Clinical trial results:
Randomised placebo-controlled study of grass pollen allergen immunotherapy tablet (AIT) for seasonal rhinitis: time course of nasal, cutaneous and immunological outcomes

Summary

EudraCT number	2013-003732-72
Trial protocol	GB
Global end of trial date	01 March 2017

Results information

Result version number	v2 (current)
This version publication date	12 October 2019
First version publication date	23 August 2019
Version creation reason	• New data added to full data set • Correction of full data set Statistical data and minor changes needs to be corrected on the posted file

Trial information

Trial identification

Sponsor protocol code	13IC0847

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02005627
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Imperial College London
Sponsor organisation address	Norfolk Place, London, United Kingdom, W2 1PG
Public contact	Nabila Youssouf , Imperial College London, +44 (0)2033110206, nabila.youssouf08@imperial.ac.uk
Scientific contact	Nabila Youssouf , Imperial College London, +44 (0)2033110206, nabila.youssouf08@imperial.ac.uk

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	07 January 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 March 2017
Global end of trial reached?	Yes
Global end of trial date	01 March 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To understand the time course of clinical and immunological actions of grass pollen allergen immunotherapy tablets in the treatment of seasonal allergic rhinitis.

Protection of trial subjects:

This trial was conducted in compliance with the protocol, current Good Clinical Practice (GCP) guidelines and all
applicable regulatory requirements. All participants read, signed, and dated the consent form before participating in the
study. Participant's privacy and confidentiality were preserved by assigning a sequential identification number used to collect, store, and report participant information.
Grazax sublingual immunotherapy is commonly associated with local side effects of itching and swelling in the mouth that may last up to 30 minutes after taking each tablet. Systemic side effects after Grazax are very rare and generally of mild intensity. The first Grazax® or Grazax® placebo was administered under the supervision of a trial physician and the participant observed for one hour thereafter before discharge from the clinic.

Background therapy:

All atopic participants were provided with anti-allergic rescue medications (antihistamine tablets, topical intranasal corticosteroids, and eye-drops) throughout the pollen season.

Evidence for comparator:

Sublingual immunotherapy tablet is a fast-dissolving tablet that is registered throughout Europe for sublingual use in patients aged 5–65 years (18–65 years in UK). The tablet is administered daily for a minimum of 2 months before and during the grass pollen season to be taken for at least 3 years. In a double-blind trial of Grazax® that included a withdrawal phase, efficacy was maintained for 2–3 years with continuous treatment and at 1 year following withdrawal.

Actual start date of recruitment	01 September 2013
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	United Kingdom: 46
Worldwide total number of subjects	46
EEA total number of subjects	46

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)	46
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants who were having severe allergic rhinoconjunctivitis were recruited during out of pollen season from September to March 2014. All participants were recruited from United Kingdom.

Pre-assignment

Screening details:

Individuals with severe grass pollen hay fever, with or without associated seasonal asthma were recruited after the 2013 grass pollen season, between December 2013 and April 2014. Screening of 94 participants was completed before 46 eligible atopic participants were randomized to one of the following two treatment arms in a 1:1 ratio.

Period 1

Period 1 title	Overall Trial (overall period)
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 active Grazax tablets and placebo were prepared as identical tablet and provided in identical packages. Throughout the study, participants, data analysist and investigators remained blinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	Grazax

Arm description:

The active treatment arm received active grass pollen immunotherapy tablet (AIT), Grazax Oral Lyophilisate 75,000 standardised quality units tablet (SQ-T) once daily.

Arm type	Active comparator
Investigational medicinal product name	GRAZAX
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Sublingual tablet
Routes of administration	Sublingual use

Dosage and administration details:

Active Grazax Oral Lyophilisate 75,000 standardised quality units tablet (SQ-T) once daily.

Arm title	Grazax Placebo

Arm description:

The placebo treatment arm received placebo tablet, Grazax placebo tablet (SQ-T) once daily.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Sublingual tablet
Routes of administration	Sublingual use

Dosage and administration details:

Grazax placebo tablet (SQ-T) sublingually once daily.

Number of subjects in period 1	Grazax	Grazax Placebo
Started	23	23
Completed	21	19
Not completed	2	4
Consent withdrawn by subject	1	2
Lost to follow-up	1	2

Baseline characteristics

Reporting groups	
Reporting group title	Grazax
Reporting group description:	
The active treatment arm received active grass pollen immunotherapy tablet (AIT), Grazax Oral Lyophilisate 75,000 standardised quality units tablet (SQ-T) once daily.	
Reporting group title	Grazax Placebo
Reporting group description:	
The placebo treatment arm received placebo tablet, Grazax placebo tablet (SQ-T) once daily.	

