Allergy Therapeutics (UK) Ltd.: PQGrass306
Study Protocol

Status: **final**

Clinical Trial Title:	A randomised, double-blind, placebo-controlled clinical trial to evaluate the efficacy and safety of PQ Grass in subjects with seasonal allergic rhinitis and/or rhinoconjunctivitis induced by grass pollen exposure
NCT05540717	
Investigational Product:	PQ Grass
Clinical Phase:	Phase III
Sponsor:	Allergy Therapeutics (UK) Ltd. Dominion Way BN14 8SA Worthing United Kingdom
Date:	June 20, 2023

Protocol Title:

A randomised, double-blind, placebo-controlled clinical trial to evaluate the efficacy and safety of PQ Grass in subjects with seasonal allergic rhinitis and/or rhinoconjunctivitis induced by grass pollen exposure.

Short Title:

Randomised efficacy and safety clinical trial of PQ Grass in subjects with seasonal allergic rhinitis and/or rhinoconjunctivitis induced by grass pollen.

Phase: Phase III

Sponsor: Allergy Therapeutics (UK) Ltd, Dominion Way, Worthing, West Sussex, BN14 8SA, United Kingdom.

Study centres: The clinical trial will be conducted in the United States of America (US) and in 5 countries in Europe at approximately 90 clinical trial sites. 15 study sites in total (7 centres in the EU and 8 centres in the US).

Rationale:

The PQGrass306 (G306) clinical trial is the pivotal Phase III efficacy clinical trial of PQ Grass. The aim of the G306 pivotal clinical trial is to confirm the efficacy and safety of the optimal effective dose of PQ Grass 27600 SU. This will be determined through the measurements of the effect of PQ Grass on the symptoms of seasonal allergic rhinitis (SAR)/rhinoconjunctivitis and the use of relief medications to control these symptoms during the peak grass pollen season (GPS).

Number of subjects planned:

The trial will apply an adaptive group sequential design with one interim analysis that will be performed on the subjects randomised in Year 1 (N=555). In case the decision is taken to progress the study to a second season after the interim analysis, the sample size will be recalculated.

Study period: Estimated first subject enrolled (Q3/2023) and last subject last visit (Q3/2024). The end of study (EoS) is defined as the date of the last 6 months telephone follow-up call of the last subject in the study.

Objectives and Endpoints:

Objectives	Endpoints
Primary Efficacy	
To evaluate the efficacy of PQ Grass 27600 SU in subjects with grass pollen induced SAR and/or rhinoconjunctivitis based on symptoms and medications.	• CSMS averaged over the peak GPS.
Secondary Efficacy	
To evaluate the treatment effect of PQ Grass on the CSMS over the entire GPS.	• CSMS averaged over the entire (or truncated) GPS.
To evaluate the quality of life.	• RQLQ(S) measured within the peak GPS.
To evaluate the effect of PQ Grass 27600 SU on IgG4.	• Serum grass specific IgG4 at Visit 7 compared to baseline.
To evaluate the treatment effect of PQ Grass on the dSS and dMS components of the CSMS over the GPS.	• dSS component of the CSMS averaged over the peak GPS and entire (or truncated) GPS. • dMS component of the CSMS averaged over the peak GPS and entire (or truncated) GPS.
To evaluate the potential of PQ Grass 27600 SU to reduce symptom burden and the need for medication use.	• The number of well days during the peak GPS.
Safety	
To evaluate the safety and tolerability of PQ Grass in subjects with grass pollen induced SAR and/or rhinoconjunctivitis.	• Frequency, severity and relationship of AEs to treatment. • Frequency of AEs leading to premature discontinuation from treatment or clinical trial. • Frequency of AESI. • Changes in clinical laboratory values (serum chemistry, haematology and urinalysis) between screening and Visit 11. • Changes in vital signs at all treatment visits.

Abbreviation sAE = adverse event; AESI = adverse event of special interest; CSMS = combined symptom and medication score; dMS = daily medication score; dSS = daily symptom score; GPS = grass pollen season; Ig = immunoglobulin; RQLQ(S) = Rhinoconjunctivitis Quality of Life Questionnaire with standardised activities; SAR = seasonal allergic rhinitis; SU = standardised units;

Overall Design (Brief Summary):

This is a multi-centre, randomised, parallel group, double-blind, placebo-controlled clinical trial to confirm the efficacy and safety of the optimal effective dose of PQ Grass (27600 SU). The trial will have an adaptive group sequential design with one planned interim analysis.

Subjects will be assigned in a ratio of 1:1 (PQ Grass:Placebo) with treatment course to be completed prior to the onset of the grass pollen season (GPS):

- **PQ Grass:** 6 injections of PQ Grass (900, 2700, 6000, 6000, 6000, 6000 SU sequentially) *or*
- **Placebo:** 6 injections of placebo

The study includes 4 periods, encompassing 11 visits to the study site and at least 2 follow-up telephone calls. Subjects will be provided with enough relief medication to cover them through this period by the study site.

Period 1 (Screening [**Visit 1 ± Visit 1a**]): This includes the screening visit at which subjects' eligibility for the clinical trial will be assessed.

Period 2 (Randomisation and treatment [**Visit 2 to Visit 7**]): At Visit 2, subjects will be randomly allocated in a randomisation ratio of 1:1 to the active treatment (PQ Grass) or the placebo treatment group and will receive the first injection.

After Randomization at Visit 2, subjects will thereafter return to the study site at subsequent visits during the treatment period (Visit 3 to Visit 7) to receive the remaining injections. The average duration of the treatment period will be approximately 16 weeks.

Treatment with either 6 injections of active treatment (900, 2700, 6000, 6000, 6000 and 6000 SU sequentially) to achieve a cumulative nominal dose of 27600 SU, or 6 injections of placebo will be administered prior to the onset of the GPS.

Period 3 During the GPS, subjects will record their allergic rhinitis/rhinoconjunctivitis symptoms and use of relief medications in an electronic diary (eDiary). The symptom and medication scores during the peak GPS and the entire (or truncated) GPS calculated according to the European Academy of Allergy and Clinical Immunology (EAACI) recommendations for the CSMS (primary endpoint) will be compared between the active and placebo treatment groups. The following 4 visits will be performed:

- Visit 8 (pre-GPS)
- Visit 9 (≈ onset of GPS)
- Visit 10 (during GPS)
- Visit 11 (≈ end of GPS)

Period 4 (Telephone safety follow-up): This consists of safety telephone calls at approximately 12 weeks and 24 weeks after the last injection to ascertain occurrence of any AEs.

Target population: Adult (18 to 65 years inclusive) subjects with seasonal allergic rhinitis and/or rhinoconjunctivitis due to grass pollen exposure (with or without allergic asthma that is well controlled).

Study treatments, dosage and mode of treatment:

Active Treatment:

Each PQ Grass injection will consist of extracts of grass pollen, which are chemically modified by treatment with glutaraldehyde and adsorbed to L-tyrosine.

The injections will be supplied at concentrations of 900, 2700, and 6000 SU per 1.0 milliliter (mL) and 50 microgram (µg)/1.0 mL of MPL adjuvant, 2% weight per volume (w/v) L-tyrosine and 0.5% (w/v) phenol.

Reference Therapy:

Placebo (Buffered saline with L-tyrosine 2% [w/v] and phenol 0.5% [w/v])

The average duration of treatment will be approximately 11 to 18 weeks.

Dose/Dose schedule:

PQ Grass or placebo will be administered during Visits 2 to 7. Visits 2 to 4 will be approximately 1 week apart, Visit 5 to 7 will be approximately 4 weeks apart.

Statistical methods

This is the pivotal Phase III study with PQ Grass. The primary endpoint of the study will be the CSMS averaged over the peak GPS.

The difference in CSMS between PQ Grass and placebo will be evaluated using a linear mixed model. Subjects with missing daily CSMS during the peak GPS will be included in the primary analysis by using multiple imputation methods to impute missing values on a by-day level.

The statistical analysis will be performed using a linear mixed model. In the context of the adaptive design, a 1-sided testing will be used using group sequential Pocock boundaries chosen such that an overall 1 sided type 1 error rate of 2.5% was preserved.

For the interim analysis after Year 1, the 1-sided p-value was therefore to be compared with $\alpha = 0.01419$ for a statistically significant superiority of the active treatment over placebo.

The difference between PQ Grass and placebo will be estimated using least squares (LS) means. Two-sided appropriate confidence intervals (CIs) for the difference between treatment groups

will be provided. The difference between treatment groups will also be presented in percent relative to the LS mean in the placebo group.

The secondary endpoints will generally be analyzed using a similar statistical approach as the primary endpoint. The statistical hypotheses for the key secondary endpoints will only to be tested in a confirmatory sense if the analysis of the primary endpoint is statistically significant. Multiplicity in the key secondary endpoints will be addressed.

The frequency, relationship and severity of AEs and frequency of premature discontinuations from treatment or study due to AEs will be assessed within each treatment group.

Adjudication Committee: Yes

Trial Oversight Committee: Yes

Schedule of activities

	Period 1 Screening	Period 2 Randomisation and Treatment						Period 3 ^ Pre/During/End of GPS Assessments				Period 4 ^ Follow-up	
Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**12w after last injection**	**24w after last injection**
Informed consent	X												
Inclusion/exclusion criteria	X												
Demographics	X												
Medical history (including asthma and allergy history)	X												
Physical examination	X										X		
Height and weight	X												
Mental health status assessment	X												
Skin prick testing	X												
Spirometry	X												
PEFR	X	X	X	X	X	X	X	X	X	X	X		
Vital signs	X	X	X	X	X	X	X	X	X	X	X		
RQLQ(S)		X							X	X			
Safety laboratory tests	X										X		
Urinalysis	X										X		
Urine pregnancy test	X	X	X	X	X	X	X	X	X	X	X		
IgE, and IgG4	X						X			X			
AEs	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomisation		X											
Investigational drug/placebo administration		X	X	X	X	X	X						
eDiary recording of daily symptoms/daily medication use								X					
Telephone safety follow-up												X	X

Main Inclusion criteria

Subjects will be eligible to be included in the study only if all of the following criteria apply:

1. Capable of giving signed informed consent
2. Subject had to be 18 to 65 years of age inclusive, at the time of signing the ICF.
3. Male or female.
4. Good general health, as determined by the Investigator, based on a medical evaluation, including medical history, physical examination, mental status assessment, and laboratory tests.
5. Positive history of moderate to severe symptoms of SAR/rhinoconjunctivitis ascribed to grass (*Pooideae*) pollen exposure of ≥2 seasons duration
6. A positive skin prick test (SPT) to histamine (wheals [longest diameter] ≥3 mm) and a negative SPT to the negative control (wheal diameter = 0 mm) at Screening.
7. A positive SPT for grass pollen (wheals [longest diameter] ≥3 mm).
8. Grass-specific IgE class ≥2 as documented by an ImmunoCAP test at Screening.
9. FEV_1 ≥80% of predicted, with a FEV_1/FVC ratio ≥70% and PEFR ≥75% predicted at screening.

Main Exclusion criteria

A subject will be excluded from this study if one or more of the following criteria apply:

1. Pregnant or lactating subject.
2. Presence of any medical history of moderate to severe allergy symptoms (verified by a positive SPT or positive specific IgE [Class ≥2] at Screening) to any other seasonal allergen (other than grass) or perennial allergens.
3. Moderate to severe symptoms during the 3 years prior to Visit 1 to any other seasonal or perennial allergen not tested in the SPT or by specific IgE done at Screening that cannot be avoided during the Period 1 to Period 3 of the clinical trial and the symptoms of which may interfere with administration of treatment and/or impact the data collected.
4. Presence of any medical condition that may reduce the ability to survive a serious allergic reaction.
5. Presence of severe or poorly controlled or uncontrolled asthma
6. Clinical history of type 1 diabetes or poorly controlled type 2 diabetes.
7. Clinical history of severe systemic reaction or serious systemic reaction in response to AIT in the past.
8. Clinical history of severe or life-threatening anaphylactic reactions to foods, insect venom, exercise, drugs, or idiopathic anaphylaxis.
9. Clinical history of allergy, hypersensitivity or intolerance to the excipients of the investigational drug/placebo.

10. Clinical history of allergy, hypersensitivity or intolerance to the relief medications (for relief of allergy symptoms during Period 3) provided for use in this clinical trial.
11. Unable to receive epinephrine therapy (ie, use of epinephrine is contraindicated such as in subjects with hyperthyroidism, uncontrolled hypertension, cardiac arrhythmias, closed angle glaucoma, or subjects taking other sympathomimetics).
12. Tyrosine metabolism disorders, especially tyrosinemia, and alkaptonuria.
13. Clinical history of drug or alcohol abuse, which, in the Investigator's opinion, could interfere with the subject's ability to participate in the clinical trial.
14. Any history of AIT for grass pollen allergy in the past or history of AIT for any other type of allergy (excluding food allergy) in the past 5 years.
15. Inability to adhere to the washout periods listed in with respect to Screening and to refrain from using the medications indicated until after Visit 11.
16. Treatment with a preparation containing MPL (eg, Cervarix, Shingrix, Fendrix) within 2 years prior to Visit 1 and until after completion of Visit 11 (with the exception of the investigational drug).
17. Previous history of epinephrine auto-injector use.
18. β-blocker medication (local or systemic, including eye drops) for any indication.
19. Monoamine oxidase inhibitors and tricyclic antidepressants.
20. Any previous therapy (within the previous 5 years) or current therapy with anti-IgE (eg, omalizumab [Xolair]) or anti-interleukins (eg, mepolizumab).
21. Current or past therapy (within the previous 5 years) with any other immunomodulatory biologics.
22. Unable to refrain from any vaccination (including influenza vaccine and COVID-19 vaccine) during the clinical trial (unless administered >30 days prior to randomisation).
23. Participation in a clinical research trial with any investigational drug within 4 weeks of Visit 1 or concomitantly with this clinical trial.
24. Personal, financial or other dependent relationship (eg, employee or immediate relative) with the clinical trial site, Sponsor, Sponsor's representative, or another individual who has access to the clinical trial protocol.
25. Vulnerable subjects or those in judicial or governmental detention, detainment, or imprisonment in a public institution.