Clinical trial results:
Evaluation of the efficacy and safety of AVANZ® Phleum pratense in grass pollen-induced allergic rhinitis during controlled exposure in an environmental challenge chamber

Summary

EudraCT number	2013-005130-38
Trial protocol	DE
Global end of trial date	15 October 2015

Results information

Result version number	v2 (current)
This version publication date	05 November 2016
First version publication date	07 October 2016
Version creation reason	• Correction of full data set spelling error

Trial information

Trial identification

Sponsor protocol code	AV-G-03

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02166268
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	ALK
Sponsor organisation address	Bøge Alle 1, Hørsholm, Denmark, 2970
Public contact	Global Clinical Development, ALK, 0045 45747576, clinicaltrials@alk.net
Scientific contact	Global Clinical Development, ALK, 0045 45747576, clinicaltrials@alk.net

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 August 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 October 2015
Global end of trial reached?	Yes
Global end of trial date	15 October 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of AVANZ® Phleum pratense 15000 SQ+ compared to placebo in the treatment of grass pollen-induced allergic rhinitis using a Environmental Challenge Chamber.

Protection of trial subjects:

Safety surveillance
Access to symptomatic pharmacotherapy (except during specified washout period prior to and during ECC visits)

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 June 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 140
Worldwide total number of subjects	140
EEA total number of subjects	140

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	140
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited from 15 trial sites in Germany.
First subject first visit 5 June 2014
Last subject last visit 15 October 2015

Pre-assignment

Screening details:

Main selection criteria
- Adults (18-65 years)
- History of moderate-severe grass pollen rhinoconjunctivitis +/- asthma despite treatment with symptom-relieving medication during the previous 2 grass pollen seasons
- Positive SPT and IgE against Phleum pratense
- Minimum level of rhinitis symptoms in a grass pollen challenge (TNSS at least 6)

Period 1

Period 1 title	Trial period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Avanz

Arm description:

Active treatment group: Avanz Phleum pratense 15,000 SQ+

Arm type	Experimental
Investigational medicinal product name	Avanz
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects were randomised to either Avanz (active treatment) or placebo. Subjects randomised to active treatment received a treatment schedule comprised by an updosing phase with 5 injections and a maintenance phase with 8 maintenance injections. During the updosing phase, injections were given in 1 week intervals; once the maintenance dose was reached, the dosage interval was increased stepwise to 2, 4, and 6 weeks. Subjects randomised to placebo received matched placebo product according to the same dosing schedule, i.e. 5 injections in the updosing treatment phase followed by 8 maintenance injections.

Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects were randomised to either Avanz (active treatment) or placebo. Subjects randomised to active treatment received a treatment schedule comprised by an updosing phase with 5 injections and a maintenance phase with 8 maintenance injections. During the updosing phase, injections were given in 1 week intervals; once the maintenance dose was reached, the dosage interval was increased stepwise

to 2, 4, and 6 weeks. Subjects randomised to placebo received matched placebo product according to the same dosing schedule, i.e. 5 injections in the updosing treatment phase followed by 8 maintenance injections.

Number of subjects in period 1	Avanz	Placebo
Started	71	69
Completed	62	66
Not completed	9	3
Consent withdrawn by subject	3	2
Subject had to leave Germany for work reasons	-	1
Adverse event, non-fatal	4	-
Pregnancy	1	-
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Avanz
Reporting group description:	
Active treatment group: Avanz Phleum pratense 15,000 SQ+	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Avanz	Placebo	Total
Number of subjects	71	69	140
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	71	69	140
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	34	34	
standard deviation	± 11	± 12	-
Gender categorical Units: Subjects			
Female	35	31	66
Male	36	38	74

Subject analysis sets	
Subject analysis set title	FAS
Subject analysis set type	Full analysis

Subject analysis set description:

Full analysis set (FAS) – all randomised subjects, in accordance with the ICH intent-to-treat principle; FAS was the primary set for all efficacy analyses and for all baseline/demography tables, efficacy tables, and subject listings. The safety set was identical to FAS; the safety set was used for safety tables and subject listings.

FAS comprised 140 subjects; 71 subjects in the Avanz group and 69 subjects in the placebo group.

Reporting group values	FAS		
Number of subjects	140		
Age categorical Units: Subjects			
In utero	0		

Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	140		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean	34		
standard deviation	± 11		
Gender categorical			
Units: Subjects			
Female	66		
Male	74		

End points

End points reporting groups

Reporting group title	Avanz
Reporting group description:	
Active treatment group: Avanz Phleum pratense 15,000 SQ+	
Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
Full analysis set (FAS) – all randomised subjects, in accordance with the ICH intent-to-treat principle; FAS was the primary set for all efficacy analyses and for all baseline/demography tables, efficacy tables, and subject listings. The safety set was identical to FAS; the safety set was used for safety tables and subject listings. FAS comprised 140 subjects; 71 subjects in the Avanz group and 69 subjects in the placebo group.	

