

UK Immunotherapy Study: Reanalysis by a combined symptom and medication score



To the Editor:

Subcutaneous immunotherapy is widely used for therapy of patients with allergic rhinoconjunctivitis with or without allergic asthma.¹⁻³ The strength of clinical evidence supporting this treatment varies between different allergen immunotherapy (AIT) products. In addition, AIT products are not directly comparable because they differ in allergen content, allergen structure (chemically modified allergens/intact allergens), adjuvants used, or application formulations. Consequently, clinical efficacy must be documented individually for each product.^{2,3}

The efficacy of Alutard SQ *Phleum pratense* (ALK-Abelló, Hørsholm, Denmark) for AIT in patients with grass pollen allergy has been demonstrated in several controlled clinical trials in adults and children,⁴⁻⁷ both at the maximum dose for maintenance treatment of 100,000 SQ-U and also at a lower dose of 10,000 SQ-U.⁴ Supplementary references on clinical trials with the product and identical manufactured products can be found in the [Methods](#) section in this article's Online Repository at www.jacionline.org.

In a large randomized, double-blind, placebo-controlled clinical trial in 26 UK hospital clinics conducted in 2002, the UK22 trial, subjects were randomized in a 1:1:2 ratio to receive placebo or 10,000 SQ-U or 100,000 SQ-U Alutard SQ *Phleum pratense* as a maintenance dose. Details of inclusion and exclusion criteria, subjects' characteristics, dosage schedules, and individual primary and secondary outcome parameters have been published previously.⁴ As (co-)primary end points, symptom scores and medication use were evaluated separately. Although symptom scores were significantly lower compared with placebo for both doses, medication scores were statistically significantly decreased only with the higher dose (100,000 SQ-U). Responders to AIT were 76.6% of subjects with 100,000 SQ-U, 66.3% with 10,000 SQ-U, and 55.0% with placebo according to subjective evaluations of symptoms (subjects who reported improvement compared with previous years, see [Table E1](#) in this article's Online Repository at www.jacionline.org). There was a clear dose-dependent effect on the responder rate: the surprisingly high placebo responder rate was likely a result of the participant's free and open access to usual antiallergic drugs, such that all 3 groups responded. The tolerability of treatment was also dose dependent, with fewer adverse events on the 10,000 SQ-U maintenance dose, although local and delayed side effects were generally mild. Clinically significant early and delayed systemic side effects were confined to the 100,000 SQ-U group.⁴ In this group urticaria or asthma graded as early, non-life-threatening grade 3 reactions according to the European Academy of Allergy and Clinical Immunology (EAACI) grading scheme were reported in 4.4% of subjects, and urticaria, wheezing, asthma, or angioedema as delayed systemic side effects were graded as moderate in 14% of subjects and severe in 2%.⁴ This is in line with results from other trials with the 100,000 SQ-U maintenance dose.⁵⁻⁷

After completion of the UK22 trial, a World Allergy Organization (WAO) task force⁸ recommended combining symptom and medication scores as key primary end points in AIT trials, and in a recent Position Paper of the EAACI,⁹ a consensus definition for the combined symptom and medication

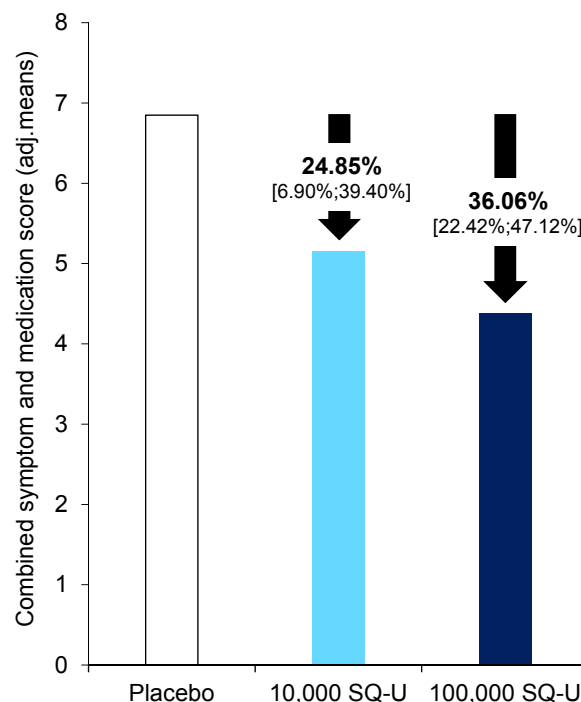


FIG 1. Adjusted means of the composite end point combining symptom and medication scores in the reanalysis for placebo and active doses of 10,000 SQ-U and 100,000 SQ-U (whole grass pollen season), with relative differences between groups and 95% CIs. All relative differences were statistically significant. *adj.*, Adjusted.

score (CSMS) has been published. The CSMS used as the primary outcome parameter for efficacy in clinical trials of AIT equally takes into account both symptom severity and the need for antiallergic medication. A very important aim of this recommendation by international experts in AIT was to standardize the clinical end points of AIT trials internationally and thereby improve the quality and comparability of AIT trials.⁹

We have applied this principle to the UK22 trial⁴ and reanalyzed the trial data *post hoc* by calculating a composite score for symptoms and medication use. In the UK22 trial nasal, eye, and lung symptoms were recorded on daily diary cards by using a 4-point scale (none, mild, moderate, and severe) to assess daily symptom scores. The daily medication score had been weighted as follows: sodium cromoglicate, 1 per drop; fluticasone nasal spray, 2 per puff; acrivastine (8 mg), 2 per capsule; prednisolone (5 mg), 2 per tablet; and salbutamol (100 µg), 1 per puff. For this *post hoc* analysis, the same data were used as for the primary analysis of the study, meaning that data were included from all subjects who had evaluable diary data ($n = 365$, full analysis set) during the grass pollen season. A composite combined score was then calculated as the sum of the total daily symptom score and the total daily medication score averaged over the pollen season, as described above. The response variable was analyzed with a linear mixed effect (LME) model. More details on the statistical methods can be found in the [Methods](#) section in this article's Online Repository.

The composite combined scores evaluated over the whole season in the reanalysis were significantly reduced compared with those in the placebo group (6.85 score points) both for the 100,000 SQ-U group (by 2.47 score points [$P < .0001$], with a relative

difference of 36.06% to placebo) and for the 10,000 SQ-U group (by 1.70 score points [$P = .0098$], with a relative difference of 24.85% to placebo; Fig 1). These changes were not statistically different between the 2 immunotherapy groups.

Thus the relative differences in composite combined scores versus the placebo group for both doses are of clinical relevance, according to the minimum criterion of 20% or greater improvement recommended by the WAO for judging the efficacy of allergy immunotherapy products.⁸ The numerically larger clinical effect size of treatment with 100,000 SQ-U was associated with a greater frequency of adverse events compared with the 10,000 SQ-U dose.⁴ This implies that it might be possible to use a patient-individualized treatment schedule comparable with other pharmaceutical treatments for which different treatment doses are available. Patients could be up dosed to a maintenance dose of 10,000 SQ-U, for which a clinically relevant effect has been proved in this study. If patients remain unacceptably symptomatic during the first grass pollen season after the start of AIT, they could be considered to be further up dosed to 100,000 SQ-U to achieve an increased clinical effect. With this approach, it might be possible to achieve an optimal outcome for patients, taking into account both tolerability and clinical effectiveness.

The results of this *post hoc* analysis confirm the main outcome of the UK22 trial, as published previously,⁴ and additionally show that the lower maintenance dose of 10,000 SQ-U induces a clinically relevant effect in the first pollen season after 5 to 8 preseasonal/seasonal maintenance injections. The importance of this *post hoc* analysis is that it was performed in line with the recommendation of international experts to combine a symptom score together with a medication score equally weighted for analysis of the primary end point in field trials. Although the definition of the end point analyzed here differs slightly from the CSMS as recommended by the EAACI⁹ (because data from slightly modified symptom and medication domains were available for this analysis, see Table E2 in this article's Online Repository at www.jacionline.org), the demonstrated effect size indicates a better discrimination capability of a combined score compared with individual symptom scores and medication scores as end points, as originally published.⁴ This *post hoc* analysis confirms earlier data showing that SQ-standardized subcutaneous immunotherapy with *Phleum pratense* allergens with either 10,000 SQ-U or 100,000 SQ-U was clinically effective in a phase III (field) trial.

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Risk factors for *Haemophilus influenzae* and pneumococcal respiratory tract colonization in CVID



To the Editor:

Disease-specific studies focused on infection risk in common variable immune deficiencies (CVIDs) are needed to define strategies for controlling respiratory infections predominantly due to bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae*.¹ Little information is available on the rate of airway bacterial carriage and its consequence in

METHODS

Treatment was handled as a fixed class effect, and region was handled as a random class variable.

Different residual errors for each treatment group were specified in the LME model. Each of the 2 active dose groups (100,000 SQ-U and 10,000 SQ-U) was compared with the placebo group by using a *t* test in the LME model. Adjusted means and the difference in adjusted means for each active dose group compared with the placebo group (placebo-active) were calculated together with associated 95% CIs. Relative differences of adjusted means were also reported with 95% confidence limits calculated based on the Fieller theorem.

AIT products

For Alutard SQ *Phleum pratense*, long-term clinical efficacy has been demonstrated in a randomized, double-blind, placebo-controlled, long-term clinical trial for 3 years after 3 to 4 years of treatment with a maintenance dose of 100,000 SQ-U,^{E1} with low risk of bias according to the recently published EAACI guidelines on AIT in allergic rhinitis^{E2} and a 3-year randomized, double blind, placebo-controlled clinical trial.^{E3}

A reduction in the risk of development of asthma in children with allergic rhinoconjunctivitis has been shown in an open randomized trial 7 years after discontinuation of a 3-year treatment with grass and/or birch allergens,^{E4} with high risk of bias according to the EAACI guidelines on AIT in allergic rhinitis and allergy prevention.^{E2,E5}

The efficacy of a maximum dose equivalent to 10,000 SQ-U (1,000 SE-U) has been demonstrated for the first pollen season after treatment in randomized, double-blind, placebo-controlled trials with an identically manufactured product (ALK7) containing grasses, rye,^{E6} and tree allergens,^{E7} with high quality and low risk of bias according to the EAACI guidelines on AIT in allergic rhinitis.^{E2}

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TABLE E1. Subjective evaluation of treatment

	100,000 SQ-U (n = 203), no. (%)	10,000 SQ (n = 104), no. (%)	Placebo (n = 103), no. (%)	Overall (n = 410), no. (%)
No. of subjects with an evaluation	180 (100.0)	89 (100.0)	91 (100.0)	360 (100.0)
How has your hay fever been this year compared with previous years?				
A lot worse	0	2 (2.2)	3 (3.3)	5 (1.4)
Worse	1 (0.6)	0	2 (2.2)	3 (0.8)
A little worse	3 (1.7)	1 (1.1)	1 (1.1)	5 (1.4)
No change	8 (4.4)	10 (11.2)	16 (17.6)	34 (9.4)
A little better	30 (16.7)	17 (19.1)	19 (20.9)	66 (18.3)
Better	44 (24.4)	24 (27.0)	24 (26.4)	92 (25.6)
A lot better	94 (52.2)	35 (39.3)	26 (28.6)	155 (43.1)

Subjects with ratings of “better” or “a lot better” were used for calculation of responder rates according to Frew et al.^{E8}

TABLE E2. Symptom scores, medication scores, and combined scores according to the EAACI^{E9}/WAO^{E10} compared with scores applied in reanalysis of UK22

Scoring according to EAACI ^{E9}	Symptom score	Scores applied in reanalysis of UK22	Symptom score
Nasal symptoms	Score 0-3 (0 = no, 1 = mild, 2 = moderate, 3 = severe symptoms)	Nasal symptoms	Score 0-3 (0 = no, 1 = mild, 2 = moderate, 3 = severe symptoms)
Itchy nose	0-3	Itchy nose	0-3
Sneezing	0-3	Sneezing	0-3
Runny nose	0-3	Runny nose	0-3
Blocked nose	0-3	Blocked nose	0-3
Conjunctival symptoms		Conjunctival symptoms	0-3
Itchy/red eyes	0-3	Gritty-feeling/red/itchy eyes	0-3
Watery eyes	0-3	Watery eyes	0-3
(Lung symptoms)*		Lung symptoms	0-3
		Cough	0-3
		Wheeze	0-3
		Tightness/dyspnea	0-3
		Exercise-induced symptoms	0-3
Total daily symptom score (dSS)	0-3 (maximum score = 3 [ie, 18 points/divided by 6 symptoms])	Total daily symptom score (DSS)	0-30 (maximum score = 30, sum of 10 symptoms)
Medication score		Medication score	
Oral and/or topical (eyes or nose) non-sedative H1A	1	Sodium cromoglicate	1 per drop
INS with/without H1A	2	Acrivastine (8 mg)	2 per capsule
Oral corticosteroids with/without INS, with without H1A	3	Fluticasone propionate nasal spray	2 per puff
		Prednisolone (5 mg)	2 per tablet
		Salbutamol (100 µg)	1 per puff
Total daily medication score (dMS)	0-3	Total daily medication score (DMS)	
Combined symptom and medication score (CSMS)		Total combined symptom and medication score (TCS)	
CSMS = dSS (0-3) + dMS (0-3)	0-6	TCS = DSS (0-30) + DMS	

H1A, H1 antihistamines; INS, Intranasal corticosteroids.

*According to the WAO task force recommendation, "Bronchial symptoms must be included in patients with symptoms from the lower airways if a claim for asthma is requested for the trial."^{E10}