



Clinical trial results:

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

Summary

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

Results information

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

Trial information

Trial identification

| | |
|-----------------------|-------|
| Sponsor protocol code | GT-12 |
|-----------------------|-------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | ALK-Abelló |
| Sponsor organisation address | Bøge Allé 1, Hørsholm, Denmark, 2970 |
| Public contact | Clinical Development, ALK-Abelló, +45 4574 7576, ClinicalTrials@alk.net |
| Scientific contact | Clinical Development, ALK-Abelló, +45 4574 7576, ClinicalTrials@alk.net |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|-------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 21 September 2007 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 21 September 2007 |
| Global end of trial reached? | Yes |
| Global end of trial date | 21 September 2007 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

Safety surveillance

Use of symptomatic medications allowed

Background therapy:

Rescue Medication

Rhinoconjunctivitis: Loratadine tablets (10 mg), levocabastine eye drops (0.5 mg/ml), budesonide nasal spray

(50 µg), prednisolone tablets (5 mg).

Asthma: Salbutamol inhaler or spray (0.10%), fluticasone inhaler or spray (125 or 250 µg),

prednisolone tablets

(5 mg).

Evidence for comparator:

Placebo comparator

| | |
|---|------------------|
| Actual start date of recruitment | 22 November 2006 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------|
| Country: Number of subjects enrolled | Germany: 253 |
| Worldwide total number of subjects | 253 |
| EEA total number of subjects | 253 |

Notes:

Subjects enrolled per age group

| | |
|---|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 140 |

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

Subject disposition

Recruitment

Recruitment details:

253 subjects were recruited by 26 investigators in Germany

Pre-assignment

Screening details:

307 subjects were screened, 54 were screening failures

Period 1

| | |
|------------------------------|---|
| Period 1 title | Overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

Blinding implementation details:

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

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | Placebo |

Arm description: -

| | |
|--|-------------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Sublingual tablet |
| Routes of administration | Sublingual use |

Dosage and administration details:

1 fast-dissolving tablet per day

| | |
|------------------|--------|
| Arm title | Grazax |
|------------------|--------|

Arm description:

Active treatment

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

Dosage and administration details:

1 fast-dissolving tablet per day

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

Baseline characteristics

Reporting groups

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

| Reporting group values | Placebo | Grazax | Total |
|---|---------|--------|-------|
| Number of subjects | 127 | 126 | 253 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 81 | 86 | 167 |
| Adolescents (12-17 years) | 46 | 40 | 86 |
| Adults (18-64 years) | 0 | 0 | 0 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Children 5-16 years | 0 | 0 | 0 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 10.1 | 10.1 | |
| standard deviation | ± 3.1 | ± 2.9 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 44 | 43 | 87 |
| Male | 83 | 83 | 166 |

End points

End points reporting groups

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

Primary: Rhinoconjunctivitis Symptom Score

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

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

Notes:

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

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

Statistical analyses

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

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

Secondary: Rhinoconjunctivitis medication score

| | |
|---|--------------------------------------|
| End point title | Rhinoconjunctivitis medication score |
| End point description: The average daily rhinoconjunctivitis medication scores over the entire grass pollen season | |
| End point type | Secondary |
| End point timeframe: During the entire grass pollen season | |

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

Notes:

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

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

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Analysis of average rhinoconjunctivitis medication |
| Statistical analysis description: Analysis of average rhinoconjunctivitis medication score, entire grass pollen season (FAS) | |
| Comparison groups | Placebo v Grazax |
| Number of subjects included in analysis | 238 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[5] |
| P-value | = 0.0156 |
| Method | Wilcoxon (Mann-Whitney) |
| Parameter estimate | Hodges-Lehmann estimate |
| Point estimate | 0.31 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.01 |
| upper limit | 0.68 |
| Variability estimate | Standard deviation |

Notes:

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

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From signing of informed consent to end of trial

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|-----|
| Dictionary version | 6.1 |
|--------------------|-----|

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description: -

| | |
|-----------------------|--------|
| Reporting group title | Grazax |
|-----------------------|--------|

Reporting group description:

Active treatment

| Serious adverse events | Placebo | Grazax | |
|---|-----------------|-----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 127 (1.57%) | 2 / 126 (1.59%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | 0 / 126 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 2 / 126 (1.59%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | 0 / 126 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Placebo | Grazax | |
|---|--------------------|--------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 106 / 127 (83.46%) | 109 / 126 (86.51%) | |
| Gastrointestinal disorders | | | |
| Oral pruritus | | | |
| subjects affected / exposed | 3 / 127 (2.36%) | 39 / 126 (30.95%) | |
| occurrences (all) | 3 | 49 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 12 / 127 (9.45%) | 6 / 126 (4.76%) | |
| occurrences (all) | 15 | 6 | |
| Cough | | | |
| subjects affected / exposed | 14 / 127 (11.02%) | 8 / 126 (6.35%) | |
| occurrences (all) | 17 | 9 | |
| Infections and infestations | | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 11 / 127 (8.66%) | 12 / 126 (9.52%) | |
| occurrences (all) | 18 | 14 | |
| Viral infection | | | |
| subjects affected / exposed | 13 / 127 (10.24%) | 23 / 126 (18.25%) | |
| occurrences (all) | 14 | 25 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

| |
|----------------|
| Not applicable |
|----------------|

Notes:

Online references

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