Primary: Average TNSS measured during the EOT ECC visit

End point title	Average TNSS measured during the EOT ECC visit
End point description:	
The rhinoconjunctivitis symptoms included 4 rhinitis symptoms (runny nose, blocked nose, sneezing, and itchy nose) and 2 conjunctivitis symptoms (gritty feeling/red/itchy eyes and watery eyes) which were scored from 0 to 3 as follows: 0 = no symptoms 1 = mild symptoms (i.e. symptom clearly present but hardly noticeable; easily tolerated) 2 = moderate symptoms (i.e. symptom clearly uncomfortable/bothersome but tolerable) 3 = severe symptoms (i.e. symptom that is hard to tolerate) The TNSS consisted of symptom scores from the 4 nose symptoms, resulting in a TNSS scale ranging from 0-12. TNSS was calculated pre-challenge and every 20 minutes during the 3-hour challenge in the ECC. The average TNSS at each ECC visit was calculated for each subject as the average of non-missing TNSS collected from hour 1 to 3 during the ECC session.	
End point type	Primary
End point timeframe:	
Average TNSS measured during the EOT ECC visit after approximately 11 months of treatment	

End point values	Avanz	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	69		
Units: 0-12				
least squares mean (confidence interval 95%)	4.87 (3.91 to 5.84)	5.56 (4.58 to 6.54)		

Statistical analyses

Statistical analysis title	Analysis of the average TNSS during the EOT ECC
Statistical analysis description:	
'Average TNSS during EOT ECC' is analysed using a linear mixed effect (LME) model. Treatment is a fixed class effect, TNSS at baseline ECC is a fixed regression variable and chamber cohort is a random class variable. Different residual errors for each treatment group	

is specified in the LME model. The LME model is estimated using the method of REML. The primary outcome is the difference in adjusted means between active and placebo with coherent p-values and confidence limits.

Comparison groups	Avanz v Placebo
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.112
Method	Linear mixed effect (LME) model
Parameter estimate	Mean difference (final values)
Point estimate	0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.16
upper limit	1.54

Secondary: Average TNSS measured during the M3 ECC visit

End point title	Average TNSS measured during the M3 ECC visit

End point description:

The rhinoconjunctivitis symptoms included 4 rhinitis symptoms (runny nose, blocked nose, sneezing, and itchy nose) and 2 conjunctivitis symptoms (gritty feeling/red/itchy eyes and watery eyes) which were scored from 0 to 3 as follows:
0 = no symptoms
1 = mild symptoms (i.e. symptom clearly present but hardly noticeable; easily tolerated)
2 = moderate symptoms (i.e. symptom clearly uncomfortable/bothersome but tolerable)
3 = severe symptoms (i.e. symptom that is hard to tolerate)
The TNSS consisted of symptom scores from the 4 nose symptoms, resulting in a TNSS scale ranging from 0-12. TNSS was calculated pre-challenge and every 20 minutes during the 3-hour challenge in the ECC. The average TNSS at each ECC visit was calculated for each subject as the average of non-missing TNSS collected from hour 1 to 3 during the ECC session.

End point type	Secondary

End point timeframe:

Average TNSS measured during the M3 ECC visit after approximantely 4 months of treatment.

End point values	Avanz	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	69		
Units: 0-12				
least squares mean (confidence interval 95%)	4.94 (4.23 to 5.65)	5.61 (4.88 to 6.33)		

Statistical analyses

Statistical analysis title	Analysis of the average TNSS during M3 ECC

Statistical analysis description:

'Average TNSS during M3 ECC' is analysed using a linear mixed effect (LME)

model. Treatment is a fixed class effect, TNSS at baseline ECC is a fixed regression variable and chamber cohort is a random class variable. Different residual errors for each treatment group is specified in the LME model. The LME model is estimated using the method of REML. The primary outcome is the difference in adjusted means between active and placebo with coherent p-values and confidence limits.

