Integrated Clinical Trial Report

Trial ID: AV-M-01

Trial title

An open trial to assess the tolerability of AVANZ® Mite mix immunotherapy

Investigational medicinal product:	AVANZ® Mite mix (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae)*
EudraCT no.:	2011-002017-11
Development phase:	II/III
Indication:	Allergic rhinoconjunctivitis
First subject first visit:	17/01/2012
Last subject last visit:	16/07/2012
Investigators:	9 investigators in Spain
	Signatory investigator: [redacted]
Trial sites:	9 trial sites in Spain
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Version:	Final
Date:	28 June 2013

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

Synopsis – Trial AV-M-01

Title of trial

An open trial to assess the tolerability of AVANZ® Mite mix (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae)* immunotherapy.

Investigators

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

Trial sites

9 trial sites in Spain: [redacted], Spain), [redacted], Spain), [redacted], Spain), [redacted], Spain), [redacted], Spain), [redacted], Spain), [redacted], Spain), [redacted], Spain), [redacted], Spain).

Publication

None.

Trial period

First subject first visit: 17 January 2012.
Last subject last visit: 16 July 2012.

Objectives

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

Primary objective:

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

Secondary objectives:

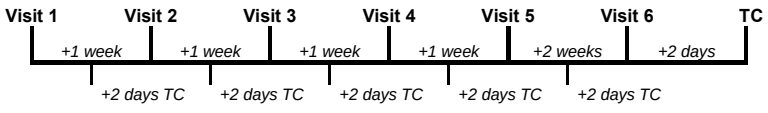
- Frequency of patients with systemic reactions, according to the European Academy of Allergy and Clinical immunology (EAACI) classification.
- Increase in IgG4 and in IgE-blocking factor.
- Reduction in immediate skin reactivity.

Methodology

This was a national, multi-center, open-label, single-arm, phase II/III clinical trial conducted in Spain.

The trial was initiated in autumn 2011 and subjects received treatment for 6 weeks, including an up-dosing phase followed by a maintenance dose. Thereafter, patients 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.
- 103 screened.
- 1 screening failure.
- 102 included.
- 102 treated.
- 8 discontinuations during treatment: 2 due to adverse events (AEs); 1 lost to follow-up; 2 non-compliance with protocol; 3 for other reasons.
- 94 completed.

Main selection criteria

Key inclusion criteria:

Male and female patients of 18-65 years of age with a clinical history of house dust mite (HDM)-induced allergic rhinoconjunctivitis with or without asthma, with a positive skin prick test (SPT) to *Dermatophagoides pteronyssinus* or *Dermatophagoides farinae* (wheal diameter ≥ 3 mm) and a positive specific IgE against *Dermatophagoides pteronyssinus* or *Dermatophagoides farinae* (≥ 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; clinically relevant history of symptomatic perennial allergic rhinitis and/or conjunctivitis caused by an allergen to which the subject is regularly exposed and sensitized; 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, β-blockers, mono amine oxidase inhibitors (MAOIs) and other drugs containing alum (e.g. antacids) taken on a daily basis; previous treatment by other allergen concomitant IT or immunotherapy with HDM 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 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® Mite mix, standardised allergen extract derived from house dust mite mix (50:50) *Dermatophagoides pteronyssinus* (Der pte) and *Dermatophagoides farinae* adsorbed on aluminium hydroxide, 600 immunologically enhanced standardised quality units (SQ+)/ml (vial A, batch number 0000136648, expiry date 31 March 2013) and 30,000 SQ+/ml (vial B, batch number 0000136649, expiry date 31 March 2013).

AVANZ® Mite mix 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: 0000136648)	**Dose ml**	**SQ+ administered**
600 SQ+/ml	0.5	300
	1	600
Vial B (batch number: 0000136649)	**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 *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* specific IgG_4 and IgE-blocking factor (secondary endpoint).
- Immediate skin response to *Dermatophagoides* mix 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 (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 patients who received at least one dose of treatment according to the International Conference on Harmonisation (ICH) intention-to-treat principle.
- The per-protocol (PP) analysis set comprised all subjects in the FAS without major protocol deviations that would affect the primary endpoint. In other words, these subjects met the screening criteria, and did not commit important protocol deviations during the trial.
- The safety analysis set 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	29.3±7.7
Male, n (%)	54 (52.9)
Ethnic origin, n (%):	
Caucasian	96 (94.1)
Hispanic	2 (2.0)
Asian	2 (2.0)
Other	2 (2.0)
Height (cm), mean±SD	169.7±10.0
Weight (kg), mean±SD	71.5±16.3
Body mass index (kg/m^2), mean±SD	24.7±4.6
Vital signs, mean±SD:	
Systolic blood pressure (mmHg)	118.4±12.9
Diastolic blood pressure (mmHg)	70.4±8.1
Heart rate (bpm)	73.5±10.5
Smoking habits, n (%):	
Non-smoker	69 (67.6)
Smoker	22 (21.6)
Previous smoker	11 (10.8)
IgE *Dermatophagoides pteronyssinus* CAP class, n (%):	
0˚	1 (1.0)
1	0 (0.0)
2	10 (9.8)
3	29 (28.4)
4	31 (30.4)
5	20 (19.6)
6	11 (10.8)
IgE *Dermatophagoides farina* CAP class, n (%):	
0*	1 (1.3)
1	0 (0.0)
2	9 (11.4)
3	28 (35.4)
4	21 (26.6)
5	13 (16.5)
6	7 (8.9)
Main concomitant illness, n (%):	
Conjunctivitis	56 (54.9)
Asthma	49 (48.0)
Rhinitis allergic	44 (43.1)

bpm, beats per minute; IgE, immunoglobulin E; SD, standard deviation.
*Subject 05-010 was withdrawn for non-fulfilment of inclusion criteria no. 5..

Pharmacodynamic results

- Treatment with AVANZ® Mite mix induced statistically significant increases in IgG_4 and in IgE-blocking factor to both *D. pteronyssinus* and *D. farinae* from visit 1 to visit 6 ($p<0.001$).
- Immediate skin reactivity (measured after 15 minutes) to *Dermatophagoides* mix decreased from visit 1 to visit 6. The cutaneous tolerance index was 1.44 (95% CI, 1.04-1.98).

Safety results

- The trial showed an acceptable safety profile for the up-dosing schedule of AVANZ® Mite mix.
- A total of 81 subjects (79.4%) reported 363 AEs during the trial. The majority of the reported AEs were mild (98.9%) or moderate (1.1%) in severity. No severe AEs were reported during the trial.
- 117 (32.2%) of the AEs reported by 52 (51.0%) subjects were considered to be related to the IMP. Most of the reported IMP-related AEs i.e. adverse drug reactions, were mild in severity (99%), did not require any modification of the IMP administration (97.4%) and fully recovered (98.2%).
- Adverse drug reactions were reported at all dosing steps (300 SQ+ to 15,000 SQ+).
- 101 local adverse drug reactions in 48 (47.1%) of subjects and 7 systemic adverse drug reactions in 5 (4.9%) of subjects were reported.
    - All local adverse drug reactions were non-serious, did not require any modification of the IMP administration, and fully recovered. The most frequently reported local adverse drug reaction was injection site reaction (25.5%), followed by (diffuse) swelling (15.7%), and itching (pruritus) (11.8%).
    - All the reported systemic adverse drug reactions were classified according to the EAACI classification as delayed, grade I, non-serious, and mild in severity. These systemic adverse drug reactions included allergic rhinitis, dyspnoea, cough and nasal obstruction.
- Two (2%) subjects withdrew due to a total of 4 AEs.
- No safety concerns were found for vital signs and physical examination.

Conclusions

Primary objective:

- The up-dosing schedule for AVANZ® Mite mix had an acceptable tolerability profile

Secondary objectives:

- Systemic adverse drug reactions classified according to the EAACI classification were reported in less than 5% of the subjects, whereas local adverse drug reactions were shown in almost 50% of the total population. Adverse drug reactions were, except for one event, mild in severity.
- Treatment with AVANZ® Mite mix induced statistically significant immunological responses in terms of increases in IgG4 and IgE-blocking factor, while it enabled immediate skin reactivity to be decreased.

Date of the report

Final, 28 June 2013.

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