Clinical trial results:
GAP - Grazax Asthma Prevention
Summary

EudraCT number	2009-011235-12
Trial protocol	FR DE FI DK GB SE AT ES
Global end of trial date	30 September 2015

Results information

Result version number	v2 (current)
This version publication date	20 July 2016
First version publication date	05 June 2016
Version creation reason	• Correction of full data set correction of data

Trial information

Trial identification

Sponsor protocol code	GT-21

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	ALK
Sponsor organisation address	Bøge Alle 1, Hørsholm, Denmark, 2970
Public contact	Global Clinical Development, ALK, 45 45747576, clinicaltrials@alk.net
Scientific contact	Global Clinical Development, ALK, 45 45747576, 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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 May 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 September 2015
Global end of trial reached?	Yes
Global end of trial date	30 September 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the effect of Grazax compared to placebo on the risk of developing asthma during 3 treatment years and 2 post-treatment years

Protection of trial subjects:

Safety surveillance
Access to symptomatic pharmacotherapy if needed.

Background therapy:

Allergic rhinoconjunctivitis pharmacotherapy:
At the winter visits, the subjects were provided with one standard panel box of ARC pharmacotherapy for use on a voluntarily basis:
•Loratadine tablets, 10 mg or desloratadine syrup 0.5 mg/ml
•Olopatadine eye drops, 1 mg/ml
•Budesonide nasal spray, 32 or 64 µg/dose or fluticasone propionate nasal spray 50 µg/dose (in UK)
Any other use of ARC medication was allowed but not provided by the sponsor.

Asthma pharmacotherapy:
A standard panel of asthma pharmacotherapy was at the investigators disposal. The asthma pharmacotherapy provided was:
•Salbutamol for inhalation, 100 µg/dose
•Fluticasone for inhalation, 100 µg/dose
•Prednisolone tablets, 5 mg
It was at the discretion of the investigator’s to prescribe asthma pharmacotherapy to the subjects. Any other use of asthma medication was acceptable, except for medication listed as prohibited concomitant medication.

Evidence for comparator:

Placebo comparator

Actual start date of recruitment	24 November 2009
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	Norway: 36
Country: Number of subjects enrolled	Poland: 103
Country: Number of subjects enrolled	Spain: 106
Country: Number of subjects enrolled	Sweden: 119
Country: Number of subjects enrolled	United Kingdom: 24
Country: Number of subjects enrolled	Austria: 25
Country: Number of subjects enrolled	Denmark: 117

Country: Number of subjects enrolled	Finland: 44
Country: Number of subjects enrolled	France: 112
Country: Number of subjects enrolled	Germany: 110
Country: Number of subjects enrolled	Switzerland: 16
Worldwide total number of subjects	812
EEA total number of subjects	796

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)	754
Adolescents (12-17 years)	58
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited from 101 sites in 11 countries (AT, CH, DE, DK, ES, FI, FR, GB, NO, PL, SE)
First subject first visit 24 November 2009
Last subject last visit 30 September 2015

Pre-assignment

Screening details:

Selection criteria
Females or males 5-12 years of age at time of randomisation, clinically relevant history of grass pollen ARC requiring symptomatic treatment for 2 years, positive SPT response and specific IgE to Phleum pratense, no other relevant allergies overlapping the grass pollen season, no signs or symptoms of asthma

Period 1

Period 1 title	Trial 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	Grazax

Arm description:

Active treatment group: Grazax 75,000 SQ-T

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

Dosage and administration details:

The daily dose of IMP was one lyophilisate [tablet], preferably taken in the morning. The tablet was placed under the tongue, and swallowing was to be avoided for one minute. In addition, eating and drinking was not allowed within 5 minutes after intake of IMP.

Arm title	Placebo

Arm description: -

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:

The daily dose of IMP was one lyophilisate [tablet], preferably taken in the morning. The tablet was placed under the tongue, and swallowing was to be avoided for one minute. In addition, eating and drinking was not allowed within 5 minutes after intake of IMP.

Number of subjects in period 1	Grazax	Placebo
Started	398	414
Completed	300	308
Not completed	98	106
Consent withdrawn by subject	14	22
Adverse event, non-fatal	39	13
Lost to follow-up	14	22
not specified	11	25
Protocol deviation	20	24

Baseline characteristics

Reporting groups	
Reporting group title	Grazax
Reporting group description:	
Active treatment group: Grazax 75,000 SQ-T	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Grazax	Placebo	Total
Number of subjects	398	414	812
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)	372	382	754
Adolescents (12-17 years)	26	32	58
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	8.5	8.7	
standard deviation	± 2.1	± 2.1	-
Gender categorical			
Units: Subjects			
Female	143	158	301
Male	255	256	511

Subject analysis sets	
Subject analysis set title	FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
The FAS was used for efficacy analyses. The safety analysis set and FAS were identical and comprised a total of 812 subjects; 398 subjects in the Grazax group, and 414 subjects in the placebo group	

Reporting group values	FAS		
Number of subjects	812		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		

Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	754		
Adolescents (12-17 years)	58		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean	8.6		
standard deviation	± 2.1		
Gender categorical			
Units: Subjects			
Female	301		
Male	511		

End points

End points reporting groups

Reporting group title	Grazax
Reporting group description:	
Active treatment group: Grazax 75,000 SQ-T	
Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
The FAS was used for efficacy analyses. The safety analysis set and FAS were identical and comprised a total of 812 subjects; 398 subjects in the Grazax group, and 414 subjects in the placebo group	

Primary: time to onset of asthma according to protocol definition

End point title	time to onset of asthma according to protocol definition
End point description:	
The primary endpoint was the time to onset of asthma according to protocol definition measured in days from randomisation	
End point type	Primary
End point timeframe:	
from randomisation to end of trial	

End point values	Grazax	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	398	414		
Units: number of subject with dagnosis	34	39		

Statistical analyses

Statistical analysis title	Time to onset of asthma by protocol criteria
Statistical analysis description:	
The primary endpoint was the time to onset of asthma by protocol criteria measured in days from randomisation (largely based on reversible impairment of lung function). For subjects with not fulfilling the asthma criteria, the time was right-censored at the end of trial visit . Subjects who discontinued were right-censored at the date of discontinuation.	
Comparison groups	Grazax v Placebo
Number of subjects included in analysis	812
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.67
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	1.43

Secondary: Asthma status at end of trial

End point title	Asthma status at end of trial

End point description:

Number of subjects
Odds-ratio for not experiencing asthma symptoms or using asthma medication

End point type	Secondary

End point timeframe:

the last 'between visits' period trial of the trial - roughly from January 2015- August 2015, with observations carried forward for subjects not compleeting the trial

End point values	Grazax	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	377	398		
Units: number of subjects without symptoms/med	318	317		

Statistical analyses

Statistical analysis title	Asthma symptom and medication status

Statistical analysis description:

Asthma symptom and medication status since last visit at end of trial; the analysis of the odds for not having any asthma symptoms and any asthma medication use was performed with a generalised logistic regression analysis. The adjusted OR for having an asthma symptom and asthma medication free period at the end of trial visit was estimated with the two-sided 95% CI. For subjects discontinuing prematurely, last observation was carried forward

Comparison groups	Grazax v Placebo
Number of subjects included in analysis	775
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.036
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.03
upper limit	2.22

Secondary: Allergic rhinoconjunctivitis VAS score

End point title	Allergic rhinoconjunctivitis VAS score

End point description:

The allergic rhinoconjunctivitis symptoms were evaluated yearly at the GPS visits by answering 'How has your hay fever been the last week?' on a VAS. The VAS score was evaluated on a scale from 0 (no symptoms) to 100 mm (severe symptoms).

End point type	Secondary

End point timeframe:

Measured for each of the 5 grass pollen seasons in the trial - reported here for year 5 (2015) - the second treatment-free follow year of the trial

End point values	Grazax	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	300[1]	309[2]		
Units: VAS score				
arithmetic mean (confidence interval 95%)	19.6 (16 to 23.3)	25.5 (21.7 to 29.3)		

Notes:

[1] - Subjects reporting VAS score during the 2015 grass pollen season

[2] - Subjects reporting VAS score during the 2015 grass pollen season

Statistical analyses

Statistical analysis title	VAS scoring of rhinoconjunctivitis symptoms

Statistical analysis description:

The yearly VAS scoring of ARC symptoms at the GPS visits was evaluated with a repeated measures analysis. Treatment, visit and treatment by visit were included as fixed effects, baseline VAS as covariate and country as random effect.
Data included here is for the fifth year of the trial (2015) - the second treatment-free follow-up year.

Comparison groups	Grazax v Placebo
Number of subjects included in analysis	609
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	5.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.18
upper limit	9.43

Secondary: Allergic rhinoconjunctivitis medication score

End point title	Allergic rhinoconjunctivitis medication score

End point description:

The use of allergic rhinoconjunctivitis medication was recorded daily during the 14 days prior to the grass pollen visit in 2015. The total daily allergic rhinoconjunctivitis medication score was calculated as the sum of the total daily scores for each medication (Antihistamine tablet: 6 points per tablets, eye drops: 1.5 points per drop, nasal spray: 1 point per puff). The average allergic rhinoconjunctivitis medication score was calculated as the average of total daily allergic rhinoconjunctivitis medication score based on observed data during the 14 days of recording.

End point type	Secondary

End point timeframe:

14 days prior to the grass pollen visit in 2015

End point values	Grazax	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	241[3]	263[4]		
Units: Medication score				
arithmetic mean (confidence interval 95%)	15.17 (12.71 to 17.85)	19.54 (16.9 to 22.38)		

Notes:

[3] - Subjects reporting daily medication for 14 days prior to the grass pollen season visit 2015

[4] - Subjects reporting daily medication for 14 days prior to the grass pollen season visit 2015

Statistical analyses

Statistical analysis title	Allergic rhinoconjunctivitis medication score

Statistical analysis description:

The average daily allergic rhinoconjunctivitis medication score prior to the 2015 GPS visit was evaluated with a LME model. The average allergic rhinoconjunctivitis medication score was the response variable, treatment was a fixed class effect and country was a random class variable.

Comparison groups	Grazax v Placebo
Number of subjects included in analysis	504
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	4.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.35
upper limit	7.41

Adverse events

Adverse events information

Timeframe for reporting adverse events:

During the entire trial

Adverse event reporting additional description:

All events meeting the definition of an AE were collected and reported from the first trial-related activity after the subject signed the informed consent and until the end of trial.
Adverse events were defined according to ICH Harmonised Tripartite Guideline E2A, Step 5

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

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	30 / 414 (7.25%)	43 / 398 (10.80%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign salivary gland neoplasm			
subjects affected / exposed	1 / 414 (0.24%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibroadenoma of breast			
subjects affected / exposed	0 / 414 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian adenoma			
subjects affected / exposed	0 / 414 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			

Orthostatic hypotension			
subjects affected / exposed	0 / 414 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Tympanoplasty			
subjects affected / exposed	1 / 414 (0.24%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Device malfunction			
subjects affected / exposed	0 / 414 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 414 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 414 (0.24%)	0 / 398 (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			
Menorrhagia			
subjects affected / exposed	0 / 414 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metrorrhagia			
subjects affected / exposed	1 / 414 (0.24%)	0 / 398 (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			

Adenoidal hypertrophy			
subjects affected / exposed	0 / 414 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	0 / 414 (0.00%)	2 / 398 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 414 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal polyps			
subjects affected / exposed	0 / 414 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngeal oedema			
subjects affected / exposed	1 / 414 (0.24%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vocal cord disorder			
subjects affected / exposed	0 / 414 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Somatisation disorder			
subjects affected / exposed	0 / 414 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 414 (0.24%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Craniocerebral injury			
subjects affected / exposed	2 / 414 (0.48%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial bones fracture			
subjects affected / exposed	0 / 414 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaw fracture			
subjects affected / exposed	0 / 414 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint injury			
subjects affected / exposed	0 / 414 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	1 / 414 (0.24%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus injury			
subjects affected / exposed	1 / 414 (0.24%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle strain			
subjects affected / exposed	1 / 414 (0.24%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	0 / 414 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			

subjects affected / exposed	0 / 414 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	0 / 414 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	0 / 414 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Hereditary haemochromatosis			
subjects affected / exposed	1 / 414 (0.24%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningomyelocele			
subjects affected / exposed	0 / 414 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 414 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 414 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 414 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Migraine			
subjects affected / exposed	0 / 414 (0.00%)	2 / 398 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 414 (0.00%)	3 / 398 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tension headache			
subjects affected / exposed	0 / 414 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 414 (0.24%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune thrombocytopenic purpura			
subjects affected / exposed	0 / 414 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Tympanic membrane perforation			
subjects affected / exposed	0 / 414 (0.00%)	2 / 398 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 414 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			

subjects affected / exposed	0 / 414 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crohn's disease			
subjects affected / exposed	0 / 414 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 414 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 414 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salivary gland cyst			
subjects affected / exposed	1 / 414 (0.24%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Liver injury			
subjects affected / exposed	1 / 414 (0.24%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermal cyst			
subjects affected / exposed	0 / 414 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urethral meatus stenosis			
subjects affected / exposed	0 / 414 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 414 (0.24%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	0 / 414 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Knee deformity			
subjects affected / exposed	1 / 414 (0.24%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myositis			
subjects affected / exposed	1 / 414 (0.24%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	2 / 414 (0.48%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	4 / 414 (0.97%)	6 / 398 (1.51%)	
occurrences causally related to treatment / all	0 / 4	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			
subjects affected / exposed	2 / 414 (0.48%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Borrelia infection			
subjects affected / exposed	0 / 414 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bronchitis			
subjects affected / exposed	0 / 414 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
bronchopneumonia			
subjects affected / exposed	0 / 414 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear infection			
subjects affected / exposed	1 / 414 (0.24%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterovirus infection			
subjects affected / exposed	0 / 414 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	2 / 414 (0.48%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis norovirus			
subjects affected / exposed	1 / 414 (0.24%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	0 / 414 (0.00%)	2 / 398 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 414 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media			

subjects affected / exposed	1 / 414 (0.24%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pilonidal cyst			
subjects affected / exposed	0 / 414 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 414 (0.48%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 414 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal osteomyelitis			
subjects affected / exposed	1 / 414 (0.24%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheitis			
subjects affected / exposed	0 / 414 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis bacterial			
subjects affected / exposed	0 / 414 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Type 1 diabetes mellitus			
subjects affected / exposed	2 / 414 (0.48%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	1 / 2	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	385 / 414 (93.00%)	380 / 398 (95.48%)	
Nervous system disorders			
Headache			
subjects affected / exposed	37 / 414 (8.94%)	45 / 398 (11.31%)	
occurrences (all)	82	74	
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	29 / 414 (7.00%)	16 / 398 (4.02%)	
occurrences (all)	37	17	
Pyrexia			
subjects affected / exposed	30 / 414 (7.25%)	28 / 398 (7.04%)	
occurrences (all)	39	35	
Immune system disorders			
Allergy to animal			
subjects affected / exposed	13 / 414 (3.14%)	22 / 398 (5.53%)	
occurrences (all)	16	28	
Seasonal allergy			
subjects affected / exposed	22 / 414 (5.31%)	22 / 398 (5.53%)	
occurrences (all)	29	29	
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	224 / 414 (54.11%)	145 / 398 (36.43%)	
occurrences (all)	393	248	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	19 / 414 (4.59%)	21 / 398 (5.28%)	
occurrences (all)	21	25	
Oral pruritus			
subjects affected / exposed	7 / 414 (1.69%)	131 / 398 (32.91%)	
occurrences (all)	7	164	
Tongue pruritus			

subjects affected / exposed	1 / 414 (0.24%)	22 / 398 (5.53%)	
occurrences (all)	6	23	
Vomiting			
subjects affected / exposed	20 / 414 (4.83%)	26 / 398 (6.53%)	
occurrences (all)	23	36	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	50 / 414 (12.08%)	28 / 398 (7.04%)	
occurrences (all)	74	42	
Cough			
subjects affected / exposed	83 / 414 (20.05%)	68 / 398 (17.09%)	
occurrences (all)	129	106	
Dyspnoea			
subjects affected / exposed	41 / 414 (9.90%)	30 / 398 (7.54%)	
occurrences (all)	62	40	
Dyspnoea exertional			
subjects affected / exposed	22 / 414 (5.31%)	10 / 398 (2.51%)	
occurrences (all)	32	18	
Oropharyngeal pain			
subjects affected / exposed	21 / 414 (5.07%)	26 / 398 (6.53%)	
occurrences (all)	24	36	
Rhinitis allergic			
subjects affected / exposed	23 / 414 (5.56%)	17 / 398 (4.27%)	
occurrences (all)	29	23	
Throat irritation			
subjects affected / exposed	5 / 414 (1.21%)	52 / 398 (13.07%)	
occurrences (all)	5	61	
Wheezing			
subjects affected / exposed	32 / 414 (7.73%)	19 / 398 (4.77%)	
occurrences (all)	48	28	
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	27 / 414 (6.52%)	24 / 398 (6.03%)	
occurrences (all)	31	27	
Infections and infestations			

Nasopharyngitis			
subjects affected / exposed	248 / 414 (59.90%)	211 / 398 (53.02%)	
occurrences (all)	781	655	
Bronchitis			
subjects affected / exposed	29 / 414 (7.00%)	29 / 398 (7.29%)	
occurrences (all)	44	47	
Conjunctivitis			
subjects affected / exposed	24 / 414 (5.80%)	26 / 398 (6.53%)	
occurrences (all)	30	34	
Ear infection			
subjects affected / exposed	15 / 414 (3.62%)	22 / 398 (5.53%)	
occurrences (all)	22	23	
Gastroenteritis			
subjects affected / exposed	71 / 414 (17.15%)	65 / 398 (16.33%)	
occurrences (all)	104	89	
Influenza			
subjects affected / exposed	54 / 414 (13.04%)	49 / 398 (12.31%)	
occurrences (all)	67	63	
Otitis media			
subjects affected / exposed	13 / 414 (3.14%)	22 / 398 (5.53%)	
occurrences (all)	16	26	
Pharyngitis			
subjects affected / exposed	53 / 414 (12.80%)	43 / 398 (10.80%)	
occurrences (all)	78	76	
Respiratory tract infection			
subjects affected / exposed	15 / 414 (3.62%)	22 / 398 (5.53%)	
occurrences (all)	26	48	
Rhinitis			
subjects affected / exposed	29 / 414 (7.00%)	26 / 398 (6.53%)	
occurrences (all)	36	32	
Tonsillitis			
subjects affected / exposed	43 / 414 (10.39%)	41 / 398 (10.30%)	
occurrences (all)	61	70	
Upper respiratory tract infection			
subjects affected / exposed	21 / 414 (5.07%)	23 / 398 (5.78%)	
occurrences (all)	29	34	

Viral infection subjects affected / exposed occurrences (all)	56 / 414 (13.53%) 85	60 / 398 (15.08%) 89	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 April 2010	Changes to pharmacotherapy and asthma diagnosis criteria (after PEI scientific advice)
04 February 2011	Update to the master patient/parent/guardian information sheet and informed consent (all subjects were asked to re-consent)
30 June 2011	Change in discontinuation criteria (deletion of requirement of less than 100 days of IMP interruption)
27 February 2012	Change of timing of primary analyses from year 3 (after end of treatment) to year 5 (end of trial)
28 January 2015	Addition of allergic rhinoconjunctivitis pamphlet for GPS 2015 Addition of blood sample for future pharmacogenetic analyses Specification of immunological analyses Clarify that worst case severity of AEs should be kept throughout the trial Clarify that the authorship policy listed in the Vancouver Declaration will be followed for the primary publication

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.

No objective asthma diagnosis exists. The diagnosis used was based on advice from experts and regulators; it relied on symptoms and reversible impairment of lung function. However, lung function tests in this population turned out to lack sensitivity

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/21999887