Reporting group values	Grazax	Grazax Placebo	Total
Number of subjects	23	23	46
Age categorical Units: Subjects			
Adults (18-64 years)	23	23	46
Age continuous Units: years			
median	31.5	36.9	
standard deviation	± 2.12	± 1.97	-
Gender categorical Units: Subjects			
Female	10	5	15
Male	13	18	31
Specific IgE Units: kU/l			
median	14.4	14.17	
standard deviation	± 3.12	± 2.81	-

End points

End points reporting groups

Reporting group title	Grazax
Reporting group description:	
The active treatment arm received active grass pollen immunotherapy tablet (AIT), Grazax Oral Lyophilisate 75,000 standardised quality units tablet (SQ-T) once daily.	
Reporting group title	Grazax Placebo
Reporting group description:	
The placebo treatment arm received placebo tablet, Grazax placebo tablet (SQ-T) once daily.	

Primary: Total nasal symptom scores mean differnce

End point title	Total nasal symptom scores mean differnce
End point description:	
The total nasal symptom score at one hour after grass pollen nasal allergen challenge in active versus placebo treated participants at 12 months. Score ranges from 0-12 points. Higher score is more severe symptoms.	
End point type	Primary
End point timeframe:	
60 minutes	

End point values	Grazax	Grazax Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	23		
Units: Score on scale				
geometric mean (confidence interval 95%)	3.37 (2.7 to 4.05)	4.71 (4 to 5.4)		

Statistical analyses

Statistical analysis title	Total symptom score
Comparison groups	Grazax v Grazax Placebo
Number of subjects included in analysis	46
Analysis specification	Post-hoc
Analysis type	superiority
P-value	< 0.05
Method	t-test, 2-sided

Secondary: Delta Peak nasal inspiratory flow

End point title	Delta Peak nasal inspiratory flow

End point description:

End point type	Secondary

End point timeframe:

60 minutes

End point values	Grazax	Grazax Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	23		
Units: L/min				
geometric mean (confidence interval 95%)	-29.2 (-44.8 to -13.5)	-72.5 (-88.8 to -56.1)		

Statistical analyses

Statistical analysis title	Peak nasal inspiratory flow
Comparison groups	Grazax v Grazax Placebo
Number of subjects included in analysis	46
Analysis specification	Post-hoc
Analysis type	superiority
P-value	< 0.05
Method	t-test, 2-sided

Secondary: Early phase Intradermal test

End point title	Early phase Intradermal test

End point description:

End point type	Secondary

End point timeframe:

15 minutes

End point values	Grazax	Grazax Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	23		
Units: millimeter(s)				
geometric mean (standard error)	15.3 (± 1.1)	20.2 (± 1.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Late phase intradermal test

End point title	Late phase intradermal test

End point description:

End point type	Secondary

End point timeframe:

8 hours after intradermal allergen test

End point values	Grazax	Grazax Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	23		
Units: millimeter(s)				
geometric mean (standard error)	52.6 (± 3.4)	74.6 (± 3.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: End of season global rhinitis symptoms

End point title	End of season global rhinitis symptoms

End point description:

End point type	Secondary

End point timeframe:

12 month

End point values	Grazax	Grazax Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	23		
Units: scale				
geometric mean (standard error)	40.4 (± 5.18)	54.97 (± 5.43)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

1 year

Adverse event reporting additional description:

All adverse and severe adverse events (SAEs) were recorded on the appropriate case report forms and the specific serious adverse events were to report as soon as possible and within 24 hours. Data were entered into MHRA approved clinical trial database.

Assessment type	Non-systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4

Reporting groups

Reporting group title	Grazax placebo

Reporting group description:

PLacebo non-active treated group

Reporting group title	Grazax active

Reporting group description: -

Serious adverse events	Grazax placebo	Grazax active	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 23 (0.00%)	0 / 23 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Grazax placebo	Grazax active	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 23 (86.96%)	22 / 23 (95.65%)	
Immune system disorders			
Allergic reaction			
subjects affected / exposed	3 / 23 (13.04%)	19 / 23 (82.61%)	
occurrences (all)	3	23	
Gastrointestinal disorders			
Dyspepsia	Additional description: In the SLIT-tablet group more adverse events were present especially gastrointestinal system such as dyspepsia and vomiting after taking SLIT.		
alternative dictionary used: CTCAE 5			

subjects affected / exposed	0 / 23 (0.00%)	6 / 23 (26.09%)	
occurrences (all)	0	8	
Abdominal pain			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Mucositis Oral			
subjects affected / exposed	1 / 23 (4.35%)	1 / 23 (4.35%)	
occurrences (all)	1	1	
Tooth Ache			
subjects affected / exposed	0 / 23 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	2	
Vomiting			
subjects affected / exposed	0 / 23 (0.00%)	4 / 23 (17.39%)	
occurrences (all)	0	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported