Allergy Therapeutics (UK) Ltd.: PQGrass309

Statistical Analysis Plan

Status: **Final**

Study Title:	A randomised, double-blind, placebo-controlled exploratory study to explore the efficacy and safety of PQ Grass 27600 SU in subjects with seasonal allergic rhinitis and/or rhinoconjunctivitis induced by grass pollen exposure
NCT04687059	
Investigational Product:	PQ Grass
Clinical Phase:	Phase II/III
Sponsor:	Allergy Therapeutics (UK) Ltd. Dominion Way Worthing West Sussex BN14 8SA United Kingdom
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1 LIST OF ABBREVIATIONS

Abbreviation	Text
ANCOVA	Analysis of Covariance
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical Classification
aTCS	adapted Total Combined Score
BDRM	Blind Data Review Meeting
BMI	Body Mass Index
BPS	Birch Pollen Season
CI	Confidence Interval
CPT	Conjunctival Provocation Test
CRA	Clinical Research Associate
CRP	C-Reactive Protein
CSMS	Combined Symptom and Medication Score
CSMS-dMS	daily Medication Score component of the Combined Symptom and Medication Score
CSMS-dSS	daily Symptom Score component of the Combined Symptom and Medication Score
CSR	Clinical study report
DF	Degrees of Freedom
dMS	daily Medication Score
dSS	daily Symptom Score
EAACI	European Academy of Allergy and Clinical Immunology
eCRF	electronic Case Report Form
eDiary	Electronic Diary
EU	European Union
FAS	Full Analysis Set
FEV_1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
GEE	Generalised Estimating Equation
GGT	Gamma-Glutamyl Transferase
GINA	Global Initiative for Asthma
GPS	Grass Pollen Season
HEP	Histamine Equivalent Potency units
ICH	International Council for Harmonization
Ig	Immunoglobulin
IMP	Investigational Medicinal Product

Abbreviation	Text
kg	Kilograms
LDH	Lactate Dehydrogenase
LS	Least Square
MCT	Microcrystalline Tyrosine
MedDRA	Medical Dictionary for Regulatory Activities
miRNA	microRNA (Ribonucleic Acid)
MSE	Mean Squared Errors
PBMC	Peripheral Blood Mononuclear Cells
PD	Protocol Deviation
PEFR	Peak Expiratory Flow Rate
PPS	Per Protocol Set
PT	Preferred term
PQ	POLLINEX® Quattro
PQ Grass	Pollinex® Quattro Grass 1.0 mL
Q-Q plot	Quantile-Quantile plot
RBC	Red Blood Cells
RQLQ(S)	Rhinoconjunctivitis Quality of Life Questionnaire with standardised activities
SAE	Serious Adverse Event
SAF	Safety Set
SAP	Statistical Analysis Plan
SAR	Seasonal Allergic Rhinitis and/or Rhinoconjunctivitis
SAS	Statistical Analysis System
SD	Standard Deviation
SE	Standard Error
SOC	System organ class
SOP	Standard Operating Procedure
SPT	Skin Prick Test
SU	Standardised Unit
TCS	Total Combined Score
TCS-dMS	daily Medication Score component of the Total Combined Score
TCS-dSS	daily Symptom Score component of the Total Combined Score
TEAE	Treatment Emergent Adverse Event
TSS	Total Symptom Score
US	United States of America
WBC	White Blood Cells
WHO	World health organization

2 GENERAL

This statistical analysis plan follows the principles of the Guidelines ICH Topic E3 and ICH Topic E9. It gives all details for the final statistical analysis of this study.

2.1 Analyses

The final analysis of the study data will be performed after all subjects have completed Visit 15.

An additional analysis will be performed once all data of the 3 and 6-month safety follow-up is available and the final analysis will be amended with these results.

Additional exploratory and sensitivity analyses will be performed as specified in an additional analysis plan of exploratory analyses.

No formal interim analyses are planned.

2.2 SOPs to be followed

The analysis will be carried out according to Standard Operating Procedures (SOPs).

2.3 Study design

This is a multi-centre, randomised, parallel group, double-blind, placebo-controlled exploratory study conducted in approximately 7 centres in the EU and 8 centres in the US. The assigned treatment will be administered prior to the onset of the GPS, in a randomisation ratio of 2:2:1:1 to:

- PQ Grass (conventional posology)
- PQ Grass (extended posology)
- Placebo containing MCT
- Placebo without MCT

3 GENERAL ASPECTS OF THE STATISTICAL ANALYSIS

3.1 Populations for analyses

The populations used for the statistical analyses are specified in Table 1.

