Shortened up-dosing with 7 injections of subcutaneous allergy immunotherapy (Alutard SQ) is safe and well tolerated

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Allergic rhinoconjunctivitis (ARC) affects 10-25% of the global population [1], and in Europe, it is mainly caused by allergens from grass pollen, Fagales tree pollen (hazel, alder, birch) and house dust mites (HDM) [2,3].

Allergy immunotherapy (AIT) can be applied by the subcutaneous or sublingual route, and it is the only treatment of ARC that has the potential for long-term effect and disease-modification [4,5].

When subcutaneous AIT (SCIT) is administered, high doses are applied with 4-8-week intervals. The optimal maintenance dose is reached safely and effectively by performing up-dosing over several weeks [6]. The convenience and practicability of SCIT as perceived by patients and physicians depend greatly on the number of injections needed for up-dosing [7]. Short up-dosing has previously been reported to be safe [8-10].

We, therefore, investigated the safety and tolerability of a 7-injection up-dosing schedule with the registered and widely used AIT product Alutard SQ (ALK, Denmark), using either 6-grasses and rye, birch or HDM allergens in comparison with the established 11-injection up-dosing schedule for grass pollen allergens in a partly randomised, parallel-group, controlled (open-label), multi-center trial. The trial was conducted in Germany and Spain in 2017-2018 (EudraCT 2017-000971-97).

Subjects treated with grass allergen extracts were randomised 1:1, either to up-dosing by 11 weekly injections (grass-11) or 7 weekly injections (grass-7). Subjects treated with birch

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(tree-7) or HDM (HDM-7) allergen extracts were treated only by the 7-injection schedule (Supplementary figure 1). Because the tolerability of SCIT with grass, tree and HDM allergens was expected to be similar, it was considered adequate to apply the 11-injection schedule with one product only. The 11 injection up-dosing schedule with Alutard SQ 6-grasses and rye was chosen as it is the most frequently used up-dosing schedule for all Alutard SQ in Germany (baseline characteristics of subjects in Supplementary table 1, and injection volumes and vial concentrations of the 7- and 11-injection schedules in Supplementary figure 2).

Male and female subjects aged 12-65 years with moderate to severe ARC to grass or birch pollen or HDM despite treatment with pharmacotherapy during the previous 2 grass or birch pollen seasons or 2 years (for allergy to HDM), with or without asthma, were eligible for the trial (in- and exclusion criteria, sample size estimation as well as safety and statistical analyses, see supporting information).

The primary endpoint was the number of treatment-related adverse events (TRAEs).

357 subjects were screened and 340 treated (Consort diagram in Supplementary figure 3).The proportion of subjects who discontinued was higher for the grass-7 group (15%) compared to the grass-11 group (7%), and the tree-7 (2%) and HDM-7 (6%) groups.

In total, 302 (89%) subjects experienced 2755 adverse events (AEs), and 269 (79%) experienced 2162 TRAEs. All AEs and TRAEs in the 4 treatment groups are displayed in the Table (all AEs and TRAEs in adolescent and adult subgroups, see Supplementary table 2).

More TRAEs were reported in the grass-11 group than in the groups with the short up-dosing schedule (grass-11: 711, grass-7: 561, tree-7: 444, HDM-7: 446) as primary endpoint of the trial, but no major differences in the proportion of subjects who experienced TRAEs were observed between the treatment groups (grass-11: 76%, grass-7: 80%, tree-7: 76%, HDM-7: 84%), (Supplementary figure 4 A and B). A majority of TRAEs typically occurred within the first 30-40 days of treatment (i.e. during the up-dosing phase). The majority of the TRAEs were mild (90%) or moderate (9%) in severity with a similar pattern in all treatment groups.

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There were no major differences in the proportion of subjects experiencing TRAEs between the adolescent and adults subgroups (adolescents: 71-86%, adults: 73-85%) or in severity, seriousness, changes to treatment and outcome. 14 (4%) subjects reported 23 TRAEs that were assessed as severe (grass-11: 7 (8%) subjects, number of events: e=8; grass-7: 6 (7%), e=14; tree-7: none, HDM-7: 1 (1%), e=1).

