COVER PAGE SU-G-01 STATISTICAL ANALYSIS PLAN

Official trial title	A randomised, parallel-group, double-blind, placebo-controlled phase III trial assessing the efficacy and safety of 5-grass mix SLIT-drops in adults with grass pollen-induced rhinoconjunctivitis
NCT number	NCT04881461
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Statistical Analysis Plan

Trial ID: SU-G-01

A randomized, parallel-group, double-blind, placebo-controlled phase III trial assessing the efficacy and safety of 5-grass mix SLIT-drops in adults with grass pollen-induced rhinoconjunctivitis

Sponsor: ALK A/S
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DK-2970 Hørsholm

Investigational medicinal product: 5-grass mix SLIT-drops

Phase: III

EudraCT No.: 2020-000455-12

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ALK approval of statistical analysis plan

Trial statistician:

[redacted]

Signature _____ Date _____

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[redacted]

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[redacted]

Signature _____ Date _____

Head of GPCD:

[redacted]

Signature _____ Date _____

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Version history

This statistical analysis plan (SAP) for trial SU-G-01 is based on protocol version 4.0 dated 12-Nov-2021.

SAP Version	Date	Change	Rationale
1	12-JUL-2023	Not applicable	Original version

1 List of abbreviations

AAS	Asthma analysis set
AE	Adverse event
AIT	Allergy immunotherapy
ALT	Alanine aminotransferase
ARC	Allergic rhinoconjunctivitis
AST	Aspartate aminotransferase
ATS	American Thoracic Society
BP	Blood pressure
BUN	Blood urea nitrogen
DBL	Database lock
DMS	Daily medication score
DPS	Data points sets
DSS	Daily symptom score
eCRF	Electronic case report form
EGPS	Entire grass pollen season
EMA	European medicines agency
[redacted]	[redacted]
ESI	Events of special interest
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAS	Full analysis set
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GCP	Good clinical practice
GLMM	Generalised linear mixed model
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICS	Inhaled corticosteroids
IE	Intercurrent event
IgE	Immunoglobulin E

[redacted]	[redacted]
[redacted]	[redacted]
IMP	Investigational medicinal product
ITT	Intention-to-treat
IRT	Interactive response technology
LABA	Long-acting bronchodilator inhalers
LDH	Lactate dehydrogenase
LSLV	Last subject last visit
MAR	Data missing at random
MCAR	Missing completely at random
MCH	Mean corpuscular haemoglobin
MCID	Minimal clinically important difference
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effect model for repeated measurement
MNAR	Data missing at not random
PGPS	Peak grass pollen season
pH	Potential of hydrogen
PRO	Patient reported outcome
PT	Preferred term
RQLQ	Rhinitis quality of life questionnaire
SABA	Short-acting β_2-agonist
SAE	Serious adverse event
SAP	Statistical analysis plan
SAF	Safety analysis set
SAS®	Computer software for statistical programming
SD	Standard deviation
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SLIT	Sublingual immunotherapy
SOC	System organ class
SPT	Skin prick test
TCS	Total combined score
TEAE	Treatment emergent adverse event
TOS	Total analysis set
WHO	World Health Organization

2 Table of definitions

AE	An AE is any untoward medical occurrence in a clinical trial subject, and which does not necessarily have a causal relationship with the administered IMP.
Completed treatment	A subject is considered to have completed treatment if he/she has been randomized and has not discontinued treatment.
Completed subject	A randomised subject is considered completed if he/she has not discontinued the trial before V9.
Completion date	For each completed subject, the date of the last scheduled procedure/end of trial visit(V9).
Concomitant medication	All medications being continued by a subject on entry into the trial and all medications given in addition to the background treatment during the trial.
Date of last contact	Date of the last contact, either by telephone or in a visit.
End of trial	The end of the trial is defined as the date of V9.
Estimand	A precise description of the treatment effect reflecting the clinical question of interest posed by the trial objective. It summarises at a population-level what the outcomes would be in the same patients under different treatment conditions being compared (ICH 2020).
Grass pollen season	• Start date: The first day of 3 consecutive days with (non-missing) pollen count larger than or equal to 10 grains/m^3. • Stop date: The last day before 3 consecutive days with (non-missing) pollen count less than 10 grains/m^3.
Peak grass pollen season	The 15 days period with the highest average pollen count during the entire grass pollen season.
IMP	A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products with a marketing authorisation used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form.
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or existence of the measurements associated with the clinical question of interest. It is necessary to address intercurrent events when describing the clinical question of interest in order to precisely define the treatment effect that is to be estimated (ICH 2020).
LSLV	Last scheduled physical visit for any subject (V9).
Primary trial completion date	Date of the last data collection for the primary endpoint (ClinicalTrials.gov) is the last scheduled physical visit for any subject (V9).
Rescue medication	Medicinal products provided by ALK when the efficacy of the IMP is not sufficient or likely to cause an AE to the subject or to manage an emergency situation in relation to grass pollen allergy symptoms in agreement with the EMA Definition of IMPs and Use of AMPs Consultation Document (EMA 2016) The rhinoconjunctivitis rescue medication in this trial is: • Antihistamine tablets • Antihistamine eye drops • Corticosteroid nasal spray.
Source documents	Source documents are original documents, data, and records from which the subjects' electronic case report form (eCRF) data are obtained. These include, but are not limited to, hospital records (from which medical history and

	concomitant medication may be summarised into the eCRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.
Systemic corticosteroids	Oral, intramuscular, or intravenously administered corticosteroids.
TEAE	TEAEs are defined as AEs with start date and/or time on or after the time of first IMP administration and no later than 7 days after last IMP administration.
Trial completion	The trial is completed once the CSR is signed.
Withdrawal from trial date	Date of subject withdrawal from trial. In case of subjects lost to follow-up, the withdrawal date is defined as the date the investigator/sponsor decides to withdrawal the subject.

3 Introduction

The SAP supplements the statistical section in the protocol and provides additional details regarding estimands, analysis sets, endpoints and statistical analyses. In Section 9.1 detailed descriptions of pollen seasons, derivation of endpoints, imputation of dates, and the statistical analyses are provided. In supplementary document to the SAP: Documentation of Trial Analysis Sets, the various subject related listings are provided.

Changes to the analyses and changes that might (or can) impact the analyses described in the protocol are documented in Section 6.5.

This SAP has been written and approved before database lock and unblinding.

3.1 Objectives and endpoints

Objectives	**Endpoints**
Primary	
The primary objective is to compare the efficacy of 5-grass mix SLIT-drops to placebo in relieving grass rhinoconjunctivitis symptoms and on the use of symptom-relief medication during the 2nd PGPS.	The primary efficacy endpoint is the average daily allergic rhinoconjunctivitis TCS during the 2nd PGPS
Key secondary	
To measure the impact of treatment with 5-grass mix SLIT-drops compared to placebo on health-related quality of life as a result of grass pollen-induced rhinoconjunctivitis during the 2nd PGPS.	The average weekly overall RQLQ score during the 2nd PGPS.
To compare the efficacy of 5-grass mix SLIT-drops to placebo in relieving grass rhinoconjunctivitis symptoms and on the use of symptom-relief medication during the 1st PGPS.	The average daily allergic rhinoconjunctivitis TCS during the 1st PGPS.
To measure the impact of treatment with 5-	The average weekly overall RQLQ score

grass mix SLIT-drops compared to placebo on health-related quality of life as a result of their grass pollen-induced rhinoconjunctivitis during the 1st PGPS.	during the 1st PGPS.
Supportive secondary	
To measure the impact of treatment with 5-grass mix SLIT-drops compared to placebo on health-related quality of life as a result of their grass pollen-induced rhinoconjunctivitis during the 1st - EGPS and during the 2nd EGPS.	• The average weekly overall RQLQ score during the 1st EGPS. • The average weekly overall RQLQ score during the 2nd EGPS.
To compare the efficacy of 5-grass mix SLIT-drops to placebo in relieving grass rhinoconjunctivitis symptoms and in use of symptom-relief medication during the 1st EGPS and during the 2nd EGPS.	• The average daily allergic rhinoconjunctivitis TCS during the 1st EGPS. • The average daily allergic rhinoconjunctivitis TCS during the 2nd EGPS.
To compare the efficacy of 5-grass mix SLIT-drops to placebo in relieving grass rhinoconjunctivitis symptoms during the 1st and during the 2nd PGPS, and during the 1st EGPS and during the 2nd EGPS.	• The average daily allergic rhinoconjunctivitis DSS during the 1st PGPS. • The average daily allergic rhinoconjunctivitis DSS during the 2nd PGPS. • The average daily allergic rhinoconjunctivitis DSS during the 1st EGPS. • The average daily allergic rhinoconjunctivitis DSS during the 2nd EGPS.
To compare the efficacy of 5-grass mix SLIT-drops to placebo in use of symptom-relief medication during the 1st and during the 2nd PGPS, and during the 1st and during the 2nd EGPS.	• The average daily allergic rhinoconjunctivitis DMS during the 1st PGPS. • The average daily allergic rhinoconjunctivitis DMS during the 2nd PGPS. • The average daily allergic rhinoconjunctivitis DMS during the 1st EGPS. • The average daily allergic rhinoconjunctivitis DMS saduring the 2nd EGPS.
To measure (or compare) the safety and tolerability of 5-grass mix SLIT-drops and (or to) placebo. To measure safety and treatment tolerability of patients who have grass pollen-induced rhinoconjunctivitis and who receive	• TEAEs • ESIs • IMP-related TEAEs

either 5-grass mix SLIT-drops or placebo at randomisation and at the end of trial.	• Treatment-emergent SAEs • TEAEs leading to discontinuation of treatment (using definitions of reasons for discontinuing treatment as in estimand framework in section 6.1.2) • Time to discontinuation of treatment due to TEAEs (using definitions of reasons for discontinuing treatment as in estimand framework in section 6.1.2) • Vital signs during the trial • Physical examination at randomisation and end of trial • Lung function tests at randomisation • Clinical laboratory assessments at randomisation and end of trial
Exploratory	
[redacted]	

3.1.1 Estimands

The formal statistical analysis of primary, key secondary, and some supportive secondary endpoints consists of two strategies (hypothetical and treatment policy defined in Sections 3.1.1.2 and 3.1.1.3, respectively), supporting and supplementary analysis. Each strategy aims to answer a different clinical question of interest by using different ways to address intercurrent events. Definitions of relevant intercurrent events for this trial are provided in Section 3.1.1.1. Each strategy consists of a main approach and sensitivity analysis estimands. Different assumptions are made in each estimand analysis to predict the behaviour of the missing data so that predictions are aligned with the interpretation of the estimand. Sections 6.2.1 and 6.2.2 provide the handling of missing data for each estimand. Hypothetical strategy main analytical approach estimand is referred to as primary estimand, and treatment policy strategy main analytical estimand is referred to as secondary estimand.

The supportive analysis investigates alternative approaches regarding missing data. One supportive analyses are planned for this trial: tipping-point analysis described in Section 6.2.7.1. Two supplementary analyses for hypotetical strategy's main approach estimand are planned: ongoing asthma subgroup analysis described in Section 6.3.1.1 and patients from the same household described in Section 6.3.1.2.

3.1.1.1 Intercurrent events

IE are events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest. It is necessary to address IEs when describing the clinical question of interest to precisely define the treatment effect that is to be estimated.

The IEs that have been identified as relevant is discontinuation of trial treatment. No additional IEs were identified during the conduct of the trial.

Due to the long duration of allergy immunotherapy, rescue medication is dispensed to every subject for ethical reasons. The use of rescue medication is, therefore, part of the treatment policy and as such, it is not classified as an intercurrent event for this trial.

3.1.1.2 Primary estimand

Primary estimand is referred to as the ‘trial product estimand’. The trial product estimand assesses the anticipated effect of the 5-grass SLIT-drops if it is taken as instructed. This estimand is considered to be of most relevance to the patient population, as it describes the potential benefit they could obtain from the 5-grass SLIT-drops if they adhere to treatment for the planned duration. Adherence to treatment is considered important in immunotherapy since the optimal effect of immunotherapy is expected when taken consistently for a longer period.

Using the framework proposed in the ICH 2020, the trial product estimand can be described by:

A. **Treatment:** 5-grass mix SLIT-drops, where rescue medication is taken as required
B. **Population**: adults with grass pollen-induced rhinoconjunctivitis
C. **Variables**: average daily allergic rhinoconjunctivitis TCS during 2nd PGPS
D. **How to account for intercurrent events:** under the hypothetical situation where all subjects have completed treatment for the planned duration (hypothetical strategy).
E. **Population summary**: absolute difference in means between treatment (see Section 9.5).

A hypothetical strategy is used to address the intercurrent event of discontinuation of trial treatment. As such, if a subject discontinues trial treatment, only diary data up until the time of discontinuation is included in the analysis. Any diary data recorded after the discontinuation of trial treatment will be excluded from the analysis. Details of the handling of IEs for primary estimand main estimator are provided in section 6.2.1.

Put differently, the hypothetical assumption is that subjects remain on randomised treatment, but this does not necessarily imply that all subjects randomised to the same treatment experience similar benefits of that treatment. The determining factor is discontinuation of IMP due to following reasons (see section 6.1.2):

- due to “lack of efficacy”
- due to “IMP-related AEs”
- due to “other reasons”

Under the primary estimand, the assumption is that subjects who discontinue IMP due to “lack of efficacy” would not have experienced a treatment benefit other than that observed in the placebo arm. Contrary, subjects discontinuing for either of the two other reasons would have experienced a treatment benefit similar to the observed among subjects randomised to the same treatment arm.

These considerations imply that under the primary estimand, the only observed data used for analysis are obtained before discontinuation of IMP, while data obtained after discontinuation will be treated as missing. It further follows that imputation of missing data or data treated as missing will condition on the reason for discontinuation as outlined above. Moreover, data can be missing even for subjects not discontinuing IMP (e.g. due to low compliance). The reasoning for this type of missingness is ignorable and, consequently, this missing data will be imputed under the assumption that subjects experience a treatment benefit similar to that observed among subjects randomised to the same treatment arm. For further details, see section 6.2.1.

3.1.1.3 Secondary estimand

This estimand is referred to as the ‘treatment policy estimand’. The treatment policy estimand assesses the treatment effect regardless of adherence to treatment and provides a broad perspective of the treatment effect in clinical practice in the expected population of patients. This estimand is in line with the ‘intention to treat’ principle and provides a robust assessment of the efficacy of the 5-grass SLIT-drops.

The treatment policy estimand can similarly to the trial product estimand be described by:

A. **Treatment:** 5-grass mix SLIT-drops, where rescue medication is taken as required.
B. **Population**: Adults with grass pollen-induced rhinoconjunctivitis
C. **Variable**: average daily allergic rhinoconjunctivitis TCS during 2nd PGPS
D. **How to account for intercurrent events:** regardless of whether subjects have complete treatment for the planned duration (treatment policy strategy).
E. **Population summary**: absolute difference in means between treatment (see Section 9.5).

A treatment policy strategy is used to address the intercurrent event of discontinuation of trial treatment. As such, if a subject discontinues trial treatment, all available diary data will be included in the analysis, regardless of adherence to treatment. Details of the handling of IEs for secondary estimand main estimator are provided in section 6.2.2.

The secondary estimand's main feature is that subjects complete the trial though not necessarily, while still exposed to IMP. Therefore, all observed data is used in the analysis of this estimand irrespective of adherence to IMP, and only truly missing data needs to be imputed.

3.2 Study design

This is a phase III, randomised, parallel-group, double-blind, placebo-controlled trial of 5-grass mix SLIT-drops in adults with grass pollen-induced moderate to severe allergic rhinoconjunctivitis, with or without asthma. The trial was conducted over two grass pollen seasons.

A total of 440 adult subjects were planned to be randomised (1:1) to continuously receive either active treatment (grass SLIT-drops) or placebo treatment once daily

All subjects should receive daily treatment continuously from at least 16 weeks before the anticipated start of the 1st EGPS through the 2nd EGPS (definitions are provided in Section 9.1), corresponding to approximately 26 months of treatment (see Figure 1). Open-label rescue medication for AR/C was provided during the GPS. The subjects were asked to complete a RQLQ diary at V3 during the off-season for grass and tree pollen and then weekly during the EGPSs. The subjects were furthermore asked to fill in an eDiary daily during the EGPSs to capture information on rhinitis and/or conjunctivitis symptoms, use of symptom-relieving medications, and impact of rhinitis and/or conjunctivitis quality of life.

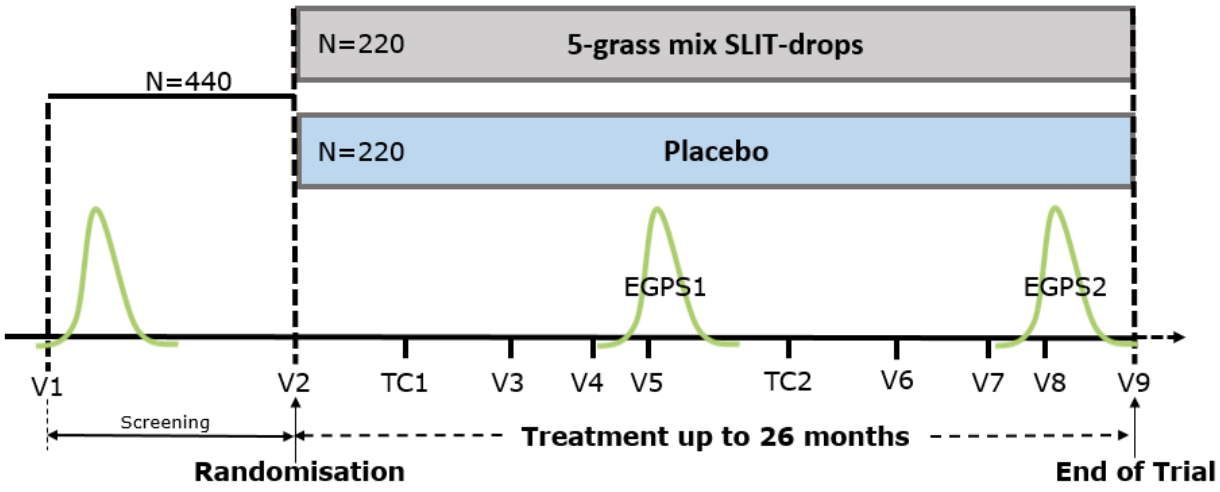

Figure 1 Trial design

Data for the primary endpoint were collected by the subjects by completing questions related to their daily symptoms and medication use in an electronic diary (eDiary).

No interim analysis was planned.

Routine safety surveillance was conducted throughout the trial. The follow-up visit was conducted via a telephone call approximately one week after the end of trial visit.

The first subject was randomised 15-Aug-2022 and subjects were planned to received treatment for 26 months. A total of 445 subjects were randomised and dosed.

3.2.1 Flow chart

The flow chart can be found in protocol.

3.2.2 Actual trial timelines

The actual trial timelines are presented in Table 1.

Table 1 Trial timelines

First subject first visit (FSFV)	02-May-2021
Last subject randomised	31-Dec-2021
Last subject last visit (LSLV)	22-Sep-2023

3.2.3 Randomisation

The randomisation list was generated by a trial-independent statistician and will not be accessible to trial personnel involved in the conduct of the trial, until the database has been locked and all protocol deviations that have been identified, evaluated, classified, categorised and closed.

The randomisation was administered centrally via IRT and treatment allocation was stratified based on pre-existing diagnosis of asthma to ensure equal distribution of subjects with or without asthma across the treatments.

Randomisation errors

During the conduct of the trial, one randomisation error has occurred. An overview of the error can be found in supplementary document to the SAP: Documentation of Trial Analysis Sets. The randomisation error was included in the FAS. If missing data have occurred, it will be handled using the estimand framework.

4 Statistical hypotheses

4.1 Multiplicity adjustment

The trial product estimand is the primary estimand for all endpoints. The analyses for the primary and for the three key secondary endpoints will be controlled for multiplicity to ensure a family wise type I error rate is no larger than 5%.

The multiplicity will be controlled by employing a hierarchical testing procedure by pre-specifying the order of the hypothesis to be tested. For the primary and key secondary endpoints the null hypothesis tested, is the hypothesis no difference between placebo and 5-grass mix SLIT-drops treatment group.

The testing order of hypothesis is:

1. The primary efficacy analysis of the average daily allergic rhinoconjunctivitis TCS during the 2nd PGPS.
2. The key secondary efficacy analysis of average weekly overall RQLQ score during the 2nd PGPS.

3. The key secondary efficacy analysis of average daily allergic rhinoconjunctivitis TCS during the 1st PGPS.
4. The key secondary efficacy analysis of average weekly overall RQLQ score during the 1st PGPS.

The primary endpoint is the 1st hypothesis in the hierarchy and will be tested on a 5% significance level. The testing of endpoints from the 2nd to the 4th in the hypothesis hierarchy will only be is only carried out formally if all previously tested hypotheses are statistically significant at the 5% level.

Additional endpoints and analyses are supportive in nature, thus they will not be controlled for multiplicity.

5 Analysis sets

5.1 Population sets

For the purposes of analyses, the following subject analysis sets are defined: TOS, FAS, SAF and AAS. The definitions are provided in Table 2.

Table 2 Population sets

Subject analysis sets	Description
Total Analysis Set (TOS)	All subjects who signed informed consent and thus includes screening failures.
Full Analysis Set (FAS)	FAS consists of all randomised subjects. Subjects are analysed as randomised i.e. according to their randomised assignment of treatment.
Safety Analysis Set (SAF)	SAF consists of all randomised subjects who received at least one dose of IMP. Subjects are analysed as treated i.e. according to treatment they actually received.
Asthma Analysis Set (AAS)	The AAS is a subgroup of the FAS and consists of subjects that have ongoing asthma at randomisation. Subjects are analysed as randomised i.e. according to their randomised assignment of treatment.

The TOS will be used for subject disposition output. The FAS will be used for baseline tables, all efficacy endpoints reporting; SAF will be used for safety data reporting; and AAS will be used for selected summary tables.

5.2 Data point sets

The following DPS are defined:

Table 3 Data point sets and observation periods.

DPS	Description
DPS1 (On-treatment observation period)	This includes all assessments that are observed while a subject is on treatment and within grass pollen season. For subjects who completed the trial, all assessments will be included, and for a subject that discontinued trial treatment, all assessments will be used until the treatment discontinuation. For relevant endpoints, baseline observation will also be included ([redacted]).
DPS2 (In-trial observation period)	This includes all assessments that are observed while a subject is in trial and within grass pollen season. For relevant endpoints, baseline observation will also be included ([redacted]).

FAS and DPS1 will be used to estimate the hypothetical strategy estimand, whereas FAS and DPS2 will be used to estimate the treatment policy estimand. Note that the on-treatment study period is only applicable for subjects exposed to randomised treatment.

6 Statistical analyses

Statistical analyses will be carried out by ALK, Biometrics, Hørsholm, Denmark. All computation will be performed using the statistical analysis system (SAS), SAS® version 9.4 or later.

The analyses described in this section along with the supporting information supplied in Section 9 specify the statistical analyses.

6.1 General considerations

The efficacy data will be analyzed using estimand framework. The primary and first key secondary endpoints will be analyzed based on on-treatment (DPS1) and in-trial (DPS2) data, while the rest of the endpoints will be analyzed based on on-treatment (DPS1) data. Different approaches of handling missing data will be applied. Overview of analysis methods and analysis sets to be used are summarized in **Error! Reference source not found.**.

Table 4 Summary of analyses

Endpoint	Analysis methods	Analysis sets	Data type
Primary endpoint:TCS during 2nd PGPS Key secondary enpoind: RQLQ during 2nd PGPS	Trial product estimand – main approach	FAS	Imputed, DPS1
	Trial product estimand – sensitivity analysis		
	Treatment policy estimand – main approach		Imputed, DPS2
	Treatment policy estimand – sensitivity analysis		
	Supportive analysis: Tipping-point analysis under the trial estimand – main approach		Imputed, DPS1
	Supplementary analysis: Ongoing asthma subgroup analysis		
	Supplementary analysis: Subjects from the same household		
	Supplementary analysis: Symptoms-score tertiles analysis		Observed, DPS1
	Descriptive analysis	FAS/AAS	
Key secondary enpoind: TCS during 1st EGPS RQLQ during 1st EGPS	Trial product estimand – main approach	FAS	Imputed, DPS1
	Trial product estimand – sensitivity analysis		
	Treatment policy estimand – main approach		Imputed, DPS1
	Treatment policy estimand – sensitivity analysis		
	Descriptive analysis		Observed, DPS1
Secondary endpoints: TCS, RQLQ, DMS and DSS	Trial product estimand – main approach	FAS	Imputed, DPS1
	Descriptive analysis		Observed, DPS1
Secondary endpoints: safety and tolerability	Descriptive analysis	SAF	Observed
[redacted]			

Unless otherwise mentioned all the statistical tests described in this section will use a significance level of 5% and all tests and confidence intervals will be two-sided. All null hypotheses are "*no differences in means between treatment arms*" and the alternative hypotheses will always be "*a (not specified) difference*".

Descriptive statistics for efficacy endpoints will be based on observed on-treatment data. Descriptive statistics for numerical (continuous) variables include displaying treatment group mean, SD, median, minimum and maximum. Descriptive statistics for categorical variables will include frequency tables displaying the numbers and percentages.

Adjusted or "estimated" treatment group means (least squares means) will be estimated using coefficients across classification effects and, where relevant, continuous covariates proportional to those found in the relevant analysis set at baseline.

In addition to the inferential analyses, all efficacy endpoints will be presented in summary tables.

Where appropriate, summaries for the endpoints will be provided for 1st and 2nd seasons (eDiary data) and PGPS/EGPS, or by visits (vital signs, clinical laboratory assessments, physical examinations, and lung-function tests).

6.1.1 Considerations regarding countries

Variation between different countries and sites are expected due to variation in geography and climate and thus grass exposure which may affect assessments. Further, variation in standard treatment procedures, and possible differences in the conduct of the trial are expected to vary between countries. Variation between sites (centres) is also expected but is assumed to be small compared to the variation between countries. The major source of variability is expected to be pollen exposure. Some sites can have very few subjects making it unreasonable to include sites as a covariate in the analysis model. In this trial, country is used as a covariate in the models.

6.1.2 IMP discontinuation

As pointed to previously, reasons for discontinuation of IMP will be categorised into three categories: 1) due to "IMP-related AE" 2) due to "lack of efficacy" and 3) due to "other reasons". As the eCRF defined that trial- and treatment discontinuation reasons are not corresponding to this tripartite split the following mapping form the observed data in the eCRFs to the three categories will be performed:

Treatment discontinuation reasons presented in the eCRF's "Visit Status"-form are:

- Severe or persistent symptoms of eosinophilic oesophagitis

- Pregnancy
- Physician's decision
- Adverse event(s)
- Asthma difficult to control
- Treatment is unblinded

while withdrawal from trial reasons presented in eCRF's "End of study"-form are:

- Screening failure
- Withdrawal of consent
- Adverse event(s)
- Lost to follow-up
- Non-compliance with protocol
- Pregnancy
- Death
- Lack of efficacy
- Randomisation code broken
- Other

Before DBL, the discontinuation of treatment is re-defined and the subject specific list of discontinuations and their classifications to fit the estimand framework is in supplementary document to the SAP: Documentation of Trial Analysis Sets.

Discontinuation due to AEs

A subject is considered discontinued from the treatment due to IMP-related AE if the following conditions are met:

1. If, in the "Visit status"-form or End of study"-form reported reason for treatment discontinuation or withdrawal from trial is:
    - Severe or persistent symptoms of eosinophilic oesophagitis
    - Adverse event(s)
    - Asthma difficult to control
2. And AEs related to discontinuation are classified as possibly or probably related.

Discontinuation due to lack of efficacy

A subject is considered discontinued from the treatment due to lack of efficacy if the following conditions are fulfilled:

1. If, in the "End of study"-form, it is noted that the subject withdrawal from trial due to "Lack of efficacy".

Discontinuation due to "other reasons"

A subject is considered discontinued from the treatment due to other reasons if the subject discontinues treatment or withdrawal from trial due to other reasons than mentioned above.

6.2 Analyses

The main estimator and sensitivity estimator for both estimands will be based on an identical method of statistical analysis .The estimator for all estimand will be based on MMRM with treatment, year, treatment and year interaction, and ongoing asthma status as fixed effects and country and year interaction as random class effect (more details specified Section 9.5.2). Exposure to pollen can vary yearly; thus, treatment effects may differ each year. Therefore, the model contains treatment and year interaction as a fixed effect. Pollen count depends on local geography and weather and can vary locally yearly. Thus, the model comprises country and year interaction as a random effect.

The actual data used in each analysis may vary according to the different strategies taken for the handling of IEs and missing data. In the trial product estimand, data until treatment discontinuation will be included in the analysis and treatment policy estimand all observed data will be included.

Imputations will be done on the average scores, but not daily/weekly values. To calculate an average score, only one observation is needed.

Missing data will be imputed by sampling from an appropriate pool that matches the subject's characteristics. Missing data for 1st year will be imputed from observed data in 1st year, and missing data for 2nd year will be imputed from the observed data in 2nd year. Thus, PGPS data will be imputed from observed PGPS data and EGPS from observed EGPS. Missing data for subjects with ongoing asthma will be imputed from subjects with ongoing asthma, and missing data for subjects without ongoing asthma will be imputed from subjects without ongoing asthma following the rules defined below.

If the IE occurred after 1st season, then the missing data imputation in the 1st year will be handled disregarding the IE and imputed under assumption MAR (data will be imputed from the subject's own treatment arm for both estimands). The missing data of 2nd season will be handled based on IE. If IE occurred after 2nd, the missing data will be handled disregarding IE in both seasons. For more details, see Sections 6.2.1 and 6.2.2.

The imputation pool of subjects will consist of subjects with all and partially observed data. In other words, if subject will be used in the analysis, they will also be used in the pool of the subjects to impute from.

Rubin's (Rubin 1987) multiple imputation strategy will be used to pool results of multiple analysis.

6.2.1 Handling of intercurrent events and missing data for the trial product estimand – main approach

The relevant endpoints will be compared between treatment groups using the trial product estimand with population FAS and data point DPS1. This means that subjects for whom the endpoint is missing (the exclusion of daily diary data due to discontinuation of trial treatment) will still be included in the analysis through multiple imputations under the hypothetical situation where subjects continued to take trial treatment as planned. The missing data imputation is done using the following rules:

- For subjects that discontinue trial treatment due to lack of efficacy, multiple imputation of the missing endpoint will be taken from the placebo group. This assumes that had the subject continued to take trial treatment, they would have experienced similar efficacy to subjects in the placebo arm. Data are assumed to be missing not at random (MNAR).

- For subjects that discontinue trial treatment due to IMP-related AEs, multiple imputation of the missing endpoint will be taken from their own treatment group. This assumes that the level of efficacy that would have been experienced by the subject if they had continued to take trial treatment is unrelated to the occurrence of the AE and, if they had continued to take trial treatment, they would have experienced similar efficacy to subjects in their own treatment group irrespective to randomised treatment. Data is assumed to be missing at random (MAR).
- For subjects that discontinue trial treatment due to any other non-IMP-related reason or subjects that have missing data but completed the trial, multiple imputation of the missing endpoint will be from their own treatment group. This assumes that the level of efficacy that would have been experienced by the subject had they continued to take trial treatment is not related to their discontinuation of trial treatment. Data is assumed to be MAR.

In summary, missing data is imputed based on the following observed on-treatment data (Table 5):

Table 5: Sources of observed data used for imputation under the primary estimand.

Missing data or data treated as missing in 2022, 2023 or in both years.			Observed data as source for bootstrap: sampling from subjects with complete 1st and 2nd year data for the pollen-period under consideration	
Randomised treatment	Discontinuation reason	Ongoing asthma status at screening	Randomised treatment	Ongoing asthma status at screening
Active	Lack of efficacy[A]	Yes	Placebo	Yes
Active	IMP-related AEs[A]	Yes	Active	Yes
Active	Other[A]	Yes	Active	Yes
Active	Data is missing[B]	Yes	Active	Yes
Active	Lack of efficacy[A]	No	Placebo	No
Active	IMP-related AEs[A]	No	Active	No
Active	Other[A]	No	Active	No
Active	Data is missing[B]	No	Active	No
Placebo	Lack of efficacy[A]	Yes	Placebo	Yes
Placebo	IMP-related AEs[A]	Yes	Placebo	Yes
Placebo	Other[A]	Yes	Placebo	Yes
Placebo	Data is missing[B]	Yes	Placebo	Yes
Placebo	Lack of efficacy[A]	No	Placebo	No
Placebo	IMP-related AEs[A]	No	Placebo	No
Placebo	Other[A]	No	Placebo	No
Placebo	Data is missing[B]	No	Placebo	No

[A]: Data is either (actually) missing or treated as missing because of “earlier” treatment discontinuation

[B]: Data is missing prior to any observed date of treatment discontinuation

6.2.2 Handling of intercurrent events and missing data for the trial product estimand – sensitivity analysis

The sensitivity analysis for the trial product estimand will use the multiple imputation policy described above for the main analysis except:

- For subjects that discontinue the trial treatment due to IMP-related AEs, multiple imputation of the missing endpoint will be from the placebo group. This assumes subjects reporting IMP-related AEs would have experienced a level of efficacy similar to subjects in the placebo group if they had continued to take trial treatment. Data is assumed to be MNAR. See Table 6.

Table 6: Sources of observed data used for imputation under the sensitivity analyses of the primary estimand.

Missing data or data treated as missing in 2022, 2023 or in both years.			Observed data as source for bootstrap: sampling from subjects with complete 1st and/or 2nd year data for the pollen-period under consideration	
Randomised treatment	Discontinuation reason	Ongoing asthma status at screening	Randomised treatment	Ongoing asthma status at screening
Active	Lack of efficacy[$]	Yes	Placebo	Yes
Active	IMP-related AEs[A]	Yes	Placebo	Yes
Active	Other[A]	Yes	Active	Yes
Active	Data is missing[B]	Yes	Active	Yes
Active	Lack of efficacy[A]	No	Placebo	No
Active	IMP-related AEs[A]	No	Placebo	No
Active	Other[A]	No	Active	No
Active	Data is missing[B]	No	Active	No
Placebo	Lack of efficacy[A]	Yes	Placebo	Yes
Placebo	IMP-related AEs[A]	Yes	Placebo	Yes
Placebo	Other[A]	Yes	Placebo	Yes
Placebo	Data is missing[B]	Yes	Placebo	Yes
Placebo	Lack of efficacy[A]	No	Placebo	No
Placebo	IMP-related AEs[A]	No	Placebo	No
Placebo	Other[A]	No	Placebo	No
Placebo	Data is missing[B]	No	Placebo	No

[A]: Data is either (actually) missing or treated as missing because of “earlier” treatment discontinuation

[B]: Data is missing prior to any observed date of treatment discontinuation

Otherwise, the sensitivity analyses will be similar to the main analyses.

6.2.3 Handling of intercurrent events and missing data for the treatment policy estimand – main approach

The relevant endpoints will be compared between treatment groups using the treatment policy estimand using FAS and DPS2. For subjects discontinuing trial treatment, all diary data (including data collected after discontinuation of trial treatment) will be included in the derivation of the relevant endpoint. Subjects for whom the primary endpoint is missing will be included in the analysis through multiple imputation as follows:

- For subjects discontinuing trial treatment due to IMP-related AEs or lack of efficacy, multiple imputation of the missing endpoint will be from the placebo group. This assumes that missing data following treatment-related discontinuation of trial treatment is MNAR

and that subjects no longer taking active treatment for these reasons would have shown similar efficacy to subjects receiving placebo.

- For subjects discontinuing trial treatment due to other reasons than IMP-related AEs or lack of efficacy reasons or subject have missing data, multiple imputation of the missing endpoint will be taken from their own treatment group. This assumes that the missing data are MAR.

Otherwise, the analyses of the secondary estimand are similar to the main analyses of the primary estimand. The summary of missing data imputation is provided in Table 7

Table 7: Sources of observed data used for imputation under the secondary estimand.

Missing data in 2022, 2023 or in both years			Observed data as source for bootstrap: sampling from subjects with complete 1st and/or 2nd year data for the pollen-period under consideration	
Randomised treatment	Discontinuation reason	Ongoing asthma status at screening	Randomised treatment	Ongoing Asthma status at screening
Active	Lack of efficacy	Yes	Placebo	Yes
Active	IMP-related AEs	Yes	Placebo	Yes
Active	Other	Yes	Active	Yes
Active	Data is missing[A]	Yes	Active	Yes
Active	Lack of efficacy	No	Placebo	No
Active	IMP-related AEs	No	Placebo	No
Active	Other	No	Active	No
Active	Data is missing[A]	No	Active	No
Placebo	Lack of efficacy	Yes	Placebo	Yes
Placebo	IMP-related AEs	Yes	Placebo	Yes
Placebo	Other	Yes	Placebo	Yes
Placebo	Data is missing[A]	Yes	Placebo	Yes
Placebo	Lack of efficacy	No	Placebo	No
Placebo	IMP-related AEs	No	Placebo	No
Placebo	Other	No	Placebo	No
Placebo	Data is missing[A]	No	Placebo	No

[A]: Data is missing prior to any observed date of treatment discontinuation

The sensitivity analysis for the treatment policy estimand will use multiple imputation from the placebo group for all subjects that discontinue trial treatment regardless of the reason for discontinuation.

6.2.4 Handling of intercurrent events and missing data for the treatment policy estimand – sensitivity analysis

The sensitivity analysis for the treatment policy estimand will use multiple imputation from the placebo group for all subjects that discontinue trial treatment regardless of the reason for discontinuation. For subject, that has missing data but completed the trial data is imputed from they own treatment arm.

6.2.5 Missing data examples

Several examples are provided to illustrate how missing data will be handled according to the rules defined above. Importantly "missing data" under the primary estimand does not necessarily mean that data were not observed but rather actually missing data and observed data that is considered missing due to treatment discontinuation.

For each year (1st and 2nd season), calculating average TCS, DSS, DMS, and RQLQ is a simple average of the diaries' observed records (no imputation of daily data) for some specific period.

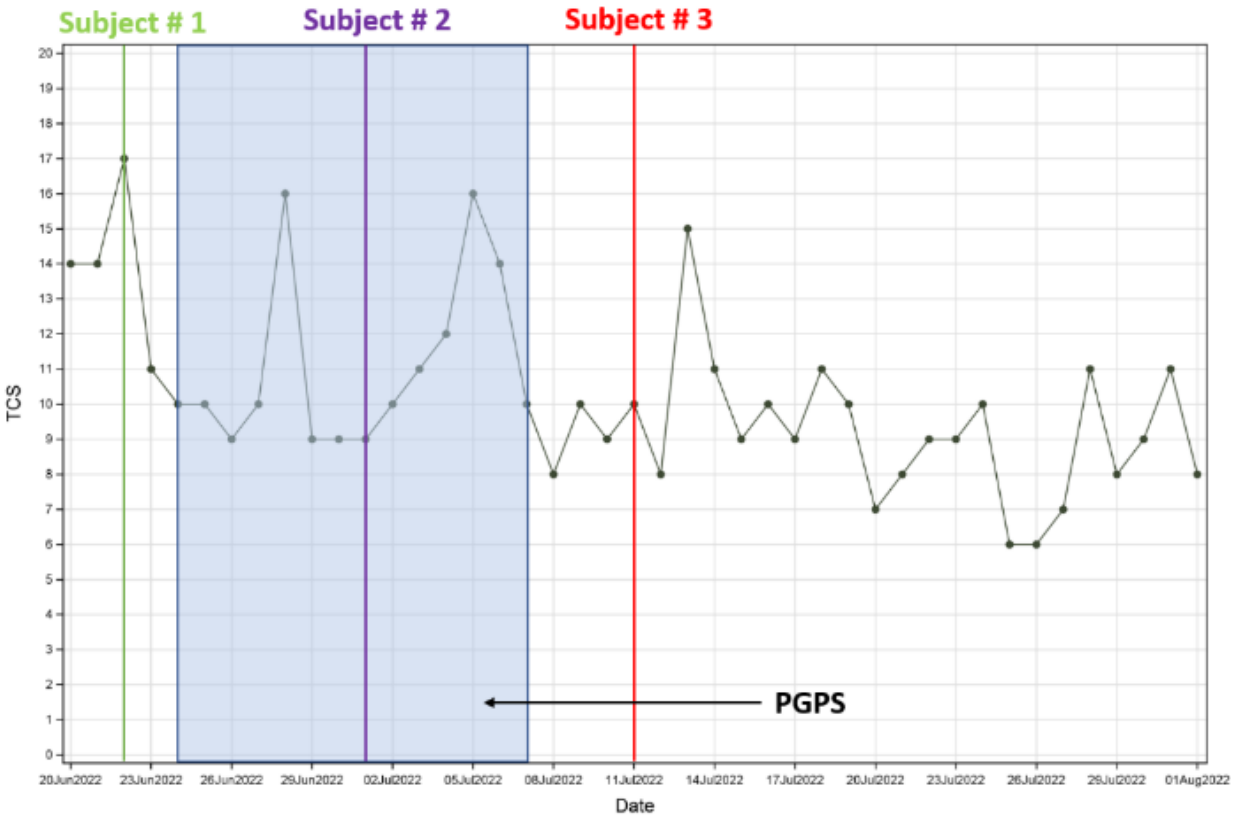

Figure 2: TCS trajectory.

The Figure 2 shows three imaginary subjects between the 20th of June, 2022 and the 1st of August, 2022, as an example of daily records of TCS. The hypotetical grass pollen season is from 20th of June to 1st of August, 2022. The three subjects have identical TCS trajectories but discontinue treatment at three different time points. Also, we consider the case for the PGPS (the case for the EGPS and the year 2023 are dealt with similarly).

For these subjects, the 2022-PGPS lies between 24th of June and 7th of July, 2022.

- Subject (#1) discontinues IMP on 22nd.of June. Thus, the entire PGPS lies after IMP discontinuation; therefore, this subject has no observations. Consequently, all records pertaining to the PGPS in 2022 and 2023 must be imputed. The observed data until 22nd of June will be used for the estimation of average endpoints for EGPS for 2022.
- Subject (#2) discontinues IMP on 1st of July. This subject has observations between 24th June and 1st of July from the PGPS, and only these observations will be used as the basis for the subject's 2022 PGPS record. This subject is thus fully observed in 2022's EGPS and PGPS. Consequently, only imputations for 2023 will be performed.
- Subject (#3) discontinues IMP after the end of the PGPS 2022. All the subject's records from the PGPS will be used to calculate the average TCS, and consequently, only imputations for 2023 will be performed.

Consider one more subject, which is not illustrated in Figure 2:

- Subject (#4) discontinued IMP before 20th of June, 2022. Though this subject might have some recordings before the actual start EGPS 2022, but all the average endpoints will have to be imputed for both years.

There are several observations to be aware about from the example above:

- The pattern of missingness (and consequently the pattern of imputation) may differ within the same subject for EGPS and PGPS. This pattern is (for each endpoint/pollen season) either:
  - Completely missing (both years 2022 and 2023 are missing)
  - Observed in 2022 but missing in 2023 (monotone missing pattern)
  - Missing in 2022 and observed in 2023 (this can happen if diary data is, in fact, missing during, the relatively short PGPS (2 weeks) in 2022 but the subject otherwise completed the trial and treatment) (not monotone missing pattern)
- "Completer" is a subject that is observed during both years.
- The number of observations upon which a subject's observed (EGPS and PGPS) average data depend considerably among subjects.

6.2.6 Exploratory endpoint analysis

[redacted]

6.2.7 Supportive analyses

6.2.7.1 Tipping point analysis under the primary and secondary estimand

The objective of tipping point analysis is to investigate the feasibility of alternative assumptions regarding missing data, leading to a change in conclusions. In other words, it aims to determine the threshold at which the evidence of a treatment effect no longer remains.

The tipping point analysis will be performed as follows: a penalty (a number) is added to all imputed values in the active treatment group, and the analysis is repeated. The considered penalty step for TCS will be 0.5 and for RQLQ will be 0.05. The penalty is gradually increased until the point, the tipping point, where the null hypothesis is no longer rejected. If the value of the tipping-point is considered a clinical plausible this analysis does not support rejecting primary hypothesis.

The tipping point analysis will be performed for primary and first key secondary endpoints using trial product estimand main approach.

6.3 Supplementary analyses

6.3.1.1 Asthma subgroup analysis

The subgroup analysis will test if the effect of treatment differs between subjects with and without ongoing asthma at screening. The analysis will be performed on imputed data using primary and secondary estimand, main analysis approaches. To be specific, data will be analysed using a Mixed Model of Repeated Measurements (MMRM) with treatment, year; treatment and year interaction, and ongoing asthma status as fixed effects and country and year interaction as random class effect and allowing unequal R-matrices among the two treatment arms.

Treatment contrasts corresponding to each level of ongoing asthma status will be output along with multivariate tests of year-specific subgroup effects: that is, for each year, the two treatment contrasts are statistically significant from one another.

6.3.1.2 Subjects from the same household

The subjective nature of PRO measure may influence the overall quality of the data Chang et al. 2019. Multiple factors can impact the truthfulness of the data, but in this supportive analysis, the aim is to investigate whether subjects from the same household can influence each other's evaluation of symptoms.

This evaluation will be done by removing all subjects from the same households from the analysis. The list of subjects will be provided in the supplementary document to the SAP: Documentation of Trial Analysis Sets before DBL. The evaluation will be done on the primary endpoint (TCS during PGPS) and the first key secondary endpoint (RQLQ during PGPS). The analysis is done using primary estimands, the main analysis approach.

If there is no, or minimal influence, the results are expected to be similar to those using all subjects' data. This analysis will be done only if in total 10 subjects will be from the same household.

6.3.1.3 Symptoms-score tertiles analysis

Howarth *et al.* (2012) examined effects of allergen immunotherapy where study sites were grouped by the level of allergic rhinoconjunctivitis symptoms (low, medium, high) among placebo-treated subjects. The hypothesis was that sites where the symptoms scores were the highest under placebo, the seasonal disease activity was the highest and, presumably, therefore an effect of the allergen immunotherapy could potentially be greater here than at sites where the symptoms scores under placebo were lower.

To address this, trial sites will be grouped into tertiles according to the trial sites' placebo mean TCS in the PGPS based purely on observed TCS values (i.e. no imputation) for each of the two years (2022 and 2023), respectively. TCS and RQLQ will be analysed for the PGPS using the

DPS1/on-treatment observation period data. The model(s) will be ANCOVAs run for each year separately. The model will include treatment, seasonal-disease-activity-subgroup and asthma strata as fixed effects and allowing unequal residual variances among the two treatment arms.

Treatment contrasts corresponding to each level of trial-site-subgroup will be output along with (multivariate) tests of (year-specific) subgroup effects: that is, for each year, whether the three treatment contrasts (corresponding to the three tertiles subgroups) are statistically significant from one another.

6.4 Safety analyses

All safety summary tables, figures and listings will be based on the SAS unless otherwise specified.

6.4.1 Extent of exposure

IMP exposure

Exposure will be assessed by calculating difference between the number of doses dispensed and the number of doses returned. Returned doses were counted by counting unopen foil bags and multiplying by number of doses in a bag (5 doses in a foin bag) Accountability by an investigator is performed at V3 (1st off-season), V4 (1st pre-EGPS), V5 (1st on-seasons), V6 (2nd off-seasons), V7 (2nd pre-EGPS), V8 (2nd on-season) and V9 (end of trial). The number of doses taken will be summarised by treatment group.

IMP duration

The duration of treatment for each subject will be calculated from the date of randomisation up until and including the date of the last IMP intake. Treatment duration will be summarised by treatment group.

IMP compliance

IMP compliance (%) will be assessed as the number of doses taken divided by the treatment duration multiplied by 100. As IMP exposure will be counted without taken into account dosses lost, thus IMP compliance will be capped to 100%. IMP compliance will be summarised by treatment group.

eDiary compliance

eDiary compliance will be summarised by treatment group and year. Here, compliance is calculated separately for the daily entries (TCS) and the weekly entries (RQLQ). Compliance is calculated as the number of actual entries to the number of intended entries. For subjects withdrawing from the trial, their withdrawal date (if during the EPGS) will serve as the cut-off when calculating the number of intended entries.

IMP interruption

IMP interruption is defined as if IMP intake is interrupted for more than 7 days and not in relation to an AE. Number of subjects that have IMP interruptions, number of IMP interruptions will be summarised by treatment group and year.

6.4.2 Adverse events

MedDRA version 23.1 will be used for reporting of AEs. All summaries will be provided using SAF.

6.4.2.1 Events of special interest

An AE is any untoward medical occurrence in a subject that does not necessarily have a causal relationship with the administered IMP. An AE is a TEAE if the time of onset is on or after the time of the first dose administration of IMP and, no later than seven days seven days after the last dose administration of IMP. Selected (non-serious or serious) AEs are considered ESIs. ESIs are events that are considered critical for the evaluation of the product's safety profile and for which additional data was collected. ESIs for this trial are:

- Systemic allergic reactions including anaphylaxis
- Events treated with adrenaline
- Severe local swelling of the mouth and/or throat
- Eosinophilic oesophagitis.

6.4.2.2 Reporting of adverse events

All TEAEs will be summarised by treatment group according to causality (IMP related or not), severity (mild, moderate, severe), seriousness (yes/no), action taken, outcome (recovered or resolved / recovered or resolved with sequelae / not recovered or not / resolved / fatal / unknown), and whether the event led to IMP discontinuation and interruption. The number of subjects in treatment group, the frequency and proportion of subjects having the event, as well as the number of events and proportion of events will be displayed. A similar summary table will be produced for all IMP-related TEAEs.

All TEAEs and all IMP-related TEAEs will be summarised (in separate tables) by treatment group, SOC, and PT, displaying number of subjects in treatment group, and number and frequency of subjects having the event. The tables will be sorted according to most frequent SOC and PT in the active treatment group, and the most common TEAEs defined as those that are present in at least 2% of subjects in the active treatment group will be marked.

Severe TEAEs will be listed only if there are fewer than 10 events in total. Otherwise, severe TEAEs will also be summarised and presented by SOC and PT similar to how TEAEs are presented. The same follows for SAEs, TEAEs leading to IMP discontinuation, and IMP-related TEAEs leading to IMP interruption.

For most frequent IMP-related TEAEs (present in at least 2% of subject in the active treatment group) onset and duration will be presented as follows: time to onset and average duration both in days, will be presented by SOC and PT and treatment. In addition, for day 1 of treatment average time to onset in minutes will be presented by SOC PT and treatment.

In addition, most frequent non-serious TEAEs reported in at least 5% of subjects in any treatment group by SOC and PT.

For the most frequent IMP-related TEAEs which are recurrent, the average daily duration and the average duration in days from first to last occurrence will be presented by PT and treatment.

A table with the overall summary of the safety profile will be produced showing number of subjects with TEAEs, IMP-related TEAEs, IMP-related severe TEAEs, IMP-related treatment-emergent SAEs, IMP-related TEAEs leading to IMP discontinuation and each type of IMP-related treatment-emergent ESI by treatment group.

Serious TEAEs, severe TEAEs, TEAEs leading to IMP discontinuation, IMP-related TEAEs leading to IMP interruption, individual ESIs, TEAEs, and all non-treatment-emergent AEs for the total analysis set will be listed. Medication errors will also be listed. Pregnancies will be listed if fewer than 10 cases have been reported; otherwise summarised.

6.4.3 Additional safety assessments

Shift tables will be produced for clinical laboratory assessments (haematology, blood chemistry and urinalysis) assessments including the categories low, normal, high, and missing as relevant, where the shift table will include the categories normal, abnormal not clinically significant, and abnormal clinically significant.

Vital signs and the pulmonary function test parameters (FVC, FVC percent predicted, FEV_1, and FEV_1 percent predicted) will be summarised by visit and treatment group.

Findings of urine pregnancy test will be summarised in a listing.

6.5 Changes and/or deviations to protocol-planned analyses

Several changes were made to the statistical analysis described in the trial protocol. The list of changes is summarised in this section:

- PP analysis set is removed from analysis sets used in this trial. This analysis set does not align with the estimand framework; therefore, it will not be used in this trial.
- Safety and tolerability objectives and endpoints are added as supportive secondary endpoints.
- As described in the estimand framework, the most important IE is the discontinuation of IMP. The IMP discontinuation was not collected in the relevant manner in eCRF. Discontinuation of IMP is then re-classified based on reported IMP discontinuation and trial withdrawal reason (see Section 6.1.2), and these re-classified reasons are used in the estimand framework.
- In this trial, subjects were stratified based on their history of asthma in adulthood. During the trial, it was determined that it is most relevant for interpretation of the disease and treatment is ongoing asthma status at screening. Therefore, the asthma status at screening will be used in the analysis models instead of asthma strata. Twenty one subjects were stratified as asthmatics but did not have ongoing asthma at screening. Subjects with ongoing asthma are expected to be well-balanced between treatment arms.
- In the protocol, the primary and key secondary endpoint estimator contains the trial site/country as a random effect. In SAP, county and year interaction is a random effect. The change accounts for the variability of pollen load yearly in each country.
- [redacted].
- In the protocol, the proposed MCID is 0,16. Since the protocol proposal, additional research was performed and based on published results presented new MCID for PGPS is 0,1 and EGPS 0,22 (**Blaiss et al. 2022**).
- Pollen season end date and pollen peak definition a modified to add clarity. Pollen season end date is specified that it is the last day of the last occurrence of 3 consecutive days with pollen count larger or equal to 10 grains/m^3. For the peak season it is specified the 14 consecutive days period is used as a peak.

7 Sample size determination

General considerations

In this trial, primary and secondary endpoints will be tested hierarchically to control the family-wise error rate at 5% level. Individual endpoint analyses will be based on treatment comparisons using a 2-sided t-distributed test on a 5% level of significance.

The power calculations were done in two steps. This sample size wasthen evaluated using the estimand framework. The power was calculated for both the primary endpoint (TCS) and the key secondary endpoint (RQLQ). It is expected that the treatment difference in overall RQLQ during peak season is greater than the MCID of 0.10 and during entire season greater than 0.22 (Blaiss et al. 2022).

TCS power calculation

The estimated TCS mean, standard deviation and treatment differences during the peak season from three trials is presented in Table 8. The power calculation is based on a TCS treatment difference of 21% (1.64 in absolute value) and a common standard deviation of 5.5. Under these assumptions, the trial has a power of 80% with the sample size of 180 evaluable subjects. The power is 86% for the primary estimand and 80% for the secondary estimand with the assumption that 10% out of 220 subjects will discontinue the trial, with 4.5% of subjects discontinuing due to AEs and 1% due to lack of efficacy each year.

Table 8: Mean and standard deviation of TCS during the peak of a season.

Trial	Placebo $\mu(\sigma)$	Active $\mu(\sigma)$	Difference absolute (relative)
GT-08 2006	8.44 (5.48)	5.14 (4.06)	3.3 (39%)
P05238	7.74 (6.50)	6.10 (5.09)	1.64 (21%)
P08067	5.73 (5.03)	4.56 (4.60)	1.17 (20%)
Average			2.04

RQLQ power evaluation

The estimated RQLQ mean, standard deviation and treatment differences during the peak season from 3 trials raw data is presented in Table 9 below.

Table 9: Mean and standard deviation of RQLQ during the peak of a season.

Trial	Placebo $\mu(\sigma)$	Active $\mu(\sigma)$	Difference Absolute (relative)
GT-08 2005	1.82 (1.11)	1.37 (0.97)	0.45 (25%)
GT-08 2006	1.48 (1.05)	1.05 (0.91)	0.43 (29%)
P05238	1.73 (1.34)	1.41 (1.12)	0.33 (18%)
P08067	1.73 (1.34)	1.18 (1.08)	0.15 (11%)
Average			0.34

A common standard deviation of 1.15 has been assumed in the power evaluation. An expected placebo mean is 1.60 and an expected treatment difference is 0.34. With 180 evaluable

subjects per treatment arm, the power of 98% is reached for testing if RQLQ treatment difference is greater than proposed MCID of 0.1. The power is 95% for the primary and 92% secondary estimands for the sample size of 220 subjects with the same discontinuation assumptions as for TCS.

Conclusion

The suggested sample size is 180 evaluable subjects per treatment arm. 220 subjects should be randomised in each arm, assuming a 10% discontinuation of subjects per year, where 1% discontinued due to lack of efficacy and 4.5% due to AEs. In such case, the trial has a power of at least 80% in order to detect a statistically significant difference of at least 21% with common standard deviation no larger than 5.5 for primary endpoint in observed case scenario. The trial has a power of 86% and 80% for primary endpoint for primary and secondary estimands respectively. Similarly, 95% and 92 % power for RQLQ for the primary and secondary estimand respectively. The trial has a power of at least 98% to detect treatment difference greater than 0.1 in RQLQ for observed case.

8 Demographics and baseline characteristics

Summaries for numerical variables tables will display the descriptive statistics such as: mean, SD, median, min and max.

Summaries for categorical variables frequency tables will display counts and percentages.

8.1 Screening failures

A summary of reasons for screening failure will be presented for the TOS.

8.2 Protocol deviations

Overall important PDs will be summarized by trial, country, site and subject level. Furthermore, the important PDs will be summarized by the subject level deviations and treatment. A listing with all important PDs will be presented.

8.3 Subject disposition

Subject disposition will be summarised by number and percentage of subjects screened, randomised and not treated, randomised and treated, included in the analysis sets, completed trial, withdrawal from the trial, reason of withdrawal of trial, completed IMP, discontinued IMP, and reason for IMP discontinuation by treatment group and total. Some endpoints will be also summarised by year. In addition, the reasons for discontinuation of IMP following the estimand framework will be summarised by treatment groups and total.

IMP discontinuations over time by different reasons will be visualised by a band plot showing proportions on treatment, having discontinued treatment due to AE, withdrawal by subject, and all other reasons (pooled).

8.4 Baseline characteristics

Demographic variables (age, sex, race, country) will be summarised by treatment and total groups.

Baseline characteristics (including baseline asthma status, inhaled corticosteroid use, duration of grass pollen allergy and mono/poly sensitized) are summarised by treatment groups.

In separate tables, SPT test results (including actual wheel size and results and whether subjects are mon/poly sensitised), FEV_1, percentage of predicted FEV_1 and IgE are summarised by treatment groups.

8.5 Pollen counts

Pollen season definitions are provided in Section 9.1. Pollen counts will be summarised by treatment group and total. Pollen counts will be weighted by the number of subjects in each pollen station and divided by the number of subjects in the trial. In addition, lengths of EGPS and for each year will be summarised. Lengths of EGPS will also be weighted as pollen counts.

8.6 Medical history

Medical history will be summarised by treatment groups. Medical history of allergic rhinitis, conjunctivitis, asthma, atopic dermatitis and food allergy are summarised by treatment groups.

8.7 Prior and concomitant therapy

Prior and concomitant medication will be summarised by treatment groups.

9 Supporting documentation

9.1 Definition of pollen seasons

Each trial site was allocated to a pollen station. The start and stop dates of the grass pollen seasons will be based on the daily pollen counts as defined in Table 10. The pollen EGPS dates will be within a period of expected pollen season defined trial protocol (see Trial Protocol, Appendix 5: Expected grass pollen season).

Table 10 Grass pollen season definitions.

Start date of EGPS	The first day of 3 consecutive days with (non-missing) pollen count larger than or equal to 10 grains/m^3.
Stop date of EGPS	The last day of the last occurrence of 3 consecutive days with (non-missing) pollen count lager or equal to 10 grains/m^3.
PGPS	The 14 consecutive days period with the highest average pollen count during the entire grass pollen season.

Based on the definition above, if the EGPS is shorter than 14 days, than PGPS will be equal to EGPS. In addition, a visual inspection of the pollen count (pollen grains/m3 versus time) will be made to validate the pollen counts in the season.
In case of missing pollen counts for specific pollen regions the 3 following principals will be used prior to unblinding:

- If pollen counts for maximum 2 days will be missing with at least 5 days with observed pollen counts days then the missing pollen counts (after first occurrence of pollen) will be replaced by applying the last observation carried forward method.

- If pollen counts will be completely missing or missing for extended period of time for a specific pollen station then a replacement pollen station will be manually assigned.
- In all other cases of missing pollen counts start and stop dates will be defined by visual inspection of the pollen counts for the specific pollen station and neighbouring pollen stations to approximate the general approach specified above.

Pollen seasons (i.e., actual start and end dates or start and end dates based on visual inspection) will be defined prior to database lock and further specified in Appendix B: pollen seasons start and stop dates.

9.2 Derivation of endpoints

Symptoms and medication use days was recorded daily by the subject in the eDiary. For each day it was only possible for the subject to either record both symptoms and medication use or neither. [redacted]

9.2.1 DSS

The 6 symptoms of rhinoconjunctivitis consists of 4 rhinitis symptoms (runny nose, blocked nose, sneezing, itchy nose) and 2 conjunctivitis symptoms (gritty feeling/red/itchy eyes, watery eyes). Each symptom is scored from 0 to 3 by the subject daily: 0 = no symptoms,1 = mild symptoms, 2=moderate symptoms, and 3=severe symptoms.

The DSS is the sum of the 6 individual DSS and ranges from 0 to 18.

9.2.2 DMS

The DMS is the sum of the total daily scores for each medication. The total DMS for each symptomatic medication is calculated as the unit score multiplied by the number of units entered in the daily diary by the subject (Table 11). Note that the score is capped so that for each medication the score of the recommended dose is also the maximum score, i.e. this score cannot be exceeded even though the recommended dose is exceeded. The DMS ranges from 0 to 20.

Table 11 Symptom relieving medication for rhinitis with/without conjunctivitis

Symptom-relieving medication	Score/dose unit	Maximum daily score	SUGGEST: MAX DAILY UNITS
Desloratadine tablets, 5 mg	6	6	1 (Tablets)
Olopatadine eye drops, 1 mg/mL	1.5 pr. eye	6	4 (Drops)
Mometasone nasal spray, 50 µg/dose	2	8	4 (Puffs)
Maximum daily rhinitis and/or conjunctivitis medication score	-	20	

9.2.3 TCS

The daily TCS is the sum of the DSS and the DMS and ranges from 0 to 38.

9.2.4 RQLQ

The RQLQ has 28 questions in 7 domains (activity limitation, sleep problems, nose symptoms, eye symptoms, non-nose/eye symptoms, practical problems and emotional function) (Juniper et. al 1998).

Subjects were asked how bothered they have been by their rhinoconjunctivitis during the previous week and to respond to each of the 28 questions on a 7-point scale (from 0 = not bothered/none of the time to 6 = extremely bothered/all of the time). The overall RQLQ score is the mean of all 28 responses and the individual domain scores are the means of the items in those domains.

[redacted] [redacted]

[redacted]

[redacted] [redacted]

[redacted]

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

[redacted] [redacted]

[redacted].

[redacted] [redacted]

[redacted]

[redacted]

9.3 Derivation of average endpoints

Average endpoints will be calculated for both EGPS and PGPS pollen seasons. Pollen seasons are defined above, and the average endpoints will be derived for the following endpoints:

- TCS
- RQLQ
- DSS
- DMS

Average endpoints will be derived as the simple mean of all observations (i.e. non-missing daily/weekly values) within the relevant time frame and data point set.

9.4 Imputation of dates

9.4.1 Partial dates in AE reporting

Partial dates and time for start of AEs will be imputed as follows:

- Missing day will be imputed as maximum of first day of month and day of first IMP dose.
- Missing month will be imputed as maximum of first day in January and date of first IMP.
- Missing time is calculated as the first minute of the day (i.e. if the AE start date is 16-AUG-2022 then the AE start datetime will be 16-AUG-2022 T:00:00)

Partial dates and time for end of AEs will be imputed as follows:

- Missing day will be imputed as minimum of last day in month and day of last contact.
- Missing month will be imputed as minimum last day of December and date of last contact.
- Missing time is calculated as the last minute of the day (i.e. if the AE end date is 16-AUG-2022 then the AE start datetime will be 16-AUG-2022 T:23:59)

With these imputation rules, AEs will be considered TE when dates are partial and the existing information does not exclude the possibility of the event being treatment-emergent.

9.4.2 Incomplete date for last IMP dose

Any partial date of last dose will be imputed as follows:

- Missing day is imputed as minimum of last day in month and day of last visit.
- Missing month is imputed as minimum of last day of December and date of last visit.
- Missing last IMP dose date is imputed as the date of last known visit

9.4.3 Incomplete date for Previous/Concomitant medication

No date imputation will take place on previous/concomitant medication. However, medications with partial end dates will be considered to be previous medication.

9.5 Further details pertaining to statistical analyses

Adjusted means for each treatment group, the absolute treatment difference with 95% CI and p-value, and the relative treatment difference with 95% confidence interval will be presented. The 95% confidence interval for the relative difference will be calculated using Fieller's theorem (Fieller 1954) see **Error! Reference source not found.**

Fieller's method

In statistics, Fieller's theorem allows the calculation of a confidence interval for the ratio of two means. If the two means are normally distributed Fieller's formular is exact. The method calculates limits for $\frac{a}{b}$, $\tilde{L}$ and $\tilde{U}$. Since the relative difference is $\hat{\rho}_{ii'} = \frac{(\hat{\tilde{\mu}}_i)^2-(\hat{\tilde{\mu}}_{i'})^2}{(\hat{\tilde{\mu}}_{i'})^2} = 1 - \left(\frac{\hat{\tilde{\mu}}_{i'}}{\hat{\tilde{\mu}}_{i'}}\right)^2$, Fieller's limits are (back)transformed as $L = 1 - \tilde{L}^2$ and $U = 1 - \tilde{U}^2$ (or $U = 1 - \tilde{L}^2$ and $L = 1 - \tilde{U}^2$).
Importantly, Fieller's limits are calculated on the transformed-scale and via the above transformation the limites on the back-transformed scale is derived.
Let

$$g = \left(\frac{t_{0.975,df} \cdot \mathrm{SE}(\hat{\tilde{\mu}}_{i'})}{\hat{\tilde{\mu}}_{i'}}\right)^2,$$

and

$$u = \mathrm{SE}^2(\hat{\tilde{\mu}}_i) - \frac{2\widehat{\mathrm{cov}}(\hat{\tilde{\mu}}_i, \hat{\tilde{\mu}}_{i'})\hat{\tilde{\mu}}_i}{\hat{\tilde{\mu}}_{i'}} + \left(\frac{\mathrm{SE}(\hat{\tilde{\mu}}_{i'})\hat{\tilde{\mu}}_i}{\hat{\tilde{\mu}}_{i'}}\right)^2 - g\left(\mathrm{SE}^2(\hat{\tilde{\mu}}_i) - \left(\frac{\widehat{\mathrm{cov}}(\hat{\tilde{\mu}}_i, \hat{\tilde{\mu}}_{i'})}{\mathrm{SE}(\hat{\tilde{\mu}}_{i'})}\right)^2\right),$$

then

$$L = 1 - \left(\frac{\frac{\hat{\tilde{\mu}}_i}{\hat{\tilde{\mu}}_{i'}} - g\frac{\widehat{\mathrm{cov}}(\hat{\tilde{\mu}}_i,\hat{\tilde{\mu}}_{i'})}{\mathrm{SE}^2(\hat{\tilde{\mu}}_{i'})} + \frac{t_{0.975,df}\sqrt{u}}{\hat{\tilde{\mu}}_{i'}}}{(1-g)}\right)^2$$

and

$$U = 1 - \left(\frac{\frac{\hat{\tilde{\mu}}_i}{\hat{\tilde{\mu}}_{i'}} - g\frac{\widehat{\mathrm{cov}}(\hat{\tilde{\mu}}_i,\hat{\tilde{\mu}}_{i'})}{\mathrm{SE}^2(\hat{\tilde{\mu}}_{i'})} - \frac{t_{0.975,df}\sqrt{u}}{\hat{\tilde{\mu}}_{i'}}}{(1-g)}\right)^2$$

Figure 3 Fieller's method

9.5.1 Transformations

Some endpoints will be square root transformed before (formal statistical) analysis. The square root transformation is generally applied, as this usually results in a good approximation to the normal distribution. In addition, a lot of subjects do not use rescue medication, so the average DMS score is often 0, and this will also be accounted for by using the square root transformation in contrast to the logarithmic transformation. The transformed endpoint is then included in the model as a response variable.

The p-value for the absolute difference will be reported as the test result and no back-transformation will be done. To enable reporting of relative difference on the original scale, transformed means will be back-transformed (see **Error! Reference source not found.**) and 95% CI will be calculated using the methods described in Figure 3. For the absolute difference,

the SE is approximated using the first-order Delta method (first-order Taylor approximation), and the 95% CI is calculated from this.

$\sqrt{()}$-transformation

Means, differences between means and relative differences

For $\sqrt{()}$-transformed endpoints the back-transformations (to the original scale) are :

$$\hat{\mu}_i = (\hat{\tilde{\mu}}_i)^2,$$

where $\hat{\tilde{\mu}}_i$ is the i'th treatment mean on the $\sqrt{()}$-transformed scale.
Similarly, back-transformed differences between group means are

$$\hat{\delta}_{ii'} = (\hat{\tilde{\mu}}_i)^2 - (\hat{\tilde{\mu}}_{i'})^2,$$

and relative differences are thus

$$\hat{\rho}_{ii'} = \frac{(\hat{\tilde{\mu}}_i)^2 - (\hat{\tilde{\mu}}_{i'})^2}{(\hat{\tilde{\mu}}_{i'})^2}.$$

The estimates $\hat{\tilde{\mu}}_i$, $\hat{\tilde{\mu}}_{i'}$ (that is, on the $\sqrt{()}$-transformed scale) are obtained from `proc mixed`'s `lsmeans` statement.

Standard errors

The variances of the back-transformed parameters follow from the δ-method

$$\mathrm{SE}(\hat{\mu}_i) = 2\hat{\tilde{\mu}}_i \times \mathrm{SE}(\hat{\tilde{\mu}}_i).$$

with the variance (SE) of $\hat{\delta}_{ii'}$ following alike :

$$\mathrm{SE}(\hat{\delta}_{ii'}) = 2\sqrt{\hat{\tilde{\mu}}_i^2 \mathrm{SE}^2(\hat{\tilde{\mu}}_i) + \hat{\tilde{\mu}}_{i'}^2 \mathrm{SE}^2(\hat{\tilde{\mu}}_{i'}) - 2\hat{\tilde{\mu}}_i \hat{\tilde{\mu}}_{i'} \widehat{\mathrm{cov}}(\hat{\tilde{\mu}}_i, \hat{\tilde{\mu}}_{i'})}.$$

The estimates $\hat{\tilde{\mu}}_i$, $\hat{\tilde{\mu}}_{i'}$, $\mathrm{SE}(\hat{\tilde{\mu}}_i)$ and $\mathrm{SE}(\hat{\tilde{\mu}}_{i'})$ (that is, on the $\sqrt{()}$-transformed scale) are obtained from `proc mixed`'s `lsmeans` statement.

Figure 4 Transformations

9.5.2 Analyses with multiple imputation

The imputations will be carried out using the method of unrestricted random sampling with replacement (seed = 68686) and with 1,000 multiple imputed datasets created. It means that observed data is "bootstrapped" or sampled with replacement within the strata defined in the rows of Table 5, Table 6 and Table 7 and used to substitute (impute) missing data. If the actual significance level of the performed test will be between 4%-6%, then the number of imputations will be increased from 1,000 to 10,000. This will be done to ensure the precision of estimated standard error, and thus the right hypothesis testing conclusion will be made.

Missing data for each year will be imputed based on observed cases for the same year and using subjects as source for the imputations which happen to have data in the “current” year in question.

Further, PGPS data will be imputed from observed PGPS data and EGPS from EGPS data from the corresponding year and ongoing asthma status. The ongoing asthma status might only be considered if there is enough unique permutation to impute from.

The relevant endpoints in 1st and 2nd years will be analysed using a MMRM with treatment and year interaction, and ongoing asthma status as fixed effects and country and year interaction as random class effect and allowing unequal R-matrices among the two treatment arms. After the by-imputation MMRMs, results are summaries/combined using Rubin’s method (**Rubin 1987**).

9.5.3 Model checking

The assumption of normally distributed residuals will be evaluated by visual inspection of quantile-quantile plots for the primary and key secondary endpoints. If the square root transformation does not result in a good approximation to the normal distribution, no transformation will be applied if this improves the approximation to a normal distribution.

[redacted]

[redacted]

9.5.7 Analysis of quality-of-life questioners

The overall RQLQ score during V3 (1st off-season) [redacted] at randomisation and at the end of trial will be analysed via descriptive statistics. Descriptive statistics by treatment include number of subjects, mean, standard deviation, median, minimum, and maximum.

9.5.8 Convergence issues

If any models defined above do not converge, several attempts will be made to reach convergence:

- The first step will be set the same R-matrice among the two treatment arms.
- The second step will be to change the unstructured covariance matrix to the compound symmetry matrix.
- The third step we will be to remove ongoing asthma status from the model.
- The fourth step we will be to be to pool countries into regions.
- The fifth step will be to remove the random effect of region and year interaction from the model.

10 References

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Rubin 1987: Rubin, D.B. (1987) Multiple Imputation for Nonresponse in Surveys. John Wiley & Sons Inc., New York. http://dx.doi.org/10.1002/9780470316696.

Blaiss et al. 2022: Blaiss, M. S., Gronskyte Juhl, R., Siew, L. Q., Hammerby, E., & Devillier, P. (2022). Determining the minimal important differences in the RQLQ score with grass and tree allergy immunotherapy versus placebo in adults with moderate-to-severe allergy. Allergy, 77(6), 1843-1851.

Appendix A: SAS codes

Primary efficacy analysis

```
proc mixed data=analysis_MI method=reml;
    by paramcd _imputation_;
    class avisitn trt01pn aasfl country usubjid;
    model aval = trt01pn avisitn trt01pn*avisitn aasfl / ddfm=KR
                                                         solution;
    random country(avisitn);
    repeated avisitn / subject=usubjid type=UN group=trt01pn;
    lsmeans trt01pn*avisitn / cl cov pdiff om;
run;
```

Appendix B: pollen seasons start and stop dates

Pollen station	Sites	Year	Season	Start date	Stop date	Comment
CZBRNO	207	2022	EGPS	19MAY2022	04JUL2022	
			PGPS	31MAY2022	13JUN2022	
		2023	EGPS	25MAY2023	20JUL2023	
			PGPS	20JUN2023	03JUL2023	
CZCEBU	203, 212	2022	EGPS	19MAY2022	18JUL2022	
			PGPS	02JUN2022	15JUN2022	
		2023	EGPS	22MAY2023	25JUL2023	Missing data imputed with CZJIHL.
			PGPS	29JUN2023	12JUL2023	
CZJIHL	205	2022	EGPS	18MAY2022	23JUL2022	
			PGPS	07JUN2022	20JUN2022	
		2023	EGPS	22MAY2023	25JUL2023	
			PGPS	29JUN2023	12JUL2023	
CZLIBE	209, 211, 213	2022	EGPS	24MAY2022	15JUL2022	
			PGPS	06JUN2022	19JUN2022	
		2023	EGPS	28MAY2023	16JUL2023	
			PGPS	31MAY2023	13JUN2023	
CZUORL	202, 210	2022	EGPS	31MAY2022	19JUN2022	
			PGPS	03JUN2022	16JUN2022	
		2023	EGPS	22MAY2023	25JUL2023	Missing data imputed with CZJIHL.
			PGPS	29JUN2023	12JUL2023	
EETALL	302	2022	EGPS	15JUN2022	12AUG2022	
			PGPS	17JUN2022	30JUN2022	
		2023	EGPS	15JUN2023	19JUL2023	Dates were adjusted after visual inspection.
			PGPS	15JUN2023	28JUN2023	

FRAMIE	676	2022	EGPS	09MAY2022	20JUL2022	
			PGPS	06JUN2022	19JUN2022	
		2023	EGPS	18MAY2023	16JUL2023	
			PGPS	03JUN2023	16JUN2023	
FRBRUL	635	2022	EGPS	11APR2022	29JUL2022	
			PGPS	14MAY2022	27MAY2022	
		2023	EGPS	02MAY2023	30JUL2023	
			PGPS	24MAY2023	06JUN2023	
FRCHOL	601	2022	EGPS	02MAY2022	14JUL2022	
			PGPS	14MAY2022	27MAY2022	
		2023	EGPS	05APR2023	12JUL2023	
			PGPS	26MAY2023	08JUN2023	
FRNARB	636	2022	EGPS	13APR2022	18JUL2022	
			PGPS	17MAY2022	30MAY2022	
		2023	EGPS	28APR2023	12JUL2023	
			PGPS	16MAY2023	29MAY2023	
FRORLE	632	2022	EGPS	20MAY2022	16JUL2022	
			PGPS	21MAY2022	03JUN2022	
		2023	EGPS	03MAY2023	23JUL2023	
			PGPS	22MAY2023	04JUN2023	
FRSTRA	670	2022	EGPS	07MAY2022	07JUL2022	
			PGPS	20MAY2022	02JUN2022	
		2023	EGPS	04MAY2023	20JUL2023	
			PGPS	23MAY2023	05JUN2023	
FRTOUL	631	2022	EGPS	04MAY2022	20JUN2022	
			PGPS	18MAY2022	31MAY2022	
		2023	EGPS	02MAY2023	24JUL2023	
			PGPS	23MAY2023	05JUN2023	
FRTOUN	633	2022	EGPS	29APR2022	18JUN2022	

			PGPS	18MAY2022	31MAY2022	
		2023	EGPS	10MAY2023	03JUL2023	
			PGPS	15JUN2023	28JUN2023	
LTVILN	501, 502, 503, 504, 506, 507, 508	2022	EGPS	10JUN2022	05JUL2022	
			PGPS	18JUN2022	01JUL2022	
		2023	EGPS	09JUN2023	01JUL2023	Dates were adjusted after visual inspection.
			PGPS	09JUN2023	22JUN2023	
LVRIGA	401, 402, 403, 404, 405, 406	2022	EGPS	05JUN2022	23JUL2022	
			PGPS	23JUN2022	06JUL2022	
		2023	EGPS	10JUN2023	21JUL2023	Dates were adjusted after visual inspection.
			PGPS	10JUN2023	23JUN2023	
PLBYDG	105, 106, 109,	2022	EGPS	13MAY2022	11AUG2022	
			PGPS	24JUN2022	07JUL2022	
		2023	EGPS	21MAY2023	26AUG2023	
			PGPS	25JUN2023	08JUL2023	
PLCRAC	102, 108, 110, 112, 113, 114	2022	EGPS	29MAY2022	11JUL2022	
			PGPS	24JUN2022	07JUL2022	
		2023	EGPS	26MAY2023	25JUL2023	
			PGPS	29JUN2023	12JUL2023	
PLLUBL	103	2022	EGPS	31MAY2022	10JUL2022	
			PGPS	22JUN2022	05JUL2022	
		2023	EGPS	25MAY2023	15AUG2023	
			PGPS	26JUN2023	09JUL2023	
PLPTRY	104, 115	2022	EGPS	10MAY2022	11AUG2022	
			PGPS	31MAY2022	13JUN2022	

		2023	EGPS	23MAY2023	14AUG2023	
			PGPS	25JUN2023	08JUL2023	
PLWROC	101, 107, 111	2022	EGPS	13MAY2022	20JUL2022	
			PGPS	30MAY2022	12JUN2022	
		2023	EGPS	23MAY2023	21JUL2023	
			PGPS	29MAY2023	11JUN2023	

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