Clinical trial results:
Molecular and Cellular Mechanism in the course of Immunotherapy with a Phleum pratense oral lyophilisate

Summary

EudraCT number	2012-005092-14
Trial protocol	ES
Global end of trial date	26 May 2016

Results information

Result version number	v1 (current)
This version publication date	13 July 2017
First version publication date	13 July 2017

Trial information

Trial identification

Sponsor protocol code	GT-24

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01854736
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	ALK-Abelló S.A.
Sponsor organisation address	Miguel Fleta, 19, Madrid, Spain,
Public contact	Pilar Rico Nieto, ALK-Abelló S.A., 34 913276100, pilar.rico@alk.net
Scientific contact	Santiago Martín , ALK-Abelló S.A., 34 913276100, santiago.martin@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 November 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 December 2015
Global end of trial reached?	Yes
Global end of trial date	26 May 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To identify changes in immunological markers measured in grass allergic subjects during treatment with Grazax.

Protection of trial subjects:

First Treatment Dose
Subjects stayed at the clinic for 20-30 minutes after the first dosing (visit 2 and visit 8), according to SmPC, in order to enable subject and physician to discuss any side effects and possible actions.
Subjects without significant reactions left the clinic 20-30 minutes after the first dose of IMP has been given.
Subject were instructed when leaving the clinic to contact immediately if the reaction reoccurs or a new reaction of similar severity appears. In the case of a medical emergency, the subject were instructed to dial the local emergency telephone number.
If an investigator determines that a subject cannot leave the clinic but needs further medical observation or attention not otherwise available at the clinical trials site, the subject were to be transferred to the appropriate facility including an emergency room.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 June 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	Spain: 47
Worldwide total number of subjects	47
EEA total number of subjects	47

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)	47
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment start period was from Jun2013 until Feb2014.

Pre-assignment

Screening details:

Adult subjects suffering from rhinoconjunctivitis with/without asthma due to sensitization to grass pollen.

Period 1

Period 1 title	Treatment period (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

Arms

Are arms mutually exclusive?	Yes
Arm title	Active Treatment

Arm description:

Phleum pratense grass pollen allergen extract Grazax®

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:

75000 SQ-T
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

Arm title	Placebo

Arm description:

Placebo Treatment

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

Dosage and administration details:

Placebo has not specific dose
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	Active Treatment	Placebo
Started	23	24
Completed	14	17
Not completed	9	7
Consent withdrawn by subject	1	1
Adverse event, non-fatal	1	-
Pregnancy	1	2
Lost to follow-up	4	4
Protocol deviation	2	-

Baseline characteristics

Reporting groups

Reporting group title	Treatment period

Reporting group description: -

Reporting group values	Treatment period	Total	
Number of subjects	47	47	
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)	47	47	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	34.3		
standard deviation	± 9.97	-	
Gender categorical Units: Subjects			
Female	22	22	
Male	25	25	

Subject analysis sets

Subject analysis set title	FAS
Subject analysis set type	Full analysis

Subject analysis set description:

The full analysis set (FAS) is all randomised subjects in accordance with the ICH intent-to-treat principle.

Subject analysis set title	Completed subjects
Subject analysis set type	Per protocol

Subject analysis set description:

The PP analysis set is all completed subjects in the FAS with no major protocol violations. The PP Analysis Set will be the population for efficacy analyses.

Subject analysis set title	Safety Analysis set
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety analysis set comprises all randomised subjects and is identical to the FAS.

Reporting group values	FAS	Completed subjects	Safety Analysis set
Number of subjects	47	31	47
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)	47	31	47
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	34.3	35.6	34.3
standard deviation	± 9.97	± 9.44	± 9.97
Gender categorical Units: Subjects			
Female	22	17	22
Male	25	14	25

End points

End points reporting groups

Reporting group title	Active Treatment
Reporting group description:	
Phleum pratense grass pollen allergen extract Grazax®	
Reporting group title	Placebo
Reporting group description:	
Placebo Treatment	
Subject analysis set title	FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
The full analysis set (FAS) is all randomised subjects in accordance with the ICH intent-to-treat principle.	

Subject analysis set title	Completed subjects
Subject analysis set type	Per protocol
Subject analysis set description:	
The PP analysis set is all completed subjects in the FAS with no major protocol violations. The PP Analysis Set will be the population for efficacy analyses.	

Subject analysis set title	Safety Analysis set
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety analysis set comprises all randomised subjects and is identical to the FAS.	

Primary: Ratios to baseline of specific IgE to Phl p 1 + Phl p 5

End point title	Ratios to baseline of specific IgE to Phl p 1 + Phl p 5
End point description:	
Serum specific IgE to Phl p 1 and Phl p 5 are calculated by summing the values of IgE to Phl p 1 and Phl p 5. Ratios are calculated dividing the values at each visit by the values at Visit 2	
End point type	Primary
End point timeframe:	
Along the treatment period, from baseline to end of treatment: Visit 2, Visit 3, Visit 4, Visit 5, Visit 6, Visit 7 and Visit 8	

End point values	Active Treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	17		
Units: Ratio				
arithmetic mean (standard error)	3.211 (± 0.444)	1.207 (± 0.403)		

Statistical analyses

Statistical analysis title	Analysis of IgE during the trial
Comparison groups	Active Treatment v Placebo

Number of subjects included in analysis	31
Analysis specification	Post-hoc
Analysis type	superiority[1]
Parameter estimate	Mean difference
Point estimate	-2.004
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.231
upper limit	-0.778
Variability estimate	Standard error of the mean
Dispersion value	0.6

Notes:

[1] - ANOVA for repeated measures with visits as withing factor and treatment (active or placebo) as between factor

Secondary: Global evaluation of rhinoconjunctivitis

End point title	Global evaluation of rhinoconjunctivitis

End point description:

Efficacy assessments included a subjective evaluation of rhinoconjunctivitis in a VAS and physician and patient-rated clinical global improvement for the peer protocol population. The VAS was done in visit 1 (only applicable if the visit is performed within the GPS 2013), visit 5, and visit 7. The physician and patient-rated clinical global improvement was performed in visit 5 and 7

End point type	Secondary

End point timeframe:

Visit 1, Visit 5 and visit 7, after peak of grass pollen season.

End point values	FAS			
Subject group type	Subject analysis set			
Number of subjects analysed	30			
Units: Subjects	30			

Attachments (see zip file)	Efficacy analyses.docx

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From informed consent signature to end visit	
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	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups	
Reporting group title	Active treatment
Reporting group description:	
Subjects receiving GRAZAX	
Reporting group title	Placebo
Reporting group description:	
Subjects receiving placebo	

Serious adverse events	Active treatment	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 23 (8.70%)	2 / 24 (8.33%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Pregnancy, puerperium and perinatal conditions			
Biochemical pregnancy			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Umbilical hernia			

subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Active treatment	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 23 (82.61%)	19 / 24 (79.17%)	
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 23 (13.04%)	5 / 24 (20.83%)	
occurrences (all)	5	8	
General disorders and administration site conditions			
Sensation of foreign body			
subjects affected / exposed	4 / 23 (17.39%)	1 / 24 (4.17%)	
occurrences (all)	5	1	
Chest discomfort			
subjects affected / exposed	4 / 23 (17.39%)	0 / 24 (0.00%)	
occurrences (all)	4	0	
Ear and labyrinth disorders			
Ear pruritus			
subjects affected / exposed	5 / 23 (21.74%)	0 / 24 (0.00%)	
occurrences (all)	5	0	
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	2 / 23 (8.70%)	2 / 24 (8.33%)	
occurrences (all)	2	2	
Food Allergy			
subjects affected / exposed	2 / 23 (8.70%)	1 / 24 (4.17%)	
occurrences (all)	5	1	

Oral allergy syndrome			
subjects affected / exposed	1 / 23 (4.35%)	2 / 24 (8.33%)	
occurrences (all)	2	2	
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	7 / 23 (30.43%)	7 / 24 (29.17%)	
occurrences (all)	9	9	
Gastrointestinal disorders			
Oral pruritus			
subjects affected / exposed	11 / 23 (47.83%)	1 / 24 (4.17%)	
occurrences (all)	22	1	
Oedema mouth			
subjects affected / exposed	7 / 23 (30.43%)	1 / 24 (4.17%)	
occurrences (all)	11	1	
Tongue pruritus			
subjects affected / exposed	5 / 23 (21.74%)	0 / 24 (0.00%)	
occurrences (all)	6	0	
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	2 / 23 (8.70%)	1 / 24 (4.17%)	
occurrences (all)	2	6	
Respiratory, thoracic and mediastinal disorders			
Throat irritation			
subjects affected / exposed	11 / 23 (47.83%)	0 / 24 (0.00%)	
occurrences (all)	17	0	
Cough			
subjects affected / exposed	2 / 23 (8.70%)	5 / 24 (20.83%)	
occurrences (all)	2	5	
Asthma			
subjects affected / exposed	2 / 23 (8.70%)	3 / 24 (12.50%)	
occurrences (all)	2	5	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 23 (8.70%)	1 / 24 (4.17%)	
occurrences (all)	2	1	
Infections and infestations			

Nasopharyngitis			
subjects affected / exposed	8 / 23 (34.78%)	8 / 24 (33.33%)	
occurrences (all)	10	18	
Influenza			
subjects affected / exposed	4 / 23 (17.39%)	2 / 24 (8.33%)	
occurrences (all)	7	2	
Gastroenteritis			
subjects affected / exposed	2 / 23 (8.70%)	2 / 24 (8.33%)	
occurrences (all)	3	2	
Tonsillitis			
subjects affected / exposed	1 / 23 (4.35%)	2 / 24 (8.33%)	
occurrences (all)	1	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 May 2013	This amendment is prepared in order to add a new site to clinical trial and update the information regarding in vitro evaluations to be performed
01 October 2013	This amendment is prepared in order to change one of the inclusion criteria (I4), documented positive specific IgE to Phl p 5, for documented positive specific IgE to Phleum pratense.
03 February 2015	This amendment is prepared in order to Reduce the follow-up period in the protocol. It is considered that the information obtained from the 5-year trial and from the present two-year trial covers the aims of the trial without having subjects exposed to an additional experimental year. The 5-year trial has shown that the instauration of the key immunological modifications are established during the second year of treatment. Add 20 ml of blood to the sample extraction at visits 7 and 8. The additional sample will be used to purify and freeze peripheral blood mononuclear cells (PBMC) in order to isolate in the future the specific lymphocytic populations responsible for individual B and T regulatory responses, which are at present difficult. This may lead to identify the underlying mechanisms behind the long-term tolerance induction.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported