Clinical trial results:
A phase III trial investigating the efficacy and safety of Grazax in children aged 5-16 years with grass pollen induced rhinoconjunctivitis with or without asthma

Summary

EudraCT number	2006-003415-46
Trial protocol	DE
Global end of trial date	21 September 2007

Results information

Result version number	v1 (current)
This version publication date	16 February 2016
First version publication date	26 July 2015

Trial information

Trial identification

Sponsor protocol code	GT-12

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	ALK-Abelló
Sponsor organisation address	Bøge Allé 1, Hørsholm, Denmark, 2970
Public contact	Clinical Development, ALK-Abelló, +45 4574 7576, ClinicalTrials@alk.net
Scientific contact	Clinical Development, ALK-Abelló, +45 4574 7576, ClinicalTrials@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	21 September 2007
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 September 2007
Global end of trial reached?	Yes
Global end of trial date	21 September 2007
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy and safety of specific immunotherapy with Grazax compared to placebo, in children with grass pollen induced allergic rhinoconjunctivitis.

Protection of trial subjects:

Safety surveillance
Use of symptomatic medications allowed

Background therapy:

Rescue Medication
Rhinoconjunctivitis: Loratadine tablets (10 mg), levocabastine eye drops (0.5 mg/ml), budesonide nasal spray
(50 µg), prednisolone tablets (5 mg).
Asthma: Salbutamol inhaler or spray (0.10%), fluticasone inhaler or spray (125 or 250 µg), prednisolone tablets
(5 mg).

Evidence for comparator:

Placebo comparator

Actual start date of recruitment	22 November 2006
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	Germany: 253
Worldwide total number of subjects	253
EEA total number of subjects	253

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)	140

Adolescents (12-17 years)	113
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

253 subjects were recruited by 26 investigators in Germany

Pre-assignment

Screening details:

307 subjects were screened, 54 were screening failures

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:

Placebo tablets were similar to the Grazax tablets as regards appearance, smell and taste.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description: -

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:

1 fast-disolving tablet per day

Arm title	Grazax

Arm description:

Active treatment

Arm type	Experimental
Investigational medicinal product name	Grazax
Investigational medicinal product code	
Other name	SQ grass SLIT-tablet
Pharmaceutical forms	Sublingual tablet
Routes of administration	Sublingual use

Dosage and administration details:

1 fast-disolving tablet per day

Number of subjects in period 1	Placebo	Grazax
Started	127	126
Completed	120	114
Not completed	7	12
Consent withdrawn by subject	1	-
Adverse event, non-fatal	2	4
Lost to follow-up	-	2
Protocol deviation	2	3
not specified	2	3

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Grazax
Reporting group description:	
Active treatment	

Reporting group values	Placebo	Grazax	Total
Number of subjects	127	126	253
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)	81	86	167
Adolescents (12-17 years)	46	40	86
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Children 5-16 years	0	0	0
Age continuous			
Units: years			
arithmetic mean	10.1	10.1	
standard deviation	± 3.1	± 2.9	-
Gender categorical			
Units: Subjects			
Female	44	43	87
Male	83	83	166

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Grazax
Reporting group description:	
Active treatment	

Primary: Rhinoconjunctivitis Symptom Score

End point title	Rhinoconjunctivitis Symptom Score
End point description:	
A total of 6 rhinoconjunctivitis symptoms were evaluated on a scale of 0 to 3, as follows: 0 No symptoms 1 Mild symptoms 2 Moderate symptoms 3 Severe symptoms Nose symptoms: Runny nose, Blocked nose, Sneezing, Itchy nose Eye symptoms: Gritty feeling / red/itchy eyes, Watery eyes	
End point type	Primary
End point timeframe:	
during the grass pollen season	

End point values	Placebo	Grazax		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	121[1]	117[2]		
Units: score unit				
arithmetic mean (standard deviation)	3.2 (± 2.1)	2.7 (± 2.4)		

Notes:

[1] - all who provided diary data during the grass pollen season

[2] - all who provided diary data during the grass pollen season

Statistical analyses

Statistical analysis title	Analysis of average rhinoconjunctivitis symptom sc
Statistical analysis description:	
Parametric analysis: ANOVA, square-root-transformed data, adjusted means with 95% confidence intervals backtransformed by squaring	
Comparison groups	Placebo v Grazax
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0215
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.62

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	1.15
Variability estimate	Standard deviation

Secondary: Rhinoconjunctivitis medication score

End point title	Rhinoconjunctivitis medication score

End point description:

The average daily rhinoconjunctivitis medication scores over the entire grass pollen season

End point type	Secondary

End point timeframe:

During the entire grass pollen season

End point values	Placebo	Grazax		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	121[3]	117[4]		
Units: score units				
median (confidence interval 95%)	1.19 (0.74 to 2.64)	0.78 (0.43 to 1.3)		

Notes:

[3] - Subjects with diary data during the grass pollen season

[4] - Subjects with diary data during the grass pollen season

Statistical analyses

Statistical analysis title	Analysis of average rhinoconjunctivitis medication

Statistical analysis description:

Analysis of average rhinoconjunctivitis medication score, entire grass pollen season (FAS)

Comparison groups	Placebo v Grazax
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.0156
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges-Lehmann estimate
Point estimate	0.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.01
upper limit	0.68
Variability estimate	Standard deviation

Notes:

[5] - A parametric ANOVA could not be performed for the average rhinoconjunctivitis medication score, since neither the untransformed data, nor transformed data fulfilled the assumption of normal distribution. A non-parametric analysis was performed using the Wilcoxon rank sum test.

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From signing of informed consent to end of trial	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	6.1

Reporting groups	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Grazax
Reporting group description:	
Active treatment	

Serious adverse events	Placebo	Grazax	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 127 (1.57%)	2 / 126 (1.59%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 127 (0.79%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 127 (0.00%)	2 / 126 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 127 (0.79%)	0 / 126 (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	Placebo	Grazax	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	106 / 127 (83.46%)	109 / 126 (86.51%)	
Gastrointestinal disorders			
Oral pruritus			
subjects affected / exposed	3 / 127 (2.36%)	39 / 126 (30.95%)	
occurrences (all)	3	49	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	12 / 127 (9.45%)	6 / 126 (4.76%)	
occurrences (all)	15	6	
Cough			
subjects affected / exposed	14 / 127 (11.02%)	8 / 126 (6.35%)	
occurrences (all)	17	9	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	11 / 127 (8.66%)	12 / 126 (9.52%)	
occurrences (all)	18	14	
Viral infection			
subjects affected / exposed	13 / 127 (10.24%)	23 / 126 (18.25%)	
occurrences (all)	14	25	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 October 2006	pre-trial - incorporation of comments given by competent authorities

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.

Not applicable

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/19130937