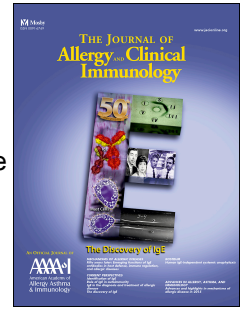


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UK Immunotherapy Study: Reanalysis by a combined symptom and medication score

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

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56 **Capsule summary**

57 Reanalysis of UK22 subcutaneous immunotherapy trial according to WAO/EAACI  
58 recommendations revealed clinically relevant improvements at both doses. Starting at the lower  
59 dose should enable efficacy with lower risk of adverse events.

60 **Key words:** Subcutaneous allergen immunotherapy, grass pollen immunotherapy, combined  
61 symptom and medication score, allergic rhinitis.

62

63 *To the Editor:*

64 Subcutaneous immunotherapy (SCIT) is widely used for therapy of patients with allergic  
65 rhinoconjunctivitis, with or without allergic asthma [1-3]. The strength of clinical evidence  
66 supporting this treatment varies between different allergen immunotherapy (AIT) products. In  
67 addition AIT products are not directly comparable as they differ in allergen content, allergen  
68 structure (chemically modified allergens/intact allergens), adjuvants used or application  
69 formulations. Consequently, clinical efficacy must be documented individually for each product  
70 [2,3].

71 The efficacy of Alutard SQ<sup>®</sup> *Phleum pratense* (ALK, Denmark) for allergen immunotherapy for  
72 grass pollen allergic patients has been demonstrated in several controlled clinical trials with adults  
73 and children [4-7], both with the maximum dose for maintenance treatment 100,000 SQ-U, and  
74 also with a lower dose of 10,000 SQ-U [4]. Supplementary references on clinical trials with the  
75 product and identical manufactured products can be found in the online repository.

76 In a large randomized, double blind, placebo-controlled clinical trial in 26 UK hospital clinics  
77 conducted in 2002, the UK22 trial, subjects were randomized in a 1:1:2 ratio to receive placebo,  
78 Alutard SQ *Phleum pratense* 10,000 SQ-U or 100,000 SQ-U as maintenance dose. Details of  
79 inclusion and exclusion criteria, subject characteristics, dosage schedules and the individual  
80 primary and secondary outcome parameters have been published previously [4]. As (co-)primary  
81 endpoints symptom scores and medication use were evaluated separately. While the symptom  
82 scores were significantly lower compared with placebo for both doses, the medication scores were  
83 statistically significantly decreased only with the higher dose (100,000 SQ-U). Responders to AIT  
84 were 76.7% of subjects with 100,000 SQ-U, 66.3% with 10,000 SQ-U and 55.0% with placebo  
85 according to subjective evaluations of symptoms (subjects who reported improvement compared to  
86 previous years, **see Table 1 in the Online repository**). There was a clear dose-dependent effect  
87 on the responder rate – the surprisingly high placebo responder rate was likely a result of the  
88 participant's free and open access to usual anti-allergic drugs, such that all 3 groups responded.

89 The tolerability of treatment was also dose-dependent, with fewer adverse events on the 10,000  
90 SQ-U maintenance dose, although local and delayed side effects were generally mild. Clinically  
91 significant early and delayed systemic side effects were confined to the 100,000 SQ-U group. In  
92 this group urticaria or asthma graded as early non-life threatening grade 3 reactions according to  
93 the European Academy of Allergy and Clinical Immunology (EAACI) grading scheme were  
94 reported in 4.4% of subjects, and urticaria, wheezing, asthma and angioedema as delayed  
95 systemic reactions graded mild in 14% of subjects and severe in 2% [4]. This is in line with results  
96 from other trials with the 100,000 SQ-U maintenance dose [5-7].

97 After completion of the UK22 trial a World Allergy Organization (WAO) task force [8] recommended  
98 to combine symptom scores and medication scores as key primary endpoints in AIT trials, and in a  
99 recent Position Paper of the EAACI, [9] a consensus definition for the combined symptom and  
100 medication score (CSMS) has been published. The CSMS used as the primary outcome parameter  
101 for efficacy in clinical trials of AIT equally takes into account both the severity of symptoms and the  
102 need for anti-allergic medication. A very important aim of this recommendation by international  
103 experts in AIT was to standardize the clinical endpoints of AIT trials internationally and, thereby, to  
104 improve the quality and comparability of AIT trials [9].

105 We have applied this principle to the UK22 trial [4] and reanalyzed the trial data post-hoc by  
106 calculating a composite score for symptoms and medication usage. In the UK22 trial nasal, eye  
107 and lung symptoms were recorded on daily diary cards using a 4-point scale (none, mild,  
108 moderate, severe) to assess the daily symptom score. The daily medication score had been  
109 weighted as sodium cromoglicate, 1 per drop; fluticasone nasal spray, 2 per puff; acrivastine (8  
110 mg), 2 per capsule; prednisolone (5 mg), 2 per tablet, salbutamol (100 µg), 1 per puff. For this  
111 post-hoc analysis the same data were used as for the primary analysis of the study, meaning that  
112 data were included from all subjects who had evaluable diary data (N=365, full analysis set) during  
113 the grass pollen season. A composite combined score was then calculated as the sum of the total  
114 daily symptom score and the total daily medication score averaged over the pollen season as

115 described above. The response variable was analyzed with a linear mixed effect (LME) model.  
116 More details on the statistical methods can be found in the online repository.

117 The composite combined scores evaluated over the whole season in the reanalysis were  
118 significantly reduced compared with placebo (6.85 score points) both for the 100,000 SQ-U group  
119 (by 2.47 score points ( $p < 0.0001$ ) with a relative difference of 36.06% to Placebo), and for the  
120 10,000 SQ-U group (by 1.70 score points ( $p = 0.0098$ ) with a relative difference of 24.85% to  
121 Placebo), (**Fig 1**). These changes were not statistically different between the two immunotherapy  
122 groups.

123 Thus, the relative differences of the composite combined score vs. placebo for both doses are of  
124 clinical relevance, according to the minimum criterion of  $\geq 20\%$  improvement recommended by  
125 WAO for judging the efficacy of allergy immunotherapy products [8]. The numerically larger clinical  
126 effect size of treatment with 100,000 SQ-U was associated with a higher frequency of adverse  
127 events compared to the 10,000 SQ-U dose [4]. This implies that it may be possible to use a  
128 patient-individualized treatment schedule, comparable to other pharmaceutical treatments for  
129 which different treatment doses are available. Patients could be up-dosed to a maintenance dose  
130 of 10,000 SQ-U for which a clinically relevant effect has been proven in this study. If patients  
131 remain unacceptably symptomatic during the first grass pollen season after start of AIT they could  
132 be considered to be further up-dosed to 100,000 SQ-U to achieve an increased clinical effect. With  
133 this approach it may be possible to achieve an optimal outcome for patients taking into account  
134 both tolerability and clinical effectiveness.

135 The results of this post-hoc analysis confirm the main outcome of the UK22 trial as published  
136 previously [4] and additionally show that the lower maintenance dose of 10,000 SQ-U induces a  
137 clinically relevant effect in the first pollen season, after 5 to 8 pre-seasonal/seasonal maintenance  
138 injections. The importance of this post-hoc analysis is that it was performed in line with the  
139 recommendation of international experts to combine a symptom scoring together with a medication

140 scoring equally weighted for the analysis of the primary endpoint in field trials. Though the  
141 definition of the endpoint analyzed here slightly differs from the CSMS as recommended by the  
142 EAACI (as data from slightly modified symptom and medication domains were available for this  
143 analysis [9], **see Table 2 in the Online repository**), the demonstrated effect size indicates a better  
144 discrimination capability of a combined score compared to the individual symptom scores and  
145 medication scores as endpoints, as originally published [4]. This post-hoc analysis confirms earlier  
146 data showing that SQ<sup>®</sup>-standardized SCIT with *Phleum pratense* allergens with either 10,000 SQ-  
147 U or 100,000 SQ-U was clinically effective in a phase III (field) trial.

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168

## 169 **Author contribution**

170 AJF, OP, HW and EW participated in designing research hypotheses. CL performed the statistical  
171 reanalysis. AJF, CJC, RJP and SRD were the main investigators in the UK22 clinical trial. HW, AJF  
172 and OP wrote the first draft of the manuscript. All authors contributed to the manuscript from the  
173 first draft and critically revised where needed. The manuscript was finalized by AJF and OP. All  
174 authors gave their approval for the submission of this article.

175

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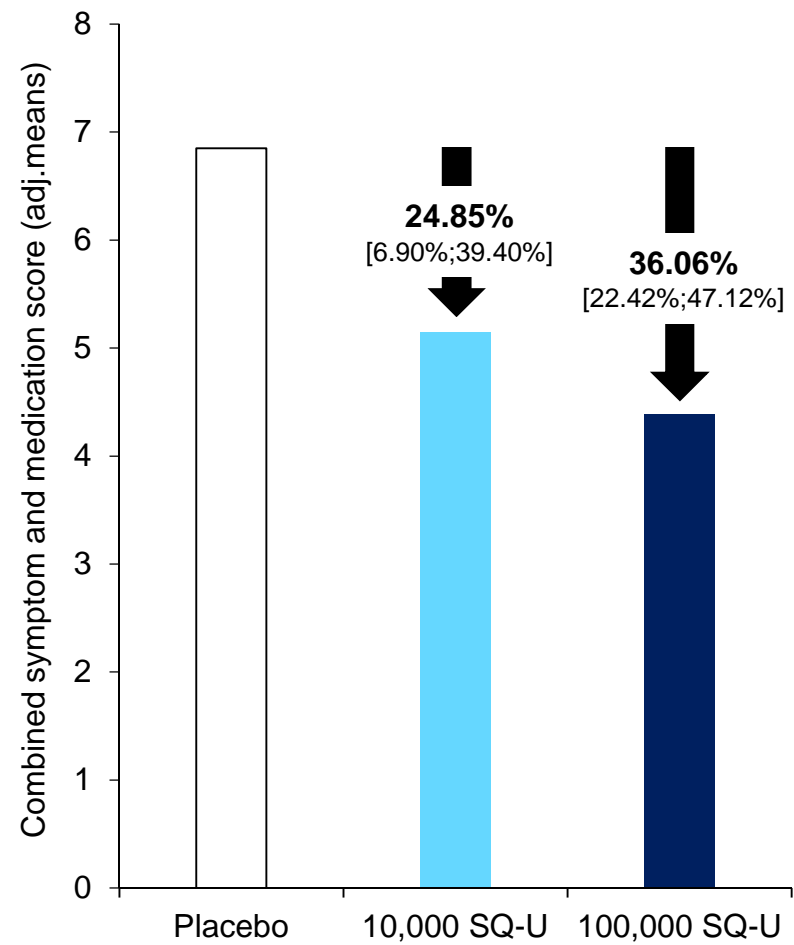
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- 204

205 **Figure Legends**

206 Figure 1. Adjusted means of the composite endpoint combining symptom scores and medication  
207 scores in the reanalysis for placebo and active doses of 10,000 SQ-U and 100,000 SQ-U (whole  
208 grass pollen season), with relative differences between groups and 95% CI. All relative differences  
209 were statistically significant. *Adj.*, *Adjusted*.

210



1 Supplementary data

2 *Details of statistical methods*

3 *Treatment was handled as a fixed class effect and Region as a random class variable.*  
4 *Different residual errors for each treatment group were specified in the LME model. Each of the*  
5 *two active dose groups (100,000 SQ-U and 10,000 SQ-U) was compared to placebo using a t-test*  
6 *in the LME model. Adjusted means and the difference in adjusted means for each active dose*  
7 *group compared to placebo (placebo-active) were calculated together with the associated 95%*  
8 *confidence intervals. The relative differences of the adjusted means were also reported with 95%*  
9 *confidence limits, calculated based on Fieller's theorem.*

10

11 *Supplementary data on AIT product*

12 *For Alutard SQ Phleum pratense long-term clinical efficacy has been demonstrated in a*  
13 *randomized, double blind, placebo-controlled long-term clinical trial for 3 years after 3 to 4 years of*  
14 *treatment with a maintenance dose of 100,000 SQ-U [1] with low risk of bias according to the*  
15 *recently published EAACI Guidelines on AIT in Allergic Rhinitis [2] and a 3-year randomized,*  
16 *double blind, placebo-controlled clinical trial [3].*

17 *A reduction of the risk of development of asthma in children with allergic rhinoconjunctivitis has*  
18 *been shown in an open randomized trial 7 years after discontinuation of a 3-year treatment with*  
19 *grass and/or birch allergens [4] with high risk of bias according to the EAACI Guidelines on AIT in*  
20 *Allergic Rhinitis and Allergy Prevention [2,5].*

21 *The efficacy of a maximum dose equivalent to 10,000 SQ-U (1,000 SE-U) has been demonstrated*  
22 *for the first pollen season after treatment in randomized double-blind placebo-controlled trials with*  
23 *an identically manufactured product (ALK7) containing grasses, rye [4] and tree allergens [5] with*  
24 *high quality and low risk of bias according to the EAACI Guidelines on AIT in Allergic Rhinitis [2].*

25

26 **Supplementary Table 1. Subjective evaluation of treatment**

	<b>100,000 SQ-U</b>	<b>10,000 SQ</b>	<b>Placebo</b>	<b>Overall</b>
	<b>(N=203)</b>	<b>(N=104)</b>	<b>(N=103)</b>	<b>(N=410)</b>
	<b>n (%)</b>	<b>n (%)</b>	<b>n (%)</b>	<b>n (%)</b>
Number 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 to previous years?				
a lot worse	0	2 (2.2)	3 (3.3)	5 (1.4)
worse	1 (0.6)	0	2 (2.2)	3 (0.9)
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)

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28 Subjects with ratings "better" or "a lot better" were used for calculation of responder rates according to [10].

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41 **Supplementary Table 2. Symptom scores, medication scores and combined scores**  
 42 **according to EAACI [8] /WAO [9] compared to the scores applied in reanalysis of UK22**

Scoring according to EAACI [8]	Symptom score	Scores applied in reanalysis of UK22	Symptom score
<i>Nasal symptoms</i>	score 0-3 (0=no, 1=mild, 2=moderate, 3=severe symptoms)	<i>Nasal symptoms</i>	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
<i>Conjunctival symptoms</i>		<i>Conjunctival symptoms</i>	0-3
itchy/red eyes	0-3	gritty feeling/red/itchy eyes	0-3
watery eyes	0-3	watery eyes	0-3
<i>(Lung symptoms)*</i>		<i>Lung symptoms</i>	0-3
		cough	0-3
		wheeze	0-3
		tightness/dyspnea	0-3
		exercised-induced symptoms	0-3
Total daily symptom score (dSS)	0-3 ( <i>max. score is 3, i.e. 18 points / divided by 6 symptoms</i> )	Total daily symptom score (DSS)	0-30 ( <i>max. score is 30, sum of 10 symptoms</i> )
<i>Medication score</i>		<i>Medication score</i>	
oral and/or topical (eyes or nose) non-sedative H1 antihistamines (H1A)	1	sodium cromoglicate	1 per drop
intranasal corticosteroids (INS) with/without H1A	2	acrivastine (8mg)	2 per capsule
oral corticosteroids with/without INS, with without H1A	3	fluticasone propionate nasal spray	2 per puff
Total daily medication score (dMS)	0-3	prednisolone (5 mg)	2 per tablet
		salbutamol (100µg)	1 per puff
Combined symptom and medication score		Total daily medication score (DMS)	
<b>CSMS = dSS (0-3) + dMS (0-3)</b>	0-6	Combined symptom score and medication score	
		<b>CS = DSS (0-30) + DMS</b>	

43

44 \*according to WAO task force recommendation: “*Bronchial symptoms must be included in patients*  
45 *with symptoms from the lower airways if a claim for asthma is requested for the trial.*” [9]

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