



## 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<br>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,<br>clinicaltrials@alk.net |
| Scientific contact           | Global Clinical Development, ALK, 45 45747576,<br>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:

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### 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    |
| <b>Arm title</b>             | 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.

|                  |         |
|------------------|---------|
| <b>Arm title</b> | 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.

| <b>Number of subjects in period 1</b> | 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 completing 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                                 |

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**Secondary: Allergic rhinoconjunctivitis VAS score**

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|                 |  |
|-----------------|--|
| 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

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| End point values                          | Grazax             | Placebo             |  |  |
|---|--------------------|---------------------|--|--|
| Subject group type                        | Reporting group    | Reporting group     |  |  |
| Number of subjects analysed               | 300 <sup>[1]</sup> | 309 <sup>[2]</sup>  |  |  |
| 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                           |

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**Secondary: Allergic rhinoconjunctivitis medication score**

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|                 |   |
|-----------------|---|
| 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 <sup>[3]</sup>     | 263 <sup>[4]</sup>    |  |  |
| 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**

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | 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 %

| <b>Non-serious adverse events</b>                     | 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 | 56 / 414 (13.53%) | 60 / 398 (15.08%) |  |
| occurrences (all)           | 85                | 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<br>Addition of blood sample for future pharmacogenetic analyses<br>Specification of immunological analyses<br>Clarify that worst case severity of AEs should be kept throughout the trial<br>Clarify that the authorship policy listed in the Vancouver Declaration will be followed for the primary publication |

Notes:

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### 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:

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### Online references

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