Tolerability and Immunological Effect of Short Up-Dosing Immunotherapy With 2 Standardized Native Allergen Extracts Derived From the Pollen of *Salsola kali* and *Cupressus arizonica*

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Salsola kali is one of the main causes of summer pollinosis in countries with dry and temperate climates [1]. The prevalence of pollinosis caused by cypress pollen has been observed to increase simultaneously with the extensive use of cypress trees as ornamental plants and hedges in residential areas. The pollen of *Cupressus arizonica* is thought to have higher allergenic potential than other species [2].

Allergen immunotherapy (AIT) is considered the only treatment that ameliorates symptoms, modulates the natural course of the disease, and provides long-lasting effects in patients with IgE-mediated allergic diseases [3,4]. Subcutaneous immunotherapy (SCIT) has been widely used and has proven to be efficacious and well-tolerated. It also provides long-term benefit to patients with allergic rhinitis, conjunctivitis, or asthma [5,6].

Two new SCIT products containing allergenic pollen extracts of *S kali* (AVANZ *Salsola*) and *C arizonica* (AVANZ *Cupressus*) have been developed based on previous SCIT products. We present the results of 2 open-label, single-arm, phase II, national (Spain), multicenter clinical trials (EudraCT No.: 2013-001728-20 and 2013-004720-11). Adults with a clinically relevant history of allergic rhinoconjunctivitis with(out) asthma caused by sensitization to pollen of *S kali* or *C arizonica* (mean age, 36 and 41 years, respectively) and who had not received AIT with the corresponding allergen extracts in the previous 5 years or concomitantly with any other allergen extract received a 6-week course of SCIT (5 weekly updosing injections and a maintenance dose 2 weeks later). The primary endpoint for both studies was the percentage of

patients experiencing at least an adverse drug reaction (ADR). An ADR was defined as any noxious and unintended response to any dose of the investigational medicinal product (primary objective) based on a 30-minute observation period after dosing, subsequent telephone interview, and examination of patients' diaries. ADRs were classified as immediate (within 30 minutes after the injection), delayed (>30 minutes after the injection), local (reactions occurring at the injection site), or systemic (generalized signs/symptoms occurring away from the injection site). All local reactions were recorded, regardless of size. Systemic reactions were graded 0-IV by the investigator according to EAACI guidelines [7].

The secondary objective in both studies was to assess changes in specific IgG4 and IgE levels, which, in immediate skin reactivity, were evaluated before the first SCIT injection and 6 weeks later. The change in the immediate skin response

Table. Summary of Adverse Drug Reactions

	Salsola kali n=51		*Cupressus arizonica* n=52	
	No. of Events	No. (%)	No. of Events	No. (%)
Adverse drug reaction	97	35 (68.6)	111	40 (76.9)
Severity				
Mild	93	35 (68.6)	104	40 (76.9)
Moderate	4	4 (7.8)	6	6 (11.5)
Severe	0	0	1	1 (1.9)
Change in treatment schedule				
None	95	35 (68.6)	106	40 (76.9)
Temporarily interrupted	0	0	0	0
Modified	2	2 (3.9)	4	4 (7.7)
Discontinued	0	0	1	1 (1.9)
Prior to first intake	0	0	0	0
Onset after SCIT administration				
Immediate (less than 30 minutes)	7	6 (11.8)	27	13 (25.0)
Delayed (more than 30 minutes)	90	35 (68.6)	84	35 (67.3)
Classification according to MedDRA				
Local reactions	87	32 (62.7)	96	37 (71.2)
(Diffuse) swelling	8	5 (9.8)	3	1 (1.9)
Redness (erythema)	0	0 (0)	2	2 (3.8)
Pain	1	1 (2.0)	4	2 (3.8)
Itching (pruritus)	14	10 (19.6)	25	14 (29.6)
Urticaria	0	0 (0)	0	0 (0)
"Injection site reaction" (≥2 local symptoms)	64	26 (51.0)	62	31 (59.6)
Systemic reactions	9	7 (13.7)	7	5 (9.6)
Allergic rhinitis	4	4 (7.8)	3	2 (3.8)
Conjunctivitis allergic	0	0 (0)	2	1 (1.9)
Eye irritation	1	1 (2.0)	0	0 (0)
Eye pruritus	1	1 (2.0)	0	0 (0)
Sneezing	1	1 (2.0)	0	0 (0)
Upper respiratory tract congestion	1	1 (2.0)	0	0 (0)
Pruritus generalised	1	1 (2.0)	1	1 (1.9)
Nasal discomfort	0	0 (0)	1	1 (1.9)
Grade 0/Nonspecific	1	1 (2.0)	8	6 (11.5)
Eye pruritus	0	0 (0)	2	2 (3.8)
Eyelids eczema	0	0 (0)	2	1 (1.9)
Allergic conjunctivitis	0	0 (0)	1	1 (1.9)
Pruritus	0	0 (0)	1	1 (1.9)
Pruritus generalised	0	0 (0)	1	1 (1.9)
Somnolence	0	0 (0)	1	1 (1.9)
Ulcerative colitis	1	1 (2.0)	0	0 (0)
Dose				
300 SQ+	7	6 (11.8)	10	10 (19.2)
600 SQ+	10	9 (17.6)	10	10 (19.2)
3000 SQ+	29	25 (49.0)	26	24 (46.2)
6000 SQ+	21	19 (37.3)	28	24 (46.2)
15 000 SQ+	22	19 (37.3)	25	24 (46.2)
15 000 SQ+ (maintenance)	8	7 (13.7)	12	12 (23.1)

Abbreviations: LR, local reactions; SCIT, subcutaneous immunotherapy; SQ+, standardised quality units; SR, systemic reactions.

(after 15 minutes) was measured by means of skin prick tests using 3×5-fold concentrations of *S kali* and *C arizonica* allergen extracts and with histamine and saline solution as positive and negative controls. The parallel-line assay was used to estimate changes in the skin response, which were expressed by the cutaneous tolerance index (CTI).

According to the primary endpoint for both studies, 69% of patients treated with *S kali* and 77% of those treated with *C arizonica* reported at least 1 ADR. With *S kali* SCIT (51 patients), 97 ADRs were reported. These were all nonserious, with 93 that were mild in intensity, 87 that were local (62.7%), 9 systemic (13.7%), and 1 nonspecific (Table). With *C arizonica* SCIT (52 patients), 111 ADRs were reported. These were all nonserious, with 104 that were mild in intensity, 96 that were local (71.2%), 7 systemic (9.6%), and 8 nonspecific (Table). Between visits 1 and 6, statistically significant increases in IgG4 levels were observed with both formulations (*S kali*, 0.12 [0.18] vs 0.37 [0.62], [*P*<.005]; *C arizonica*, 0.07 [0.08] vs 0.40 [0.83], [*P*<.01]) and IgE (*S kali*, 9.25 [10.92] vs 18.19 [18.03], [*P*<.001]; *C arizonica*, 14.36 [17.85] vs 33.57 [30.98], [*P*<.001]). After 6 weeks of SCIT, no significant change in immediate skin reactivity was observed with *S kali* (CTI, 1.05 [95%CI, 0.66-1.68]; *P*>.05); whereas with *C arizonica* a statistically significant reduction was achieved (CTI, 2.51 [95%CI, 1.53-4.04]; *P*<.01).

It is encouraging to find that no moderate or severe systemic reactions were reported and that all systemic reactions found during the studies were mild in intensity (grade I, EAACI classification), and no measures had to be implemented. The number and nature of the ADRs were overall as expected; all reactions occurred at all dosing steps and were mild in severity, with a higher proportion of local reactions (89.7% with *S kali* and 86.5% with *C arizonica*), which resolved completely at the end of the studies. One patient, who was receiving SCIT with *C arizonica*, experienced a severe adverse event (injection site reaction) that led to discontinuation, although the patient recovered fully. As for *S kali*, another patient discontinued the trial because of a severe adverse event (ulcerative colitis) that was considered unlikely to be related to the investigational medicinal product.

Findings from the clinical trial reported by Moreno et al [8], which included 93 patients who received the same SCIT formulation containing *Olea europaea*–derived pollen, showed similar results to those in the present studies, in terms of number and nature of ADRs. A lower number of participants reported ADRs, although we found that these were generally mild in intensity, occurred across all dosing steps, and were mostly related to the injection site. In a similar open-label clinical trial conducted by Tabar et al [9] (102 patients) to examine the tolerability profile of the 5-week updosing schedule of a SCIT formulation with house dust mite–derived allergen extracts, around half of the study participants reported at least 1 of the 117 ADRs recorded during the trial. Approximately 5% of the affected participants reported mild, grade I systemic reactions, and 47% of the participants reported at least a local reaction that resolved fully before completion of the study.

The induction of specific IgE and IgG4 antibodies is consistent with previous findings for AIT with other allergen extracts [8,9]. Additionally, the significant reduction in the immediate skin response seen with *C arizonica* is similar to that observed with mites and olive SCIT [8,9].

In conclusion, these 2 new SCIT products derived from *S kali* and *C arizonica* administered in a 4-week updosing schedule were well tolerated and induced an early and significant immunological effect.

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Conflicts of Interest

Alicia Marín is an employee of the Medical Department at ALK-Abelló, S.A. Dr Ethel Ibáñez Echevarría acted as trial coordinator but received no remuneration for her participation in the study. All of the other co-authors were study investigators who received remuneration from ALK-Abelló, SA for their involvement in the trial.

Previous Presentation

The results from the study with *Salsola kali* were presented as a poster at the SEAIC Congress 2015. The results from the study with *Cupressus arizonica* were presented as poster at the SEAIC Congress 2016.

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