Integrated Clinical Trial Report

Trial ID: AV-X-01

Trial title

An open trial to assess the tolerability of AVANZ Olive immunotherapy

Investigational medicinal product:	AVANZ Olive
EudraCT no.:	2011-004852-20
Development phase:	II/III
Indication:	Allergic rhinoconjunctivitis
First subject first visit:	26/09/2012
Last subject last visit:	12/04/2013
Investigators:	10 investigators in Spain
	Signatory investigator: [redacted] MD, PhD [redacted] Spain
Trial sites:	10 trial sites in Spain
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Version:	Final
Date:	12 March 2014

This trial was conducted in compliance with the principles of ICH Good Clinical Practice.

Synopsis – Trial AV-X-01

Title of trial

An open trial to assess the tolerability of AVANZ Olive immunotherapy.

Investigators

Coordinating investigator: [redacted], MD, PhD.
Investigators: [redacted], MD; [redacted], MD; [redacted], MD; [redacted], MD; [redacted], MD; [redacted], MD, PhD; [redacted], MD, PhD; [redacted], MD, PhD; [redacted], MD, PhD.

Trial sites

10 trial sites in Spain: [redacted] Spain), [redacted] Spain), [redacted] Spain), [redacted] Spain), [redacted] Spain), [redacted] Spain), [redacted] Spain), [redacted] Spain), [redacted] Spain) and [redacted] Spain).

Publication

None.

Trial period

First subject first visit: 26 September 2012.
Last subject last visit: 12 April 2013.

Objectives

This trial was intended to assess the tolerability of AVANZ® Olive.

Primary objective:

- To assess the tolerability of the up-dosing phase of AVANZ® Olive. The frequency of patients with adverse reactions was the primary endpoint.

Secondary objectives:

- Frequency of patients with systemic reactions according to the European Academy of Allergy and Clinical immunology (EAACI) classification.
- Increase in IgG_4 and in IgE.
- Reduction in immediate skin reactivity.

Methodology

This was a national, multi-centre, open-label, single-arm, phase II/III clinical trial conducted in Spain. The trial was initiated after olive pollen season 2012 and subjects received treatment for 6 weeks, including a 4-week up-dosing phase followed by a maintenance dose. Thereafter, subjects were telephonically contacted 2 days after each visit for a follow-up.

The overall trial design is shown below:

TC: telephone contact (2 days after dose administration)

Number of subjects planned and analysed

- 100 planned.
- 96 screened.
- 3 screening failures.
- 93 included.
- 93 treated.
- 3 discontinuations during treatment: 1 non-compliance with protocol; 1 withdrew consent; 1 pregnancy.
- 90 completed.

Main selection criteria

Key inclusion criteria:

Male and female subjects of 18-65 years of age, with a clinical history of olive pollen induced allergic rhinoconjunctivitis with or without asthma at least one year prior to trial entry, a positive skin prick test (SPT) to olive pollen (wheal diameter ≥ 3 mm), and a positive specific IgE against olive pollen (≥ IgE class 2; ≥0.70 KU/L) documented within the last 5 years.

Key exclusion criteria:

Forced expiratory volume within one second (FEV_1) <70% of predicted value at screening; uncontrolled or severe asthma; a history of severe asthma exacerbation or emergency room visit or admission for asthma in the previous 12 months; at screening, current symptoms of, or treatment for, upper respiratory tract infection, acute sinusitis, acute otitis media or other relevant infection; treatment with parenteral corticosteroids, oral corticosteroids or anti-IgE in the previous 3 months or during the study (except for steroids if needed as rescue medication); being treated with angiotensin converting enzyme (ACE) inhibitors, tricyclic antidepressants, β-blockers, mono amine oxidase inhibitors (MAOIs) and any other drug containing alum (i.e. antacids) taken on a daily basis; previous treatment by other allergen concomitant IT or immunotherapy with *Olea europaea* extracts within the previous 5 years; history of anaphylactic shock due to food, insect venom, exercise or drug; history of severe and recurrent angioedema; any contraindication detailed in the Investigator's Brochure; use of an investigational drug within 30 days prior to screening; a mental condition rendering the subject unable to understand the nature, scope and possible consequences of the trial, and/or evidence of an uncooperative attitude; history of allergy, hypersensitivity or intolerance to the excipients of the IMP (except olive pollen) or symptomatic medications; lactating women; Being the investigator, trial staff or their immediate families, defined as the investigator's/staff's spouse, parent, child, grandparent, or grandchild

Investigational medicinal product, dose and mode of administration, batch number

AVANZ® Olive, biologically standardised allergen extract at 600 immunologically enhanced standardised quality units (SQ+)/ml (vial A, batch number 0000181198, expiry date 7 June 2014) or 30,000 SQ+/ml (vial B, batch number 0000181199, expiry date 7 June 2014) adsorbed on aluminium hydroxide.

AVANZ® Olive was administered subcutaneously using a 5-step up-dosing schedule and subjects received one maintenance dose:

- Up-dosing phase: 5 weekly injections administered subcutaneously until reaching maintenance dose (15,000 SQ+).

Vial A (batch number: 0000181198)	**Dose (ml)**	**SQ+ administered**
600 SQ+/ml	0.5	300
	1	600
Vial B (batch number: 0000181199)	**Dose (ml)**	**SQ+ administered**
30,000 SQ+/ml	0.1	3,000
	0.2	6,000
	0.5	15,000

- Maintenance phase: 1 subcutaneous administration of 15,000 SQ+ (0.5 ml of vial B) 2 weeks after reaching maintenance dose.

Reference therapy, dose and mode of administration, batch number

Not applicable.

Additional therapy

Not applicable.

Duration of treatment

6 weeks.

Criteria for evaluation – Pharmacodynamics

- Quantification of *Olea europaea* specific IgG_4 and IgE (secondary endpoint).
- Immediate skin response to *Olea europaea* measured by parallel line assay (secondary endpoint).

Criteria for evaluation – Safety

- Incidence of adverse drug reactions (ADRs) (primary endpoint).
- Incidence of systemic ADRs (grade I or higher) according to the EAACI classification (secondary endpoint).
- Incidence of local ADRs (secondary endpoint).

Statistical methods

The following analysis sets were used:

- The full analysis set (FAS) comprised all subjects who received at least one dose of IMP according to the International Conference on Harmonisation (ICH) intent-to-treat principle.
- The per-protocol (PP) analysis set comprised all subjects who have completed the the treatment without major protocol violations/deviations.
- The safety analysis set was identical to the FAS.

Changes in specific IgG_4 and IgE levels between visit 1 and visit 6 were performed using Student's t-test for paired samples. Safety was analysed by descriptive statistics.

Missing data were not considered in the analyses and a significance level of 0.05 was used for statistical testing. The statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 17.0 ([redacted] USA).

Demography of trial population (FAS)

Characteristics	Value
Age (years), mean±SD	35.7±10.3
Female, n (%)	62 (66.7)
Ethnic origin, n (%):	
Caucasian	89 (95.7)
Hispanic	3 (3.2)
Arabian	1 (1.1)
Height (cm), mean±SD	166.4±9.2
Weight (kg), mean±SD	72.1±14.7
BMI (kg/m^2), mean±SD	25.9±4.2
Vital signs, mean±SD:	
Systolic blood pressure (mmHg)	120.2±13.7
Diastolic blood pressure (mmHg)	73.7±8.8
Heart rate (bpm)	74.2±8.1
Smoking habits, n (%):	
Non-smoker	72 (77.4)
Smoker	14 (15.1)
Previous smoker	7 (7.5)
IgE *Olea europaea* CAP class, n (%):	
2	16 (17.2)
3	32 (34.4)
4	28 (30.1)
5	12 (12.9)
6	5 (5.4)
Main concomitant illness, n (%):	
Asthma	64 (68.8)
Conjunctivitis	54 (58.1)
Rhinitis allergic	26 (28.0)
Conjunctivitis allergic	14 (15.1)

bpm, beats per minute; IgE, immunoglobulin E; SD, standard deviation.

Pharmacodynamic results

- Treatment with AVANZ® Olive induced statistically significant increases in IgG4 and IgE levels from visit 1 to visit 6 ($p<0.001$).
- Immediate skin reactivity (measured after 15 minutes) to *Olea europaea* decreased statistically significantly ($p<0.01$) from visit 1 to visit 6. The cutaneous tolerance index was 2.34 (95% CI, 1.72-3.19).

Safety results

- The trial showed a good safety profile for the up-dosing schedule of AVANZ® Olive.
- A total of 48 (51.6%) subjects reported 179 AEs during the trial. The vast majority of them were mild (99.4%) in severity and no serious AEs were reported during the trial.
- 95 (53.0%) of the AEs reported by 34 (36.6%) subjects were considered to be related to the IMP. All the reported IMP-related AEs were mild in severity, non-serious, and subjects were fully recovered.
- The most frequent AEs were injection site reaction, injection site pruritus, and headache, which were reported in 23.7%, 16.1% and 12.9%, respectively.
- ADRs were reported at all dosing steps (300 SQ+ to 15,000 SQ+).
- A total of 85 local ADRs were reported in 32 (34.4%) subjects, and 9 systemic ADRs were reported in 4 (4.3%) subjects.
- All local ADRs were non-serious, did not require any modification of the IMP administration, and subjects were fully recovered. The most frequently reported local ADR was injection site reaction (61.2%), followed by itching (pruritus) (29.4%), (diffuse) swelling (4.7%), and pain (3.5%).
- All the reported systemic ADRs were delayed, mild in severity, grade I according to the EAACI classification, and non-serious. These systemic ADRs included asthma (4 events), pharyngeal pruritus (3 events), ear pruritus (1 event) and chest tightness (1 event).
- No safety concerns were found for vital signs and physical examination.

Conclusions

The up-dosing schedule of AVANZ® Olive had a good tolerability profile where all ADR were mild in severity and mostly local. Systemic ADRs classified according to the EAACI guidelines were reported in less than 5% of the subjects, whereas local ADRs were shown in over 34% of the total population. None of the ADRs led to withdrawal.

Treatment with AVANZ® Olive induced statistically significant immunological responses in terms of statistically significant increases in the levels of IgG_4 and IgE, while it enabled immediate skin reactivity to be decreased.

Date of the report

Final, 12 March 2014.

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