



## Clinical trial results:

### Randomised placebo-controlled study of grass pollen allergen immunotherapy tablet (AIT) for seasonal rhinitis: time course of nasal, cutaneous and immunological outcomes

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2013-003732-72 |
| Trial protocol           | GB             |
| Global end of trial date | 01 March 2017  |

#### Results information

|                                |   |
|--------------------------------|---|
| Result version number          | v2 (current)  |
| This version publication date  | 12 October 2019   |
| First version publication date | 23 August 2019  |
| Version creation reason        | <ul style="list-style-type: none"><li>• New data added to full data set</li><li>• Correction of full data set</li></ul> Statistical data and minor changes needs to be corrected on the posted file |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | 13IC0847 |
|-----------------------|----------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02005627 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Imperial College London  |
| Sponsor organisation address | Norfolk Place, London, United Kingdom, W2 1PG  |
| Public contact               | Nabila Youssouf , Imperial College London, +44 (0)2033110206, nabila.youssouf08@imperial.ac.uk |
| Scientific contact           | Nabila Youssouf , Imperial College London, +44 (0)2033110206, nabila.youssouf08@imperial.ac.uk |

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:

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**Results analysis stage**

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|  |                 |
|--|-----------------|
| Analysis stage                                       | Final           |
| Date of interim/final analysis                       | 07 January 2018 |
| Is this the analysis of the primary completion data? | Yes             |
| Primary completion date                              | 01 March 2017   |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 01 March 2017   |
| Was the trial ended prematurely?                     | No              |

Notes:

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**General information about the trial**

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Main objective of the trial:

To understand the time course of clinical and immunological actions of grass pollen allergen immunotherapy tablets in the treatment of seasonal allergic rhinitis.

Protection of trial subjects:

This trial was conducted in compliance with the protocol, current Good Clinical Practice (GCP) guidelines and all applicable regulatory requirements. All participants read, signed, and dated the consent form before participating in the study. Participant's privacy and confidentiality were preserved by assigning a sequential identification number used to collect, store, and report participant information. Grazax sublingual immunotherapy is commonly associated with local side effects of itching and swelling in the mouth that may last up to 30 minutes after taking each tablet. Systemic side effects after Grazax are very rare and generally of mild intensity. The first Grazax® or Grazax® placebo was administered under the supervision of a trial physician and the participant observed for one hour thereafter before discharge from the clinic.

Background therapy:

All atopic participants were provided with anti-allergic rescue medications (antihistamine tablets, topical intranasal corticosteroids, and eye-drops) throughout the pollen season.

Evidence for comparator:

Sublingual immunotherapy tablet is a fast-dissolving tablet that is registered throughout Europe for sublingual use in patients aged 5–65 years (18–65 years in UK). The tablet is administered daily for a minimum of 2 months before and during the grass pollen season to be taken for at least 3 years. In a double-blind trial of Grazax® that included a withdrawal phase, efficacy was maintained for 2–3 years with continuous treatment and at 1 year following withdrawal.

|   |                   |
|---|-------------------|
| Actual start date of recruitment                          | 01 September 2013 |
| Long term follow-up planned                               | No                |
| Independent data monitoring committee (IDMC) involvement? | No                |

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 46 |
| Worldwide total number of subjects   | 46                 |
| EEA total number of subjects         | 46                 |

Notes:

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**Subjects enrolled per age group**

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|          |   |
|----------|---|
| In utero | 0 |
|----------|---|

|   |    |
|---|----|
| Preterm newborn - gestational age < 37 wk | 0  |
| Newborns (0-27 days)                      | 0  |
| Infants and toddlers (28 days-23 months)  | 0  |
| Children (2-11 years)                     | 0  |
| Adolescents (12-17 years)                 | 0  |
| Adults (18-64 years)                      | 46 |
| From 65 to 84 years                       | 0  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Participants who were having severe allergic rhinoconjunctivitis were recruited during out of pollen season from September to March 2014. All participants were recruited from United Kingdom.

### Pre-assignment

Screening details:

Individuals with severe grass pollen hay fever, with or without associated seasonal asthma were recruited after the 2013 grass pollen season, between December 2013 and April 2014. Screening of 94 participants was completed before 46 eligible atopic participants were randomized to one of the following two treatment arms in a 1:1 ratio.

### 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:

The active Grazax tablets and placebo were prepared as identical tablet and provided in identical packages. Throughout the study, participants, data analyst and investigators remained blinded.

### Arms

|                              |        |
|------------------------------|--------|
| Are arms mutually exclusive? | Yes    |
| <b>Arm title</b>             | Grazax |

Arm description:

The active treatment arm received active grass pollen immunotherapy tablet (AIT), Grazax Oral Lyophilisate 75,000 standardised quality units tablet (SQ-T) once daily.

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

Dosage and administration details:

Active Grazax Oral Lyophilisate 75,000 standardised quality units tablet (SQ-T) once daily.

|                  |                |
|------------------|----------------|
| <b>Arm title</b> | Grazax Placebo |
|------------------|----------------|

Arm description:

The placebo treatment arm received placebo tablet, Grazax placebo tablet (SQ-T) once daily.

|  |                   |
|--|-------------------|
| 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:

Grazax placebo tablet (SQ-T) sublingually once daily.

| <b>Number of subjects in period 1</b> | Grazax | Grazax Placebo |
|---------------------------------------|--------|----------------|
| Started                               | 23     | 23             |
| Completed                             | 21     | 19             |
| Not completed                         | 2      | 4              |
| Consent withdrawn by subject          | 1      | 2              |
| Lost to follow-up                     | 1      | 2              |

## Baseline characteristics

### Reporting groups

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

Reporting group description:

The active treatment arm received active grass pollen immunotherapy tablet (AIT), Grazax Oral Lyophilisate 75,000 standardised quality units tablet (SQ-T) once daily.

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

Reporting group description:

The placebo treatment arm received placebo tablet, Grazax placebo tablet (SQ-T) once daily.

| Reporting group values                | Grazax | Grazax Placebo | Total |
|---------------------------------------|--------|----------------|-------|
| Number of subjects                    | 23     | 23             | 46    |
| Age categorical<br>Units: Subjects    |        |                |       |
| Adults (18-64 years)                  | 23     | 23             | 46    |
| Age continuous<br>Units: years        |        |                |       |
| median                                | 31.5   | 36.9           | -     |
| standard deviation                    | ± 2.12 | ± 1.97         | -     |
| Gender categorical<br>Units: Subjects |        |                |       |
| Female                                | 10     | 5              | 15    |
| Male                                  | 13     | 18             | 31    |
| Specific IgE<br>Units: kU/l           |        |                |       |
| median                                | 14.4   | 14.17          | -     |
| standard deviation                    | ± 3.12 | ± 2.81         | -     |

## End points

### End points reporting groups

|  |                |
|--|----------------|
| Reporting group title  | Grazax         |
| Reporting group description:<br>The active treatment arm received active grass pollen immunotherapy tablet (AIT), Grazax Oral Lyophilisate 75,000 standardised quality units tablet (SQ-T) once daily. |                |
| Reporting group title  | Grazax Placebo |
| Reporting group description:<br>The placebo treatment arm received placebo tablet, Grazax placebo tablet (SQ-T) once daily.  |                |

### Primary: Total nasal symptom scores mean difference

|  |  |
|--|--|
| End point title  | Total nasal symptom scores mean difference |
| End point description:<br>The total nasal symptom score at one hour after grass pollen nasal allergen challenge in active versus placebo treated participants at 12 months. Score ranges from 0-12 points. Higher score is more severe symptoms. |  |
| End point type   | Primary                                    |
| End point timeframe:<br>60 minutes   |  |

| End point values                         | Grazax             | Grazax Placebo  |  |  |
|--|--------------------|-----------------|--|--|
| Subject group type                       | Reporting group    | Reporting group |  |  |
| Number of subjects analysed              | 23                 | 23              |  |  |
| Units: Score on scale                    |                    |                 |  |  |
| geometric mean (confidence interval 95%) | 3.37 (2.7 to 4.05) | 4.71 (4 to 5.4) |  |  |

### Statistical analyses

|   |                         |
|---|-------------------------|
| Statistical analysis title              | Total symptom score     |
| Comparison groups                       | Grazax v Grazax Placebo |
| Number of subjects included in analysis | 46                      |
| Analysis specification                  | Post-hoc                |
| Analysis type                           | superiority             |
| P-value                                 | < 0.05                  |
| Method                                  | t-test, 2-sided         |

### Secondary: Delta Peak nasal inspiratory flow

|                 |                                   |
|-----------------|-----------------------------------|
| End point title | Delta Peak nasal inspiratory flow |
|-----------------|-----------------------------------|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

60 minutes

| End point values                         | Grazax                 | Grazax Placebo         |  |  |
|--|------------------------|------------------------|--|--|
| Subject group type                       | Reporting group        | Reporting group        |  |  |
| Number of subjects analysed              | 23                     | 23                     |  |  |
| Units: L/min                             |                        |                        |  |  |
| geometric mean (confidence interval 95%) | -29.2 (-44.8 to -13.5) | -72.5 (-88.8 to -56.1) |  |  |

### Statistical analyses

| Statistical analysis title              | Peak nasal inspiratory flow |
|---|-----------------------------|
| Comparison groups                       | Grazax v Grazax Placebo     |
| Number of subjects included in analysis | 46                          |
| Analysis specification                  | Post-hoc                    |
| Analysis type                           | superiority                 |
| P-value                                 | < 0.05                      |
| Method                                  | t-test, 2-sided             |

### Secondary: Early phase Intradermal test

|                 |                              |
|-----------------|------------------------------|
| End point title | Early phase Intradermal test |
|-----------------|------------------------------|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

15 minutes

| End point values                | Grazax          | Grazax Placebo  |  |  |
|---------------------------------|-----------------|-----------------|--|--|
| Subject group type              | Reporting group | Reporting group |  |  |
| Number of subjects analysed     | 23              | 23              |  |  |
| Units: millimeter(s)            |                 |                 |  |  |
| geometric mean (standard error) | 15.3 (± 1.1)    | 20.2 (± 1.1)    |  |  |

### Statistical analyses



No statistical analyses for this end point

### Secondary: Late phase intradermal test

|                 |                             |
|-----------------|-----------------------------|
| End point title | Late phase intradermal test |
|-----------------|-----------------------------|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

8 hours after intradermal allergen test

| End point values                | Grazax            | Grazax Placebo    |  |  |
|---------------------------------|-------------------|-------------------|--|--|
| Subject group type              | Reporting group   | Reporting group   |  |  |
| Number of subjects analysed     | 23                | 23                |  |  |
| Units: millimeter(s)            |                   |                   |  |  |
| geometric mean (standard error) | 52.6 ( $\pm$ 3.4) | 74.6 ( $\pm$ 3.4) |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: End of season global rhinitis symptoms

|                 |  |
|-----------------|--|
| End point title | End of season global rhinitis symptoms |
|-----------------|--|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

12 month

| End point values                | Grazax             | Grazax Placebo      |  |  |
|---------------------------------|--------------------|---------------------|--|--|
| Subject group type              | Reporting group    | Reporting group     |  |  |
| Number of subjects analysed     | 23                 | 23                  |  |  |
| Units: scale                    |                    |                     |  |  |
| geometric mean (standard error) | 40.4 ( $\pm$ 5.18) | 54.97 ( $\pm$ 5.43) |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

1 year

Adverse event reporting additional description:

All adverse and severe adverse events (SAEs) were recorded on the appropriate case report forms and the specific serious adverse events were to report as soon as possible and within 24 hours. Data were entered into MHRA approved clinical trial database.

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

### Dictionary used

|                 |       |
|-----------------|-------|
| Dictionary name | CTCAE |
|-----------------|-------|

|                    |   |
|--------------------|---|
| Dictionary version | 4 |
|--------------------|---|

### Reporting groups

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

Reporting group description:

PLacebo non-active treated group

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

Reporting group description: -

| Serious adverse events                            | Grazax placebo | Grazax active  |  |
|---|----------------|----------------|--|
| Total subjects affected by serious adverse events |                |                |  |
| subjects affected / exposed                       | 0 / 23 (0.00%) | 0 / 23 (0.00%) |  |
| number of deaths (all causes)                     | 0              | 0              |  |
| number of deaths resulting from adverse events    | 0              | 0              |  |

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

| Non-serious adverse events                            | Grazax placebo   | Grazax active    |  |
|---|--|------------------|--|
| Total subjects affected by non-serious adverse events |  |                  |  |
| subjects affected / exposed                           | 20 / 23 (86.96%)   | 22 / 23 (95.65%) |  |
| Immune system disorders                               |  |                  |  |
| Allergic reaction                                     |  |                  |  |
| subjects affected / exposed                           | 3 / 23 (13.04%)  | 19 / 23 (82.61%) |  |
| occurrences (all)                                     | 3  | 23               |  |
| Gastrointestinal disorders                            |  |                  |  |
| Dyspepsia   | Additional description: In the SLIT-tablet group more adverse events were present especially gastrointestinal system such as dyspepsia and vomiting after taking SLIT. |                  |  |
| alternative dictionary used: CTCAE 5                  |  |                  |  |

|                             |                |                 |  |
|-----------------------------|----------------|-----------------|--|
| subjects affected / exposed | 0 / 23 (0.00%) | 6 / 23 (26.09%) |  |
| occurrences (all)           | 0              | 8               |  |
| Abdominal pain              |                |                 |  |
| subjects affected / exposed | 0 / 23 (0.00%) | 1 / 23 (4.35%)  |  |
| occurrences (all)           | 0              | 1               |  |
| Mucositis Oral              |                |                 |  |
| subjects affected / exposed | 1 / 23 (4.35%) | 1 / 23 (4.35%)  |  |
| occurrences (all)           | 1              | 1               |  |
| Tooth Ache                  |                |                 |  |
| subjects affected / exposed | 0 / 23 (0.00%) | 2 / 23 (8.70%)  |  |
| occurrences (all)           | 0              | 2               |  |
| Vomiting                    |                |                 |  |
| subjects affected / exposed | 0 / 23 (0.00%) | 4 / 23 (17.39%) |  |
| occurrences (all)           | 0              | 4               |  |

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported