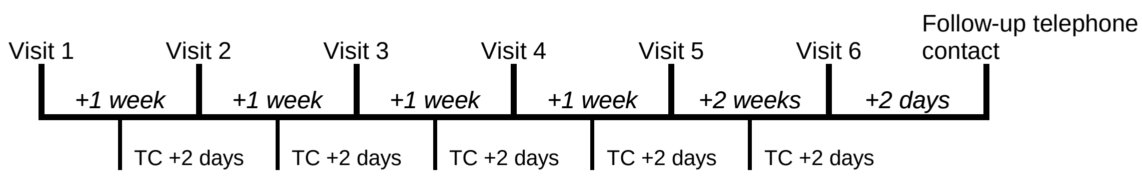
Synopsis – trial AV-G-01

Title of trial An open trial to assess the tolerability of AVANZ® *Phleum pratense* immunotherapy
Investigators 20 investigators in Spain. Coordinating investigator: [redacted], MD, PhD. Other principal investigators: [redacted], MD, PhD; [redacted], MD, PhD; [redacted], MD; [redacted], MD; [redacted], MD; [redacted], MD, PhD; [redacted], MD; [redacted], MD; [redacted], MD; [redacted], MD, PhD; [redacted], MD; [redacted], MD, PhD; [redacted], MD, PhD; [redacted], MD, PhD; [redacted], MD, PhD; [redacted], MD, PhD; [redacted], MD, PhD; [redacted], MD, PhD; [redacted], MD, PhD
Trial sites 20 trial sites in Spain: [redacted] ([redacted] Spain), [redacted] ([redacted], Spain), [redacted] ([redacted], Spain), [redacted] ([redacted], Spain), [redacted] ([redacted], Spain), [redacted] ([redacted], Spain), [redacted] ([redacted] Spain), [redacted] ([redacted], Spain), [redacted] ([redacted], Spain), [redacted] ([redacted], Spain), [redacted] ([redacted], Spain), [redacted] ([redacted], Spain), [redacted] ([redacted], Spain), [redacted] ([redacted], Spain), [redacted] ([redacted], Spain), [redacted] ([redacted], Spain), [redacted] ([redacted], Spain), [redacted] ([redacted], Spain), [redacted] ([redacted], Spain) and [redacted] ([redacted], Spain)
Publication None
Trial period First subject first visit: 06 July 2011 Last subject last visit: 02 March 2012
Objectives This trial was intended for investigating the tolerability of AVANZ® *Phleum pratense* <u>Primary objective:</u> • To assess the tolerability of the up-dosing phase of AVANZ® *Phleum pratense*. The frequency of subjects with adverse drug reactions was the primary endpoint <u>Secondary objectives:</u> • Frequency of systemic adverse drug reactions, based on EAACI classification • Increase in IgG_4 and in IgE-blocking factor • Reduction in immediate skin reactivity
Methodology This was a national, multi-site, open-label, single-arm, phase II/III trial performed in Spain. The trial was conducted outside the grass pollen season. Subjects received treatment for 6 weeks with an up-dosing phase followed by one maintenance dose; subjects were telephonically contacted 2 days after receiving each dose in order to ascertain if any adverse event had occurred The overall trial design is shown below:    TC: telephone contact (2 days after dose administration)

Number of subjects planned and analysed

- 200 planned
- 199 screened
- 3 screening failures
- 196 included
- 4 discontinuations before treatment
- 192 treated
- 19 discontinuations during treatment: 14 due to adverse events; 1 lost to follow-up; 1 for personal reasons; 1 for delay between administrations of IMP (Investigational medicinal product); 1 for suspicion of tuberculosis infection (confirmed to be negative in the following days); 1 for unknown reason
- 173 completed

Main selection criteria

Key inclusion criteria:

Male and female subjects of 18-65 years of age with a clinical history of grass pollen induced allergic rhinoconjunctivitis with or without asthma, a positive skin prick test (SPT) to *Phleum pratense* (wheal diameter≥3 mm) and a positive specific IgE against *Phleum pratense* (≥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 (GINA (Global Initiative for Asthma) step 4); history of severe asthma exacerbation or emergency room visit 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 (serous otitis media is not an exclusion criterion); treatment with parenteral corticosteroids, oral corticosteroids or anti-IgE in the previous 3 months or during the trial (except for steroids if needed as rescue medication); currently treated with angiotensin converting enzyme (ACE) inhibitors, tricyclic antidepressants, mono amine oxidase inhibitors (MAOIs) and other drugs containing alum (e.g. antacids) taken on a daily basis; previous treatment with immunotherapy with grass pollen allergen within the previous 5 years (initiation of subcutaneous immunotherapy is acceptable if treatment has been discontinued before reaching maintenance dose; for SLIT 3 months in the last 5 years is accepted); history of anaphylactic shock due to e.g. food, insect venom, exercise or drug, history of severe and recurrent angioedema; any contraindication according to the Investigator's Brochure; use of an investigational drug within 30 days prior to screening

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

AVANZ® *Phleum pratense*, standardised allergen extract adsorbed on aluminium hydroxide, 600 SQ+/ml (vial A, batch number 0000135149, expiry date 31 January 2013) and 30,000 SQ+/ml (vial B, batch number 0000135150, expiry date 31 January 2013)

AVANZ® *Phleum pratense* 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	Dose (ml)	SQ+ administered
600 SQ+/ml	0.5	300
	1	600
Vial B	**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 *Phleum pratense* specific IgG_4 and IgE-blocking factor (secondary endpoint)
- Immediate skin response to *Phleum pratense* as measured by parallel line assay (secondary endpoint)

Criteria for evaluation – Safety

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

Statistical methods

The following analysis sets were used:

- The full analysis set (FAS) comprised all the subjects who received at least one dose of treatment according to the ICH intention-to-treat principle
- The per-protocol (PP) analysis set comprised all FAS subjects without important deviations from the protocol that affected the primary endpoint. In other words, they met the screening criteria and did not commit important deviations from the protocol during the trial
- The safety analysis set (SS) was identical to the FAS

Changes in IgG_4 and IgE-blocking factor 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

Characteristics	Value
Age (years), mean±SD	32.8±9.4
Female, n (%)	98 (51.0)
Ethnic origin, n (%):	
Caucasian	140 (72.9)
Hispanic	49 (25.5)
African	2 (1.0)
Arab	1 (0.5)
Height (cm), mean±SD	168.2±10.3
Weight (kg), mean±SD	73.3±15.2
Body mass index (BMI) (kg/m^2), mean±SD	25.8±4.4
Vital signs, mean±SD:	
Systolic blood pressure (mmHg)	118±13.3
Diastolic blood pressure (mmHg)	72.3±10.7
Heart rate (bpm)	71.6±10.6
Smoking habits, n (%):	
Non-smoker	150 (78.1)
Smoker	26 (13.5)
Previous smoker	16 (8.3)
IgE *Phleum pratense* CAP class, n (%):	
2	16 (8.3)
3	60 (31.3)
3.4[a]	1 (0.5)
4	55 (28.6)
5	37 (19.3)
6	23 (12.0)
Asthma history, n (%):	
Subjects with asthma history	93 (48.4)
Subjects with asthma ongoing at baseline	92 (47.9)
Main concomitant illness (frequency ≥5%), n (%):	
Conjunctivitis	165 (87.0)
Asthma	92 (47.9)
Rhinitis allergic	28 (14.6)

[a] 3.4 was recorded as CAP class in the CRF (case report form); bpm: beats per minute; IgE: immunoglobulin E; SD: standard deviation

Pharmacodynamic results

- Treatment with AVANZ® *Phleum pratense* induced statistically significant increases in IgG_4 and in IgE-blocking factor from visit 1 to visit 6 ($p<0.001$)
- Immediate skin reactivity (measured after 15 minutes) to *Phleum pratense* decreased from visit 1 to visit 6. The cutaneous tolerance index was 1.8 [95% CI 1.5; 2.2]

Safety results

- The trial showed an acceptable tolerability profile for the up-dosing schedule of AVANZ® *Phleum pratense*
- A total of 154 subjects (80%) reported 686 adverse events during the trial. The majority of the reported adverse events were mild or moderate in severity; 91% were mild and 8% were moderate. 2 of the 686 adverse events (0.3%) were considered to be severe
- 432 (63%) of the adverse events reported by 133 (69%) subjects were considered to be related to the IMP. IMP-related adverse events i.e. adverse drug reactions were primarily mild or moderate in severity; 88% were mild and 12% were moderate. 2 of the adverse drug reactions (0.5%) were considered to be severe
- The most frequently reported adverse drug reactions were injection site erythema, injection site pruritus, injection site reaction, injection site swelling, hypersensitivity, rhinitis allergic and urticaria with injection site reactions being the far most frequently reported adverse events – reported in 47% of subjects
- Adverse drug reactions were reported at all dosing steps (300 SQ+ to 15,000 SQ+)
- 278 local adverse drug reactions in 109 (57%) subjects and 136 systemic adverse drug reactions in 66 (34%) subjects were reported. The systemic adverse drug reactions classified according to the EAACI classification were primarily delayed grade I and II reactions and included a variety of different adverse drug reactions. The most frequently reported systemic adverse drug reactions included allergic rhinitis, urticaria and hypersensitivity. 2 of the 136 adverse drug reactions were classified as grade III, no grade IV reactions were reported
- 3 subjects experienced serious adverse events during the trial
- 14 subjects (7%) withdrew due to a total of 20 adverse events
- No safety concerns were found for vital signs and physical examination

Conclusions

Primary objective:

- The up-dosing schedule for AVANZ® *Phleum pratense* had an acceptable tolerability profile

Secondary objectives:

- Systemic adverse drug reactions classified according to the EAACI classification were reported in approximately one third of the subjects. Adverse drug reactions were, except for 2 events, mild or moderate adverse drug reactions (grade I or II)
- Treatment with AVANZ® *Phleum pratense* induced statistically significant immunological responses (increases in IgG_4 and IgE-blocking factor) and immediate skin reactivity decreased

Date of the report

Final, 11 April 2013

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