

Allergy Therapeutics (UK) Ltd.: PQGrass309 Study Protocol

Status:

final

Clinical Trial 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.
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United Kingdom

Date:

August 3, 2021

Protocol 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.

Short Title: *An exploratory study of PQ Grass 27600 SU.*

Phase: Phase II/III

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

Study centres: The study is expected to be conducted in the European Union (EU) (Germany and/or Poland) and the United States of America (US) and include approximately 15 study sites in total (7 centres in the EU and 8 centres in the US).

Rationale:

The PQGrass309 (G309) clinical trial is the exploratory Phase II/III field study with PQ Grass. The aim of the G309 pivotal clinical trial is to explore the efficacy and safety of the optimal effective dose of PQ Grass 27600 SU using 2 pre-seasonal treatment regimens ~ (conventional and extended). The efficacy will be assessed 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 study will enrol enough subjects to allow treatment of approximately 150 subjects.

Study period: Estimated first subject enrolled (Q3/2020) and last subject last visit (Q3/2021). 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	
To explore the efficacy of PQ Grass 27600 SU in grass pollen induced seasonal allergic rhinitis and/or rhinoconjunctivitis in a field setting.	The CSMS averaged over the peak grass pollen season (GPS).
Secondary	
Efficacy	

Objectives	Endpoints
To explore the treatment effect of PQ Grass on the CSMS and TCS over the GPS.	CSMS averaged over the entire (or truncated) GPS. TCS averaged over the peak GPS. TCS averaged over the entire (or truncated) GPS.
To explore 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 explore the treatment effect of PQ Grass on the dSS and dMS components of the TCS over the GPS.	dSS component of the TCS averaged over the peak GPS and entire (or truncated) GPS. dMS component of the TCS averaged over the peak GPS and entire (or truncated) GPS.
To explore the relationship between TSS during CPT and CSMS, TCS, dSS (for CSMS and TCS) and dMS (for CSMS and TCS) over the GPS compared to baseline.	TSS during CPT, CSMS, TCS, dSS (for CSMS and TCS) and dMS (for CSMS and TCS) over the peak and entire (or truncated) GPS for subjects with a positive CPT at baseline.
To evaluate well days and severe days during the GPS.	The probability of well days and severe days during the peak and entire (or truncated) GPS.
To evaluate TSS during CPT at the same dose eliciting a positive response at baseline.	Pre-GPS (Visit 12) TSS measured during CPT.
To evaluate immunological parameters.	Serum Ig responses (total IgE; grass-specific IgE and IgG4; specific IgE/total IgE and specific IgE/specific IgG4) at Visit 12 and Visit 15.
To evaluate the quality of life.	Rhinoconjunctivitis quality of life questionnaire with standardised activities (RQLQ(S)) measured within the GPS.

Objectives	Endpoints
Safety	
To evaluate the safety and tolerability of PQ Grass in subjects with grass pollen induced seasonal allergic rhinitis and/or rhinoconjunctivitis.	<p>Frequency, severity and relationship of AEs to treatment.</p> <p>Frequency of AEs leading to premature discontinuation from treatment or study.</p> <p>Frequency of AESI.</p> <p>Changes in clinical laboratory values (chemistry, haematology, urinalysis) between screening and Visit 15.</p> <p>Changes in vital signs (all subjects) and PEFr (only in subjects with past or current asthma) at all treatment visits.</p>
Abbreviations: AE = adverse events; AESI = adverse events of special interest; CPT = conjunctival provocation test; CSMS = combined symptom and medication score; dMS = daily medication score; dSS = daily symptom score; GPS = grass pollen season; Ig = immunoglobulin; PEFr = peak expiratory flow rate; RQLQ(S) = rhinoconjunctivitis quality of life questionnaire with standardised activities; SU = standardised units; TCS = total combined score; TSS = total symptom score.	

Overall design:

This will be a multi-centre, randomised, parallel group, double-blind, placebo-controlled exploratory study to explore the efficacy and safety of PQ Grass. Subjects will be assigned in a ratio of 2:2:1:1 (PQ Grass conventional posology, PQ Grass extended posology, placebo containing MCT and placebo without MCT, respectively) to receive one of the following treatment options prior to the onset of the grass pollen season (GPS):

- **PQ Grass conventional posology:** 4 injections of placebo without MCT followed by 6 injections of PQ Grass (900, 2700, 6000, 6000, 6000 and 6000 SU sequentially), to achieve a cumulative dose of 27600 SU *or*
- **PQ Grass extended posology:** 4 injections initially of PQ Grass (900, 2700, 6000, 6000 SU sequentially) followed by 1 injection of placebo without MCT, followed by 1 injection of PQ Grass (6000 SU), followed by 3 injections of placebo without MCT and thereafter 1 injection of PQ Grass (6000 SU) to achieve a cumulative dose of 27600 SU *or*
- **Placebo containing MCT:** 4 injections of placebo without MCT followed by 6 injections of placebo containing MCT *or*
- **Placebo without MCT:** 10 injections of placebo without MCT.

The study includes 4 periods, encompassing 15 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. Eligible subjects will be randomised to either PQ Grass (conventional posology), PQ Grass (extended posology), placebo containing MCT or placebo without MCT treatment groups and will receive the first injection at the study. Subjects will thereafter return to the study site at subsequent visits during the treatment period (Visit 3 to Visit 11) to receive the remaining injections. The average duration of the treatment period will be approximately 16 weeks.

During the GPS, subjects will record their allergic rhinitis/rhinoconjunctivitis symptoms and use of relief medications in an electronic diary (eDiary). The primary 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.

Subjects will return to study site for a follow-up visit approximately 2 weeks after Visit 12 (Visit 13) and 5 weeks after Visit 13 (Visit 14). At Visit 15 (approximately 5 weeks after Visit 14), subjects will return their eDiaries and relief medications, and post-treatment assessments for safety and efficacy parameters will be carried out.

A safety follow-up will be conducted by telephone at 3 and 6 months following the last injection.

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:

2 forms of placebo will be used; placebo containing MCT (L-tyrosine 2% [w/v] and phenol 0.5% [w/v]) and placebo without MCT (Buffered saline with 0.5% phenol [w/v]).

Dose/Dose schedule:

PQ Grass or placebo will be administered during Visits 2 to 11. Visits 2 to 4 will be approximately 1 week apart, Visit 4 to 5 will be approximately 4 weeks apart, Visit 5 to 6 will be approximately 3 weeks apart and Visits 6 to 11 will be approximately 1 week apart.

Statistical methods

This is an exploratory field study which will aim to randomise 150 subjects, with approximately 50, 50, 25 and 25 subjects randomised to PQ Grass 27600 SU (conventional posology), PQ Grass 27600 SU (extended posology), placebo containing MCT and placebo without MCT, respectively. This number is considered adequate for an exploratory study to verify the assumptions for the coefficient of variation (CV) of the placebo and the average reduction in CSMS after treatment with PQ Grass compared to placebo (both expressed as percentages and as absolute differences) during the peak GPS. The findings from this exploratory study will support the sample size calculations of a subsequent pivotal Phase III study for PQ Grass (PQGrass306).

The primary endpoint of the study will be the CSMS averaged over the peak GPS.

The difference in CSMS between PQ Grass (conventional posology) and placebo (i.e., the placebo containing MCT group and the placebo without MCT group) and the difference between PQ Grass (extended posology) and the placebo groups will be evaluated using parametric (i.e., linear mixed effects model) / non-parametric models as appropriate. The 2 placebo groups will both be combined and analysed as separate groups if there is <5% effect-size difference and similar variability between the 2 groups. Otherwise, they will only be analysed as independent groups.

Secondary efficacy endpoints derived from the CSMS, TCS, daily symptom score (dSS) and daily medication score (dMS) (for both the CSMS and TCS) and for the peak/entire (or truncated) GPS, immunological responses, probability of well days and quality of life will be evaluated using comparable linear mixed effects model and sensitivity analyses as in the primary efficacy analysis.

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. Changes in vital signs, clinical laboratory parameters and peak expiratory flow rate (PEFR) in subjects with past or current asthma will be analysed using descriptive statistics and 2-sided 95% confidence intervals (CIs) within each treatment group. All other safety data will be analysed descriptively.

Trial Oversight Committee: Yes.

Adjudication Committee: Yes.

Schedule of activities

	Period 1 Screening	Period 2 Randomisation and Treatment					Period 3 Pre/during/end of GPS Assessments				Period 4	
Visit Number	V1	V2	V3-4	V5	V6	V7-11	V12	V13	V14	V15	3 M	6 M
Informed consent	X											
Inclusion/exclusion criteria	X	X										
Demographics	X											
Medical and allergy history	X											
Physical examination (including height, weight and mental health assessment at V1 only)	X									X		
Skin prick testing	X											
Spirometry	X											
PEFR	X	X	X	X	X	X	X	X	X	X		
Vital signs	X	X	X	X	X	X	X	X	X	X		
Safety laboratory tests and urinalysis ⁸	X									X		
Urine pregnancy test	X	X	X	X	X	X	X	X	X	X		
CPT	X	X					X					
AEs	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
Randomisation		X										
Study drug administration		X	X	X	X	X						
Post-dose observation and 24 hour, 4 and 7 days post-dose call		X	X	X	X	X						
eDiary recording of daily symptoms/daily medication use							X					
Issue relief medications							X	X	X			
RQLQ(S)		X						X	X			
Telephone safety follow-up at 3 and 6 months following the last injection											X	X

Abbreviations: AE = adverse event; CPT = conjunctival provocation test; eDiary= electronic diary; Ig = immunoglobulin; IMP = investigational medicinal product; M = months; PEFR = peak expiratory flow rate; RQLQ(S) = Rhinoconjunctivitis Quality of Life Questionnaire with standardised activities; SPT = skin prick test; TEAE =treatment emergent adverse event; V = visit.

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 must 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, and laboratory tests.

5. Positive history of moderate to severe symptoms of seasonal allergic rhinitis and/or rhinoconjunctivitis ascribed to grass (*Pooideae*) pollen exposure that required repeated use of antihistamines, nasal corticosteroids, and/or leukotriene modifiers for relief of symptoms during the last 2 consecutive seasons prior to the study, confirmed by subject records.
6. A positive SPT for grass pollen (wheals [longest diameter] ≥ 3 mm and histamine ≥ 3 mm) and a negative SPT to the negative control (wheal diameter=0) at screening.
7. Grass specific IgE class ≥ 2 as documented by an ImmunoCAP test at screening.
8. FEV₁ $\geq 80\%$ of predicted, with a FEV₁/FVC ratio $\geq 70\%$ and PEFR $\geq 75\%$ 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. Moderate to severe allergy symptoms during the screening and treatment periods, and/or GPS caused by perennial allergens or seasonal allergens (other than grass) as verified by medical history and positive SPT.
3. Moderate to severe symptoms during the 3 years prior to Visit 1 to another seasonal or perennial allergen not tested in the SPT that cannot be avoided during the study and the symptoms of which may interfere with administration of treatment and/or impact the data collected, as determined by the investigator.
4. Presence of any medical condition that may reduce the ability to survive a serious allergic reaction.
5. Presence of severe or uncontrolled or partly controlled asthma
6. Emergency room visit or hospitalisation for asthma in the 12 months prior to screening and randomisation or any history of a life-threatening asthma attack.
7. Clinical history of severe or serious SR in response to AIT treatment 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 IMP.
10. Tyrosine metabolism disorders, especially tyrosinemia and alkaptonuria.

Prior/concomitant therapy

11. History of any allergen SIT.

12. Inability to adhere to the washout periods listed in the table Prohibited Medications/Therapies
13. Treatment with a preparation containing MPL (e.g., Cervarix, Shingrix, Fendrix) within 2 years prior to Visit 1 and until after completion of Visit 15 (with the exception of the IMP).
14. Unable to receive epinephrine therapy (i.e., use of epinephrine is contraindicated such as in subjects with hyperthyroidism, uncontrolled hypertension, cardiac arrhythmias, closed angle glaucoma or subjects taking other sympathomimetic).
15. Previous history of epinephrine device use.
16. β -blocker medication (including eye drops), for any indication.
17. Monoamine oxidase inhibitors and tricyclic antidepressants (tricyclic antidepressants should be avoided at least 2 weeks prior to screening).
18. Any previous therapy (within 12 months prior to screening) or current therapy with anti-IgE (e.g., Xolair) or anti-interleukins (e.g., mepolizumab) or any other therapy with a biologic agent.

Other exclusions

19. Clinical history of drug or alcohol abuse which, in the investigator's opinion, could interfere with the subject's ability to participate in the study.
20. Participation in a clinical research trial with any IMP within 4 weeks of Visit 1 or concomitantly with this study
21. Personal, financial or other dependent relationship (e.g., employee or immediate relative) with the study site, Sponsor, Sponsor's representative, or another individual who has access to the study protocol.
22. Vulnerable subjects or those in judicial or governmental detention, detainment or imprisonment in a public institution.