

# Days with severe symptoms: an additional efficacy endpoint in immunotherapy trials

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efficacy; endpoint; immunotherapy; severe; symptoms.

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## Abstract

**Background:** In immunotherapy trials, primary and secondary endpoints often focus on average symptom and medication scores during the pollen season or on days with low symptoms and low medication use. Thus, there is a need for endpoints describing the treatment effect on the most troublesome days in the pollen season.

**Aims of the study:** A possible additional efficacy endpoint, days with severe symptoms during the pollen season, was investigated using data from a multicentre, double-blind, randomized, placebo-controlled trial of the SQ-standardized grass allergy immunotherapy tablet (AIT) (Grazax, *Phleum pratense*, 75 000 SQ-T/2,800 BAU, ALK, Hørsholm, Denmark).

**Methods:** The trial included 634 subjects ( $N_{\text{Grass AIT}} = 316$ ;  $N_{\text{Placebo}} = 318$ ) with grass pollen-induced rhinoconjunctivitis. Six different definitions of a day with severe symptoms were suggested. The number of days with severe symptoms was analysed and odds ratios were calculated.

**Results:** The number and percentage of days with severe symptoms differed between definitions, but overall the analysis of days with severe symptoms showed consistent results (odds ratios: 2.0–3.4) for the different definitions. All definitions showed a reduced risk of having days with severe symptoms in the grass AIT group when compared to the placebo group.

**Conclusions:** Days with severe symptoms during the pollen season is a relevant additional efficacy endpoint, which can be used in immunotherapy trials to support the clinical interpretation of commonly used efficacy endpoints.

Pollen-induced rhinoconjunctivitis is a disease with extreme day-to-day variation in the severity of symptoms. This is unlike many other allergic and nonallergic medical conditions. The variation in symptoms is caused by a significant day-to-day variation in the level of airborne pollens. During the pollen season, days with high pollen counts are alternating with days with very low pollen counts. Thus, even subjects with very severe pollen allergy will experience days with no or only mild symptoms alternating with days with severe symptoms (1).

Average rhinoconjunctivitis symptom and medication scores during the grass pollen season are often chosen as primary efficacy endpoints in immunotherapy trials. These endpoints focus on average scores during the pollen season and secondary endpoints such as rhinoconjunctivitis well days often focus on days with low symptoms and low medication use. Therefore, there is a need for endpoints describing the treatment effect on the most troublesome days in the pollen season.

For this purpose, a new additional efficacy endpoint, days with severe symptoms during the grass pollen season, was investigated using data from a multicentre, double-blind, randomized, placebo-controlled trial of the SQ-standardized grass allergy immunotherapy tablet (AIT). Days with severe symptoms during the pollen season are days with significant impact on allergic subjects' daily life (2, 3).

## Material and methods

Data from a multicentre, double-blind, randomized placebo-controlled trial (4) were analysed. The trial was conducted at 51 centres in eight countries (Austria, Denmark, Germany, Italy, The Netherlands, Spain, Sweden and United Kingdom). The trial included a total of 634 subjects suffering from grass pollen-induced rhinoconjunctivitis, with or without mild to moderate asthma, receiving grass AIT (Grazax, *Phleum pratense*, 75 000 SQ-T/2,800 BAU, ALK, Hørsholm,

Denmark) (316 subjects) or corresponding placebo (318 subjects). The tablet was administered once daily sublingually as self-administration initiated prior to the grass pollen season 2005 and continuing throughout the entire grass pollen season.

A total of six rhinoconjunctivitis symptoms were rated (four nose symptoms and two eye symptoms): runny nose, blocked nose, sneezing, itchy nose, gritty feeling/red/itchy eyes and watery eyes. Each day, the subjects rated their rhinoconjunctivitis symptoms on a scale from 0 to 3 (0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms and 3 = severe symptoms). In case of rhinoconjunctivitis symptoms, subjects had access to symptomatic medication in a stepwise manner (desloratadine tablets, budesonide nasal spray and prednisone tablets) depending on the persistence and severity of their symptoms. The final symptom and medication scores were calculated as the average of the daily scores during the whole grass pollen season.

Six definitions of a day with severe symptoms were suggested:

- A. Severe symptoms in one of the six symptom categories.
- B. Severe symptoms in three of the six symptom categories.
- C. Severe symptoms in one of the two eye symptom categories or severe symptoms in two of the four nose symptom categories.
- D. A total score of  $\geq 3$  in the eye symptom categories or  $\geq 3$  in the nose symptom categories.
- E. A total score of  $\geq 3$  in the eye symptom categories or  $\geq 6$  in the nose symptom categories.
- F. Use of budesonide nasal spray.

Written informed consent was obtained before entering the trial, and the trial was performed in accordance with current GCP standards and the Declaration of Helsinki.

## Subjects

The main inclusion criteria in the trial were age 18–65; clinical history of significant, troublesome symptoms of seasonal allergic rhinoconjunctivitis of a duration of at least 2 years with/without mild–moderate grass pollen-induced asthma during the grass pollen season; positive (wheal diameter  $\geq 3$  mm) skin prick test to *Phleum pratense* (Soluprick® SQ, ALK, Hørsholm, Denmark) and with positive specific IgE ( $\geq$ CAP allergy class 2) to *Phleum pratense*. The main criteria for exclusion included the following: significant asthma outside the grass pollen season;  $FEV_1 < 70\%$  of predicted value; significant rhinoconjunctivitis (requiring medication) caused by other allergens than grass pollen during the planned treatment period; significant recurrent acute sinusitis or chronic sinusitis; conjunctivitis, rhinitis or asthma at the screening or randomization visits; history of anaphylaxis or angioedema; presence of serious underlying conditions; immunosuppressive treatment; hypersensitivity to excipients of trial medications or rescue medications; having received immunotherapy with grass pollen allergen within the previous 5–10 years or any other allergen within the previous 5 years; or pregnancy.

## Statistical analysis

The level of airborne grass pollen was measured on a daily basis in all geographical regions in the trial. For each pollen region, the start date of the grass pollen season was defined as the first day of three consecutive days with a pollen count larger than or equal to 10 grains/m<sup>3</sup>. The stop date of the grass pollen season was defined as the last day before three consecutive days with a pollen count  $< 10$  grains/m<sup>3</sup>. The peak grass pollen season was defined as the 15-day period with the highest average pollen count of all 15-day periods fully contained in the entire grass pollen season. Days with severe symptoms were analysed using a generalized linear mixed model with a logit link function, treatment group as a fixed effect and subject within treatment and pollen region as random effect. The auto-correlation was calculated to assess the day-to-day correlation for pollen counts within each pollen region and the day-to-day correlation for symptom scores for each subject.

## Results

A total of 634 subjects were randomized and of these, 568 subjects had diary data in the grass pollen season. The mean age was 34.2 years, and all subjects had a history of moderate–severe rhinoconjunctivitis symptoms (4). Grass pollen counts were obtained from 33 pollen stations in the participating countries. The average grass pollen season lasted 57.8 days (SD: 13.9; range: 16–86 days).

Overall efficacy and safety data from the trial have been reported previously (4). Treatment with the grass AIT was well tolerated and clinically effective as treatment of grass pollen-induced rhinoconjunctivitis and adherence to immunotherapy was high; compliance based on drug accountability (calculated as number of tablets used divided by number of treatment days) was 99% (5) and dropout rate was 13% (4).

## Variability in grass pollen exposure and rhinoconjunctivitis symptoms

Significant geographical differences in the timing, duration and intensity of the grass pollen season were observed (Fig. 1). Within each pollen region, large day-to-day variations in the grass pollen counts were also observed. Because of the variation in pollen exposure, subjects experiencing no symptoms 1 day may have significant symptoms the next day. Overall, the day-to-day correlation in pollen counts in all pollen regions decreased rapidly (mean correlation coefficient 1 day apart: 0.47, mean correlation coefficient 2 days apart: 0.26). The fluctuations in pollen exposure resulted in daily fluctuations in the symptoms score (mean correlation coefficient 1 day apart: 0.41; mean correlation coefficient 2 days apart: 0.24).

## Days with severe symptoms

The percentage of subjects with days with severe symptoms during the grass pollen season using Definition A (severe symptoms in one of the six symptom categories) is illustrated

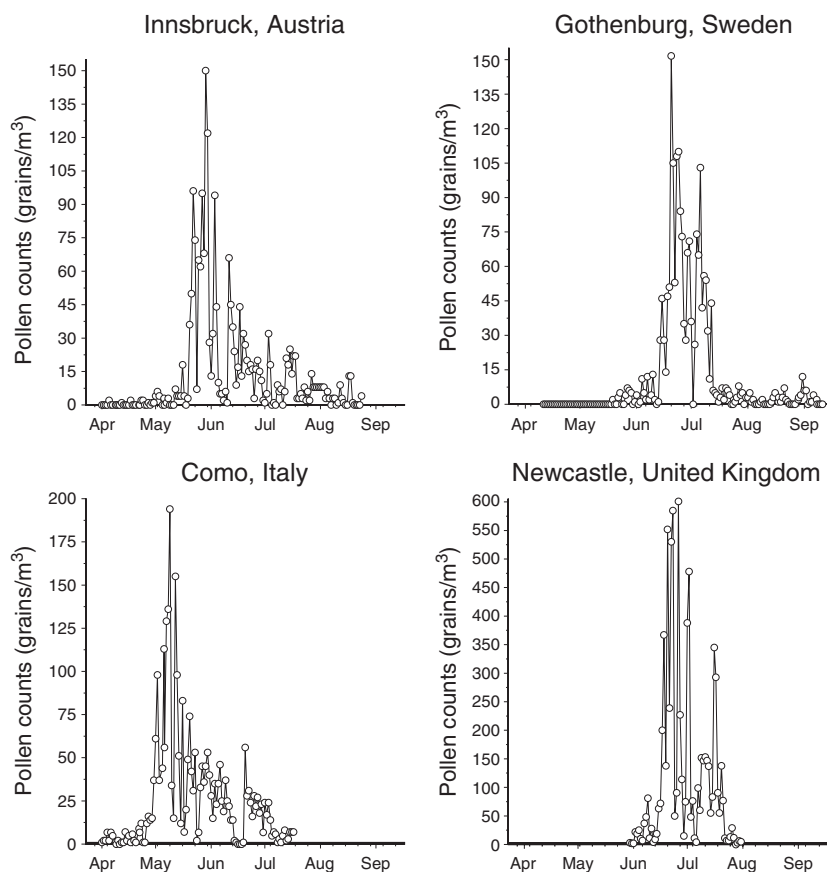


**Figure 1** Daily grass pollen counts during the grass pollen season 2005 for four arbitrarily chosen pollen regions (Innsbruck, Austria; Gothenburg, Sweden; Como, Italy and Newcastle, UK).

together with average grass pollen counts in Fig. 2. On days with high pollen counts, the percentage of subjects who experienced a day with severe symptoms increased. The percentage of subjects with days with severe symptoms was lower in the grass AIT group.

The analysis of days with severe symptoms showed consistent results for all definitions with odds ratios for having a day with severe symptoms in the entire grass pollen season (placebo *vs* grass AIT) ranging from 2.0 to 2.8 for Definition A–E (Table 1). For the last definition (Definition F), which was based on the use of budesonide nasal spray, the odds ratio was somewhat higher (3.4). For the peak grass pollen season, the odds ratio and 95% CI for the six definitions were approximately the same as for the entire grass pollen season [A: 2.8; (1.9, 4.2), B: 2.5; (1.4, 4.5), C: 2.9; (1.9, 4.5), D: 2.1; (1.5, 3.0), E: 2.5; (1.8, 3.5), F: 3.3; (1.9, 5.7)].

## Discussion

A new additional efficacy endpoint in immunotherapy trials: days with severe symptoms during the pollen season has been investigated.

Six different definitions of a day with severe symptoms were suggested. As illustrated in Table 1, the number and percentage of days with severe symptoms differed for the different definitions, but overall, all definitions showed a similar

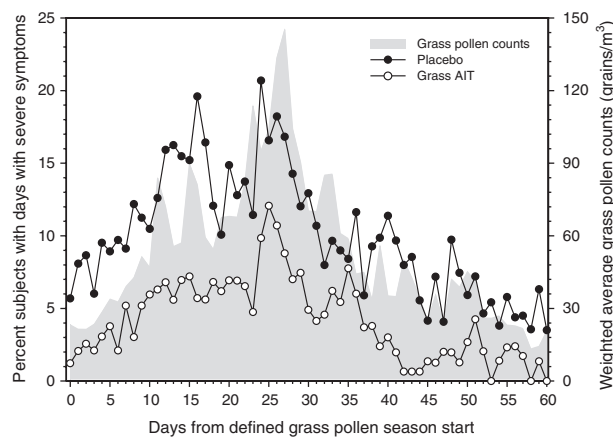


**Figure 2** Percent subjects with days with severe symptoms (using Definition A) superimposed on the weighted average grass pollen counts during the grass pollen season 2005.

and consistent pattern, i.e. a reduced risk of having days with severe symptoms in the grass AIT group when compared to the placebo group. Five of the six suggested definitions of a day with severe symptoms (Definitions A–E) are linked to the rhinoconjunctivitis symptom score. Details of the level of rhinoconjunctivitis symptoms in the analysed trial have

**Table 1** Distribution of days with severe symptoms during the grass pollen season 2005 using six different definitions of a day with severe symptoms

| Definition | Placebo |                                        | Grass AIT |                                        | Odds ratio<br>OR (95% CI) |
|------------|---------|----------------------------------------|-----------|----------------------------------------|---------------------------|
|            | % Days  | No. of days<br>with severe<br>symptoms | % Days    | No. of days<br>with severe<br>symptoms |                           |
| A          | 10.6    | 1253                                   | 4.5       | 543                                    | 2.4 (1.7; 3.3)            |
| B          | 2.8     | 332                                    | 0.88      | 106                                    | 2.6 (1.6; 4.2)            |
| C          | 7.5     | 888                                    | 2.9       | 351                                    | 2.8 (1.9; 3.9)            |
| D          | 50      | 5894                                   | 38        | 4581                                   | 2.0 (1.6; 2.6)            |
| E          | 25      | 3003                                   | 16        | 1934                                   | 2.1 (1.6; 2.7)            |
| F          | 17      | 1970                                   | 9.9       | 1186                                   | 3.4 (2.1; 5.5)            |

Based on 12 013 diary days (Grass AIT) and 11 830 diary days (placebo) in the entire grass pollen season.

% days, % days with severe symptoms in the entire grass pollen season; OR, odds ratio; CI, confidence interval; A, Severe symptoms in one of the six symptom categories; B, Severe symptoms in three of the six symptom categories; C, Severe symptoms in one of the two eye symptom categories or severe symptoms in two of the four nose symptom categories; D, A total score of  $\geq 3$  in the eye symptom categories or  $\geq 3$  in the nose symptom categories; E, A total score of  $\geq 3$  in the eye symptom categories or  $\geq 6$  in the nose symptom categories; F, Use of budesonide nasal spray; AIT, allergy immunotherapy tablet.

previously been described in (4) and is in line with the level commonly observed in other immunotherapy trials (6).

It has previously been reported that subjects treated with placebo generally used significantly more symptomatic medication than subjects treated with grass AIT (4). This is also reflected in the days with severe symptoms (Definition F). The percentage of days with use of budesonide nasal spray was approximately halved in the grass AIT group when compared to the placebo group (9.9% vs 17%).

The days with severe symptoms endpoint describes – in contrast to commonly used efficacy endpoints – the treatment effect on the most troublesome days in the pollen season.

Days with severe symptoms during the pollen season are days with significant impact on allergic subjects' daily life. The severe symptoms impact subjects' well-being, daily work or school life, sleep and in general, their quality of life. The endpoint reflects the impact on subject's daily life on a day-to-day basis in contrast to traditionally measurements of rhinoconjunctivitis quality of life, where subjects are asked to think about how they have been feeling over a longer well-defined time period e.g. on a weekly basis (2).

The six different suggested definitions were in relation to this paper defined *post-hoc* and the results may therefore only be considered to be exploratory. To confirm the validity and the most appropriate definition, the endpoint is to be further investigated in a separate trial with days with severe symptoms as a predefined endpoint. However, as the comparisons across all suggested definitions are very consistent, the results are robust and indicate the suitability of the days with severe symptoms endpoint.

In conclusion, the endpoint, days with severe symptoms, is a suitable additional endpoint that can be used in immunotherapy trials to support the clinical interpretation of commonly used efficacy endpoints.

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