Comparison groups	Avanz v Placebo
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.092
Method	Linear mixed effect (LME) model
Parameter estimate	Mean difference (final values)
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.11
upper limit	1.44

Secondary: Average TSS measured during the EOT ECC visit

End point title	Average TSS measured during the EOT ECC visit

End point description:

The rhinoconjunctivitis symptoms included 4 rhinitis symptoms (runny nose, blocked nose, sneezing, and itchy nose) and 2 conjunctivitis symptoms (gritty feeling/red/itchy eyes and watery eyes) which were scored from 0 to 3 as follows:
0 = no symptoms
1 = mild symptoms (i.e. symptom clearly present but hardly noticeable; easily tolerated)
2 = moderate symptoms (i.e. symptom clearly uncomfortable/bothersome but tolerable)
3 = severe symptoms (i.e. symptom that is hard to tolerate)
The TSS consisted of symptom scores from the 4 nose symptoms and the 2 eye symptoms, resulting in a TSS scale ranging from 0-18. TSS was calculated pre-challenge and every 20 minutes during the 3-hour challenge in the ECC. The average TSS at each ECC visit was calculated for each subject as the average of non-missing TSS collected from hour 1 to 3 during the ECC session.

End point type	Secondary

End point timeframe:

Average TSS measured during the EOT ECC visit after approximately 11 months of treatment.

End point values	Avanz	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	69		
Units: 0-18				
least squares mean (confidence interval 95%)	5.85 (4.55 to 7.16)	7.1 (5.75 to 8.46)		

Statistical analyses

Statistical analysis title	Average TSS measured during the EOT ECC visit

Statistical analysis description:

'Average TSS during EOT ECC' is analysed using a linear mixed effect (LME) model. Treatment is a fixed class effect, TNSS at baseline ECC is a fixed regression variable and chamber cohort is a random class variable. Different residual errors for each treatment group is specified in the LME model. The LME model is estimated using the method of REML. The primary outcome is the difference in adjusted means between active and placebo with coherent p-values and confidence limits.

Comparison groups	Avanz v Placebo
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.038
Method	Linear mixed effect (LME) model
Parameter estimate	Mean difference (final values)
Point estimate	1.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.07
upper limit	2.43

Secondary: Average TSS measured during the M3 ECC visit

End point title	Average TSS measured during the M3 ECC visit

End point description:

The rhinoconjunctivitis symptoms included 4 rhinitis symptoms (runny nose, blocked nose, sneezing, and itchy nose) and 2 conjunctivitis symptoms (gritty feeling/red/itchy eyes and watery eyes) which were scored from 0 to 3 as follows:
0 = no symptoms
1 = mild symptoms (i.e. symptom clearly present but hardly noticeable; easily tolerated)
2 = moderate symptoms (i.e. symptom clearly uncomfortable/bothersome but tolerable)
3 = severe symptoms (i.e. symptom that is hard to tolerate)
The TSS consisted of symptom scores from the 4 nose symptoms and the 2 eye symptoms, resulting in a TSS scale ranging from 0-18. TSS was calculated pre-challenge and every 20 minutes during the 3-hour challenge in the ECC. The average TSS at each ECC visit was calculated for each subject as the average of non-missing TSS collected from hour 1 to 3 during the ECC session.

End point type	Secondary

End point timeframe:

Average TSS measured during the M3 ECC visit after approximately 4 months of treatment.

End point values	Avanz	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	69		
Units: 0-18				
least squares mean (confidence interval 95%)	6.33 (5.3 to 7.35)	7.51 (6.43 to 8.59)		

Statistical analyses

Statistical analysis title	Average TSS measured during the M3 ECC visit

Statistical analysis description:

'Average TSS during M3 ECC' is analysed using a linear mixed effect (LME) model. Treatment is a fixed class effect, TNSS at baseline ECC is a fixed regression variable and chamber cohort is a random class variable. Different residual errors for each treatment group is specified in the LME model. The LME model is estimated using the method of REML. The primary outcome is the difference in adjusted means between active and placebo with coherent p-values and confidence limits.

Comparison groups	Avanz v Placebo
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.033
Method	Linear mixed effect (LME) model
Parameter estimate	Mean difference (final values)
Point estimate	1.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	2.27

Secondary: Average TOSS measured during the EOT ECC visit

End point title	Average TOSS measured during the EOT ECC visit

End point description:

The rhinoconjunctivitis symptoms included 4 rhinitis symptoms (runny nose, blocked nose, sneezing, and itchy nose) and 2 conjunctivitis symptoms (gritty feeling/red/itchy eyes and watery eyes) which were scored from 0 to 3 as follows:
0 = no symptoms
1 = mild symptoms (i.e. symptom clearly present but hardly noticeable; easily tolerated)
2 = moderate symptoms (i.e. symptom clearly uncomfortable/bothersome but tolerable)
3 = severe symptoms (i.e. symptom that is hard to tolerate)
The TOSS consisted of symptom scores from the 2 eye symptoms, resulting in a TOSS scale ranging from 0-6. TOSS was calculated pre-challenge and every 20 minutes during the 3-hour challenge in the ECC. The average TOSS at each ECC visit was calculated for each subject as the average of non-missing TOSS collected from hour 1 to 3 during the ECC session.

End point type	Secondary

End point timeframe:

Average TOSS measured during the EOT ECC visit after approximately 11 months of treatment.

End point values	Avanz	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	69		
Units: 0-6				
least squares mean (confidence interval 95%)	0.97 (0.62 to 1.32)	1.58 (1.17 to 1.99)		

Statistical analyses

Statistical analysis title	Average TOSS measured during the EOT ECC visit

Statistical analysis description:

'Average TOSS during EOT ECC' is analysed using a linear mixed effect (LME) model. Treatment is a fixed class effect, TNSS at baseline ECC is a fixed regression variable and chamber cohort is a random class variable. Different residual errors for each treatment group is specified in the LME model. The LME model is estimated using the method of REML. The primary outcome is the difference in adjusted means between active and placebo with coherent p-values and confidence limits.

Comparison groups	Avanz v Placebo
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007
Method	Linear mixed effect (LME) model
Parameter estimate	Mean difference (final values)
Point estimate	0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.17
upper limit	1.05

Secondary: Average TOSS measured during the M3 ECC visit

End point title	Average TOSS measured during the M3 ECC visit

End point description:

The rhinoconjunctivitis symptoms included 4 rhinitis symptoms (runny nose, blocked nose, sneezing, and itchy nose) and 2 conjunctivitis symptoms (gritty feeling/red/itchy eyes and watery eyes) which were scored from 0 to 3 as follows:
0 = no symptoms
1 = mild symptoms (i.e. symptom clearly present but hardly noticeable; easily tolerated)
2 = moderate symptoms (i.e. symptom clearly uncomfortable/bothersome but tolerable)
3 = severe symptoms (i.e. symptom that is hard to tolerate)
The TOSS consisted of symptom scores from the 2 eye symptoms, resulting in a TOSS scale ranging from 0-6. TOSS was calculated pre-challenge and every 20 minutes during the 3-hour challenge in the ECC. The average TOSS at each ECC visit was calculated for each subject as the average of non-missing TOSS collected from hour 1 to 3 during the ECC session.

End point type	Secondary

End point timeframe:

Average TOSS measured during the M3 ECC visit after approximately 4 months of treatment.

End point values	Avanz	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	69		
Units: 0-6				
least squares mean (confidence interval 95%)	1.37 (0.95 to 1.8)	1.91 (1.45 to 2.37)		

Statistical analyses

Statistical analysis title	Average TOSS measured during the M3 ECC visit

Statistical analysis description:

'Average TOSS during M3 ECC' is analysed using a linear mixed effect (LME) model. Treatment is a fixed class effect, TNSS at baseline ECC is a fixed regression variable and chamber cohort is a random class variable. Different residual errors for each treatment group is specified in the LME model. The LME model is estimated using the method of REML. The primary outcome is the difference in adjusted means between active and placebo with coherent p-values and confidence limits.

Comparison groups	Avanz v Placebo
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.015
Method	Linear mixed effect (LME) model
Parameter estimate	Mean difference (final values)
Point estimate	0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	0.97

Secondary: Pre- to post-treatment change in IgG4 against Phleum pratense

End point title	Pre- to post-treatment change in IgG4 against Phleum pratense

End point description:

End point type	Secondary

End point timeframe:

Pre- to post-treatment change in IgG4 against Phleum pratense, i.e. change in levels from the screening visit to the final visit after approximately 11 months of treatment.

End point values	Avanz	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	69		
Units: 0				
least squares mean (confidence interval 95%)	1.134 (1.05 to 1.22)	0.068 (0 to 0.14)		

Statistical analyses

Statistical analysis title	Change from baseline in IgG4 (Phleum pratense)

Statistical analysis description:

Analysis via LDA with change from baseline as the response variable, treatment, visit and their two-factor interaction as fixed class variables, the immunological baseline value as a fixed regression variable, subject as a random class variable and adjusted for different error variation for each treatment group.

Comparison groups	Avanz v Placebo
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	LDA model
Parameter estimate	Mean difference (final values)
Point estimate	1.066
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.95
upper limit	1.18

Adverse events

Adverse events information

Timeframe for reporting adverse events:

During the entire trial.

Adverse event reporting additional description:

Adverse events meeting the definition of an AE were recorded and reported from the time the subject signed the informed consent and until the final visit.
An AE was defined according to ICH Harmonised Tripartite Guideline E2A, Step 5.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18

Reporting groups

Reporting group title	Placebo

Reporting group description: -

Reporting group title	Avanz

Reporting group description:

Active treatment group: Avanz Phleum pratense 15,000 SQ+

Serious adverse events	Placebo	Avanz	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 69 (1.45%)	5 / 71 (7.04%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Surgical and medical procedures			
Knee arthroplasty			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 69 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 69 (0.00%)	2 / 71 (2.82%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Urticaria			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 69 (0.00%)	2 / 71 (2.82%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteochondrosis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 69 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 69 (1.45%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo	Avanz	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	41 / 69 (59.42%)	61 / 71 (85.92%)	
Nervous system disorders			
Headache			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 69 (2.90%)	10 / 71 (14.08%)	
occurrences (all)	2	12	
General disorders and administration site conditions			
Injection site erythema			
alternative assessment type: Non-systematic			
subjects affected / exposed	14 / 69 (20.29%)	21 / 71 (29.58%)	
occurrences (all)	63	109	
Injection site nodule			
alternative assessment type: Non-systematic			

subjects affected / exposed	7 / 69 (10.14%)	1 / 71 (1.41%)	
occurrences (all)	16	1	
Injection site pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	9 / 69 (13.04%)	6 / 71 (8.45%)	
occurrences (all)	27	8	
Injection site pruritus			
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 69 (8.70%)	24 / 71 (33.80%)	
occurrences (all)	27	78	
Injection site swelling			
alternative assessment type: Non-systematic			
subjects affected / exposed	20 / 69 (28.99%)	32 / 71 (45.07%)	
occurrences (all)	86	119	
Injection site urticaria			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 69 (2.90%)	11 / 71 (15.49%)	
occurrences (all)	3	16	
Injection site warmth			
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 69 (7.25%)	12 / 71 (16.90%)	
occurrences (all)	22	62	
Respiratory, thoracic and mediastinal disorders			
Cough			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 69 (1.45%)	4 / 71 (5.63%)	
occurrences (all)	1	4	
Skin and subcutaneous tissue disorders			
Pruritus			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 69 (1.45%)	5 / 71 (7.04%)	
occurrences (all)	1	6	
Urticaria			
alternative assessment type: Non-systematic			

subjects affected / exposed	2 / 69 (2.90%)	7 / 71 (9.86%)	
occurrences (all)	2	7	
Infections and infestations			
Nasopharyngitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	15 / 69 (21.74%)	17 / 71 (23.94%)	
occurrences (all)	17	21	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 February 2014	Amendment 1 to the protocol: The following updates has been made to the protocol. Section 4.1 Inclusion Criteria • Wording of Inclusion criterion I3 altered An update of section 8 has been made to reflect that both AVANZ® Phleum pratense and the grass pollen (Dactylis glomeratis) that are used in the ECC is considered IMP. Section 8.1 IMP • Dactylis glomeratis added to the section. Dactylis glomeratis will be considered as an IMP. Section 8.2 NIMP • Section updated to reflect that the subjects will be offered an antihistamine after the grass pollen challenge in the ECC.
05 May 2014	Amendment 2 to the protocol: The following updates has been made to the protocol. Protocol synopsis: Synopsis updated to reflect that first baseline ECC visit will be conducted from end of August 2014. Section 1.2: Section updated to correct the information provided on the doses used in the pre-clinical study in mice. Section 3.1: Section updated to reflect that the first baseline ECC visit will be conducted from end of August 2014. Section 4.1: Footnote to inclusion criterion I5 updated to reflect that the that skin prick test is invalid if the reaction to the positive control is <3 mm. Section 6.3: Instructions for code break updated. Section 7: Text added to instruct the sites that the ECC visits should be postponed (or cancelled if a postponement is not possible), if the subject has taken restricted medication. Section 10: • Instructions for the procedures performed at the ECC visits updated. Pre- and post challenge interviews by physician added. • Instruction given at the post challenge interview at the ECC visits added. • Instructions for scheduling of the 3rd maintenance ECC 4visit and the EOT ECC visit added to visit 10 and 16, for subjects receiving an antihistamine before IMP treatment. Section 11.8: Section updated to reflect that vital signs will be measured before and after the grass pollen challenge at the ECC visits. Section 11.16: An column has been added to Table 10 to list the post grass pollen challenge activities performed at the ECC site. Section 11.20: Additional risk minimisation activities added. In case the subjects peak flow drops with 20 % from baseline for two consecutive measurements the subject will be offered treatment with a β2-agonist. Section 11.21: New section added to describe the risk minimisation activities performed during the ECC visit, not mentioned in section 11.16 (environmental challenge chamber) or 11.20 (peak flow). Section 13: Text on interim analysis deleted.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported