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	v1
This version publication date	23 August 2019
First version publication date	23 August 2019

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
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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 January 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	September 2014 to March 2015 (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:

Placebo controlled trial.

Arms

Are arms mutually exclusive?	Yes
Arm title	Active

Arm description:

Grazax active tablet

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:

75,000 SQ fast dissolving sublingual tablet.

Arm title	Placebo arm

Arm description: -

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

Dosage and administration details:

Placebo sublingual tablet without active ingredient

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Consent withdrawn by subject	1	2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

Baseline characteristics

End points

End points reporting groups

Reporting group title	Active
Reporting group description: Grazax active tablet	
Reporting group title	Placebo arm
Reporting group description: -	
Subject analysis set title	Active SLIT
Subject analysis set type	Intention-to-treat
Subject analysis set description: Allergic rhinitis were randomised to 12 months treatment with grass pollen allergen tablet immunotherapy or matched placebo and clinical, surrogate clinical and immunological outcomes monitored. The primary outcome was total nasal symptom score at 0-1 hour after nasal allergen challenge with grass pollen allergen extract. Secondary endpoints included peak nasal inspiratory flow after nasal allergen challenge, seasonal symptom visual analogue scale and skin test sensitivity to allergen.	
Subject analysis set title	Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description: Hay fever participants	

Primary: The area under the curve (AUC) of the early phase response (total nasal symptom score, TNSS, 0-60 minutes)

End point title	The area under the curve (AUC) of the early phase response (total nasal symptom score, TNSS, 0-60 minutes)
End point description:	
End point type	Primary
End point timeframe: The area under the curve (AUC) of the early phase response (total nasal symptom score, TNSS, 0-60 minutes) following grass pollen nasal allergen challenge in active versus placebo treated participants at 12 months.	

End point values	Active	Placebo arm	Active SLIT	Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	23[1]	23	23	23
Units: 0- 12 points	23	23	23	23

Notes:

[1] - active group hay fever

Statistical analyses

Statistical analysis title	non-parametric statistics
Comparison groups	Active SLIT v Placebo

Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
P-value	< 0.05
Method	Kruskal-wallis
Parameter estimate	Odds ratio (OR)
Confidence interval	
level	95 %
sides	1-sided

Notes:

[2] - Intent-to-treat (ITT) samples are all randomized participants, regardless of the medication actually received. Per-protocol (PP) sample will be defined as ITT sample participants who remain in the study for 12 months and in whom the primary endpoints were assessed. Safety sample (SS) will be defined as all randomized participants who received at least one dose of study medication.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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.

Adverse event reporting additional description:

Systemic reactions related to either AIT tablet treatment were graded according to the WAO SCIT Systemic Reaction Grading System. Reference: Cox L, Larenas-Linnemann D, Lockey RF, et al. Editors speaking the same language: The World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System J Allergy Clin Immunol 2010;125:569-

Assessment type	Systematic

Dictionary used

Dictionary name	World allergy organi
Dictionary version	n/a

Reporting groups

Reporting group title	Active group

Reporting group description:

Active SLIT group-Grazax

Reporting group title	Placebo group

Reporting group description:

PLacebo non-active treated group

Serious adverse events	Active group	Placebo group	
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			

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

Non-serious adverse events	Active group	Placebo group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 23 (86.96%)	18 / 23 (78.26%)	
Gastrointestinal disorders			
Local reaction	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	20 / 23 (86.96%)	18 / 23 (78.26%)	
occurrences (all)	33	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