Clinical trial results:
A multi-centre, randomised, double blind, placebo controlled study to determine the optimal effective and safe dose of Pollinex Quattro Grass 1.0 mL (Allergy Therapeutics, (UK) Ltd.) for the treatment of patients with seasonal allergic rhinoconjunctivitis due to grass pollen

Summary

EudraCT number	2017-000333-31
Trial protocol	DE AT PL
Global end of trial date	05 April 2018

Results information

Result version number	v1 (current)
This version publication date	20 April 2019
First version publication date	20 April 2019

Trial information

Trial identification

Sponsor protocol code	PQGrass205

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Allergy Therapeutics (UK) Ltd.
Sponsor organisation address	Dominion Way, Worthing, United Kingdom, BN14 8SA
Public contact	Clinical Research Management, Bencard Allergie GmbH, +49 0893681198, denise.lee@allergytherapeutics.com
Scientific contact	Clinical Research Management, Bencard Allergie GmbH, +49 0893681198, denise.lee@allergytherapeutics.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 April 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 April 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the dose-response of Pollinex Quattro Grass 1.0 mL in patients with grass pollen-induced rhinoconjunctivitis.

Protection of trial subjects:

The conduct of this trial met all local legal and regulatory requirements. The study was conducted in accordance with the principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization (ICH) Guideline E6: Good Clinical Practice (GCP). An informed consent form explaining the procedures of the study including the potential hazards was reviewed and approved by the responsible IEC/IRB before its use.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 September 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 152
Country: Number of subjects enrolled	Austria: 19
Country: Number of subjects enrolled	Germany: 276
Worldwide total number of subjects	447
EEA total number of subjects	447

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	447

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted in 43 investigational sites in three countries: Austria, Germany and Poland. Overall, 546 patients were enrolled and screened, 447 patients were randomised and received the study drug. A total of 426 patients were included in the analysis set.

Pre-assignment

Screening details:

Male or female aged 18 to 50 years with a positive history of moderate to severe seasonal allergic rhinoconjunctivitis ascribed to grass pollen exposure requiring treatment for at least two consecutive seasons prior to study.

Period 1

Period 1 title	Visit 2 - 7 (Visit 1 = Screening)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

The identity of study medication administered was not known by the subject, investgators or other persons directly involved in the conduct of the clinical study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

6 subcutaneous injections of Placebo given sequentially at weekly intervals

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Trained site personnel administered 6 subcutaneous injections of 1.0 mL each in eligible subjects in the outer third part of the upper arm.

Arm title	5100 SU

Arm description:

2 subcutaneous injections of Placebo and 4 subcutaneous injections of PQ Grass achieving 5100 SU cumulative dose

Arm type	Experimental
Investigational medicinal product name	POLLINEX® Quattro Grass 1.0 mL; Placebo
Investigational medicinal product code	
Other name	PQ Grass
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

6 subcutaneous injections of 1.0 mL each, with 2 Placebo injections followed by active formulations at the dose strengths 300, 800, 2000 and 2000 SU/mL given sequentially at weekly intervals.

Arm title	14400 SU

Arm description:

6 subcutaneous injections of PQ Grass achieving 14400 SU cumulative dose

Arm type	Experimental
Investigational medicinal product name	POLLINEX® Quattro Grass 1.0 mL
Investigational medicinal product code	
Other name	PQ Grass
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

6 subcutaneous injections of 1.0 mL each, at the dose strengths 900, 2700, 2700, 2700, 2700 and 2700 SU/mL given sequentially at weekly intervals.

Arm title	27600 SU

Arm description:

6 subcutaneous injections of PQ Grass achieving 27600 SU cumulative dose

Arm type	Experimental
Investigational medicinal product name	POLLINEX® Quattro Grass 1.0 mL
Investigational medicinal product code	
Other name	PQ Grass
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

6 subcutaneous injections of 1.0 mL each, at the dose strengths 900, 2700, 6000, 6000, 6000 and 6000 SU/mL given sequentially at weekly intervals.

Arm title	35600 SU

Arm description:

6 subcutaneous injections of PQ Grass achieving 35600 SU cumulative dose

Arm type	Experimental
Investigational medicinal product name	POLLINEX® Quattro Grass 1.0 mL
Investigational medicinal product code	
Other name	PQ Grass
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

6 subcutaneous injections of 1.0 mL each, at the dose strengths 900, 2700, 8000, 8000, 8000 and 8000 SU/mL given sequentially at weekly intervals.

Number of subjects in period 1	Placebo	5100 SU	14400 SU
Started	89	87	92
Completed	86	86	87
Not completed	3	1	5
Consent withdrawn by subject	-	-	1
Adverse event, non-fatal	1	1	4
no post-treatment TSS available	1	-	-
Protocol deviation	1	-	-

Number of subjects in period 1	27600 SU	35600 SU
Started	93	86

Completed	88	80
Not completed	5	6
Consent withdrawn by subject	2	1
Adverse event, non-fatal	2	5
no post-treatment TSS available	-	-
Protocol deviation	1	-

Period 2

Period 2 title	Follow-up (Visit 8)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

The identity of study medication administered was not known by the subject, investgators or other persons directly involved in the conduct of the clinical study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

6 subcutaneous injections of Placebo given sequentially at weekls intervals

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	Placebo
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Trained site personnel administered 6 subcutaneous injections of 1.0 mL each in eligible subjects in the outer third part of the upper arm.

Arm title	5100 SU

Arm description:

2 subcutaneous injections of Placebo and 4 subcutaneous injections of PQ Grass achieving 5100 SU cumulative dose

Arm type	Experimental
Investigational medicinal product name	POLLINEX® Quattro Grass 1.0 mL; Placebo
Investigational medicinal product code	
Other name	PQ Grass
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

6 subcutaneous injections of 1.0 mL each, with 2 Placebo injections followed by active formulations at the dose strengths 300, 800, 2000 and 2000 SU/mL given sequentially at weekly intervals.

Arm title	14400 SU

Arm description:

6 subcutaneous injections of 1.0 mL each, at the dose strengths 900, 2700, 2700, 2700, 2700 and 2700

SU/mL given sequentially at weekly intervals.

Arm type	Experimental
Investigational medicinal product name	POLLINEX® Quattro Grass 1.0 mL
Investigational medicinal product code	
Other name	PQ Grass
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

6 subcutaneous injections of 1.0 mL each, at the dose strengths 900, 2700, 2700, 2700, 2700 and 2700 SU/mL given sequentially at weekly intervals.

Arm title	27600 SU

Arm description:

6 subcutaneous injections of PQ Grass achieving 27600 SU cumulative dose

Arm type	Experimental
Investigational medicinal product name	POLLINEX® Quattro Grass 1.0 mL
Investigational medicinal product code	
Other name	PQ Grass
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

6 subcutaneous injections of 1.0 mL each, at the dose strengths 900, 2700, 6000, 6000, 6000 and 6000 SU/mL given sequentially at weekly intervals.

Arm title	35600 SU

Arm description:

6 subcutaneous injections of PQ Grass achieving 35600 SU cumulative dose

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Trained site personnel administered 6 subcutaneous injections of 1.0 mL each in eligible subjects in the outer third part of the upper arm.

Investigational medicinal product name	POLLINEX® Quattro Grass 1.0 mL
Investigational medicinal product code	
Other name	PQ Grass
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

6 subcutaneous injections of 1.0 mL each, at the dose strengths 900, 2700, 8000, 8000, 8000 and 8000 SU/mL given sequentially at weekly intervals.

Number of subjects in period 2	Placebo	5100 SU	14400 SU
Started	86	86	87
Completed	85	86	87
Not completed	1	0	0
Lost to follow-up	1	-	-

Number of subjects in period 2	27600 SU	35600 SU
Started	88	80
Completed	88	80
Not completed	0	0
Lost to follow-up	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
6 subcutaneous injections of Placebo given sequentially at weekly intervals	
Reporting group title	5100 SU
Reporting group description:	
2 subcutaneous injections of Placebo and 4 subcutaneous injections of PQ Grass achieving 5100 SU cumulative dose	
Reporting group title	14400 SU
Reporting group description:	
6 subcutaneous injections of PQ Grass achieving 14400 SU cumulative dose	
Reporting group title	27600 SU
Reporting group description:	
6 subcutaneous injections of PQ Grass achieving 27600 SU cumulative dose	
Reporting group title	35600 SU
Reporting group description:	
6 subcutaneous injections of PQ Grass achieving 35600 SU cumulative dose	

Reporting group values	Placebo	5100 SU	14400 SU
Number of subjects	89	87	92
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	89	87	92
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	31.6	29.6	31.9
standard deviation	± 9.2	± 8.4	± 9.2
Gender categorical			
Units: Subjects			
Female	41	43	44
Male	48	44	48

Reporting group values	27600 SU	35600 SU	Total
Number of subjects	93	86	447
Age categorical			
Units: Subjects			
In utero	0	0	0

Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	93	0	361
From 65-84 years	0	86	86
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	30.3	30.2	
standard deviation	± 8.2	± 8.0	-
Gender categorical			
Units: Subjects			
Female	36	41	205
Male	57	45	242

Subject analysis sets

Subject analysis set title	Safety Set
Subject analysis set type	Full analysis

Subject analysis set description:

All patients who received at least one dose of study medication. Subjects were analysed according to the treatment that they received.

Subject analysis set title	mFAS
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subset of the Full Analysis Set that excluded all patients who did not receive exactly the full cumulative dose to which they were randomized to or who had missing values with respect to the post-treatment TSS.

Reporting group values	Safety Set	mFAS	
Number of subjects	447	426	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	447	426	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	30.8	30.7	
standard deviation	± 8.6	± 8.6	

Gender categorical Units: Subjects			
Female	205	192	
Male	242	234	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
6 subcutaneous injections of Placebo given sequentially at weekly intervals	
Reporting group title	5100 SU
Reporting group description:	
2 subcutaneous injections of Placebo and 4 subcutaneous injections of PQ Grass achieving 5100 SU cumulative dose	
Reporting group title	14400 SU
Reporting group description:	
6 subcutaneous injections of PQ Grass achieving 14400 SU cumulative dose	
Reporting group title	27600 SU
Reporting group description:	
6 subcutaneous injections of PQ Grass achieving 27600 SU cumulative dose	
Reporting group title	35600 SU
Reporting group description:	
6 subcutaneous injections of PQ Grass achieving 35600 SU cumulative dose	
Reporting group title	Placebo
Reporting group description:	
6 subcutaneous injections of Placebo given sequentially at weekls intervals	
Reporting group title	5100 SU
Reporting group description:	
2 subcutaneous injections of Placebo and 4 subcutaneous injections of PQ Grass achieving 5100 SU cumulative dose	
Reporting group title	14400 SU
Reporting group description:	
6 subcutaneous injections of 1.0 mL each, at the dose strengths 900, 2700, 2700, 2700, 2700 and 2700 SU/mL given sequentially at weekly intervals.	
Reporting group title	27600 SU
Reporting group description:	
6 subcutaneous injections of PQ Grass achieving 27600 SU cumulative dose	
Reporting group title	35600 SU
Reporting group description:	
6 subcutaneous injections of PQ Grass achieving 35600 SU cumulative dose	
Subject analysis set title	Safety Set
Subject analysis set type	Full analysis
Subject analysis set description:	
All patients who received at least one dose of study medication. Subjects were analysed according to the treatment that they received.	
Subject analysis set title	mFAS
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Subset of the Full Analysis Set that excluded all patients who did not receive exactly the full cumulative dose to which they were randomized to or who had missing values with respect to the post-treatment TSS.	

Primary: Post-treatment TSS following CPT

End point title	Post-treatment TSS following CPT

End point description:

The primary objective of this study was to evaluate the dose-response of PQ Grass in patients with grass pollen-induced rhinoconjunctivitis. The MCP-Mod (multiple comparison procedure - modeling methodology) was used to test for and to characterise a dose-response relationship using the placebo (0 SU) and the 5100, 14400, 27600, and 35600 SU treatment arms as dose levels.

End point type	Primary

End point timeframe:

Approximately four weeks after the last injection.

End point values	Placebo	5100 SU	14400 SU	27600 SU
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	85	86	87	88
Units: Score				
arithmetic mean (standard deviation)	-1.9 (± 2.2)	-3.0 (± 2.9)	-3.5 (± 3.0)	-3.7 (± 2.9)

End point values	35600 SU			
Subject group type	Reporting group			
Number of subjects analysed	80			
Units: Score				
arithmetic mean (standard deviation)	-3.1 (± 2.8)			

Attachments (see zip file)	PQGrass205-attachment-primary endpoint-MCP

Statistical analyses

Statistical analysis title	MCP-Mod
Comparison groups	Placebo v 35600 SU v 5100 SU v 14400 SU v 27600 SU
Number of subjects included in analysis	426
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	MCP-Mod

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Within the time period from the first injection of study medication until Visit 8	
Adverse event reporting additional description:	
AEs were summarised by treatment group and primary SOC, preferred term, additionally by causality assessment and intensity	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	5100 SU
Reporting group description: -	
Reporting group title	14400 SU
Reporting group description: -	
Reporting group title	27600 SU
Reporting group description: -	
Reporting group title	35600 SU
Reporting group description: -	

Serious adverse events	Placebo	5100 SU	14400 SU
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 89 (0.00%)	0 / 87 (0.00%)	0 / 92 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Serious adverse events	27600 SU	35600 SU	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 93 (0.00%)	0 / 86 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo	5100 SU	14400 SU
Total subjects affected by non-serious adverse events			
subjects affected / exposed	53 / 89 (59.55%)	76 / 87 (87.36%)	78 / 92 (84.78%)
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	15 / 89 (16.85%)	50 / 87 (57.47%)	55 / 92 (59.78%)
occurrences (all)	21	130	190
Injection site swelling			
subjects affected / exposed	11 / 89 (12.36%)	52 / 87 (59.77%)	56 / 92 (60.87%)
occurrences (all)	22	132	183
Injection site pruritus			
subjects affected / exposed	5 / 89 (5.62%)	40 / 87 (45.98%)	41 / 92 (44.57%)
occurrences (all)	5	87	109
Injections site pain			
subjects affected / exposed	18 / 89 (20.22%)	20 / 87 (22.99%)	23 / 92 (25.00%)
occurrences (all)	36	39	41
Injection site urticaria			
subjects affected / exposed	1 / 89 (1.12%)	7 / 87 (8.05%)	8 / 92 (8.70%)
occurrences (all)	1	14	18
Injection site warmth			
subjects affected / exposed	1 / 89 (1.12%)	3 / 87 (3.45%)	10 / 92 (10.87%)
occurrences (all)	1	4	15
Injection site nodule			
subjects affected / exposed	2 / 89 (2.25%)	4 / 87 (4.60%)	6 / 92 (6.52%)
occurrences (all)	3	8	10
Headache			
subjects affected / exposed	5 / 89 (5.62%)	4 / 87 (4.60%)	0 / 92 (0.00%)
occurrences (all)	6	5	0
Infections and infestations			
Viral upper respiratory tract infection			
subjects affected / exposed	17 / 89 (19.10%)	12 / 87 (13.79%)	8 / 92 (8.70%)
occurrences (all)	20	13	9
Pharyngitis			
subjects affected / exposed	6 / 89 (6.74%)	4 / 87 (4.60%)	2 / 92 (2.17%)
occurrences (all)	6	4	2

Non-serious adverse events	27600 SU	35600 SU	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	84 / 93 (90.32%)	76 / 86 (88.37%)	
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	65 / 93 (69.89%)	59 / 86 (68.60%)	
occurrences (all)	238	204	
Injection site swelling			
subjects affected / exposed	62 / 93 (66.67%)	59 / 86 (68.60%)	
occurrences (all)	199	208	
Injection site pruritus			
subjects affected / exposed	47 / 93 (50.54%)	40 / 86 (46.51%)	
occurrences (all)	130	105	
Injections site pain			
subjects affected / exposed	30 / 93 (32.26%)	23 / 86 (26.74%)	
occurrences (all)	65	41	
Injection site urticaria			
subjects affected / exposed	9 / 93 (9.68%)	6 / 86 (6.98%)	
occurrences (all)	21	21	
Injection site warmth			
subjects affected / exposed	8 / 93 (8.60%)	5 / 86 (5.81%)	
occurrences (all)	14	1	
Injection site nodule			
subjects affected / exposed	6 / 93 (6.45%)	3 / 86 (3.49%)	
occurrences (all)	13	10	
Headache			
subjects affected / exposed	3 / 93 (3.23%)	2 / 86 (2.33%)	
occurrences (all)	3	2	
Infections and infestations			
Viral upper respiratory tract infection			
subjects affected / exposed	14 / 93 (15.05%)	10 / 86 (11.63%)	
occurrences (all)	18	11	
Pharyngitis			
subjects affected / exposed	3 / 93 (3.23%)	2 / 86 (2.33%)	
occurrences (all)	3	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 July 2017	Update to the German Final Study Protocol v 3.0.; PEI requested to incorporate further exclusion requirements.
18 September 2017	To create a global protocol version - Version 4.0. The protocol update included update of symptpom intensity for exclusion criteria table to reflect the exclusion of all birch and ash allergic patients, addition of withdrawal criterion for patients with past or current asthma who fail spirometry test prior to any IMP administration and replacement of term "rescue medication" with "relief medication".

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None

Notes: