Clinical assessment of tolerability, immunological and cutaneous reactivity effects of an abbreviated schedule with *Olea europaea* native extract of subcutaneous immunotherapy.

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ABSTRACT

Objectives:

To evaluate the tolerability and efficacy of *Olea europaea* subcutaneous immunotherapy (SCIT) on patients with rhinoconjunctivitis.

Methods:

In this open clinical trial patients were assigned to an abbreviated build-up scheme. The outcomes were: number, percentage, and severity of adverse reactions. Secondary outcomes included: changes in immunoglobulin titers and changes in dose-response skin prick tests.

Results:

Only 8 systemic reactions were registered, which represented 7/47 (14.9%) of patients and 8/429 (1.9%) of administered doses. Regarding immunological parameters the significant increases of sIgG and sIgG4 evidenced the changes in the patient immune system. Cutaneous reactivity decreased significantly.

Conclusions:

*Olea europaea* SCIT (Allergovac® depot ROXALL Medicina España S.A.) showed a good safety and tolerability profile. Immunological changes with induction of blocking IgG and decreases in cutaneous reactivity were detected in the patients.
Keywords: *Olea europaea*, subcutaneous immunotherapy, rhinoconjunctivitis, abbreviated schedule, depot extracts.

List of abbreviations

- AEs: Adverse events
- AIT: Allergen immunotherapy
- AR: Allergic rhinitis
- ARIA: Allergic Rhinitis and its Impact on Asthma
- DBU: Diagnostic biological unit
- EAACI: European Academy of Allergy and Clinical Immunology
- ELISA: Enzyme-Linked Immune Sorbent Assay
- FEV₁: Forced expiratory volume in one second
- GLP: Good Laboratory Practice
- ICH: International Conference on Harmonisation
- ITT: Intention to treat
- LR: Local reaction
- LTPs: Lipid transfer proteins
- MedDRA: Medical Dictionary for Regulatory Activities
OAS: Oral Allergy Syndrome

PP: Per Protocol

RA: Respiratory Allergy

SCIT: Subcutaneous Immunotherapy

SPT: Skin prick test

sIgE: specific immunoglobulin E

sIgG: specific immunoglobulin G

sIgG4: specific immunoglobulin G4

SLIT: Sublingual immunotherapy

SP: Safety population

SPSS: Statistical Package for Social Sciences

SR: Systemic reaction

TSU: Treatment standardized unit
**Introduction**

Allergic rhinitis (AR) secondary to olive pollinosis is one of the most important causes of respiratory allergy in Mediterranean area (1,2). In some provinces of southern Spain, *Olea europaea* pollen becomes the main allergen overtaking grass and dust mites allergens in eliciting respiratory allergy symptoms (3).

The production of olive pollen extracts may present differences in allergen composition and potency as a result of the variability in cultivars origin (4-6). Some olive tree species like Frantoio, Gordal or Arbequina are less allergenic than Loaime, Hojiblanca or Picual species, regarding immunoblot detection of Ole e 1 (7). These variations could be higher from one batch to another in the case of Ole e 7 and Ole e 9, as a consequence of the little amount of these minor allergens in the source material pollen (8). In addition, these allergenic differences could be affected by external factors in relation to geographic, climatologic and pollution conditions where these trees are cultivated; as soil quality, hours of light received, rainfall values and maturation stage of the plant.

Thus, the characterization of the olive pollen raw material by manufacturers is crucial during the supplier selection process, in order to assure the presence of these allergens.

It is well known, that olive pollen extracts show a greatly complex and varied allergogram (9,10). Standard laboratory methods have detected at least 20 protein bands with allergenic activity (11). One of the most studied allergens is Ole e 1, it seems to be involved in pollen hydration or germination processes (12). This protein is considered a major allergen, because almost 70% of allergic patients to *Olea europaea* recognise it (13). Other olive pollen allergens belong to panallergens family, such as profilin (Ole e 2) (14) and calcium binding proteins (Ole e 3 and Ole e 8) (15-17). Ole e 2 is responsible for cross reactivity to vegetable foods and oral allergy syndrome (OAS), and the two latter are related to polysensitization observed with olive pollinosis (9). Ole e 7 belongs to the well-known family of Lipid Transfer Proteins (LTPs) associated with...
fruit anaphylaxis (9,18,19). In addition, the prevalence of asthma is significantly higher in patients sensitized to Ole e 7 (20). On the contrary, patients sensitized to 1,3-β-glucanase (Ole e 9) have more connection with poor tolerance to allergen immunotherapy and show more severe adverse reactions (11,21).

ROXALL Medicina España S.A. developed a sensitive and specific two-site sandwich ELISA for quantification of Ole e 1 (22). This method is especially useful in the manufacturing procedure to guarantee the quality and standardization of allergenic extracts from olive tree pollen, intended for diagnostic and therapeutic clinical use. In addition, the drug substance (Olea europaea allergenic extract) used for manufacturing these products has been characterized and the presence of main olive tree pollen allergens has been detected (Ole e 1, Ole e 2, Ole e 3; Ole e 5, Ole e 8, Ole e 9, Ole e 10, and Ole e 11) by Western-blot and mass spectrometry (ROXALL internal files).

On the other hand, two kind of products are available for SCIT, chemically modified or native allergen extracts. Both of them are absorbed into aluminium hydroxide, in order to reduce the number and severity of systemic adverse reactions by binding and slowly releasing allergens (23). Furthermore, this is the most common adjuvant used in allergen immunotherapy (AIT) (24), being able to induce the immune system response although the mechanism is not fully understood (25). According to European Pharmacopeia, the maximum amount of aluminium (Al) content per human dose is restricted to 1.25 mg/mL or lower (26). In spite of the Al concerns regarding safety and tolerability (24,27,28), until now, there are no major safety issues in commercially available registered SCIT product (29).

Traditionally, depot SCIT required large series of injections, which included a long up-dosing phase increasing allergen weekly dose until achievement of maintenance dose after 3-4 months. Abbreviated schedules, using higher concentrations at the beginning,
allowed to shorten this process maintaining a good tolerability profile (30-32).

Therefore, an open multicentre clinical trial in adult patients with allergic
rhinoconjunctivitis (with or without asthma) using standardized native depot *Olea
europaea* extract was conducted. The main aim of the current clinical trial was to
establish the tolerability and safety of an abbreviated treatment schedule in patients with
allergic rhinoconjunctivitis sensitized to olive tree pollen. Finally, the effects on
immunological and cutaneous reactivity were also evaluated.

**Materials & Methods**

**Study design and ethical considerations**

This open, multicentre and phase I clinical trial, was conducted at 5 hospitals in Spain.
The aim of the study was to establish the tolerability and safety of native depot *Olea
europaea* pollen extract administered by subcutaneous immunotherapy in patients with
allergic rhinoconjunctivitis (with or without asthma). Patients were assigned to a new
abbreviated schedule comprising 6 visits for 5 weeks, where the concentration of the olive
pollen extract was increased gradually to reach the target maintenance dose, being whole
treatment duration of 17-weeks (Table 1). Tolerability was assessed taking into account
the number, percentage and severity of adverse reactions and safety, testing
haematological and biochemical parameters. The efficacy was measured through
evaluation of immunological parameters and performing skin prick tests (SPTs), as
secondary efficacy endpoints.

The study was conducted in accordance with the principles of the Declaration of
Helsinki and the ICH guideline on Good Clinical Practice. It was approved by relevant
ethics committees and by the Spanish regulatory authorities, (EudraCT 2014-001569-29). Prior to their participation, written informed consent was given by every patient.

Study population

Patients were included in the study if they followed these inclusion criteria: patients aged 18–60 years with seasonal AR due to *Olea europaea* and clinical history of AR induced by olive tree pollen for at least 2 years prior to the study inclusion. Regarding asthma, only patients with concurrent mild asthma were allowed to participate. A positive SPT against *Olea europaea* (wheal diameter ≥ 3 mm) and specific immunoglobulin E (sIgE) levels ≥ 0.7 kUA/L determined by ImmunoCAP® (Thermo Fisher Scientific, Uppsala, Sweden) were also required. Women of childbearing age should present a negative urine pregnancy test before first vaccine dose administration.

Patients were excluded from study participation if they had received immunotherapy against *Olea europaea* or a cross-reactive allergen in the 5 years prior the study inclusion, or if currently they were receiving immunotherapy for any other allergen. In spite of the good control of asthma, patients with moderate to severe asthma and a forced expiratory volume in 1st second (FEV$_1$) < 70%, were ineligible. Patients were also excluded if they presented additional clinically relevant sensitization different of *Olea europaea* or met any of the following criteria: a history of anaphylaxis; chronic urticaria; moderate to severe atopic dermatitis; immunological, cardiac, renal or hepatic diseases; current treatment with immunosuppressants, anti-IgE, tricyclic antidepressants, psychotropic drugs, beta-blockers, or angiotensin-converting enzyme inhibitors and women who were pregnant or breast-feeding.

Study interventions
A standardized native extract of *Olea europaea* adsorbed onto 0.2% aluminium hydroxide, was used for patients’ SCIT treatment, (Allergovac® depot, ROXALL Medicina España S.A., Zamudio, Spain). Injections were administered by trained nurses under supervision of qualified allergologists in Immunotherapy Units.

During the first 5-weeks, patients received increasing doses of *Olea europaea* extract at weekly intervals (±2 days) to reach the target maintenance dose from the maximum concentration (vial 3, 1000 Treatment Standardized Units (TSU)/mL). The concentration of the major allergen Ole e 1 was 11.28 μg/mL. The build-up schedule comprised 6 doses: 3 doses (0.2, 0.5 and 1 mL) from vial 2 (100 TSU/mL), and 3 subsequent administrations (0.2, 0.5 and 1 mL) from vial 3 (Table 1). Dose modifications were allowed in the event of adverse reactions according to the recommendations of Alvarez-Cuesta *et al.* (33).

**Outcome measures**

Adverse events were collected and recorded for tolerability assessment. As a primary outcome, the incidence of adverse reactions was recorded at Immunotherapy Units during the 30 minutes after each vaccine administration. Likewise, adverse reactions were also collected by checking the patients’ diaries designed to register any unpleasant experience outside participating centres. Adverse reactions were defined as all noxious and unintended responses to any dose of the investigational allergen vaccine administered. These reactions were classified as immediate (within 30 minutes after the vaccine administration) or delayed (> 30 minutes after vaccine administration).

In the same way, adverse reactions were classified as local (LR, reactions taking place at the arm where vaccine was administered), or systemic (SR, generalised symptoms taking place far away from the administration site). According to LRs extension, we consider clinically significant the immediate LR ≥5 cm and the delayed LR ≥10 cm or those implying a dose modification in the next administration. Additionally, LRs were
described as diffuse inflammation, redness, erythema, local painfulness, pruritus, or reaction in injection site (when two or more local symptoms took place simultaneously).

SRs were classified by the investigators according to the European Academy of Allergy and Clinical Immunology EAACI guidelines (33) and the Medical Dictionary for Regulatory Activities (MedDRA).

Skin prick testing was performed using four increasing concentrations of *Olea europaea* extract (100, 1,000, 10,000 and 100,000 DBU/mL, Diagnostic Biologic Units) as well as positive (histamine 10 mg/mL) and negative (saline) controls. The change in cutaneous reactivity (wheal area in mm$^2$) from baseline to the final visit was measured.

Regarding the immunological effects assessment, serum samples were obtained at baseline and final visits to determinate specific immunoglobulin levels (IgE, IgG and IgG4) against *Olea europaea* whole extract by ELISA (Enzyme-Linked Immune Sorbent Assay) as previously described (34). Samples were frozen and sent to ROXALL’s central laboratory for bioanalysis in accordance with Good Laboratory Practices (GLPs).

Statistical methods

We performed tolerability and safety assessment and descriptive statistical analyses in the safety population (patients who received at least one dose of treatment). Efficacy statistical analyses were applied using the intention-to-treat (ITT) population (patients who met all inclusion/exclusion criteria, received at least one dose of treatment and had available data on efficacy variables) and the per-protocol (PP) population (patients who met previous criterial and moreover achieved their target maintenance dose and completed the study without any major protocol deviation).

For descriptive statistics, we displayed categorical variables by absolute and relative frequencies and continuous variables by the standard deviation and the mean.
Changes in immunoglobulin levels and SPT values from baseline to final visit, were analysed by means of the Wilcoxon non-parametric test for paired samples. A bilateral statistical significance level of 0.05 was applied to all statistical tests. Statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS) version 17.

Sample size was calculated considering a percentage of adverse events of 71% (35). Establishing a confidence interval of 95% with a precision of ± 13 percentage unit and assuming a 5% of drop outs, the number of patients to provide adequate data on the primary endpoint was 49.

Results

Descriptive data

A total of 49 subjects were enrolled in two out-season periods: from 1/9/15 to 28/2/16 and from 1/9/16 to 28/2/17. Two of them were screening failures, so 47 ones were assigned to receive AIT and were analysed in safety population (SP). Based on a rigorous clinical history and allergy diagnosis tests, sensitization to *Olea europaea* was confirmed, so that a vaccine of olive tree pollen extract 100% was indicated. The intention to treat (ITT) population included 44 patients since 3 patients were excluded due to the absence of data on immunoglobulins or dose-response SPT at final visit. Finally, 42 patients remained in the per protocol population (PP), mainly as a result of major protocol deviations. Moreover, one of these two patients were excluded from the PP population dropout from the study because of presenting asthma not related with the treatment administration (under investigator opinion). Patient’s distribution is shown in Figure 1.
Most patients (70%) showed sIgE class ≥4 against complete *Olea europaea* extract.

Subjects’ baseline demographic and clinical characteristics are presented in table 2.

**Tolerability and safety**

One hundred and fifty-five adverse events (AEs) were described in the study, being only 37 (23.87%), related to study vaccine administration. In addition, 31 patients (66.0%) reported at least one adverse event (interestingly, one patient reported 17 AEs). The most frequent AE reported by > 5% of patients were, headache (23 events in 8 patients, 17.0%), upper respiratory tract infections (8 events in 7 patients, 14.9%), pharyngitis (11 events in 7 patients, 14.9%), back pain (17 events in 6 patients, 12.8%), cutaneous reaction (11 events in 5 patients, 10.6%), dysmenorrhea (7 events in 3 patients, 6.4%), myalgia (3 events in 3 patients, 6.4%) and pruritus (3 events in 3 patients 6.4%). All AEs were non-serious and most of them (82.6%) were mild or moderate intensity. Only 27 (17.4%) were reported as severe, being headache the most frequent severe AE. In the majority of cases (106) were resolved with symptomatic medication.

During the study period, 5 clinically relevant delayed LR in 5 patients (10.6%) were recorded (Table 3). There were no immediate clinically relevant LR.

Regarding systemic reactions, only 8 SRs in 7 patients (14.9%) were recorded; five grade 0 (8.5%) described as: general discomfort, isolated eye itchy, nasal herpes, lonely oral pruritus and oral pruritus plus nausea. With regards to systemic reactions grade I (2.1%), only one described as rhinoconjunctivitis was recorded. Finally, two systemic reactions grade II (4.3%) were documented as generalized urticaria and asthma. There were no systemic reactions grade III or IV. All these SRs occurred during the build-up phase (Table 3). Systemic reactions represented 1.9% of the vaccine administrations.

Most of ARs were of mild intensity and took place in the initiation period. Symptomatic treatment or a change in the next administration dose was the most common action
required (Table 3). All patients recovered of the ARs at the end of the study. None of
the patients failed to reach the maintenance dose established in the study protocol, in
spite of the schedule dose modifications due to 8 adverse reactions.

No clinically relevant changes in blood laboratory parameters were observed following
treatment in any patient.

**Immunoglobulin levels**

For ITT population, mean changes in immunoglobulin levels against *Olea europaea*
between baseline and final visit are described (Figure 2). Statistically significant
increases in serum specific IgG and IgG4 titers at final visit were observed compared
with basal visit (both \( p < 0.001 \); Wilcoxon test). Serum specific IgE levels to *Olea
europaea* slightly decreased at final visit, achieving statistical significance (\( p < 0.001 \);
Wilcoxon test). As it was expected, these results were maintained in PP population.

**Cutaneous reactivity**

A dose-response SPT was performed with four ten-fold increasing concentrations (vials
1 to 4). Cutaneous reactivity to *Olea europaea* decreased at final visit compared with
baseline values in ITT population. Mean values of wheal area in mm\(^2\) were significantly
reduced at final visit compared with baseline in each one of the four tested vials (Figure
3). Moreover, a statistical significance was achieved with any vial tested (\( p < 0.001 \);
Wilcoxon test from vial 1 to vial 4). These cutaneous results were also reproducible in
the PP population.
Discussion

In Mediterranean countries and especially in provinces of southern Spain (Córdoba and Jaén), rhinoconjunctivitis due to olive tree pollen is one of the most frequent consultations to allergologist (36). It is also a health problem due to the large surface area devoted to this crop in Andalusia (37).

Allergen-specific immunotherapy is the unique etiologic treatment that can alter the course of the respiratory allergy condition, presenting a disease modifying effect and inducing tolerance to the antigen (38). Traditionally, clinicians prescribed allergy immunotherapy following two defined schedules as perennial or pre-seasonal. The first one was generally used in respiratory allergy secondary to perennial allergens, (i.e. mites and moulds) while the pre-seasonal schedule was usually preferred in pollinosis.

Both immunotherapy schedules have been shown to be effective in terms of clinical and immunological parameters (39). Currently, perennial schedules are more commonly used in AIT clinical practice with independency of the kind of the allergen responsible. Pre-seasonal and co-seasonal schedules are more frequently used in sublingual immunotherapy (SLIT) (40).

In the event of performing a perennial subcutaneous schedule with pollen allergens, it is recommended that the scale up be carried out outside the pollen season to diminish the risk of adverse reactions. Not only for the effect of the induction phase, which it is related to a significantly higher number of systemic reactions (40), but also for the “priming effect,” due to the natural exposition to a high amount of grain pollens.

Consequently, the vaccine tolerance can be reduced, because of these two factors (41).

On the other hand, classic AIT comprises a build-up phase with increasing doses of allergen extracts administered at short regular intervals until the optimal dose is reached. Afterwards, a maintenance period where the optimal dose is administered approximately at monthly intervals for 3 to 5 years. According to the initiation
Increasing doses schedule, immunotherapy is categorized as rush, cluster, abbreviated and conventional. Conventional schedules implies that maintenance dose is achieved after a long period of time, between 2-3 months (42). The modern tendency is to provide a treatment schedule that allows the attainment of the maintenance dose in the shortest period with the fewest adverse events and the best patient adherence to treatment. For these reasons, the abbreviated schedule can be considered a good AIT option.

A potential risk of fast schedules (rush, accelerated and abbreviated) is an increase in adverse reactions, especially systemic ones (42), although in other published article, an accelerated schedule versus a conventional one with grass SCIT seems to be similar between both regimens (43). The pattern and intensity of adverse reactions in our trial were similar to those reported in other studies, in spite of the difficulties to compare trials due to the differences in the products (44-46). The maintenance dose of 1000 TSU/mL was reached by all study participants. Only 8 systemic reactions in 7 patients (14.9%) and 1.9% of administered doses were recorded and no one was grade III or higher. A randomized unblinded controlled study with SCIT containing a standardized extract of *Olea europaea* reported good clinical results in nasal and bronchial symptoms with a rate of systemic reactions of 8.7% (44). Another open label clinical trial (45) with 93 patients treated with a short up-dosing SCIT containing *Olea europaea* extract, showed a slightly lower rate of systemic reactions 4.3%. However, non-specific or grade 0 reactions were not taken into consideration for the analysis. Other multicentre randomized clinical trials evaluated the tolerability of two five-step up-dosing schedules for SCIT with grasses. The incidence of systemic adverse reactions was 22.5% for group 1 and 35.1% for group 2 in Jung K. (31), and 21% or 33% of patients of group 1 and 2 respectively according to Pfaar O. (32).
Regarding to the early immunological response produced by the new up-dosing SCIT depot formulation, in five steps, it could be confirmed the statistically significant increments of sIgG and sIgG4 levels to Olea europaea, after 3 months of therapy. Similar results could be observed in other studies, where a rapid increase in sIgG and sIgG4 can be associated with the effect of blocking IgE-binding to allergens and B cells (39,45,46).

With respect to cutaneous reactivity to the causative allergen, a statistically significant reduction in immediate skin reactivity to the different concentrations of Olea europaea extract was observed, expressed as a decrease in the mean wheal area produced by each concentration tested. This result is in the line of another clinical trial (45) with an extract of Olea europaea after a short course of AIT.

Since the main objective of this study was tolerability, the trial was designed without a placebo group. This fact must be taken into account when interpreting the reported subrogate efficacy results because the comparison was made with each patient comparing with himself.

Conclusions

The results of this clinical trial show that the assayed abbreviated schedule with native depot Olea europaea SCIT, (Allergovac® depot ROXALL Medicina España), has a good tolerability profile, with few systemic and clinically significant local reactions. In addition, it induces a preliminary positive efficacy response. This fact is ascertained by a significant immunological and cutaneous reactivity changes in subjects suffering from allergic rhinoconjunctivitis with or without asthma due to sensitization to olive pollen. In spite of these good preliminary efficacy results, the reduction of rhinoconjunctivitis symptoms remains to be demonstrated in further clinical trials.
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Blanca Sáenz-De San Pedro, María Pilar Mur, Lucía Valverde, María Angela Gonzalo-Garijo and Mercedes Hernández are the sites principal investigators disposed according to highest recruitment. María Cruz Gómez-Fernández was the sponsor’s designated project manager and drafted the manuscript. Juan Andrés Asturias was responsible of the immunological analysis blood samples Begoña Madariaga, Leire Begoña and Alberto Martínez contributed in the conception, design, development, data analysis, data interpretation, drafting of the manuscript and manuscript revision.

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Conflicts of interest

Blanca Saenz-De San Pedro has received research fees from ALK-Abello, Leti, Novartis, Diater, Meda, Shire and Bial. María Pilar Mur has received research fees from ALK-Abello, Leti, Diater, GSK, Chiesi, Astra and Roxall. Lucía Valverde has received collaboration fees from ALK-Abello. María Angela Gonzalo-Garijo has
received collaboration fees from ALK-Abelló, Allergy Therapeutics, Bial/Roxall, Diater, Leti, Merck-Allergopharma and Stallergenes. Begoña Madariaga, Juan Andrés Asturias, Leire Begoña, Alberto Martínez and Mª Cruz Gómez are fulltime employees of ROXALL Medicina España S.A. Mercedes Hernández has no conflicts of interest to declare. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

FIGURE LEGENDS:

Figure 1:
Title: Study flow chart.
Legend: Patient’s disposition along the study.

Figure 2:
Title: Changes in specific Olea europaea immunoglobulins.
Legend: Changes in specific Olea europaea pollen extract immunoglobulins. Corresponding P-values according to Wilcoxon test are indicated.

Figure 3:
Title: Change in mean wheal area at final visit versus baseline to Olea europaea.
Legend: Change in mean wheal area after SPT with to Olea europaea pollen extract at final visit versus baseline. P-values according to Wilcoxon test are indicated.

TABLES AND FIGURES

Manuscript accepted for publication
Table I: Treatment Schedule

<table>
<thead>
<tr>
<th>Week</th>
<th>VIAL No</th>
<th>INJECTION VOLUME (mL)</th>
<th>CONCENTRATION (TSU/mL)</th>
<th>DOSE INTERVAL</th>
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<tbody>
<tr>
<td>1</td>
<td>0.2</td>
<td>20</td>
<td>NA</td>
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<tr>
<td>2</td>
<td>0.5</td>
<td>50</td>
<td>1 week</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>100</td>
<td>1 week</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0.2</td>
<td>200</td>
<td>1 week</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0.5</td>
<td>500</td>
<td>1 week</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>1000</td>
<td>1 week</td>
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**Build up phase treatment schedule**

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<thead>
<tr>
<th>Week</th>
<th>VIAL No</th>
<th>INJECTION VOLUME (mL)</th>
<th>CONCENTRATION (TSU/mL)</th>
<th>DOSE INTERVAL</th>
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<td>10</td>
<td>1</td>
<td>1000</td>
<td>4 weeks</td>
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<tr>
<td>14</td>
<td>1</td>
<td>1000</td>
<td>4 weeks</td>
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<tr>
<td>18</td>
<td>1</td>
<td>1000</td>
<td>4 weeks</td>
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**Maintenance phase treatment schedule**
Table II. Patients’ baseline clinical characteristics

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<th>Baseline characteristics</th>
<th>Abbreviated schedule</th>
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<tr>
<td>Number of patients (SP)(^a)</td>
<td>47</td>
</tr>
<tr>
<td>Age (years), mean ± (SD)(^b)</td>
<td>37.7 ± 11.82</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>28 (59.6)</td>
</tr>
<tr>
<td>Rhinitis ARIA classification (47)</td>
<td></td>
</tr>
<tr>
<td>Intermittent mild n (%)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Persistent mild n (%)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Intermittent moderate-severe n (%)</td>
<td>2 (4.3)</td>
</tr>
<tr>
<td>Persistent moderate-severe n (%)</td>
<td>45 (95.7)</td>
</tr>
<tr>
<td>Main concomitant illness</td>
<td></td>
</tr>
<tr>
<td>Asthma n (%)</td>
<td>27 (57.4)</td>
</tr>
<tr>
<td>Time from diagnostic (years), mean ± SD</td>
<td>9.8 ± 7.5</td>
</tr>
<tr>
<td>IgE <em>Olea europaea</em> CAP class n (%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>8 (17.0)</td>
</tr>
<tr>
<td>3</td>
<td>6 (12.8)</td>
</tr>
<tr>
<td>4</td>
<td>16 (34.0)</td>
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<tr>
<td>5</td>
<td>8 (17.0)</td>
</tr>
<tr>
<td>6</td>
<td>9 (19.1)</td>
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</table>

\(^a\) safety population, \(^b\) standard deviation.
Table III. Summary of adverse drug reactions by administration doses. (N=423 doses administered)

<table>
<thead>
<tr>
<th>Description</th>
<th>Initiation Phase</th>
<th>Maintenance Phase</th>
<th>Intensity</th>
<th>Action Taken</th>
<th>Recovery</th>
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<tr>
<td>Clinically relevant immediate LRs</td>
<td>0 (0)</td>
<td>0 (0%)</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Skin reaction&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>mild</td>
<td>dose change</td>
<td>yes</td>
</tr>
<tr>
<td>Erythema + oedema&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>mild</td>
<td>symptomatic treatment</td>
<td>yes</td>
</tr>
<tr>
<td>Clinically relevant delayed LRs</td>
<td>4&lt;sup&gt;a&lt;/sup&gt; (0.95)</td>
<td>1&lt;sup&gt;b&lt;/sup&gt; (0.23)</td>
<td>Localized oedema&lt;sup&gt;a&lt;/sup&gt;</td>
<td>mild</td>
<td>dose change</td>
</tr>
<tr>
<td>Erythema&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>mild</td>
<td>none</td>
<td>yes</td>
</tr>
<tr>
<td>Injection site reaction&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>severe</td>
<td>dose change</td>
<td>yes</td>
</tr>
</tbody>
</table>

Systemic reactions
<table>
<thead>
<tr>
<th>Grade</th>
<th>Number (Percentage)</th>
<th>Symptoms</th>
<th>Severity</th>
<th>Treatment</th>
<th>Relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>0c</td>
<td>5 (1.2)</td>
<td>General discomfort&lt;sup&gt;c&lt;/sup&gt;</td>
<td>mild</td>
<td>none</td>
<td>yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Eye pruritus&lt;sup&gt;c&lt;/sup&gt;</td>
<td>mild</td>
<td>none</td>
<td>yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nasal herpes&lt;sup&gt;c&lt;/sup&gt;</td>
<td>mild</td>
<td>symptomatic treatment</td>
<td>yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mouth pruritus&lt;sup&gt;c&lt;/sup&gt;</td>
<td>mild</td>
<td>none</td>
<td>yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pruritus + nausea&lt;sup&gt;c&lt;/sup&gt;</td>
<td>moderate</td>
<td>none</td>
<td>yes</td>
</tr>
<tr>
<td>1d</td>
<td>1 (0.2)</td>
<td>Rhinconjunctivitis&lt;sup&gt;d&lt;/sup&gt;</td>
<td>moderate</td>
<td>none</td>
<td>yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Asthma&lt;sup&gt;e&lt;/sup&gt;</td>
<td>severe</td>
<td>change + treatment</td>
<td>yes</td>
</tr>
<tr>
<td>2e</td>
<td>2 (0.5)</td>
<td>Urticaria&lt;sup&gt;e&lt;/sup&gt;</td>
<td>mild</td>
<td>change + treatment</td>
<td>yes</td>
</tr>
</tbody>
</table>

n (%) number and percentage of adverse reactions, LR (local reaction), * Clinically relevant delayed LRs during initiation phase, † Clinically relevant delayed LRs during maintenance phase, ‡ Systemic reaction grade 0, § Systemic reaction grade I and ‖ Systemic reaction grade II.
Figure 1
Figure 2
Figure 3

Wheal area (mm²)

- Basal visit
- Final visit

Comparisons:
- p < 0.001
- p < 0.001
- p < 0.001
- p < 0.001