The most frequently reported TRAEs (≥ 5% of subjects in any group) in all treatment groups were typically injection site reactions related to the subcutaneous administration (Supplementary figure 5). Median onset was on the first day of treatment, typically 1-2 hours after treatment and median durations were 2-3 days.

Four systemic allergic reactions were identified in the grass-11 group (all serious) and three in the grass-7 group (1 serious and 2 non-serious), (details in Supplementary information, subheading Systemic allergic reaction and Supplementary table 3).

In total, 14 (4%) subjects discontinued treatment due to 26 AEs (grass-11: 2 (2%), grass-7: 9 (11%), tree-7: none, HDM-7: 3 (4%) subjects), and, of these, 11 (3%) subjects experienced 20 TRAEs leading to discontinuation. More subjects discontinued due to TRAEs in the grass-7 group (7 subjects, 8%) than in the grass-11 group (1 subject, 1%) and the HDM-7 group (3 subjects, 4%). 6 (2%) subjects experienced 6 serious AEs (grass-11: 4; grass-7: 2; tree-7: none; HDM-7: none) of which 5 were assessed as treatment-related (grass-11: 4; grass-7: 1; tree-7: none, HDM-7: none), (Supplementary table 2).

Serious TRAEs, systemic allergic reactions and severe TRAEs were predominantly seen in the grass groups, however, no indications were detected that the grass-7 group was less safe or less tolerated than the grass-11 group.

Limitations of this trial are the challenges of comparing treatment schedules of different durations and lack of corresponding comparators (11- or 16-injection up-dosing schedule) for the tree-7 and HDM-7 groups. The trial was not powered to detect differences in systemic allergic reactions, since these reactions rarely occur.

Overall, the 7-injection up-dosing schedules were well tolerated consistent with observations made in previous trials with a similar up-dosing period, but higher number of injections with the same product [8,9].

Our results suggest that potentially the 7-injection up-dosing schedules for grass, tree and HDM have an acceptable safety and tolerability profile, overall comparable to the 11-injection up-dosing schedule for grass, for adolescents and adults (12-65 years) with moderate to severe ARC induced by the respective allergen. SCIT with Alutard SQ with the 7-injection up-dosing schedules may improve the convenience of treatment and, thus, facilitate patients' access to the benefits of AIT.

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Previous presentation

The design of the study and the results have been presented in abstract and poster form at the European Academy of Allergy and Clinical Immunology (EAACI) Congress, 26-30 May 2018, Munich, Germany, at the Annual Meeting of the American Academy of Allergy Asthma and Immunology, 22-25 February 2019, San Francisco, CA, USA and at the EAACI Congress, 01-05 June 2019, Lisbon, Portugal.

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Conflict of interest

A. Horn reports grants during the conduct of the study.

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Table. All AEs and TRAEs in the four treatment groups

	Grass-11 (N=85) n (%), e	**Grass-7 (N=85)** n (%), e	**Tree-7 (N=87)** n (%), e	**HDM-7 (N=83)** n (%), e
All AEs	74 (87), 859	79 (93), 729	75 (86), 611	74 (89), 556
TRAEs	65 (76), 711	68 (80), 561	66 (76), 444	70 (84), 446
Severity, mild	63 (74), 657	64 (75), 488	66 (76), 398	69 (83), 406
moderate	19 (22), 46	23 (27), 59	16 (18), 46	16 (19), 39
severe	7 (8), 8	6 (7), 14	-	1 (1), 1
Serious TRAEs	4 (5), 4	1 (1), 1	-	-
Dose not changed	63 (74), 666	64 (75), 493	65 (75), 431	69 (83), 416
Dose reduced	20 (24), 44	18 (21), 49	5 (6), 11	12 (14), 26
Treatment interrupted	-	1 (1), 4	1 (1), 2	-
Treatment withdrawn	1 (1), 1	7 (8), 15	-	3, (4), 4
Event leading to discontinuation	1 (1), 1	7 (8), 15	-	3, (4), 4
Treated by medication	30 (35), 95	31 (36), 98	18 (21), 63	28 (34), 76
Immediate onset (<30 minutes)	23 (27), 99	26 (31), 106	17 (20), 52	20 (24), 56
Delayed onset (>30 minutes)	64 (75), 612	68 (80), 455	65 (75), 392	67 (81), 390

AE=adverse event, TRAE= treatment-related adverse event