBC
Clarity	Blood	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.

4.6.4. Vital Signs and Weight/Height

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.

Weight and height are measured at screening visit 1 only.

4.6.5. 12-Lead Electrocardiography (ECG)

A standard 12-lead ECG will be performed at the screening visit 1 only. 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.

4.6.6. Physical Examination Variables

The physical examination variable values are dichotomized to normal and abnormal.

4.6.7. 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 (FEV1 [L]), FEV1/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.

4.7. Pharmacokinetic Variables

Concentrations in serum of total (free+bound to target) REGN5713, REGN5714, and REGN5715 will be determined at time points specified in the study schedule of events in Section 10.2. Pharmacokinetic variables consist of invididual antibody, as well as total drug, concentration in serum and time (both nominal and actual).

4.8. Immunogenicity Variables

The immunogenicity variables are ADA status, ADA titer, NAb status and time point/visit. Samples in this study will be collected at the clinic visits specified in Section 10.2. Samples positive in the ADA assay will be further characterized for ADA titers. 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.

Immunogenicity will be characterized by the ADA response and titer categories observed:

ADA response category:

- ADA Negative, defined as ADA negative response in the ADA assay at all time points, regardless of any missing samples.

- Pre-existing immunoreactivity: defined as either an ADA positive response in the ADA assay at baseline with all post first dose ADA results negative, OR a positive response at baseline with all post first dose ADA responses less than 9-fold over baseline titer levels.
- Treatment-emergent ADA response: defined as a positive response in the ADA assay post first dose when baseline results are negative or missing.
- Treatment-boosted ADA response: defined as a positive response in the ADA assay post first dose that is greater than or equal to 9-fold over baseline titer levels, when baseline results are positive

Titer category (Maximum titer values)

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

The NAb status is categorized as follows:

- Negative: Samples tested negative in the ADA assay, or samples positive in the ADA assay but tested negative in the NAb assay
- Positive: Samples positive in the NAb assay

4.9. Biomarker Variables

Exploratory biomarker variables include:

- Total serum IgE at baseline, day 57 (V5) and day 113 (V7)
- Allergen-specific IgE levels (birch pollen, Bet v 1) at screening visit 1 (V1) and baseline (V2)
- Allergen-specific IgE levels (Bet v 1 and other common allergens) at screening and baseline to assess sensitization status and to evaluate the relationship between response to REGN5713-5714-5715 treatment and poly/mono-sensitization
- Allergen-specific IgE levels (Bet v 1 and other common allergens) on day 57 and day 113

4.10. 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.

Birch Pollen Regions:

Clinical sites will be pooled into different pollen regions geographically. The pollen regions for this study include Belgium, Denmark, Germany, Canada, west-US and east-US.

Birch Pollen Season:

Local site-specific pollen count data will be used for each patient to determine the start and end of the birch pollen season. The start of the birch pollen season is defined as the first of 3 consecutive days with a pollen count of 10 grains/m^3 or greater. The end of the birch pollen season is defined as the last day of the last occurrence of 3 consecutive days with a pollen count of 10 grains/m^3 or greater. The peak birch pollen season is defined as the 15 consecutive days within the birch pollen season with the highest 15-day moving average pollen count.

5. STATISTICAL METHODS

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

For categorical or ordinal data, frequencies and percentages will be displayed for each category. Missing values at baseline will not be imputed unless otherwise specified.

5.1. Demographics and Baseline Characteristics

Demographics and Baseline Characteristics will be summarized by treatment groups and overall based on the FAS.

5.2. Medical History

Medical history will be summarized by primary SOC and PT for each treatment group and for study total based on the SAF. The table will be sorted by decreasing frequency of SOC followed by PT based on the overall incidence across treatment groups.

5.3. Prior/Concomitant Medications/Procedures

Number and proportion of subjects taking prior/concomitant medications, prohibited medications and will be summarized for study total based on the SAF by Anatomical Therapeutic Chemical (ATC) level 2 and ATC level 4, sorted by decreasing frequency of ATC level 2 and ATC level 4 based on the overall incidence. Subjects will be counted only once for each medication class (ATC levels 2 and 4) linked to the medication.

Number of patients taking rescue medications will be summarized by medication name based on rescue medication e-diary.

Number and proportion of patients taking prior/concomitant procedures will be summarized for study total based on the SAF, sorted by decreasing frequency of SOC and PT based on the overall incidence. Patients will be counted only once for each SOC and PT linked to the procedure.

5.4. Subject Disposition

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

- The total number of screened subjects
- The total number of randomized patients: received a randomization number from IWRS
- The total number of patients in each analysis set
- The total number of patients who discontinued the study and the reasons for discontinuation (including COVID-19 related reasons)

5.5. Extent of Study Treatment Exposure and Compliance

Treatment exposure is defined as the number of study treatment administrations for each subject. Since this is a single dose study, subjects will have 1 study treatment administration, given as 3 injections sequentially on one day. Summary of number of injections will be provided. Treatment compliance is not applicable.

The duration of observation period during the study is calculated as:

(Date of the last study visit – date of the investigational product administration) +1.

Duration of observation period will be summarized for each treatment group using number of subjects, means, SD, minimums, medians and maximums.

The number (%) of subjects with observation periods will be presented by specific time periods. The time periods of interest are specified as: ≥1 day, ≥28 days, ≥57 days, ≥85 days, and ≥113 days.

5.6. Analyses of Efficacy Variables

The analyses of efficacy variables are described in the subsections below and summarized in Appendix 10.1. The intercurrent events, strategies, and the corresponding missing data handling approaches for the primary estimands of interest for the primary endpoint are provided in Table 1

Table 1: Primary Estimand for the Primary Endpoint

Endpoint Category	Estimands			
	Endpoint(s)[1]	**Population**	**Intercurrent event(s) strategy and missing data handling**	**Population-level summary/Analysis**
Primary Endpoint	Daily CSMS, averaged over the duration of the birch pollen season	FAS	The intercurrent events will be handled as follows: • Taking rescue medications to treat allergic symptoms during the study: data after rescue medication will be utilized (Treatment policy strategy) • Taking relavant prohibited medications[2] during the study: the worst calculated CSMS score (worst observed TOSS+TNSS+DMS) during the birch pollen season from the same patient will be use to impute the daily CSMS after the medication usage (details are provided in section 5.6.1 Table 2). If the patient dose not have any data to be utilized during birch pollen season, the mean of average CSMS during the birch pollen season in the treatment that the patient is randomized to will be used for imputation. The average CSMS during the birch pollen season will be calculated based on observed and imputed daily CSMS. Missing data handling: If all TOSS and/or DMS during the birch pollen season are missing, the missing will be imputed using the mean of the average of TOSS and/or DMS during birch pollen season in the treatment group that the patient is randomized to. The average CSMS during the birch pollen season will be calculated by adding average of observed TNSS, average of observed/imputed TOSS and average of observed/imputed DMS.	Linear mixed-effect model, with the treatment group and randomization stratification factors as fixed effects and pollen region as a random effect will be used. The least squares means (LS-means) estimate for each treatment, and LS-means for between-treatment difference with its 95% confidence interval and p-value will be provided based on the model.

[1] Secondary endpoints are not included in this table but would be handled with a similar strategy as the primary endpoint.
[2] Prohibited medications will be adjudicated by study medical monitor before the database lock and corresponding data utilization rules for selected prohibited medications are listed in **Table 2** .

5.6.1. Analysis of Primary Efficacy Variable

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 (serum specific birch pollen IgE levels at screening (<17.5 kUa/L, ≥17.5 kUa/L), serum specific oak pollen IgE levels at screening (<0.7 kUa/L, ≥0.7 kUa/L for NA) and geographical region (NA, EU)) 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. Subjects with at least 1 day of post-baseline diary record with CSMS during the birch pollen season will be included. The CSMS will be calculated on all available data during the birch pollen season. The least squares means (LS-means) estimate for each treatment, and LS-means for between-treatment difference with its 95% confidence interval and p-value will be provided.

The average CSMS will be calculated based on total 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 is defined in section 4.10 for each site based on the local pollen counts.

Data after any rescue medication use will be used for the calculation of the average CSMS, but relevant prohibited medications that may have an impact on symptom measurements will result in subsequent symptoms and medication scores not be utilized in the CSMS for that subject for a specified period of time (determined by medication type). The prohibited medications will be adjudicated by study medical monitor before the database lock. A list of those relevant prohibited medication and the rules of data utilization are detailed in Table 2 .

Table 2: Data Utilization for Relevant Prohibited Medications

Name of Medication	Rule of Data Utilization
Systemic steroids (oral/ IV/ IM/ intra-articular/ other)	Data will not be used after the medication usage.
Type 2 Biologics	

In additional, if a patient has major change in birch pollen exposure (e.g. travel out of country), the data will be set to missing during this major change and no imputation will be applied.

For patients with data not utilized due to prohibited medication, the following data imputation rule will be apply:

- For a patient with at least one day data to use during the birch pollen season, the worst observed score from the same patient during the birch pollen season will be used to impute the daily TNSS, TOSS and DMS in this affected period. Daily CSMS will be calculated by adding the worst daily TOSS, TNSS and DMS. Average CSMS will be calculated based on the observed scores and imputed scores.
- For a patient without any data to use during the birch pollen season, average CSMS will be imputed using the mean of average CSMS during the birch pollen season in the treatment that the patient is randomized to.

Sensitivity analysis

A sensitivity analysis is planned to assess an alternative method to impute missing data. The alternative method of calculation of average CSMS is detailed as below:

- If TOSS and/or DMS are missing on any single day with TNSS completed, it will be assumed to be 'No ocular symptom' and/or 'No rescue use' and a score of 0 will be assigned. Daily CSMS will be calculated for days with at least TNSS completed.
- The daily CSMS will be set to missing for the days that are affected by prohibited medication and/or major change in birch pollen exposure.
- The average CSMS will be calculated only based on non-missing daily CSMS during birch pollen season.

The same linear mixed-effect model will be used for the sensitivity analysis. Patients without any data during birch pollen season will not be part of the sensitivity analysis.

5.6.2. Analysis of Secondary Efficacy Variables

Secondary efficacy variables will be analyzed using linear mixed-effect model in the same fashion as the primary analysis for primary endpoint, average CSMS during birch pollen season. 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. Data after rescue will be utilized and data after relevant prohibited medications will be set to missing according to Table 2 .

5.6.3. Adjustment for Multiple Comparison

The following multiplicity adjustment approach, a hierarchical procedure, will be used to control overall Type-1 error rate at 0.05 for the primary endpoint and the secondary endpoints. Each hypothesis will be formally tested only if the preceding one is significant at the 2-sided 0.05 significance level. The hierarchical testing order is shown as follows.

1. **Primary endpoint**: Daily CSMS, averaged over the duration of the birch pollen season, in subjects who receive a single dose of REGN5713-5714-5715 versus placebo
2. TNSS, averaged over the duration of the birch pollen season, in subjects who receive a single dose of REGN5713-5714-5715 versus placebo
3. TSS, averaged over the duration of the birch pollen season, in subjects who receive a single dose of REGN5713-5714-5715 versus placebo
4. 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
5. 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
6. TOSS, averaged over the duration of the birch pollen season, in subjects who receive a single dose of REGN5713-5714-5715 versus placebo
7. DMS, averaged over the duration of the birch pollen season, in subjects who receive a single dose of REGN5713-5714-5715 versus placebo

5.6.4. Subgroup Analysis

Subgroups described in Section 3.5 for the primary endpoint will be summarized. Treatment difference and its 95% confidence interval in subgroups of subjects will be presented in forest plots.

5.6.5. Analysis of Exploratory Efficacy Variables

For continuous exploratory efficacy variables, e.g. average ACQ-5 and change and percent change in SPT mean wheal diameter for birch homologous/cross-reactive allergens, they will be analyzed by using a linear mixed effects model similar to the analyses of primary endpoint.

For categorical exploratory variables, e.g. PFASQ and PGI-S, only descriptive summary will be provided.

For endpoints related to biomarker, e.g. serum total IgE, serum sIgE for birch and Bet v 1, analysis method will be detailed in section 5.11.

5.7. Analysis of Safety Data

The analysis of safety and tolerance will be performed on the SAF, as defined in Section 3.2.

The safety analysis will be based on the reported AEs, clinical laboratory evaluations and vital signs.

Thresholds for treatment-emergent Potential Clinically Significant Values (PCSV) in laboratory variables and vital signs are defined in Appendix 10.3. Treatment-emergent PCSV is any PCSV developed or worsened in severity compared to the baseline during the treatment and follow-up period. The baseline when determining treatment-emergent PCSV refers to the baseline value of the study.

The time interval to detect any event or abnormality is between the first injection of study medication and EOS.

5.7.1. Adverse Events

The number and proportion of subjects reporting TEAEs will be summarized on SAF as described in Section 3.2.

AE incidence tables will be presented by treatment group for the SAF as well as subgroups for safety. TEAE summaries will present the number (n) and percentage (%) of subjects experiencing an TEAE by SOC and PT, sorted by decreasing frequency of SOC and PT for the REGN 5713-5714-5715 treatment group. Multiple occurrences of AEs of the same PT (or SOC) in the same subject will be counted only once for that PT (or SOC). For tables presenting severity of events, the worst severity will be chosen for subjects with multiple instances of the same event. The denominator for computation of percentage is the number of subjects in each treatment group for safety analysis.

An overall summary of TEAEs will be provided with number and proportion of subjects with any:

- TEAE
- Serious TEAE

- Serious TEAE leading to death
- Study drug related TEAE/serious TEAE
- TEAE leading to study discontinuation
- Maximum intensity for TEAE

Note: TEAE leading to treatment discontinuation will be not provided since the study only has a single dose.

Detailed summaries of TEAEs will include:

- TEAEs
  - TEAEs by primary SOC/PT
  - TEAEs by PT
  - TEAEs by primary SOC/PT with incidence of PT ≥ 5%
  - TEAEs by severity and by primary SOC/PT
  - TEAEs related to study drug as assessed by the investigator by primary SOC/PT
- Serious TEAE
  - Serious TEAEs by primary SOC/PT
- Fatal AEs by primary SOC/PT
- TEAE leading to study discontinuation by primary SOC/PT
- AESI by AESI category (see section 10.4), primary SOC/HLT/PT

Number and proportion of subjects reporting pre-treatment adverse events will be tabulated by primary SOC and PT.

The number and proportion of subjects with injection site reaction by PT will be summarized.

5.7.2. Clinical Laboratory Measurements

Laboratory measurements include clinical chemistry, hematology and urinalysis results, and will be converted to standard international units. Summaries of laboratory variables will include:

- Descriptive statistics of laboratory result and change from baseline by visit
- The number (n) and percentage (%) of subjects with treatment-emergent PCSVs. This summary will be provided based on the subgroup of SAF subjects who did not meet the PCSV criterion at baseline
- Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for parameters of interest

The graph of mean change and/or percent change from baseline value for lab parameters by visit will be provided.

5.7.3. Analysis of Vital Signs

Summaries of vital sign variables will include:

- Descriptive statistics of vital sign variable and change from baseline by visit
- The number (n) and percentage (%) of subjects with treatment-emergent PCSV
- Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for parameters of interest

5.8. Analysis of Pharmacokinetic Data

Descriptive statistics of total REGN51713, total REGN5714, total REGN5715, and total drug (REGN5713+REGN5714+REGN5715) concentrations in serum at each sampling timepoint will be provided. Plots of mean concentration versus nominal time will be presented. Select PK parameters may be calculated.

Exposure-response analysis for biomarkers, efficacy, and safety endpoints may be conducted as appropriate, and presented in separate reports.

5.9. Analysis of Immunogenicity Data

5.9.1. Analysis of ADA Data

The immunogenicity variables described in Section 4.8 will be summarized using descriptive statistics. Analysis described in this section will be performed separately for ADA to REGN5713, ADA to REGN5714 and ADA to REGN5715 in all treatment groups unless otherwise specified.

The following analysis will be provided by treatment groups and ADA titer categories:

- Number (n) and percent (%) of ADA-negative subjects
- Number (n) and percent (%) of pre-existing immunoreactivity subjects
- Number (n) and percent (%) of treatment-emergent ADA positive subjects
- Number (n) and percent (%) of treatment-boosted ADA positive subjects

5.9.2. Analysis of Neutralizing Antibody (NAb) Data

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.

The absolute occurrence (n) and percent of subjects (%) with NAb status in the NAb analysis set will be provided by treatment groups. Analysis described in this section will be performed separately for NAb to REGN5713, NAb to REGN5714 and NAb to REGN5715 in all treatment groups unless otherwise specified.

5.10. Association of Immunogenicity with Exposure, Safety and Efficacy

5.10.1. Immunogenicity and Exposure

Potential association between immunogenicity variables and systemic exposure to REGN5713, REGN5714 or REGN5715 will be explored. Plots of drug concentration may be provided for analyzing the potential impact of ADA response status, titer and NAb status on PK.

5.10.2. Immunogenicity and Safety and Efficacy

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

- TEAEs
- SAEs
- Injection site reaction (HLT: Injection site reaction)
- Hypersensitivity (SMQ: Hypersensitivity [Narrow] followed by manual adjudication (same as AESI 'Hypersensitivity'))
- Anaphylaxis (SMQ: Anaphylactic Reaction [Narrow])

Note: TEAE leading to treatment discontinuation will be not provided since the study only has a single dose.

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

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

- ADA positive subjects, that is subjects/patients with treatment-emergent or treatment-boosted response.
- ADA negative subjects, that is subjects/patients with pre-existing immunoreactivity or negative in the ADA assay at all time points.
- NAb positive subjects, that is ADA positive subjects who were positive in the NAb assay at any time point analyzed.
- Maximum post-baseline titer in treatment-emergent or treatment-boosted ADA positive subjects:
  - Low (titer <1,000)
  - Moderate (1,000 ≤ titer ≤ 10,000)
  - High (titer >10,000)

5.11. Analysis of Biomarker Data

All biomarker analyses will be performed on the FAS using all observed data.

Descriptive statistics for the observed values and change and percent change from baseline in detectable allergen specific IgE by treatment and visit will be provided for the biomarker variables.

Baseline serum total IgE, serum birch pollen sIgE, and serum bet v 1 sIgE and the ratio of serum Bet v 1 sIgE/ serum birch pollen sIgE will be correlated to the primary and secondary clinical efficacy endpoints using spearman's rho test.

The percent of detectable IgE at each visit (V5 and V7) compared to baseline will also be correlated to the primary and secondary clinical efficacy endpoints using spearman's rho test. Both the spearman correlation coefficients and p-values will be reported. Multiple linear regression models will also be used to explore these relationships, with the efficacy endpoints as dependent variables and the IgE values at baseline (log transformed if appropriate) as dependent variables.

The poly-allergen sensitization status for each study subject will be determined by the number of allergen-specific IgE values that are equal to or above 0.35kUa/L. A descriptive report will be provided based on the allergen-specific IgE results at screening/ baseline for all concomitant or homologous allergen to birch pollen. The number of allergen that each subject were sensitized to will be correlated with the primary and secondary clinical outcomes.

6. DATA CONVENTIONS

The following analysis conventions will be used in the statistical analysis.

6.1. Definition of Baseline for Efficacy/Safety Variables

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

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

6.2. Data Handling Conventions

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

6.3. Data Handling Convention for Missing Data

Missing data will not be imputed in listings. This section includes the methods for missing data imputation for some summary analyses, if necessary.

Rules for handling missing data for primary and secondary efficacy variables are described in Section 4.5.1 and Section 4.5.2.

Adverse event

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

Adverse event start date

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

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

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

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

Adverse event end date

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

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

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

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

Prior or concomitant medication

Medication start and end date missing

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

Prior medication start date

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

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

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

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

Prior medication end date

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

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

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

Concomitant medication start date

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

Concomitant medication end date

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

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

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

Medication coding

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

PCSV

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

6.4. Analysis Visit Windows

Data analyzed by-visit-analysis (efficacy [excluding daily diary data], laboratory data, vital sign) will be summarized by the study scheduled visits described in the study protocol and SAP "Schedule of Event".

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

1. If ET visit falls in an analysis window which already has non-missing observed value of this parameter from the scheduled visit, ET will be mapped to the next scheduled visit.

2. If both ET visit and unscheduled visit of the same parameter are available in the same analysis visit window, only ET visit will be mapped.
3. If multiple unscheduled visits of the same parameter are available in the same analysis visit window, the unscheduled visis will be mapped using the following rules:
   a. The closest unscheduled visit from the target day will be selected
   b. If multiple unscheduled visits exist on the same day, the first unscheduled visit will be used.
4. If mapping distance is greater than 4 weeks, the unscheduled visit will not be mapped.

Unscheduled visits and early termination (ET) visit will be mapped per the following analysis visit windows based on the study day/visit of each parameter.

Analysis Visit Window for Efficacy Endpoints

Visit from SOE	Target Study Day*	PFASQ, SPT	PGI-S
Baseline	1	≤ 1	≤ 1
Visit 5	57		[2, 85]
Visit 7 (EOS)	113	≥ 2	≥ 86

*Study days are calculated from the day of 1st injection. Study day = (date of assessment – 1st injection date + 1) when date of assessment ≥1st injection date; otherwise study day = (date of assessment – 1st injection date). If subject never received any dose of study drug, randomization date will be used in the place of 1st injection date.

Analysis Visit Window for Safety and Biomarkers

Visit from SOE	Target Study Day*	Vital Sign	Physical Exam	Laboratory#, PK	ADA	Serum total IgE, Serum sIgE for birch pollen and Bet v 1 and other regional or relevant allergens, Serum sIgE for concomitant and homologous allergens
Baseline	1	≤ 1	≤ 1	≤ 1	≤ 1	≤ 1
Visit 5	57	≥2		[2, 85]		[2, 85]
Visit 7 (EOS)	113		≥2	≥86	≥2	≥86

* Study days are calculated from the day of 1st injection. Study day = (date of assessment – 1st injection date + 1) when date of assessment ≥1st injection date; otherwise study day = (date of assessment – 1st injection date). If subject never received any dose of study drug, randomization date will be used in the place of 1st injection date.
# Post-baseline urinalysis will not be mapping since no scheduled measurements will be collected per protocol.

6.5. Statistical Technical Issues

None.

7. INTERIM ANALYSIS

No formal interim analysis will be conducted.

8. SOFTWARE

All analyses will be done using SAS Version 9.4 or above.

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10. APPENDIX

10.1. Summary of Statistical Analyses

10.1.1. Summary of Efficacy Analyses

Endpoint	Analysis Populations	Primary Statistical Method	Supportive/Sensitive Statistical Method	Subgroup Analysis	Other Analyses
Primary Endpoints					
Daily CSMS, averaged over the duration of the birch pollen season	FAS	Linear-mixed effect model	N/A	Yes	Plot
Secondary Endpoints					
TSS, TNSS and TOSS averaged over the duration of the birch pollen season	FAS	Linear-mixed effect model	N/A	No	Plot
DMS, averaged over the duration of the birch pollen season	FAS	Linear mixed effect model	N/A	No	Plot
Change and percent change from baseline to the end of study in birch SPT mean wheal diameter	FAS	Linear mixed effect model	N/A	No	Plot
The number of “well days” in each of the treatment groups,	FAS	Linear mixed effect model	N/A	No	Plot

10.1.2. Summary of Safety Analyses

Endpoint	Analysis Populations	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Adverse Events	SAF	Descriptive statistics and model-based analyses	No	Yes, for selected AE summary	No
Laboratory Measures	SAF	Descriptive Statistics	No	No	No
Vital sign	SAF	Descriptive Statistics	No	No	No

10.2. Schedule of Time and Events

Table 3: 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

	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**	
Spirometry	X[4]	X						X
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.

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 Protocol 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 Protocol 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 Protocol 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 Protocol Section 9.2.4.1, 9.4.2.2 and 9.4.2.4 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 Protocol 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 Protocol 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 Protocol Section 9.2.4.8 procedural details.
10. Refer to for Protocol 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 Protocol 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 Protocol Section 9.2.12.

10.3. Criteria for Potentially Clinically Significant Values (PCSV)

Parameter	PCSV	Comments
Clinical Chemistry		
ALT*	>3 and ≤ 5 ULN and baseline ≤ 3 ULN* >5 and ≤ 10 ULN and baseline ≤ 5 ULN >10 and ≤ 20 ULN and baseline ≤ 10 ULN >20 ULN and baseline ≤ 20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Each category is calculated independently. * At least one level is required; multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution across the different PCSV levels, additional shift table on ≤3, >3 to ≤5, > 5 to ≤10, >10 to ≤20, and > 20 category for baseline vs. post baseline may be provided
AST*	>3 and ≤ 5 ULN and baseline ≤ 3 ULN* >5 and ≤ 10 ULN and baseline ≤ 5 ULN >10 and ≤ 20 ULN and baseline ≤ 10 ULN >20 ULN and baseline ≤ 20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Each category is calculated independently. * At least one level is required, multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution across the different PCSV levels, additional shift table on ≤3, >3 to ≤5, > 5 to ≤10, >10 to ≤20, and > 20 category for baseline vs. post baseline may be provided
Alkaline Phosphatase	>1.5 ULN and baseline ≤ 1.5 ULN	Enzyme activity must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007.
Total Bilirubin*	>1.5 and ≤ 2 ULN and baseline ≤ 1.5 ULN* >2 ULN and baseline ≤ 2.0 ULN	Must be expressed in ULN, not in µmol/L or mg/L. Categories are cumulative. Concept paper on DILI – FDA draft Guidance Oct 2007. * At least one level is required, multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution of significant level, additional shift table on ≤1.5, >1.5 to ≤2.0 and > 2.0 category for baseline vs. post baseline may be provided
(ALT or AST) and Total Bilirubin	((ALT >3 ULN or AST>3 ULN) and TBILI>2 ULN) and baseline ((ALT ≤3 ULN and AST ≤3 ULN) or TBILI ≤2 ULN))	Concept paper on DILI – FDA draft Guidance Oct 2007.
Creatinine	≥150 µmol/L (Adults) and baseline < 150 µmol/L ≥30% change from baseline and <100% change from baseline ≥100% change from baseline	Benichou C., 1994. 3 independent criteria
Uric Acid	<120 µmol/L and ≥ 120 µmol/L at baseline >408 µmol/Land ≤ 408 µmol/L at baseline	Harrison- Principles of Internal Medicine 17th Ed., 2008. Two independent criteria
Blood Urea Nitrogen (BUN)	≥17 mmol/L and <17 mmol/L at baseline	Two independent criteria
Chloride	<80 mmol/L and baseline ≥ 80 mmol/L >115 mmol/L and baseline ≤115 mmol/L	Two independent criteria
Sodium	≤129 mmol/L and baseline > 129 mmol/L ≥160 mmol/L and baseline < 160 mmol/L	Two independent criteria

Parameter	PCSV	Comments
Potassium	<3 mmol/L and baseline ≥ 3 mmol/L ≥5.5 mmol/L and baseline < 5.5 mmol/L	FDA Feb 2005. Two independent criteria
Triglycerides	≥4.6 mmol/L and < 4.6 mmol/L at baseline	Threshold for therapeutic intervention.
Glucose Hypoglycaemia Hyperglycaemia	≤3.9 mmol/L and <LLN and baseline >3.9 mmol/L or ≥ LLN ≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted) and baseline < 11.1 mmol/L (unfasted); <7 mmol/L (fasted)	ADA Jan 2008.
Albumin	≤25 g/L and >25 g/L at baseline	
Hematology		
WBC	<3.0 Giga/L and ≥3.0 Giga/L at baseline (Non-Black); <2.0 Giga/L and ≥2.0 Giga/L at baseline (Black) ≥16.0 Giga/L and < 16 Giga/L at baseline	Increase in WBC: not relevant. *The default criteria. Summary by race (black and Non-black) are optional. To be interpreted only if no differential count available.
Lymphocytes (ALC)	>4.0 Giga/L and ≤4.0 Giga/L at baseline	
Neutrophils	<1.5 Giga/L and ≥1.5 Giga/L at baseline (Non-Black); <1.0 Giga/L and ≥1.0 Giga/L at baseline (Black)	International Consensus meeting on drug-induced blood cytopenias, 1991. *The default criteria. By race (black and Non-black) are optional.
Monocytes	>0.7 Giga/L and ≤ 0.7 Giga/L at baseline	
Basophils	>0.1 Giga/L and ≤ 0.1 Giga/L at baseline	
Eosinophils	(>0.5 Giga/L and >ULN) and (≤0.5 Giga/L or ≤ ULN at baseline)	Harrison- Principles of Internal Medicine 17th Ed., 2008.
Hemoglobin	≤115 g/L and > 115 g/L at baseline for male; ≤95 g/L and> 95 g/L at baseline for Female. ≥185 g/L and <185 g/L at baseline for Male; ≥165 g/L and < 165 g/L at baseline for Female Decrease from Baseline ≥20 g/L	Three criteria are independent. *The default criteria. By gender (male and female) are optional. Criteria based upon decrease from baseline are more relevant than based on absolute value. Other categories for decrease from baseline can be used (≥30 g/L, ≥40 g/L, ≥50 g/L).
Hematocrit	≤0.37 v/v and > 0.37 v/v at baseline for Male ; ≤0.32 v/v and > 0.32 v/v at baseline for Female ≥0.55 v/v and < 0.55 v/v at baseline for Male ; ≥0.5 v/v and < 0.5 v/v at baseline for Female	Two Criteria are independent *The default criteria. By gender (male and female) are optional.

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

10.4. Search Criteria for TEAE of Special Interest

AESI	Search Criteria
Systemic or severe hypersensitivity reactions	Narrow SMQ for hypersensitivity Note: manual adjudication of relevant PTs will be required by the study medical monitor, before database lock
Severe injection site reactions	HLT=Injection Site Reactions AND Serious AE= “Yes” OR Severity= “severe”

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