Table 1 Populations for analyses

Population	Description
Full Analysis Set (FAS)	All subjects who received at least 1 injection of the IMP. The analysis will follow the intention-to-treat principle and will analyse subjects according to the treatment group to which they were randomised.
Safety Set (SAF)	All subjects who received at least 1 injection of the IMP. Subjects will be analysed according to the treatment that they actually received.
Per Protocol Set (PPS)	A subset of the FAS and will exclude all subjects with major protocol deviations, and all subject with an in-sufficient level of in-season assessments during the peak GPS.

The SAF will be used for all evaluations of safety and tolerability. No participant of the BDRM had knowledge of treatment assignments of individual subjects.

The FAS and the PPS will be used for the evaluation of efficacy; the FAS will be the primary analysis set, and the PPS will be used for sensitivity analyses. The criteria used for inclusion of each subject into the respective analysis sets are detailed in the BDRM plan and the final decisions are documented in the BDRM minutes.

3.2 Protocol deviations and other reasons for exclusion from any analysis set

Protocol deviations and other reasons for exclusion from any analysis set are reported by the study team and/or automatically via pre-programmed checks as defined in all detail in the BDRM plan. During the BDRM, all deviations until Visit 15 were classified into major (leading to exclusion from per protocol set) and minor (not leading to exclusion from any analysis set) deviations, and if needed certain unambiguous rules were defined during the BDRM to be implemented after un-blinding.

All decisions and the reasons for these decisions are documented in the BDRM minutes, which will be finalized and signed prior to database hard lock and un-blinding.

4 DEFINITIONS FOR STATISTICAL ANALYSIS

The statistical analysis will be performed after completion of the following working steps:

- All relevant electronic case report form (eCRF) data including eDiary data is available and has been checked for errors and/or inconsistencies.
- All external subject data relevant for the analysis as described below, e.g. laboratory data, is available and reconciled.
- All external non-subject data, e.g. grass pollen counts, is available.
- All queries relevant for the analysis have been answered and necessary editing of the database has been performed.

- Relevant data has been locked as further described in the Data Validation Manual. The evaluation and classification of all protocol deviations and allocation of subjects to the respective analysis sets have been completed and captured in the final BDRM minutes approved by the responsible persons.
- A detailed final statistical analysis plan is available and approved by responsible personnel.

4.1 Screen failures

For the purpose of summary tables and subject data listings, screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomized.

For screen failures, the informed consent date, the screening date and the reason for screen failure (including the violated eligibility criteria) will be listed. Additionally, demography and all adverse events observed within Period 1 (Screening) will be listed for screen failures.

The number of screen failed subjects and the reason for screen failure will be tabulated. Beyond that, screen failures will not be considered in any of the summary tables, figures or subject data listings.

4.2 Handling of withdrawals (drop-outs) and missing values

Discontinued or withdrawn subjects will not be replaced if they withdrew due an adverse event. Subjects withdrawn early from the study due to other reasons may be replaced (if there is sufficient time to complete the treatment period prior to the onset of the GPS). Data collected for subjects whose participation is terminated is evaluated with all data as collected until withdrawal and during a possible follow-up for safety.

Missing data for the primary variable on a by-subject level will be handled using multiple imputation methods

4.3 Visit definition for analysis

All scheduled visits will be analysed as defined in the protocol and the numbering is taken from the eCRF.

4.4 Baseline

A baseline measurement will be defined as the latest measurement obtained prior to the first administered dose of study medication.

4.5 Reference day for the statistical analysis

Day 1 is defined as the date of first administration of study medication. Study days for statistical analysis will be calculated relative to Day 1. There is no study Day 0 (day before first administration of study medication is day -1).

5 STATISTICAL ANALYSIS SPECIFICATION

5.1 Specifications related to whole analysis

5.1.1 Tables

Data will be summarised using suitable descriptive statistics depending on the structure of the data.

Summary tables will be grouped by treatment group and by visit, and separated by relevant periods (e.g. treatment period, entire (truncated) GPS, peak GPS) if appropriate and reasonable.

If not specified otherwise, the following treatment groups will be included:

- PQ Grass (conventional posology),
- PQ Grass (extended posology),
- PQ Grass (pooled),
- Placebo (containing MCT),
- Placebo (without MCT), and
- Placebo (pooled).

To increase the readability of the summary tables and to separate the different periods, separate summary tables will be generated for different periods (e.g. treatment period, entire (truncated) GPS, peak GPS, etc.). Summary tables for all periods combined will be presented additionally whenever appropriate.

For quantitative variables, summary statistics will be created that include the number of subjects with data available, arithmetic mean, standard deviation (SD), median, first and third quartile, minimum, maximum.

For qualitative variables, the summaries will include the number and percentage of subjects for each outcome category.

If the analysis sets FAS and SAF are identical (i.e., planned and actual treatment assignments do not differ), all baseline summary tables will be displayed for the FAS only.

5.1.2 Data listings

Individual data will be listed. In general, listings will be sorted by subject number. Each listing will contain the subject number, randomized treatment group, and most restrictive analysis set (PPS is more restrictive than FAS or SAF). The study period will be additionally displayed whenever applicable and reasonable.

Subject data listings for event-based data (e.g., adverse events or concomitant medications) will be sorted by subject number, by event start date and then alphabetically by reported term and coded term.

For all assessment dates, the study day relative to the first injection will be presented. For assessments analysed within the entire (truncated) or peak GPS (e.g., for start and end dates of adverse events within peak GPS), the day relative to the start of the entire (truncated) GPS and to the start of the peak GPS may be additionally displayed whenever reasonable.

5.1.3 Figures

If not specified otherwise, in all figures, the four treatment groups will be displayed separately, i.e. no pooled Placebo and no pooled PQ Grass group will be displayed.

5.2 Disposition of subjects

A summary table will be created including

- the number of screenings (including re-screenings),
- the number of subjects who were screened (i.e. signed the informed consent),
- the number of screen failures,
- the number of subjects who were randomised,
- the number and percentage of subjects who were treated,
- the number and percentage of subjects who completed the study including safety follow-up (only after 3 and 6 months follow-up data is available),
- the number and percentage of subjects who prematurely discontinued treatment, and
- the number and percentage of subjects who prematurely discontinued the study.

These categories will be displayed by randomised treatment group and overall and percentages will be calculated based on all randomised subjects, if applicable.

5.3 Demographics and baseline characteristics

Demographic information collected at Screening (Visit 1) will include age, sex, race, ethnicity, childbearing potential and methods of contraception, as well as smoking and alcohol consumption habits.

Height at Screening will be displayed in cm and weight at Screening in Kilograms (kg). Body Mass Index (BMI) will be calculated as

and displayed in kg/m^2.

Demographic data will be summarized by treatment group and overall for all analysis sets, and listed by subject. Childbearing potential and methods of contraception will only be tabulated for female subjects in the FAS.

5.4 Medical History and Concurrent Diseases

5.4.1 Definitions and conventions

A medical and allergy history including details regarding all illnesses, surgeries and any kind of allergies (to assess eligibility) at screening must be recorded in the eCRF. A full history for the 5 years prior to screening and any other significant medical history is to be documented. Concurrent diseases and medical history will be coded using the MedDRA dictionary (Medical Dictionary for Regulatory Activities) according to the version and update strategy as defined in the coding guideline for this study.

A concurrent disease is defined as any disease, for that either no stop date was documented or the stop date is later than the date of Visit 1. All other diseases are defined as medical history. Incomplete stop dates will be estimated using the first possible date in order to define

whether a disease is concurrent, i.e. it will be assumed that a disease is not ongoing at study start.

5.4.2 Medical History and Concurrent Diseases (non-allergy related)

Concurrent diseases and medical history not related to any allergy will be summarized by treatment group. In this summary table, the diagnoses and indications will be decoded by MedDRA preferred term (PT) and grouped under the respective system organ class (SOC). The SOCs and the PTs within will be sorted by decreasing frequency in the total column.

Separate tables will be created for non-allergy related medical history and concurrent diseases for the FAS.

Non-allergy related concurrent diseases and medical history will be listed by subject.

5.4.3 Grass pollen allergy history and status at start of study

Expressions of allergy will generally be summarized separately by whether the expression was ongoing at study start (expression of allergy occurred during the last grass pollen season before screening) or not.

Number and percentage of subject with the pre-printed expressions of grass pollen allergy (i.e. allergic conjunctivitis, allergic rhinitis, allergic cough, allergic asthma, allergic urticaria) will be provided by treatment group, differentiating further by severity, whether allergic treatment was required (i.e., anti-allergic treatment for symptom control was required for at least two consecutive seasons prior to the study) and / or allergic treatment was taken (i.e., repeated use of treatment for symptom control for at least two consecutive seasons prior to the study).

All grass pollen allergy history related information including start and end dates of expressions of grass pollen allergy will be listed by subject.

Grass pollen related concurrent diseases and medical history will be summarized for the FAS.

5.4.4 Other allergy history

Concurrent other allergies (ongoing at study start) will be summarized by treatment group and reported term (including “Other” as collected in the eCRF), differentiating further by severity and whether allergic treatment was required and/or taken for the FAS.

All other allergy history (past or present) will be listed by subject.

5.5 Previous and concomitant medication

All prescription and over-the-counter medications taken by the subject during the study until study termination are recorded at each visit (scheduled or unscheduled) in the eCRF. Relief medications taken during the GPS will be recorded by the subject in the eDiary only and are not to be recorded as concomitant medication in the eCRF.

All previous and concomitant medications will be coded using the World Health Organization (WHO) Drug dictionary according to the version and the update strategy as defined in the coding guideline for this study.

Four relevant periods will be defined for previous and concomitant medications:

- Previous medications,
- concomitant medications during the whole study,

- concomitant medications during the treatment period, and,
- concomitant medications during the entire (truncated) GPS.

5.6 Other baseline characteristics

Other baseline measures are the results of Skin Prick Test (SPT), the results of spirometry, peak expiratory flow rate (PEFR), and grass-specific IgE for eligibility (ImmunoCAP). These data will be summarised by treatment group and overall for each analysis set, and listed by subject.

5.6.1 Skin Prick Test

A skin prick test (SPT) using various allergens will be performed at screening to assess eligibility of subjects. A standard negative control will be used and histamine control solution (1.0%) will be used for the positive control.

The reaction grade (negative, positive) will be displayed in a frequency table further differentiated by case history of symptoms during the 3 years prior to Visit 1.

5.6.2 Spirometry

Spirometry will be performed at screening to determine eligibility.

Summary statistics will be created for spirometry measurements at screening by treatment group. All spirometry results will be listed by subject.

5.6.3 Peak expiratory flow rate (PEFR)

Summary statistics will be created for the baseline PEFR only containing all subjects for the calculated peak exploratory flow ratio (best result divided by predicted result) in %.

All PEFR measurements will be listed by subject, visit and timepoint. Only the system calculated values will be listed.

5.6.4 Immunoglobulins at screening

Blood samples will be collected for evaluation of the following by ImmunoCAP:

- Total IgE [ku/L]
- Grass specific IgE [ku/L]
- Grass specific IgG4 [mg/L]

These classes will be summarized by display of the absolute and relative frequencies per class by treatment group for the FAS and the SAF.

5.7 Efficacy

5.7.1 Primary efficacy variable: Average CSMS over the peak GPS

The primary efficacy variable is the daily Combined Symptom and Medication Score (CSMS) averaged over the peak Grass Pollen Season (GPS).

5.7.1.1. Definition of the Grass Pollen Season

For the purpose of statistical analysis, the start and end of the entire grass pollen seasons

(GPS) and the peak pollen seasons of each year (if applicable) will be determined based on the daily pollen counts from pollen traps local to the trial sites.

The final decisions regarding the site-specific (peak) pollen periods to be applied for the eDiary related endpoints will be determined prior to unblinding of the database and documented in the BDRM minutes for each year.

5.7.1.2. Daily Combined Symptom and Medication Score (CSMS)

The daily CSMS is the sum of the daily Symptom Score (dSS) component of the CSMS (CSMS-dSS) and the daily Medication Score (dMS) component of the CSMS (CSMS-dMS) calculated from the data recorded in the eDiary.

The CSMS-dSS is calculated as the sum of the severity of conjunctival symptoms (2 items) and nasal symptoms (4 items) divided by 6 for each subject and day (see Table 2).

The severity of symptoms is recorded on a 4-point severity scale

- 0 = No symptoms,
- 1 = Mild symptoms,
- 2 = Moderate symptoms, and
- 3 = Severe symptoms.

Table 2: Conjunctival and nasal symptoms of the CSMS

Conjunctival Symptoms	Itchy/red eyes *
	Watery eyes
Nasal Symptoms	Blocked nose
	Runny nose
	Itchy nose
	Sneezing

* Maximum of single items “Itchy eyes” and “Red eyes” is used for analysis.

The CSMS-dMS is equal to the raw score assigned to each subject and day for the medication with the highest step taken that day.

Thereby, medication is rated on a 4-point scale

- 0 = No relief medication used,
- 1 = Oral antihistamine/Ocular antihistamine (Step 1 medication),
- 2 = Intranasal corticosteroids (Step 2 medication) with Step 1 medication(s), and
- 3 = Oral corticosteroids (Step 3 medication) with Step 1 and Step 2 medications.

Hence, the CSMS-dSS and the CSMS-dMS each range from 0 to 3 and the daily CSMS thus ranges from 0 to 6.

5.7.1.3. Average CSMS over the peak GPS

The average CSMS of the peak GPS is calculated as the sum of the daily CSMS within the peak GPS divided by the number of days of the peak GPS where the CSMS has been collected.

Subjects with missing average CSMS over the peak GPS will be included in the primary analysis by using multiple imputation methods on a by-subject level.

Summary statistics will be provided for the average CSMS over the peak GPS by treatment group based on observed cases.

5.7.1.4. Primary efficacy analysis

The primary efficacy endpoint will be evaluated using a linear mixed model and non-parametric approaches.

The mixed model is accounting for the heterogeneity across countries and will include:

- Average CSMS over the peak GPS as outcome variable.
- Treatment group as main fixed effect
- Country as a random factor.

The difference between PQ Grass and placebo treatment groups will be estimated using least square (LS) means along with the corresponding 2-sided 80% confidence intervals (CIs) of the difference of LS means.

The difference in CSMS will also be presented as a relative percentage change with respect to the LS mean in the corresponding placebo group, and the CI will be calculated by approximating the standard error using the delta method.

The primary analysis specified above will be performed for all imputed datasets and the resulting least square (LS) means are averages over the analyses performed on the single imputed datasets. The difference on the relative scale will be calculated based on the combined LS means.

For linear mixed models, parameter estimation and inference is based on the assumption that the residuals are normally distributed and the random affects are normally distributed and uncorrelated. To verify the validity of the results, several plots are generated based on observed cases only:

- Scatter plots of marginal residuals against their predicted values.
- Histogram of marginal residuals.
- Q-Q plot of marginal residuals.

As a non-parametric approach the Wilcoxon Rank Sum test will be performed for pairwise comparisons without accounting for any potential covariates and country heterogeneity.

The primary efficacy analysis will be performed on the FAS.

5.7.2 Secondary efficacy variables

5.7.2.1. Average CSMS over the entire (truncated) GPS

The average CSMS over the entire (truncated) GPS is calculated in the same way as the average CSMS over the peak GPS.

The primary efficacy analysis will be repeated for the average CSMS over the entire (truncated) GPS for the FAS.

Summary statistics will be provided for the average CSMS over the entire (truncated) GPS by treatment group.

5.7.2.2. Average CSMS-dSS and CSMS-dMS over the peak and the entire (truncated) GPS

The average CSMS-dSS over the peak and the entire (truncated) GPS and the average CSMS-dMS over the peak and the entire (truncated) GPS is calculated in the same way as the average CSMS over the peak GPS.

The primary efficacy analysis will be repeated for

- the averaged CSMS-dSS over the peak GPS for the FAS,
- the averaged CSMS-dMS over the peak GPS for the FAS,
- the averaged CSMS-dSS over the entire (truncated) GPS for the FAS, and
- the averaged CSMS-dMS over the entire (truncated) GPS for the FAS.

Summary statistics will be provided for all average scores by treatment group.

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5.7.2.3. Average Total Combined Score (TCS) over the peak and entire (truncated) GPS

5.7.2.3.1. Daily Total Combined Score (TCS)

The daily TCS is the sum of the dSS component of the TCS (TCS-dSS) and the dMS component of the TCS (TCS-dMS) calculated from the data recorded in the eDiary.

The TCS-dSS is calculated as the sum of the severity of conjunctival symptoms (2 items) and nasal symptoms (4 items).

Table 3: Conjunctival and nasal symptoms of the TCS

Conjunctival Symptoms	Gritty feeling/itchy/red eyes *
	Watery eyes
Nasal Symptoms	Blocked nose
	Runny nose
	Itchy nose
	Sneezing

* Maximum of single items “Gritty feeling”, “Itchy eyes” and “Red eyes” is used for analysis.

Table 4: Relief medications and scoring of the daily medication score of the TCS

Relief medication	**Score**
No relief medications used	0
Oral antihistamine	Each tablet taken corresponds to a score of 6 with a maximum daily score of 6
Ocular antihistamine	Each drop corresponds to a score of 1.5 per eye with a maximum daily score of 6
Intranasal corticosteroid	Each spray corresponds to a score of 2 with a maximum daily score of 8
Maximum daily Medication Score (dMS)	20

For scoring of the TCS-dMS, subjects who take oral corticosteroids will be allocated the maximum daily score of 20.

Hence, the TCS-dSS ranges from 0 to 18 and the TCS-dMS ranges from 0 to 20. The daily TCS thus ranges from 0 to 38.

No single symptoms or medications within a daily assessment were missing, i.e. no strategy was needed how to deal with this issue.

TCS, TCS-dSS and TCS-dMS will be listed by subject and day. Days within the peak GPS and the entire (truncated) GPS will be flagged accordingly.

5.7.2.3.2. Average TCS,TCS-dSS and TCS-dMS over the peak and the entire (truncated) GPS

The primary efficacy analysis will be repeated for

- the averaged TCS over the peak GPS for the FAS,
- the averaged TCS -dSS over the peak GPS for the FAS,
- the averaged TCS -dMS over the peak GPS for the FAS,
- the averaged TCS over the entire (truncated) GPS for the FAS,
- the averaged TCS -dSS over the entire (truncated) GPS for the FAS, and
- the averaged TCS -dMS over the entire (truncated) GPS for the FAS.

Summary statistics will be provided for all average scores by treatment group.

5.7.2.4. Probability of well and severe days during the peak and entire (truncated) GPS

Well and severe days are defined based on the CSMS.

A **"well day"** is defined as a day with:

- No use of relief medication on the particular day, i.e. CSMS-dMS = 0.
- A total daily symptom score ≤ 2 out of 18 (CSMS-dSS < 0.34).

A **"severe day"** is defined as a day with a score of 3 in any of the 6 rhinitis/rhinoconjunctivitis symptoms used for CSMS-dSS calculation.

The probability of a well day or a severe day during the peak and the entire (truncated) GPS will be analysed using data on a by-day level per subject using generalised estimating equation (GEE).

5.7.2.5. Total Symptom Score (TSS) following Conjunctival Provocation Test (CPT)

5.7.2.5.1. Conjunctival provocation test assessment

Four symptoms (eye redness, tearing, itching and irritation) will be scored by the investigator in conjunction with the subject 10 minutes after application of negative control or allergen solution. The Total Symptom Score (TSS) at each time point will be calculated as the sum of the four individual eye symptom scores.

A frequency table will be created displaying the number of subjects who achieved a positive test result during the CPT and those who did not at each visit, i.e. Visit 1, Visit 1a, Visit 2, Visit 2a and Visit 12. This table will be contain all subjects in the respective treatment group (FAS and PPS) and also contain the category "CPT not performed". Percentages will be calculated based on the performed CPTs only.

5.7.2.6. Immunologic parameters

Immunological parameters analyses are

- total IgE [ku/L].,
- grass-specific IgE [ku/L].,
- grass-specific IgG4 [mg/L].,
- grass-specific IgE / total IgE, and
- grass-specific IgE / specific IgG4.

Summary statistics will be created per immunological parameter and visit (Baseline, Visit 12 and Visit 15 and the absolute change from baseline to Visit 12 and Visit 15) by treatment group. A 80% confidence interval will be included for the mean of the absolute changes from screening to the final visit.

The change from baseline in immunoglobulin measurements will be additionally analysed using the same linear mixed model as specified in the primary analysis with the baseline value as additional covariate. The corresponding least square (LS) mean differences (for all active treatment groups compared to placebo [separately and combined]) with 80% CIs will be presented.

The analysis will be performed for the change from baseline to Visit 12 and for the change from baseline to Visit 15.

5.7.2.7. Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ)

The RQLQ is a questionnaire which consists of 28 questions in 7 domains (activity limitation, sleep problems, nose symptoms, eye symptoms, non-nose/eye symptoms, practical problems, and emotional function). Each question is scored on a scale from 0 to 6 (0 = not impaired at all to 6 = severely impaired).

The standardised version of the RQLQ score (RQLQ (S) defined as the mean of all 28 responses) will be aggregated as an outcome variable on a subject level by taking the mean of the scores from Visits 13 and 14 that can be attributed to the entire (truncated) or peak GPS, respectively.

The RQLQ score will be calculated if at least one score at Visit 13 or 14 is reported during the entire (truncated) or peak GPS. It will be considered missing if the RQLQ questionnaire has not been filled at any of these visits. Missing values of the RQLQ score will not be imputed.

The total RQLQ score and its change from baseline (Visit 2) will be summarized by eCRF visit and treatment group for the FAS and the PPS. In addition, summary statistics will be created for the RQLQ during the entire (truncated) or peak GPS and its change from baseline.

The total RQLQ score during the entire (truncated) or peak GPS will also be analysed using similar models as defined for the primary efficacy based on observed cases only.

The linear mixed model will include the RQLQ score during the entire (truncated) or peak GPS as outcome variable, the treatment group as fixed effect and country as random factor. In addition, the baseline total RQLQ score will be included as further covariate.

The analysis will be performed for the FAS.

Missing values for the analysis of the primary efficacy endpoint or for the analysis of selected secondary efficacy endpoints will be imputed using multiple imputation. Missing values in average symptom scores will be imputed using multiple imputation on the subject. The imputation strategy allows the inclusion of all subjects from the FAS in the respective efficacy analysis.

5.8 Safety

Analysis of all safety and tolerability variables will be based on the safety population (i.e., all subjects who received at least 1 dose of IMP). Summary statistics will be provided for safety variables. Alert ranges will be defined for laboratory values lying outside the normal range to a clinically relevant degree. Any measurement fulfilling these criteria will be presented in subject listings.

5.8.1 Treatment exposure and compliance

The number and percentage of subjects having received treatment will be summarised per treatment group and treatment visit (treatment received from Visits 2/2a to 11) for the FAS (randomised treatment) and the Safety Set (actual treatment).

The actually received cumulative dose in SU is calculated based on the actually received kit and vial numbers entered in the eCRF. The planned cumulative dose is based on the randomised treatment.

Summary statistics will be provided for the cumulative dose in SU and the ratio of the cumulative dose actually received and planned for the FAS (randomised treatment) and the Safety Set (actual treatment).

5.8.2 Adverse events

All Adverse events during the course of the study will be coded using the medical dictionary of regulatory activities (MedDRA) current at the start of the study and summarised by treatment group. AEs will be summarised by treatment, primary system organ class (SOC), preferred term (PT), relationship assessment and severity.

All solicited AEs identified via separate phone calls for the US will also be entered in the general AE section of the eCRF. Therefore, no separate analysis will be conducted.

The SOCs as well as the PTs within each summary table will be sorted by frequency in the total column in decreasing order.

AEs will be reported separately as pre-treatment or screening period AEs (any AE occurring prior to the first injection of study medication) and treatment emergent AEs (any AEs after first injection of study medication).

In general, all adverse events will be listed by treatment group, subject number, and period. For AE onset and end dates, the study day relative to the first injection will be listed.

5.8.2.1. Definitions related to adverse events

Pre-Treatment adverse event: Any AE with date and time of onset prior to the first injection of study medication. Pre-treatment AEs might also be termed Screening Period AEs.

Treatment emergent AE (TEAE): Any AE with date and time of onset after first injection of study medication. In case of (partially) missing date or time that could indicate a TEAE, it will be analysed as treatment emergent.

TEAEs during the treatment period: Any AE with date and time of onset after first injection of study medication and up to and including date of last injection of study medication + 28 days.

Adverse Drug Reactions (ADRs): Any AE that is possibly, probably or definitely related to study medication or the assessment of the relationship to study medication is missing as reported in the eCRF.

Adverse events related to study procedure: Any AE that was documented with causal relationship to a study procedure of "yes" in the eCRF.

Adverse events of special interest (AESI): Any AE that was documented as "AESI confirmed by Adjudication Committee" in the eCRF.

Local AE: Any AE that is documented with the category "Local (injection site) adverse event" in the eCRF.

Systemic AE: Any AE that is documented with the category "Systemic adverse event" in the eCRF.

Other AE: Any AE that is documented with the category "Other adverse event" in the eCRF, i.e. any adverse event that is neither local nor systemic.

AEs leading to premature discontinuation of treatment: Any AE for which action taken is documented as "Permanent discontinuation of the IMP" in the eCRF.

AEs leading to temporary discontinuation of treatment: Any AE for which action taken is documented as "Temporary discontinuation of the IMP" in the eCRF.

AEs leading to premature discontinuation of study: for which action taken is documented as "Withdrawal from the Study" in the eCRF.

Duration of adverse event (expressed in [days]) is calculated as follows:

- End date/time of AE – onset date/time of AE
- In case of missing onset time or missing end time: end date of AE – onset date of AE + 1
- In case of (partially) missing onset date or (partially) missing end date no calculation will be done
- In case of ongoing end date/time (outcome = recovering, not recovered or unknown), date of study termination will be used as documented at the end of the study page or the early termination page of the eCRF.

5.8.2.2. Summary tables for analysis of adverse events

The number and percentage of subjects with

- TEAEs
- ADRs
- treatment emergent serious adverse events (SAEs)
- serious ADRs
- treatment emergent adverse events of special interest (AESIs)
- TEAEs leading to premature discontinuation of treatment
- ADRs leading to premature discontinuation of treatment
- TEAEs leading to temporary discontinuation of treatment
- ADRs leading to temporary discontinuation of treatment
- TEAEs leading to premature discontinuation of study
- ADRs leading to premature discontinuation of study
- local AEs
- systemic AEs

- other AEs, not classified as local or systemic AEs

will be summarised by treatment group, MedDRA SOC and PT.

For the analysis of the severity and the relationship of AEs, the worst severity and the strongest relationship per subject and type of AE will be used. The number and percentage of subjects with at least one AE by MedDRA SOC, PT and severity/relationship will be displayed only for

- all TEAEs
- all ADRs
- all serious adverse events (SAEs).

5.8.2.3. Overview summary tables for adverse events

An overview summary of the following AE types will be provided, presenting number and percentage of subjects experiencing at least one AE of the respective AE type in each treatment group as well as the corresponding number of events.

- Any AE
- Any ADR
- Any severe AE
- Any severe ADR
- Any AE of special interest
- Any serious AE
- Any serious ADR
- Any non-serious AE
- Any AE leading to premature discontinuation from treatment
- Any AE leading to temporary discontinuation from treatment
- Any ADR leading to premature discontinuation from treatment
- Any ADR leading to temporary discontinuation from treatment
- Any AE leading to premature discontinuation of study
- Any ADR leading to premature discontinuation of study
- Any local TEAE
- Any systemic TEAE
- Any other TEAE, not classified as local or systemic AE

Furthermore, the number and percentage of subjects with AEs, ADRs and severe AEs after each injection will be summarized by treatment group, differentiating whether the AE occurred within 24 hours after injection, after 7 days of injection or thereafter, including only TEAEs within the treatment period.

5.8.3 Safety laboratory

Blood samples for chemistry and haematology assessments will be collected at Visit 1 and Visit 15. Additionally, study sites will perform urine dipstick testing. In case of abnormal

findings, urine samples will be sent to the central laboratory for further analysis.

The laboratory tests that will be performed by the central laboratory are presented in Table 5. Laboratory test results and related normal ranges will be provided to investigators for review to assess subject eligibility and subject safety during the study.

Table 5: Safety Laboratory Assessments

Serum Chemistry	Glucose, Sodium, Uric acid, Urea, Potassium, Calcium, Creatinine, Chloride, Total protein, Phosphorus, Cholesterol, Albumin, Total Bilirubin, Alkaline phosphatase, LDH, AST, ALT, GGT, CRP
Haematology	Haemoglobin, haematocrit, total WBC and differentials, total RBC, RBC indices, and platelet count.
Urinalysis (using a urine dip-stick)	pH, Protein, Glucose, Ketones, Bilirubin, Blood, Nitrite, Urobilinogen, Leukocytes.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CRP = C-reactive protein; GGT = gamma-glutamyl transferase; LDH = lactate dehydrogenase; RBC = red blood cells; WBC = white blood cells.

Summary tables will be created for serum chemistry and haematology.

For urinalysis, a frequency table will be created summarizing the overall sample.

5.8.4 Vital signs

Vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature) will be measured after the subject has been in the supine position for at least 5 minutes at Visit 1 to Visit 15.

Summary statistics will be created per vital sign parameter and visit/timepoint (pre- and post-injection) for all scheduled treatment visits by treatment group including the absolute values per visit/timepoint and the absolute change from baseline.

5.8.5 Physical examination

A complete physical examination include assessment of the following: general appearance, skin, head, neck, eyes, ears, nose, throat, lymph nodes, abdomen, musculoskeletal, cardiovascular, respiratory and neurological systems. Rectal, breast, pelvic, gynaecological, and/or urogenital examinations will not be performed. Complete physical examination will be performed at Visit 1 and Visit 15, or at the early termination visit if applicable.

5.8.6 Other safety data

Pregnancy tests will only be performed on female subjects of childbearing potential on every visit (except 3 and 6 months safety follow-up calls). The corresponding results will only be listed by subject.

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6 SOFTWARE AND STATISTICAL PROGRAMMING

The statistical analysis will be performed using the SAS® statistical software package (Statistical Analysis System, Version 9.4 or higher) on a Windows Server 2016 System.

7 REFERENCES

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