Clinical trial results:
Molecular and cellular mechanism in rhinitis allergic patients treated with GRAZAX®

Summary

EudraCT number	2009-011453-41
Trial protocol	ES
Global end of trial date	04 September 2015

Results information

Result version number	v1 (current)
This version publication date	23 November 2016
First version publication date	23 November 2016

Trial information

Trial identification

Sponsor protocol code	GT-20

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02437786
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	ALK-Abelló S.A.
Sponsor organisation address	Miguel Fleta, 19, Madrid, Spain, 28037
Public contact	Pilar Rico, ALK-Abelló, +34 913276100, prnes@alk.net
Scientific contact	Pilar Rico, ALK-Abelló, +34 913276100, prnes@alk.net

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	04 September 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 September 2015
Global end of trial reached?	Yes
Global end of trial date	04 September 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine biomarkers which can be related to the tolerability and the clinical response to GRAZAX® treatment. A full array of specific immunoglobulins, cytokines, molecular diagnostics, poblational analyses, lymphoproliferative response to allergens and activation of basophile will be studied and related to the outcome of three-year treatment of GRAZAX® in terms of tolerance and clinical benefit, followed by a two years period without treatment. The tolerance will be evaluated according to the recording of adverse events and the efficacy will be based in a global subjective evaluation of rhinoconjunctivitis symptoms

Protection of trial subjects:

Informed Consent Form. Internal clinical Safety Group, to evaluate from time to time the adverse events ocurred during the trial period.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 September 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 58
Worldwide total number of subjects	58
EEA total number of subjects	58

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)	58
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment start period was from 14 Sep 2009 until 23 Nov 2009 in 1 investigational site in Spain

Pre-assignment

Screening details:

Adult patients suffering from rhinoconjuctivitis with/without asthma due to sensitization to grass pollen. 60 patients will be included

Period 1

Period 1 title	Treatment period
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

No randomisation and blinding will be made as this trial is non-controlled. Patients which fulfil with all selection criteria will be assigned to treatment and a subject number

Arms

Arm title	Experimental

Arm description:

All of trial subjects will receive GRAZAX® as a daily treatment.

Arm type	Experimental
Investigational medicinal product name	GRAZAX
Investigational medicinal product code	68398
Other name	
Pharmaceutical forms	Oral lyophilisate
Routes of administration	Sublingual use

Dosage and administration details:

75000SQ-T/tablet
The daily dose of trial medication is one tablet, which should preferably be taken in the morning. The tablet is placed under the tongue and swallowing should be avoided for one minute. Eating and drinking is not allowed within five minutes after trial medication intake.

Number of subjects in period 1	Experimental
Started	58
Completed	37
Not completed	21
Adverse event, serious fatal	2
Adverse event, non-fatal	4
Breast feeding	1
Lost to follow-up	13
Protocol deviation	1

Period 2	
Period 2 title	Follow up period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

No randomisation and blinding was made as this trial was non-controlled. This period was without treatment.

Arms

Arm title	Follow up

Arm description:

2 year follow up

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2	Follow up
Started	37
Completed	30
Not completed	7
Consent withdrawn by subject	2
Move out of Spain	3
Lost to follow-up	2

Baseline characteristics

Reporting groups	
Reporting group title	Treatment period
Reporting group description:	
Experimental	

Reporting group values	Treatment period	Total	
Number of subjects	58	58	
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)	58	58	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	29	29	
Male	29	29	

Subject analysis sets	
Subject analysis set title	FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
comprised all subjects who received at least one dose of IMP according to the International Conference on Harmonisation (ICH) intent-to-treat principle.The safety analysis set was identical to the FAS.	
Subject analysis set title	3 year treatment
Subject analysis set type	Per protocol
Subject analysis set description:	
Comprising all Per Protocol subjects from Visit 1 to Visit 10 (complete data until end of treatment)	
Subject analysis set title	3 year treatment + 2 year follow up
Subject analysis set type	Per protocol
Subject analysis set description:	
Visit 1 to visit 15	

Reporting group values	FAS	3 year treatment	3 year treatment + 2 year follow up
Number of subjects	58	37	30
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)	58	37	30
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical			
Units: Subjects			
Female	29	21	16
Male	29	16	14

End points

End points reporting groups

Reporting group title	Experimental
Reporting group description:	
All of trial subjects will receive GRAZAX® as a daily treatment.	
Reporting group title	Follow up
Reporting group description:	
2 year follow up	
Subject analysis set title	FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
comprised all subjects who received at least one dose of IMP according to the International Conference on Harmonisation (ICH) intent-to-treat principle.The safety analysis set was identical to the FAS.	
Subject analysis set title	3 year treatment
Subject analysis set type	Per protocol
Subject analysis set description:	
Comprising all Per Protocol subjects from Visit 1 to Visit 10 (complete data until end of treatment)	
Subject analysis set title	3 year treatment + 2 year follow up
Subject analysis set type	Per protocol
Subject analysis set description:	
Visit 1 to visit 15	

Primary: IgE to Phl p 1 + Phl p 5

End point title	IgE to Phl p 1 + Phl p 5[1]
End point description:	
The present trial is an exploratory trial of immunological changes after 3 year of treatment with GRAZAX and 2 year follow up without treatment. As an example the analysis of IgE to Phl p 1 + Phl p 5 is presented. Other analyses are a full array of specific immunoglobulins and cellular analyses.	
End point type	Primary
End point timeframe:	
Visit 1 to visit 15	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The trial is an exploratory trial. Endpoints are described by their median values during the three year treatment period at baseline and after 1 week, 1 month, four month, and after peak of grass pollen season and autumn visits. No inferential analyses have been performed.

End point values	Experimental	Follow up	3 year treatment + 2 year follow up	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	58	37	30	
Units: ku/L				
median (standard deviation)	18.27 (± 35.28)	26.92 (± 67.4)	13.59 (± 44.92)	

Statistical analyses

No statistical analyses for this end point

Secondary: Global evalutation of rhinoconjunctivitis

End point title	Global evalutation of rhinoconjunctivitis

End point description:

Subject global evaluation of rhinoconjuctivitis in a semiquantitative scale (much better, better, same, worse, much worse) comparing the actual grass pollen season to the previous

End point type	Secondary

End point timeframe:

Yearly (visit 7, 9, 11, 13 and 15) after peak of grass pollen season during 3 years of treatment and 2 years of follow up.

End point values	FAS			
Subject group type	Subject analysis set			
Number of subjects analysed	58[2]			
Units: Subjects	58			

Notes:

[2] - Efficacy results are presented in the attached file

Attachments (see zip file)	Efficacy Results_160707.pdf

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Sep 2009 until December 2014

Adverse event reporting additional description:

From the first trial related activity after the subject signed the informed consent until the follow- up telephone contact

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.0

Reporting groups

Reporting group title	Overall

Reporting group description: -

Serious adverse events	Overall		
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 58 (15.52%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Tendon rupture			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Transient ischaemic attack			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	2 / 58 (3.45%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Abortion late			

subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Device extrusion			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Pyelonephritis			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary incontinence			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Overall		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	58 / 58 (100.00%)		

Nervous system disorders			
Headache			
subjects affected / exposed	9 / 58 (15.52%)		
occurrences (all)	20		
Migraine			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	4		
Immune system disorders			
Oral allergy syndrome			
subjects affected / exposed	4 / 58 (6.90%)		
occurrences (all)	5		
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	42 / 58 (72.41%)		
occurrences (all)	197		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	8 / 58 (13.79%)		
occurrences (all)	13		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	18 / 58 (31.03%)		
occurrences (all)	53		
Throat irritation			
subjects affected / exposed	38 / 58 (65.52%)		
occurrences (all)	79		
Cough			
subjects affected / exposed	21 / 58 (36.21%)		
occurrences (all)	46		
Dyspnoea			
subjects affected / exposed	16 / 58 (27.59%)		
occurrences (all)	29		
Sneezing			
subjects affected / exposed	14 / 58 (24.14%)		
occurrences (all)	24		
Rhinitis allergic			

subjects affected / exposed	10 / 58 (17.24%)		
occurrences (all)	12		
Wheezing			
subjects affected / exposed	10 / 58 (17.24%)		
occurrences (all)	15		
nasal discomfort			
subjects affected / exposed	8 / 58 (13.79%)		
occurrences (all)	13		
Nasal congestion			
subjects affected / exposed	8 / 58 (13.79%)		
occurrences (all)	8		
Rhinorrhoea			
subjects affected / exposed	6 / 58 (10.34%)		
occurrences (all)	9		
Dry throat			
subjects affected / exposed	5 / 58 (8.62%)		
occurrences (all)	8		
Oropharyngeal pain			
subjects affected / exposed	6 / 58 (10.34%)		
occurrences (all)	8		
Pharyngeal oedema			
subjects affected / exposed	4 / 58 (6.90%)		
occurrences (all)	6		
Dysphonia			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	3		
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	8 / 58 (13.79%)		
occurrences (all)	9		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 January 2010	This amendment is prepared to include new in vitro evaluations in the serum samples and to plan an interim analysis to evaluate the in vitro parameters corresponding to the first month of treatment
08 February 2012	This amendment was prepared to add a period without IMP treatment (Grazax – Phleum allergy immunotherapy tablet) to determine which of the changes related to the immune system are sustained in the absence of Grazax treatment (sustained effect). Patients will, after the last visit during 2012 pollen season sign for a follow up period of 2 year without Grazax treatment. During the follow up, 5 visits are scheduled to draw samples for immunological assays.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/24290282