NOVARTIS

Sponsor

Novartis

Generic Drug Name

VAK694

Therapeutic Area of Trial

Seasonal rhinitis

Approved Indication

Investigational

Protocol Number

CVAK694A2201

Title

A randomized, double-blind, placebo- and calibrator-controlled exploratory study to assess the safety, tolerability, pharmacokinetics and preliminary pharmacodynamics of multiple intravenous doses of VAK694 in atopic subjects with seasonal rhinitis during natural exposure to allergen

Phase of Development

Phase IIa

Study Start/End Dates

05-Jun-2009 (FPFV) to 09-Feb-2011 (LPLV)

Study Design/Methodology

This was a multicenter, randomized, double blind, placebo and open-label calibrator controlled, parallel group study of intravenous doses of VAK694 in atopic subjects with seasonal rhinitis. VAK694 3mg/kg or matching placebo was administered once every 4 weeks for 12 weeks whilst fluticasone propionate 200 µg (calibrator) was dosed daily for 12 weeks administered prior to and during two consecutive seasons of natural ragweed allergen exposure. It was planned to recruit 60 atopic subjects with seasonal rhinitis for this study.

Centres

1 center in Canada and 1 center in USA.

Publication

None

Outcome measures

Primary outcome measures(s)

- To assess the safety and tolerability
- To assess the preliminary efficacy of multiple intravenous doses of VAK694 in atopic subjects with seasonal rhinitis during natural allergen exposure as reflected by changes in the nasal symptom subscore of the daily symptom diary score (DSDS) during the peak allergy season

Secondary outcome measures(s)

- To evaluate the pharmacokinetics
- To assess the pharmacodynamic response as reflected in serum levels of total and antigen-specific IgE and total and antigen-specific IgG
- To assess immunogenicity of multiple intravenous doses of VAK694
- To preliminary assess the efficacy as reflected in a rhinitis visual-analogue score and the use of symptom relief therapy during both the peak and entire allergy season
- To preliminary asses the durability of the pharmacodynamic response to VAK694 in atopic subjects with seasonal rhinitis during a subsequent (second) season of natural allergen exposure as reflected by symptoms and biomarkers of immunomodulation

Test Product (s), Dose(s), and Mode(s) of Administration

VAK694 3 mg/kg kg given via IV every 4 weeks for 12 weeks in Season 1 and 2.

Statistical Methods

Data for DSDS and its subscales were averaged over each weekly period from the first day of the ragweed allergy season prior to statistical analysis. Comparisons of the weekly averaged DSDS and subscales were made between VAK694 and placebo, and between fluticasone propionate and placebo, using a repeated measures analysis of covariance approach with baseline value as a continuous covariate, treatment as a fixed factor, day as repeated factor within subject and the treatment by day interaction.

In addition, DSDS and its subscales were determined over the peak ragweed allergy season from the daily pollen counts by calculating an area under the curve (AUC), and compared between VAK694 and placebo, and between fluticasone propionate and placebo treatments, using an analysis of covariance with the baseline value as a continuous covariate and treatment as a fixed factor. One-sided P values (α=0.1) were presented. In addition, the posterior density of the treatment differences for DSDS and its subscales were obtained.

Study Population: Inclusion/Exclusion Criteria and Demographics

Key Inclusion Criteria:

- Male or female adults of non-child bearing potential aged between 18-60 years of age
- Male patients were required to use a double-barrier local contraception
- BMI within 18-32 kg/m2.
- Subjects must have a history of atopy, defined as a history of seasonal allergic rhinitis for at least 2 years and evidence of atopy, defined as a positive skin prick test to ragweed allergen.

Key Exclusion criteria:

- treatment with intranasal corticosteroids within 28 days of baseline,
- history of asthma with inhaled or systemic corticosteroid treatment within 6 months of baseline,
- history of COPD,
- previous exposure to human monoclonal antibodies,
- allergy immunotherapy within 1 year of screening,
- ragweed specific allergy immunotherapy within 5 years prior to screening unless those treated >2 years previously were symptomatic in the most recent ragweed season,
- nasal symptom sub-score on the DSDS>4 with any individual score >1 at screening or baseline,
- FEV1 <70% of predicted at screening or baseline,
- history of clinically significant ECG or cardiac abnormalities,
- history of clinically significant drug allergy, hypersensitivity to the study drugs or to similar drugs,
- positive tuberculin test at screening,
- history of autoimmune disease,
- history of cancer or
- concurrent administration of live vaccines.

Participant Flow

Subject disposition[a]

	VAK694 3mg/kg n (%)	Placebo n (%)	Nasal steroid n (%)	Total n (%)
Season 1	**N=12**	**N=13**	**N=5**	**N=30**
Completed	10 (83)	10 (77)	5 (100)	25 (83)
Discontinued	2 (17)	3 (23)	0	5 (17)
Main cause of discontinuation in Season 1				
Adverse event(s)	1 (8)	0	0	1 (3)
Subject withdrew consent	0	2 (15)	0	2 (7)
Loss to follow-up	0	1 (8)	0	1 (3)
Protocol deviation	1 (8)	0	0	1 (3)
Season 2	**N=7**	**N=8**	**N=9**	**N=24**
Completed	6 (86)	8 (100)	9 (100)	23 (96)
Discontinued	1 (14)	0	0	1 (4)
Main cause of discontinuation in Season 2				
Subject withdrew consent	1 (14)	0	0	1 (4)

[a] The study planned to enroll 60 subjects; only 30 subjects were recruited in Season 1. Nineteen subjects continued into season 2 and an additional 5 subjects were recruited to the nasal steroid group at the beginning of season 2, for a total of 24 subjects participating in Season 2.

Baseline Characteristics

Demographic summary by treatment group (Safety analysis set)

		VAK694 3 mg/kg N=12	Placebo N=13	Nasal steroid N=10	All subjects N=35
Age (years)	Mean (SD)	38 (13.4)	43 (9.5)	40 (11.9)	41 (11.4)
	Range	20 – 60	24 – 60	22 – 55	20 – 60
Gender – n (%)	Male	11 (92%)	11 (85%)	9 (90%)	31 (89%)
	Female	1 (8%)	2 (15%)	1 (10%)	4 (11%)
Race – n (%)	Caucasian	11 (92%)	9 (69%)	8 (80%)	28 (80%)
	Black	1 (8%)	3 (23%)	1 (10%)	5 (14%)
	Native American	0	0	1 (10%)	1 (3%)
	Other	0	1 (7%)	0	1 (3%)
Height (cm)	Mean (SD)	175 (7.4)	176 (6.4)	175 (6.9)	176 (6.7)
	Range	165 – 191	168 – 192	159 – 182	159 – 192
Weight (kg)	Mean (SD)	77.9 (8.24)	77.4 (10.59)	84.5 (9.30)	79.6 (9.72)
	Range	62.5 – 96.5	62.5 – 100.5	72.0 – 98.0	62.5 – 100.5
BMI (kg/m^2)	Mean (SD)	25.3 (2.66)	24.8 (2.19)	27.6 (2.38)	25.8 (2.61)
	Range	22.8 – 30.7	20.6 – 28.4	22.8 – 31.2	20.6 – 31.2

BMI = body mass index

Outcome measures

All subjects were included in the safety and PD analysis sets and all subjects treated with active drugs (i.e. VAK694 or nasal steroid) were included in the PK analysis set.

Primary Outcome Result(s)

Summary of the statistical analysis of DSDS nasal sub-score AUCs over the peak allergy period in each season[a] (PD analysis set)

				Comparison with placebo	
Season	Treatment	N	LS Mean (SE)	Difference (90% CI)	P value[b]
1	Placebo	13	2.13 (0.60)		
	VAK694 3 mg/kg	11	2.27 (0.65)	0.14 (-1.37, 1.65)	0.56[b]
	Nasal steroid	5	1.16 (0.98)	-0.97 (-2.93, 0.99)	0.20
2	Placebo	8	2.47 (0.70)		
	VAK694 3 mg/kg	7	2.59 (0.75)	0.11 (-1.66, 1.89)	0.54[b]
	Nasal steroid	9	0.81 (0.66)	-1.66 (-3.34, 0.02)	0.052

[a] Pollen counts in the 2009 season (season 1) were low compared to previous years, but the counts were higher in 2010 (season 2).
[b] one-sided P value to be compared to 0.1 threshold for significance; [b] primary comparison;

Secondary Outcome Result(s)

Summary pharmacokinetic parameters of VAK694 in season 1 following 4 sequential doses of 3mg/kg via 1 hour i.v. infusion at 28 day intervals.

Parameter		Dose 1 (n=12)	Dose 4 (n=11)
Cmax (µg/mL)	Mean (SD)	58.3 (10.4)	77.7 (9.60)
	Range	38.8 – 75.8	60.1 – 91.8
	CV (%)	17.8	12.4
Tmax (hr)	Median (SD)	2.00	3.83
	Range	1.17 – 4.22	0.833 – 4.13
	CV (%)	41.2	37.3
Cmax ratio	Mean (SD)	-	1.37 (0.20)
	Range	-	1.10 – 1.77
	CV (%)	-	14.7

Summary pharmacokinetic parameters of VAK694 in season 2 following 4 sequential doses of 3mg/kg via 1 hour i.v. infusion at 28 day intervals.

Parameter		Dose 1 (n=7)	Dose 4 (n=7)
Cmax (µg/mL)	Mean (SD)	69.3 (12.8)	80.3 (10.6)
	Range	51.9 – 89.7	67.1 – 92.9
	CV (%)	18.4	13.2
Tmax (hr)	Median (SD)	2.30	2.08
	Range	1.88 – 4.25	0.917- 4.08
	CV (%)	37.2	47.2

Cmax ratio	Mean (SD)	-	1.18 (0.15)
	Range	-	1.00 – 1.42
	CV (%)	-	12.8

Immunogenicity:

	VAK694 N=12	Placebo N=13
Number of pts with detectable Antibodies to VAK694 before treatment	0	1
Number of pts with detectable Antibodies to VAK694 after treatment	0	1

Summary tables were not produced for the other secondary outcome measures. Below is a brief written summary of the data.

Summary of serum levels of total and antigen-specific IgE and total and antigen-specific IgG

No effect of VAK694 was seen on serum levels of allergen-specific IgE or IgG.

Summary of rhinitis visual-analogue scores

These data are highly variable with the majority of subjects within each treatment group having low scores. Mean scores increased from Day 1 to Day 43 or 57 and then reduced again in both seasons with very little difference evident between the treatment groups. Means were never greater than 30 at any time point reflecting that the subjects had little rhinitis during either season.

Summary of Biomarker of immunomodulation

Trends for reduced expression of IL-4 and increased expression of IFNγ on ELISPOT in season 1 were not observed in season 2, and there was no consistent effect of VAK694 on Th1/Th2 balance as judged by ELISPOT. Treatment with VAK694 did not elicit a consistent or significant effect on expression of prototypical Th1 and Th2 genes in PBMC, nor did it significantly affect T cell subsets

Safety Results

Adverse Events by System Organ Class

	VAK694 3mg/kg N=12 n (%)	Placebo N=13 n (%)	Nasal steroid N=10 n (%)
Patients with at least one AE	11 (92)	11 (85)	7 (70)
Primary system organ class			
Infections & infestations	5 (42)	6 (46)	3 (30)
Nervous system disorders	4 (33)	4 (31)	2 (20)
Respiratory, thoracic & mediastinal disorders	4 (33)	4 (31)	2 (20)
Injury, poisoning and procedural complications	4 (33)	1 (8)	4 (40)
Musculoskeletal & connective tissue disorders	4 (33)	3 (23)	0
Gastrointestinal disorders	3 (25)	3 (23)	0
General disorders & administration site conditions	3 (25)	2 (15)	1 (10)
Skin & subcutaneous tissue disorders	0	3 (23)	2 (20)
Eye disorders	1 (8)	1 (8)	1 (10)
Reproductive system & breast disorders	1 (8)	1 (8)	0
Blood and lymphatic system disorders	1 (8)	0	0
Ear and labyrinth disorders	0	0	1 (10)
Investigations	1 (8)	0	0
Psychiatric disorders	0	1 (8)	0

Most Frequently Reported AEs Overall by Preferred Term n (%)*

	VAK694 3mg/kg	Placebo	Nasal steroid
	N=12	N=13	N=10
	n (%)	n (%)	n (%)
Patients with at least one AE	11 (92)	11 (85)	7 (70)
Preferred term			
Headache	3 (25)	4 (31)	2 (20)
Nasopharyngitis	4 (33)	3 (23)	1 (10)
Fatigue	1 (8)	2 (15)	1 (10)
Nasal congestion	1 (8)	2 (15)	1 (10)
Arthralgia	3 (25)	0	0
Dental caries	2 (17)	1 (8)	0
Nausea	1 (8)	2 (15)	0
Procedural pain	2 (17)	0	1 (10)
Chest discomfort	2 (17)	0	0
Oropharyngeal pain	2 (17)	0	0

* experienced by at least 2 subjects in any one group – Safety analysis set. AEs by preferred terms are presented in descending order of frequency in total group.

Serious Adverse Events and Deaths

	VAK694 N=12	Placebo N=13	Nasal steroid N=10
Number (%) of subjects with serious or other significant events			
Death	0	0	0
SAE(s)	1*	0	0
Discontinued due to SAE(s)	0	0	0

*Hospitalization for appendicitis 85 days after last administration of study drug. Not suspected to be related to study drug

Other Relevant Findings

Summary of the statistical analysis of FEV_1 AUCs (L) over the peak allergy period in each season (PD analysis set)

				Comparison with placebo	
Season	Treatment	N	LS Mean (SE)	Difference (90% CI)	P value[a]
1	Placebo	8	3.30 (0.31)		
	VAK694 3 mg/kg	8	3.41 (0.31)	0.12 (-0.64, 0.87)	0.40
	Nasal steroid	5	3.18 (0.39)	-0.11 (-0.99, 0.76)	0.59
2	Placebo	7	3.02 (0.22)		
	VAK694 3 mg/kg	6	2.89 (0.26)	-0.12 (-0.72, 0.47)	0.64
	Nasal steroid	9	3.29 (0.20)	0.28 (-0.25, 0.80)	0.19

[a] one-sided P value to be compared to 0.1 threshold for significance.

Date of Clinical Trial Report

20 Jan 2012

Date Inclusion on Novartis Clinical Trial Results Database

14 Jun 2012

Date of Latest Update

14 Jun 2012