Integrated Clinical Trial Report

Trial ID: AV-G-02

Trial title: AVANZ® *Phleum pratense* maintenance dose

Investigational medicinal product:	AVANZ® *Phleum pratense*
EudraCT no.:	2011-000120-15
Development phase:	II/III
Indication:	Grass pollen-induced rhinoconjunctivitis with or without asthma
First subject first visit:	19 September 2011
Last subject last visit:	21 December 2012
Signatory investigator:	[redacted], Priv. Doz. Dr. med
No. of trial sites:	53
Sponsor:	Global Clinical Development ALK-Abelló A/S Bøge Allé 6-8 DK-2970 Hørsholm Phone: +45 4574 7576
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Version:	Final
Date:	9 September 2013

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

Synopsis: AV-G-02 trial

Title of trial: AVANZ® *Phleum pratense* maintenance dose

Signatory investigator: [redacted], Priv. Doz. Dr. med

Trial sites: 53

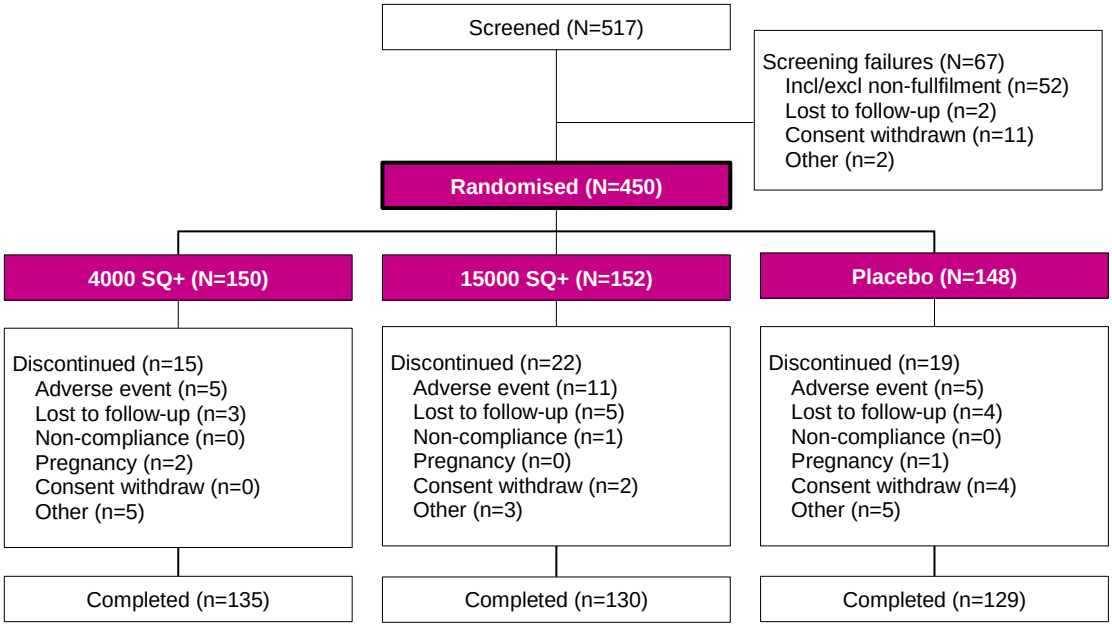
Trial period: First subject first visit – 19 September 2011
Last subject last visit – 21 December 2012

Development phase: II/III

Objectives:
Primary objective: to evaluate the efficacy of 2 dosing schedules of AVANZ® *Phleum pratense* compared to placebo in subjects suffering from grass pollen-induced allergic rhinoconjunctivitis with or without asthma. The evaluation was based on the combined rhinoconjunctivitis daily symptom score (DSS) and rhinoconjunctivitis daily medication score (DMS) during the entire grass pollen season (GPS).
Key secondary objectives: to compare efficacy between the 2 dosing schedules of AVANZ® *Phleum pratense* and placebo with respect to the average rhinoconjunctivitis DSS and DMS for the entire GPS.
Other secondary objectives: to assess the overall safety of AVANZ® *Phleum pratense* and to compare the 2 dosing schedules of AVANZ® *Phleum pratense* and placebo with respect to immunological parameters, pharmacoeconomic parameters, quality of life, asthma symptoms, and asthma medication in the GPS.

Methodology: This was a randomised (1:1:1), parallel group, double-blind, placebo-controlled, multisite trial comparing efficacy and safety of 2 dose schedules of AVANZ® *Phleum pratense* (maintenance doses of 4,000 SQ+ and 15,000 SQ+) to placebo in 5-updosing subcutaneous immunotherapy (SCIT) steps.

Number of subjects planned and analysed



Main selection criteria
Inclusion criteria:

- Written informed consent obtained before entering the trial
- Adults (≥18 to ≤64 years old) with a documented clinically relevant history of grass pollen-induced allergic rhinoconjunctivitis with or without asthma despite having received symptomatic

treatment during the GPS 2010 and 2011
- Clinical history of severe rhinoconjunctivitis interfering with usual activities or sleep, and subjects who experience an appropriate minimum level of symptoms (defined as a rhinoconjunctivitis DSS score of ≥10 on the worst day of the previous GPS) prior to randomisation
- Positive skin prick test (SPT) response (wheal diameter ≥3 mm) to *Phleum pratense*
- Positive specific IgE against *Phleum pratense* (≥IgE Class 2; ≥0.70 kU/L)
- Female subjects, who were fertile[1,2] with a negative pregnancy test and were willing to practise appropriate[3] contraceptive methods until treatment with the investigational medicinal product (IMP) has been discontinued
- Subjects who were willing and able to comply with trial protocol

Exclusion criteria:
- Clinically relevant history of symptomatic seasonal allergic rhinoconjunctivitis caused by an allergen, other than grass, overlapping the GPS. Patients with rhinoconjunctivitis caused by animal hair and dander to which they were regularly exposed to were not eligible. For patients could be sensitised to perennial allergens, e.g. house dust mites and moulds, but were not eligible if they have had symptoms induced by these allergens.
- Asthma with a reduced lung function defined as forced expiratory volume in 1 second (FEV_1) <70% of predicted value after adequate pharmacologic treatment
- Previous treatment with immunotherapy with grass pollen allergen or a cross-reacting allergen for more than 1 month within the last 5 years. Initiation of SCIT was acceptable if treatment had been discontinued before reaching maintenance dose.
- Ongoing treatment with any specific immunotherapy
- History of anaphylaxis with cardio-respiratory symptoms (food allergy, drugs or an idiopathic reaction)
- Currently treated with ACE inhibitors, β-blockers, tricyclic antidepressants, catechol-O-methyl transferase inhibitors and monoamine oxidase inhibitors
- Use of medication that was prohibited according to the specifications in the trial protocol
- Lactating women

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

IMP: AVANZ® *Phleum pratense*

Mode of administration: subcutaneous injection

Doses:

Treatment groups	Updosing phase	Maintenance phase
4000 SQ+	300; 600: 800; 1,600; 4,000 SQ+	4000 SQ+
15000 SQ+	300; 600; 3,000; 6,000; 15,000 SQ+	15000 SQ+
Placebo	Placebo in 5 steps	Placebo

Batch no.:

Vials	Batch no.	Expiry date
Vial A: ALK Flex placebo 600 SQ+/ml	137498	12.05.2013
Vial A: ALK Flex 225, *Phleum pratense* 600 SQ+/ml	138465	27.06.2013
Vial B: ALK Flex placebo 30,000 SQ+/ml	137497	12.05.2013
Vial B: ALK Flex placebo 30,000 SQ+/ml	137632	19.05.2013
Vial B: ALK Flex 225, *Phleum pratense* 8,000 SQ+/ml	138315	20.06.2013
Vial B: ALK Flex 225, *Phleum pratense* 30,000 SQ+/ml	138466	27.06.2013
Vial B: ALK Flex 225, *Phleum pratense* 30,000 SQ+/ml	137370	04.05.2013

[1] Females were considered infertile/post-menopausal when there had been no menstruation for minimum 12 months prior to randomisation.

[2] Female subjects included in Austria who were considered fertile had to agree to perform pregnancy test every 4 weeks until the end of trial visit.

[3] Adequate contraception methods included abstinence, oral contraceptives, transdermal patches or depot injection of a progesterone drug (starting at least 4 weeks prior to IMP administration), double barrier method included condom or occlusive cap (diaphragm or cervical/vault caps) plus spermicidal agent, intrauterine device, intrauterine system, implant, or vaginal ring (placed at least 4 weeks prior to IMP administration), or male partner sterilization (vasectomy with documentation of azoospermia) prior to the female subject's entry into trial and is the sole sexual partner for that female subject.

Additional therapy: The following symptomatic medications were allowed and supplied by ALK:
For rhinoconjunctivitis: desloratadine tablets, olopatadine eye drops, and fluticasone nasal spray.
For asthma: salbutamol for inhalation, and fluticasone for inhalation.

Duration of treatment: Approximately 1 year. Pre-seasonal IMP exposure was planned to include updosing and at least 2 maintenance doses.

Criteria for evaluation:

Efficacy endpoints

- Primary: combined average rhinoconjunctivitis DSS and DMS averaged over the entire GPS[4].
- Key secondary: average rhinoconjunctivitis DSS for the entire GPS and average rhinoconjunctivitis DMS for the entire GPS.
- Other secondary:
  - combined average rhinoconjunctivitis DSS and DMS for peak GPS
  - average rhinoconjunctivitis DSS for peak GPS
  - average rhinoconjunctivitis DMS for peak GPS
  - combined average weighted rhinoconjunctivitis DSS and DMS for entire and peak GPS
  - average rhinoconjunctivitis visual analogue scale (VAS) for entire and peak GPS
  - percentage of well-days for entire and peak GPS
  - maximum average rhinoconjunctivitis DSS for entire and peak GPS
  - average asthma DSS for entire and peak GPS
  - average asthma DMS for entire and peak GPS
  - percentage of severe days for entire and peak GPs
  - global evaluation of rhinoconjunctivitis

Pharmacodynamics

- Log_{10}(IgE), Log_{10}(IgG_4), and IgE-blocking factor

Pharmacoeconomic and quality of life

- EQ-5D, patient benefit index (PBI), health care utilisation, and work productivity
- Rhinoconjunctivitis quality of life questionnaire (RQLQ)

Safety

- Adverse events (AEs): serious AEs (SAEs) and IMP-related SAEs, AEs leading to discontinuation, local reaction, systemic reactions, and early/delayed reactions
- Vital signs: resting blood pressure, and heart rate
- Clinical laboratory tests: haematology, clinical chemistry, urinalysis (including level of aluminium in plasma and urine)
- Physical examination
- FEV_1

Statistical methods

3 analysis sets were defined:

- Full analysis set (FAS): all randomised subjects following the intent-to-treat ICH principle and was the primary set for efficacy analyses
- Per-protocol analysis set (PP): subjects who did not have major protocol deviations that would have affected the primary endpoint
- Safety set: all randomised subjects and was used for safety tables and listings

All statistical tests were 2-sided using a 5% significance level. The primary endpoint was analysed using a common linear mixed effect (LME) model for all treatment groups. The square root of the average combined rhinoconjunctivitis DSS and DMS was the response variable, treatment was a fixed class effect and pollen region was a random class variable. Different residual error for each treatment group was specified in the LME model. The primary outcome was the difference in (back transformed) adjusted means for each treatment group and placebo with associated p-values and

[4] Combined score for each subject was calculated as the sum of the rhinoconjunctivitis DSS and DMS during the entire GPS divided by the number of days with diary records in the entire GPS (=∑(DSS+DMS)/(Records in GPS)

95% confidence limit. The null hypothesis was that the difference in means between the active groups and the placebo group during the entire GPS was zero with the highest dose first in a test hierarchy. In addition, the relative difference of the (back transformed) adjusted means was reported together with 95% confidence limit. Supportive analyses of the primary endpoint include analysis using the same LME model based on the PP population and analysis using the same LME model and a multiple imputation method.

All statistical analyses were pre-defined in the statistical analysis plan prior to unblinding. There were no exploratory *ad hoc* analyses performed after the unblinding.

Demography of trial population

450 subjects were randomised to receive either AVANZ® 4000 SQ+ (n=150), 15000 SQ+ (n=152), or placebo (n=148). The participating countries were Austria (n=3), Germany (n=368), and Spain (n=79).

Treatment group	Placebo (N=148)		4000 SQ+ (N=150)		15000 SQ+ (N=152)		Overall (N=450)	
Sex (n,%n)								
Male	71	(48%)	82	(55%)	69	(45%)	222	(49%)
Female	77	(52%)	68	(45%)	83	(55%)	228	(51%)
Ethnic origin (n,%n)								
Caucasian	144	(97%)	143	(95%)	143	(94%)	430	(96%)
Hispanic	4	(3%)	5	(3%)	4	(3%)	13	(3%)
Other*	-	(-)	2	(2%)	5	(3%)	7	(1%)
Age (years)								
Mean (SD)	32.5 (10.0)		33.3 (10.7)		32.8 (10.8)		32.9 (10.5)	
Median	30.5		31.0		30.0		31.0	
Min–max	18–61		18–64		18–64		18–64	

N=number of subject (FAS), n=number of subjects with observations, %n=percentage of subjects with observations, SD=standard deviation

Efficacy results:

Primary efficacy

- The relative difference in the combined rhinoconjunctivitis scores for the entire GPS between:
  - 4000 SQ+ vs. placebo: 4.8% [95%CL -11.0; 18.5, FAS]; no statistically significant differences between the compared groups were observed (p=0.53).
  - 15000 SQ+ vs. placebo: 4.9% [95% CL -10.7; 18.4, FAS]; no statistically significant differences between the compared groups were observed (p=0.51).

Key secondary efficacy

- The relative difference in the average rhinoconjunctivitis DSS for the entire GPS between:
  - 4000 SQ+ vs. placebo: 7.7% [95%CL -6.6; 20.4, FAS]; no statistically significant differences between the compared groups were observed (p=0.27).
  - 15000 SQ+ vs. placebo: 9.3% [95%CL -4.9; 21.7, FAS]; no statistically significant differences between the compared groups were observed (p=0.19).
- The relative difference in the average rhinoconjunctivitis DMS for the entire GPS between:
  - 4000 SQ+ vs. placebo: 4.3% [95%CL -27.0; 28.1, FAS]; no statistically significant differences between the compared groups were observed (p=0.76).
  - 15000 SQ+ vs. placebo: 2.2% [95% CL -29.1; 25.9, FAS]; no statistically significant differences between the compared groups were observed (p=0.88).

Other secondary efficacy

- No statistically significant differences were observed between each of the 2 active groups and the placebo (p>0.05) for the following secondary endpoints:
  - Combined average rhinoconjunctivitis DSS and DMS for peak GPS
  - Average rhinoconjunctivitis DSS for peak GPS
  - Average rhinoconjunctivitis DMS for peak GPS
  - Combined average weighted rhinoconjunctivitis DSS and DMS for entire and peak GPS
  - Average rhinoconjunctivitis VAS for entire and peak GPS
  - Percentage of well-days for entire and peak GPS
  - Maximum average rhinoconjunctivitis DSS for entire and peak GPS

- Average asthma DSS for entire and peak GPS
- Average asthma DMS for entire and peak GPS
- Percentage of severe days for entire and peak GPS
- Global evaluation of rhinoconjunctivitis

Immunological response

- A statistically significant difference in the immunomodulatory effect of AVANZ® *Phleum pratense* was demonstrated by high inductions of IgE, IgG4, and IgE-blocking factor for the active groups compared with the placebo group.
- A dose-dependent increase in the immunological effect was observed. The change in the adjusted mean in the 15000 SQ+ group was higher than the 4000 SQ+ group. The changes in the immunological effect were statistically significant ($p<0.001$).

Pharmacoeconomic and quality of life

- Most subjects across all treatment groups reported via the EQ-5D questionnaires either as having 'no pain', 'no discomfort', or 'not anxious or depressed' at both screening and post-treatment visit. No major differences were observed between the active and the placebo groups.
- The overall PBI (mean, SD) for all treatment groups was 2.2 (0.9), which is considered 'relevant benefit'. Nevertheless, the differences between the active treatment group and the placebo group were not statistically significant ($p>0.05$).
- 7 (1.5%) of all subjects utilised health care services due to their rhinoconjunctivitis and/or asthma symptoms during the entire GPS 2012.
- About 75% of the subjects from each treatment group worked during GPS 2012. More subjects in the placebo group (n=22) missed work at least 1 hour during the entire GPS than subjects in the 4000 SQ+ group (n=12) and 15000 SQ+ group (n=16).
- No statistically significant differences in the RQLQ between each of the active groups and the placebo ($p>0.05$).

Safety results:

- 369 subjects (2101 AEs) reported at least 1 AE. Subjects in the 15000 SQ+ group experienced the most AEs. Most AEs (>98%) were of mild-to-moderate severity.
- 265 (1191 AEs) subjects experienced possible IMP-related AEs. Subjects in the 15000 SQ+ reported the most events.
- 214 subjects (926 AEs) experienced local reactions at the injection site. Subject from the 4000 SQ+ and 15000 SQ+ groups experienced similar number of local reactions and more than the placebo (51% vs. 54% vs. 38% of the subjects, respectively). Most of the local reactions were seen step 3 updosing for the active groups.
- 22 subjects (25 AEs) experienced systemic reaction, 18 of them were from the active group 15000 SQ+. Most the systemic reactions (20 out of 25) were delayed reactions.
- 19 (<1%) serious adverse events (SAEs) were reported, most of which were experienced by subjects from the active groups (10 in 4000 SQ+ and 7 in 15000 SQ+). The most common SAEs was preferred term (PT) *Anaphylactic reactions* with 5 events, all were possible IMP-related and all were experienced by subjects in the 15000 SQ+ group.
- 21 (<5%) subjects discontinued the trial due to AEs: almost twice as many subjects from the 15000 SQ+ as subjects from 4000 SQ+ and placebo. The most common AE leading to discontinuation was PT *Anaphylactic reaction*.
- No major differences were observed between the active groups and the placebo group in the following parameters: laboratory test, vital signs, physical examination findings, and FEV_1 measurements.
- No increase in aluminium concentration in serum and urine after almost 1 year of treatment.
- There were no reported cases of anaphylactic shock or death related to AVANZ® *Phleum pratense*.

Conclusion:

Overall, the trial did not reveal any statistically significant differences between the AVANZ® *Phleum pratense* and the placebo with respect to clinical efficacy parameters.

A dose-dependent increase in IgG4 and IgE-blocking factor was observed. The change in the adjusted mean in the 15000 SQ+ group was higher than the 4000 SQ+ group. The changes in the immunological effect were statistically significant ($p<0.001$) for both active groups. The most frequently reported IMP-related AE were mild-to-moderate local injection site reactions. Generally, subjects in the 15000 SQ+ group experienced more AEs than the subjects in the 4000 SQ+ and the placebo group did. In conclusion, an immunological response was observed in the active groups but without a corresponding clinical effect. Other factor such as the extent of the pre-seasonal treatment could have contributed to this finding, but the result was potentially influenced by the low natural pollen exposure. Overall, the tolerability profile is considered acceptable for continuing the clinical development of AVANZ® *Phleum pratense* in order to determine its potential efficacy.
Date of the summary: 9 September 2013
This trial was conducted in compliance with the principles of ICH Good Clinical Practice.