NOVARTIS

Sponsor Novartis
Generic Drug Name VAK694
Therapeutic Area of Trial Seasonal Allergic Rhinitis
Approved Indication Investigational
Protocol Number CVAK694A2205
Title Randomized, double-blind, placebo-controlled trial to determine the capacity of VAK694 to elicit long term immune tolerance when combined with subcutaneous allergen immunotherapy for the treatment of seasonal allergic rhinitis
Phase of Development Phase IIa
Study Start/End Dates Study initiation date: 19 Nov 2009 (first subject first visit) Study completion date: 20 Oct 2011 (last subject last visit)
Study Design/Methodology This study was a randomized, double-blind, placebo-controlled parallel group study of intravenous doses of VAK694 with simultaneous intermediate-dose grass-pollen specific immunotherapy (SCIT) in grass pollen-allergic subjects. VAK694 was administered intravenously as an infusion prior to the start of the grass-pollen allergy season. Subcutaneous doses of intermediate-dose grass-pollen SCIT were also administered during this period. The study consisted of three parallel treatment groups, VAK694 + SCIT, Placebo to VAK694 + SCIT and Placebo to VAK694 + Placebo to SCIT. The study planned to enroll a total of 39 subjects with a history of seasonal grass pollen-induced allergic rhinitis (13 per treatment group).
Centers 1 site in 1 Country (UK) Imperial College, Dovehouse Street, London SW3 6LY, United Kingdom
Publication None

Outcome measures

Primary outcome measures

- Change from baseline in the intradermal late phase response (LPR) (mean swelling diameter and area) to assess the induction of sustained tolerance to allergen when VAK694 is combined with subcutaneous (SC) immunotherapy for the treatment of grass pollen allergy.
- Safety and tolerability of VAK694 when administered in the context of SCIT

Secondary outcome measures

- Changes in symptoms of seasonal allergic rhinitis measured by:
    - The mini-Respiratory Quality of Life Questionnaire (RQLQm)
    - A rhinitis visual analogue scale (VAS) total score
    - Allergy season retrospective global rating
- Modulation of the immune response as evidenced by
    - Induction of regulatory T cells
    - Down regulation of Th2 cells,
    - Decrease in the seasonal rise in allergen-specific IgE
    - Induction of specific antigen-binding neutralizing antibodies (IgG4)
    - Inhibition of facilitated antigen binding (FAB)
- Differences between treatment groups in the side-effects of SCIT
- Antibody responses to immunization (While all subjects received immunization to influenza prior to receiving the first dose of VAK694, the assessment schedule did not include collection of blood for measurement of antibody responses. Thus, the study did not assess antibody responses to immunization)

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

VAK694 (3 mg/kg) or placebo was administered every four weeks as an intravenous (i.v.) infusion over one hour, using an infusion pump. A total of 4 doses were planned to be administered for the duration of the study.

Alutard Avanz (Phleum Pratense) was administered subcutaneously on a weekly basis in accordance with the manufacturer's instructions up to a maintenance dose of 30,000 SQ. A total of 13 doses were planned to be administered.

Statistical Methods

Pharmacodynamic analyses: The primary endpoint was the change from baseline in the intradermal late phase response (mean swelling diameter and area). It was analyzed using a linear mixed effect model with fixed effects for treatment (VAK694 3 mg/kg + SCIT, VAK694 placebo + SCIT, VAK694 placebo + SCIT placebo), time of measurement (categorized according to visits), and a treatment*time interaction. The baseline values were included in the model as a covariate to correct for differences in the baseline late phase response. An unstructured covariance matrix was employed to allow for correlation of measurements obtained on the same subject over time. Contrasts for treatment group differences at the different time points were provided together with 95% confidence intervals. Differences were tested for statistical significance at the two-sided 5% alpha level. The primary comparison was the comparison of the VAK694 3 mg/kg + SCIT group vs. the VAK694 placebo + SCIT group at Visit 25, one year after completion of treatment with VAK694 + SCIT.

In addition, the posterior density of the treatment differences for late phase response, were

obtained from the model. The level of confidence for the ratio of LS means being less than or equal to 1 (0.9, 0.8, 0.7, 0.6, 0.5) were calculated, with values <1 indicating VAK694 + SCIT is better than SCIT.

The change from baseline in the Mini RQLQm total score, change from baseline in Rhinitis VAS total score and the allergy season retrospective global rating were analyzed in the same way as the primary endpoint. Frequency counts were provided for the allergy season retrospective global rating.

Total IL-4 percent change from baseline was planned to be calculated for each time point and summarized by descriptive statistics. However, we only presented the summary of descriptive statistics at each timepoint, because IL-4 was not detected at baseline.

All information obtained on adverse events was displayed by treatment group and subject. All laboratory data were listed by treatment and subject, and if ranges were available abnormalities were flagged and a listing of laboratory values out of the normal range were provided.

Spirometry measurements were listed and summarized by descriptive statistics. Immunogenicity testing results were listed.

Pharmacokinetic parameters were determined using non-compartmental methods using WinNonlin Pro (Version 5.2).

Interim analysis: The first interim analysis was planned to review the safety, efficacy, biomarker and pharmacokinetics/pharmacodynamic (PK/PD) data during the study at the end of the grass pollen allergy season. The purpose of this analysis was for inferential learning of the parameters, for hypothesis generation and for determination of the ability of the study to meet the secondary and exploratory endpoints with respect to immunomodulation to enable the initiation of activities for further studies. Hypothesis testing with respect to clinical endpoints was performed, but due to the exploratory character of this study no multiplicity adjustments were done. Subjects were asked to monitor symptoms and medication use during the second grass pollen allergy season if the interim analysis suggested either significant suppression of the LPR or improvement in clinical symptoms of allergy during the pollen season in those receiving VAK694. If it was decided to monitor symptoms during the second allergy season, a second interim analysis was planned to be done before the start of the second allergy season (Visit 25) to evaluate the primary endpoint of the study.

Study Population: Inclusion/Exclusion Criteria and Demographics

The study population comprised of the following subjects, who had passed screening assessments, complied with inclusion / exclusion criteria and has provided written informed consent:

- Subjects with history of atopy, defined as a history of seasonal allergic rhinitis for at least 2 years (in relation to the grass pollen allergy season), and evidence of atopy, defined as a positive skin prick test (wheal difference allergen – negative control at least 3 mm) to grass pollen allergen at screening.
- Male or female subjects aged between 18 and 60 years (inclusive) and in good health as determined by past medical history, physical examination, vital signs, electrocardiogram and laboratory tests.
- Female subjects of non-childbearing potential (women who were postmenopausal or permanently sterilized (e.g. tubal occlusion, hysterectomy, bilateral salpingectomy). Last menstrual bleeding or surgical sterilization procedures (requiring clinical documentation) were noted in the Relevant Medical History / Current Medical Conditions section of the Case Report Form (CRF).

- Male subjects using two highly effective methods of contraception, (e.g. a barrier method condom or occlusive cap plus spermicide) plus ensuring use by the female partner of a second method of contraception. These measures were required to be in place and males were required to refrain from fathering a child in the three (3) months following the last study drug administration.
- Subjects weighing at least 50 kg with a body mass index (BMI) within the range of 18 to 32 kg/m^2 (inclusive).
- Able to communicate well with the investigator, to understand and comply with the requirements of the study.
- Subjects must have provided written informed consent prior to study participation.

Subjects treated with intranasal corticosteroids within 28 days prior to the first dose, subjects with history of asthma and treated with inhaled or systemic corticosteroids within 6 months of the first dose, subjects with history of chronic obstructive pulmonary disease (COPD) and smokers were excluded from entry into or continuation in the study.

Participant Flow

	VAK694 + SCIT N=12 n (%)	SCIT N=12 n (%)	Placebo N=13 n (%)	All Treatment N=37 n (%)
Screenings				66
Patients				
Randomized	12 (100)	12 (100)	13 (100)	37 (100)
. Completed	10 (83.3)	11 (91.7)	12 (92.3)	33 (89.2)
. Discontinued	2 (16.7)	1 (8.3)	1 (7.7)	4 (10.8)
Main cause of discontinuation				
. Lost to follow-up	1 (8.3)		1 (7.7)	2 (5.4)
. Administrative problems		1 (8.3)		1 (2.7)
. Protocol deviation	1 (8.3)			1 (2.7)

Baseline Characteristics

		VAK694 + SCIT N=12	SCIT N=12	Placebo N=13	Total N=37
Age (years)	Mean (SD)	31.8 (10.84)	34.1 (11.74)	37.5 (11.67)	34.6 (11.36)
	Median	29.5	29.5	37.0	32.0
	Range	22, 54	23, 56	21, 56	21, 56
Height (cm)	Mean (SD)	179.33 (7.101)	176.42 (7.971)	181.15 (8.980)	179.03 (8.102)
	Median	179.00	178.00	180.00	180.00
	Range	168.0, 195.0	159.0, 185.0	166.0, 196.0	159.0, 196.0
Weight (kg)	Mean (SD)	84.65 (14.390)	76.60 (13.851)	85.88 (15.295)	82.41 (14.741)
	Median	86.00	77.00	89.00	81.00
	Range	60.0, 106.0	55.0, 102.0	54.0, 109.0	54.0, 109.0
BMI (kg/m^2)	Mean (SD)	26.24 (3.566)	24.49 (3.291)	26.13 (4.156)	25.62 (3.690)
	Median	26.62	24.19	27.17	25.72
	Range	21.3, 32.4	18.2, 30.0	19.6, 31.5	18.2, 32.4
Sex	Male	12 (100.0 %)	11 (91.7 %)	12 (92.3 %)	35 (94.6 %)
	Female		1 (8.3 %)	1 (7.7 %)	2 (5.4 %)
Predominant Race	Caucasian	9 (75.0 %)	7 (58.3 %)	12 (92.3 %)	28 (75.7 %)
	Black	1 (8.3 %)	2 (16.7 %)		3 (8.1 %)
	Asian	1 (8.3 %)	3 (25.0 %)	1 (7.7 %)	5 (13.5 %)
	Other	1 (8.3 %)			1 (2.7 %)
Ethnicity	Other	10 (83.3 %)	8 (66.7 %)	12 (92.3 %)	30 (81.1 %)
	Indian (India subc)	1 (8.3 %)	2 (16.7 %)	1 (7.7 %)	4 (10.8 %)
	Mixed ethnicity	1 (8.3 %)	1 (8.3 %)		2 (5.4 %)

Baseline LPR (area) (mm^2)	Mean (SD)	13360.8 (1742.37)	10983.4 (2837.79)	11477.3 (4375.66)	11928.0 (3290.21)
	Median	12948.0	10540.5	11784.0	12192.0
	Range	10921, 17050	5877, 15529	5408, 18961	5408, 18961
Baseline LPR (diameter) (mm)	Mean (SD)	135.2 (9.46)	120.8 (15.64)	124.8 (20.45)	126.9 (16.68)
	Median	135.5	119.0	127.0	129.0
	Range	121, 155	92, 146	86, 158	86, 158
Baseline VAS	Mean (SD)	16.3 (18.71)	18.9 (23.24)	26.9 (36.12)	20.9 (27.08)
	Median	10.5	11.0	13.0	12.0
	Range	0, 55	0, 78	0, 117	0, 117
Baseline RQLQm	Mean (SD)	3.1 (3.40)	7.3 (8.91)	5.7 (5.12)	5.4 (6.32)
	Median	2.5	4.0	4.5	3.5
	Range	0, 11	0, 32	0, 17	0, 32

Primary Outcome measures

Statistical analysis of changes from baseline in late phase response - Parameter: area (mm^2)

Visit	Treatment effect /contrast	n	LS mean (SE)	Difference (SE)	95% CI	P-value (2-sided)
VISIT19	VAK694 + SCIT	11	-9985.0 (1001.65)			
	SCIT	11	-9124.8 (992.72)			
	Placebo	13	-2938.5 (913.55)			
	(VAK694 + SCIT) - SCIT			-860.2 (1426.64)	(-3775.8, 2055.5)	0.551
	(VAK694 + SCIT) - Placebo			-7046.5 (1371.92)	(-9850.0, -4243.0)	<.001
	SCIT - Placebo			-6186.3 (1341.13)	(-8932.8, -3439.9)	<.001
VISIT24	VAK694 + SCIT	11	-8822.4 (1078.32)			
	SCIT	11	-8128.7 (1071.34)			
	Placebo	12	-4967.4 (1015.63)			
	(VAK694 + SCIT) - SCIT			-693.7 (1535.26)	(-3822.1, 2434.7)	0.654
	(VAK694 + SCIT) - Placebo			-3855.0 (1494.75)	(-6899.5, -810.4)	0.015
	SCIT - Placebo			-3161.3 (1469.67)	(-6159.8, -162.7)	0.039
VISIT25	VAK694 + SCIT	11	-8600.6 (989.06)			
	SCIT	11	-6909.2 (977.11)			
	Placebo	12	-4061.4 (928.01)			
	(VAK694 + SCIT) - SCIT			-1691.4 (1406.96)	(-4559.6, 1176.8)	0.238
	(VAK694 + SCIT) - Placebo			-4539.2 (1370.56)	(-7332.2, -1746.2)	0.002
	SCIT - Placebo			-2847.8 (1340.57)	(-5583.4, -112.2)	0.042
VISIT26	VAK694 + SCIT	11	-7521.2 (1155.64)			
	SCIT	9	-7596.3 (1220.05)			

	Placebo	12	-5250.2 (1091.33)			
	(VAK694 + SCIT) - SCIT			75.1 (1694.29)	(-3376.5, 3526.8)	0.965
	(VAK694 + SCIT) - Placebo			-2270.9 (1602.31)	(-5543.1, 1001.3)	0.167
	SCIT - Placebo			-2346.1 (1630.77)	(-5675.6, 983.5)	0.161

Statistical analysis of % suppression in late phase response - Parameter: % suppression in Area

Visit	Treatment effect /contrast	n	LS mean (SE)	Difference (SE)	95% CI	P-value (2-sided)
VISIT19	VAK694 + SCIT	11	79.7 (7.90)			
	SCIT	11	76.0 (7.76)			
	Placebo	13	21.6 (7.14)			
	(VAK694 + SCIT) - SCIT			3.7 (11.21)	(-19.1, 26.6)	0.741
	(VAK694 + SCIT) - Placebo			58.2 (10.79)	(36.2, 80.1)	<.001
	SCIT - Placebo			54.4 (10.48)	(33.0, 75.8)	<.001
VISIT24	VAK694 + SCIT	11	69.5 (10.97)			
	SCIT	11	68.1 (10.90)			
	Placebo	12	35.2 (10.39)			
	(VAK694 + SCIT) - SCIT			1.4 (15.56)	(-30.4, 33.1)	0.931
	(VAK694 + SCIT) - Placebo			34.3 (15.19)	(3.3, 65.3)	0.031
	SCIT - Placebo			32.9 (15.02)	(2.2, 63.6)	0.036
VISIT25	VAK694 + SCIT	11	67.0 (9.84)			
	SCIT	11	59.2 (9.72)			
	Placebo	12	27.9 (9.30)			
	(VAK694 + SCIT) - SCIT			7.8 (13.95)	(-20.7, 36.2)	0.582
	(VAK694 + SCIT) - Placebo			39.1 (13.63)	(11.3, 66.9)	0.007
	SCIT - Placebo			31.3 (13.41)	(3.9, 58.7)	0.026
VISIT26	VAK694 + SCIT	11	59.2 (11.37)			
	SCIT	9	61.0 (11.75)			
	Placebo	12	36.2 (10.78)			
	(VAK694 + SCIT) - SCIT			-1.8 (16.42)	(-35.3, 31.7)	0.914
	(VAK694 + SCIT) - Placebo			23.0 (15.75)	(-9.1, 55.2)	0.154
	SCIT - Placebo			24.8 (15.92)	(-7.7, 57.3)	0.129

Statistical analysis of changes from baseline in late phase response - Parameter: Average diameter (mm)

Visit	Treatment effect /contrast	n	LS mean (SE)	Difference (SE)	95% CI	P-value (2-sided)
VISIT19	VAK694 + SCIT	11	-77.3 (7.58)			
	SCIT	11	-68.7 (7.49)			
	Placebo	13	-21.5 (6.85)			
	(VAK694 + SCIT) - SCIT			-8.6 (10.88)	(-30.8, 13.6)	0.437
	(VAK694 + SCIT) - Placebo			-55.8 (10.38)	(-77.0, -34.6)	<.001
	SCIT - Placebo			-47.2 (10.05)	(-67.8, -26.6)	<.001
VISIT24	VAK694 + SCIT	11	-68.9 (9.27)			
	SCIT	11	-60.5 (9.23)			
	Placebo	12	-36.1 (8.70)			
	(VAK694 + SCIT) - SCIT			-8.4 (13.26)	(-35.4, 18.6)	0.532
	(VAK694 + SCIT) - Placebo			-32.8 (12.82)	(-58.9, -6.7)	0.015

	SCIT - Placebo			-24.4 (12.61)	(-50.1, 1.3)	0.062
VISIT25	VAK694 + SCIT	11	-65.6 (8.70)			
	SCIT	11	-51.5 (8.59)			
	Placebo	12	-30.1 (8.13)			
	(VAK694 + SCIT) - SCIT			-14.2 (12.42)	(-39.5, 11.1)	0.262
	(VAK694 + SCIT) - Placebo			-35.6 (12.02)	(-60.1, -11.1)	0.006
	SCIT - Placebo			-21.4 (11.76)	(-45.4, 2.6)	0.079
VISIT26	VAK694 + SCIT	11	-55.9 (9.48)			
	SCIT	9	-56.0 (10.01)			
	Placebo	12	-40.0 (8.91)			
	(VAK694 + SCIT) - SCIT			0.1 (13.97)	(-28.3, 28.5)	0.993
	(VAK694 + SCIT) - Placebo			-15.9 (13.13)	(-42.6, 10.9)	0.236
	SCIT - Placebo			-16.0 (13.33)	(-43.2, 11.2)	0.240

Statistical analysis of % suppression in late phase response - Parameter: % suppression in Average diameter

Visit	Treatment effect /contrast	n	LS mean (SE)	Difference (SE)	95% CI	P-value (2-sided)
VISIT19	VAK694 + SCIT	11	59.0 (5.85)			
	SCIT	11	53.9 (5.76)			
	Placebo	13	16.1 (5.27)			
	(VAK694 + SCIT) - SCIT			5.1 (8.38)	(-12.0, 22.2)	0.550
	(VAK694 + SCIT) - Placebo			42.8 (8.00)	(26.5, 59.1)	<.001
	SCIT - Placebo			37.8 (7.74)	(22.0, 53.6)	<.001
VISIT24	VAK694 + SCIT	11	52.6 (7.74)			
	SCIT	11	47.8 (7.72)			
	Placebo	12	26.8 (7.29)			
	(VAK694 + SCIT) - SCIT			4.9 (11.06)	(-17.6, 27.4)	0.663
	(VAK694 + SCIT) - Placebo			25.8 (10.71)	(4.0, 47.7)	0.022
	SCIT - Placebo			21.0 (10.57)	(-0.6, 42.5)	0.056
VISIT25	VAK694 + SCIT	11	49.7 (6.90)			
	SCIT	11	41.1 (6.80)			
	Placebo	12	23.3 (6.46)			
	(VAK694 + SCIT) - SCIT			8.6 (9.83)	(-11.4, 28.7)	0.387
	(VAK694 + SCIT) - Placebo			26.4 (9.53)	(7.0, 45.9)	0.009
	SCIT - Placebo			17.8 (9.33)	(-1.2, 36.9)	0.066
VISIT 26	VAK694 + SCIT	11	42.8 (7.58)			
	SCIT	9	43.0 (7.95)			
	Placebo	12	30.4 (7.13)			
	(VAK694 + SCIT) - SCIT			-0.3 (11.11)	(-22.9, 22.3)	0.979
	(VAK694 + SCIT) - Placebo			12.4 (10.49)	(-9.0, 33.8)	0.246
	SCIT - Placebo			12.7 (10.63)	(-9.0, 34.4)	0.241

Safety and tolerability of VAK694 when administered in the context of SCIT

See safety section

Secondary Outcome Results

Statistical analysis of changes from baseline in total rhinitis VAS score

Visit	Treatment effect /contrast	n	LS mean (SE)	Difference (SE)	95% CI	P-value (2-sided)
VISIT21	VAK694 + SCIT	11	28.7 (9.17)			
	SCIT	10	17.3 (9.51)			
	Placebo	13	46.0 (8.45)			
	(VAK694 + SCIT) - SCIT			11.4 (13.19)	(-15.6, 38.3)	0.396
	(VAK694 + SCIT) - Placebo			-17.3 (12.56)	(-42.9, 8.4)	0.179
	SCIT - Placebo			-28.6 (12.76)	(-54.7, -2.6)	0.033
VISIT22	VAK694 + SCIT	12	94.6 (25.57)			
	SCIT	10	107.9 (28.01)			
	Placebo	12	99.0 (25.63)			
	(VAK694 + SCIT) - SCIT			-13.3 (37.92)	(-90.7, 64.0)	0.728
	(VAK694 + SCIT) - Placebo			-4.4 (36.21)	(-78.3, 69.4)	0.904
	SCIT - Placebo			8.9 (37.97)	(-68.5, 86.3)	0.816
VISIT23	VAK694 + SCIT	11	29.6 (10.40)			
	SCIT	10	27.7 (10.85)			
	Placebo	12	34.4 (9.94)			
	(VAK694 + SCIT) - SCIT			1.8 (15.02)	(-28.9, 32.5)	0.903
	(VAK694 + SCIT) - Placebo			-4.8 (14.39)	(-34.2, 24.6)	0.740
	SCIT - Placebo			-6.7 (14.73)	(-36.8, 23.5)	0.655
VISIT25	VAK694 + SCIT	11	74.1 (24.35)			
	SCIT	10	19.4 (25.39)			
	Placebo	12	69.4 (23.24)			
	(VAK694 + SCIT) - SCIT			54.7 (35.18)	(-17.2, 126.6)	0.131
	(VAK694 + SCIT) - Placebo			4.7 (33.68)	(-64.1, 73.5)	0.889
	SCIT - Placebo			-50.0 (34.43)	(-120.3, 20.4)	0.157

Statistical analysis of changes from baseline in total RQLQm score

Visit	Treatment effect /contrast	n	LS mean (SE)	Difference (SE)	95% CI	P-value (2-sided)
VISIT22	VAK694 + SCIT	12	13.3 (4.59)			
	SCIT	11	18.4 (4.80)			
	Placebo	11	15.6 (4.69)			
	(VAK694 + SCIT) - SCIT			-5.1 (6.78)	(-19.0, 8.7)	0.456
	(VAK694 + SCIT) - Placebo			-2.3 (6.56)	(-15.7, 11.0)	0.723
	SCIT - Placebo			2.8 (6.71)	(-10.9, 16.5)	0.682

Small values / negative differences indicate positive treatment effect, indicating improvement in quality of life

Statistical analysis of allergy season retrospective global rating

Visit	Treatment effect /contrast	n	LS mean (SE)	Difference (SE)	95% CI	P-value (2-sided)
VISIT24	VAK694 + SCIT	11	6.5 (1.19)			

	SCIT	11	6.5 (1.19)			
	Placebo	12	4.2 (1.14)			
	(VAK694 + SCIT) - SCIT			0.0 (1.68)	(-3.4, 3.4)	1.000
	(VAK694 + SCIT) - Placebo			2.4 (1.64)	(-1.0, 5.7)	0.158
	SCIT - Placebo			2.4 (1.64)	(-1.0, 5.7)	0.158
VISIT25	VAK694 + SCIT	11	5.3 (1.13)			
	SCIT	11	5.5 (1.13)			
	Placebo	12	2.0 (1.08)			
	(VAK694 + SCIT) - SCIT			-0.2 (1.59)	(-3.4, 3.1)	0.910
	(VAK694 + SCIT) - Placebo			3.3 (1.56)	(0.1, 6.5)	0.044
	SCIT - Placebo			3.5 (1.56)	(0.3, 6.6)	0.034
VISIT26	VAK694 + SCIT	11	2.0 (1.38)			
	SCIT	9	2.1 (1.54)			
	Placebo	12	1.4 (1.32)			
	(VAK694 + SCIT) - SCIT			-0.1 (2.06)	(-4.3, 4.1)	0.960
	(VAK694 + SCIT) - Placebo			0.6 (1.91)	(-3.3, 4.5)	0.762
	SCIT - Placebo			0.7 (2.03)	(-3.5, 4.8)	0.737

Summary statistics for IgE, IgG4 and FAB assay results

Parameter	Visit		VAK694 + SCIT N=12	SCIT N=12	Placebo N=13
Serum total IgE (U/mL)	**BAS**	**n**	**12**	**12**	**13**
		mean	303.81	199.16	374.31
		SD	245.324	189.823	661.763
		minimum	50.2	15.8	15.2
		median	248.50	135.00	102.00
		maximum	902.0	667.0	2019.0
	VISIT19	n	11	11	13
		mean	414.77	318.86	420.26
		SD	490.138	369.458	783.741
		minimum	63.5	21.1	23.1
		median	202.00	284.00	114.00
		maximum	1742.0	1350.0	2655.0
	VISIT22	n	12	11	12
		mean	381.87	298.17	527.48
		SD	359.892	334.462	948.981
		minimum	61.0	23.6	16.5
		median	271.50	231.00	127.00
		maximum	1158.0	1226.0	2879.0
	VISIT24	n	11	11	12
		mean	371.71	275.57	592.92
		SD	297.514	346.764	1043.396
		minimum	51.8	17.8	13.6
		median	372.00	198.00	179.50
		maximum	1008.0	1267.0	2859.0
	VISIT25	n	11	11	12
		mean	222.75	141.31	388.38
		SD	166.073	114.298	722.353
		minimum	31.5	12.6	11.0

		median	196.00	118.00	91.55
		maximum	596.0	447.0	2290.0
Grass-pollen specific IgE (U/mL)	**BAS**	**n**	**12**	**12**	**13**
		mean	48.962	30.495	25.038
		SD	51.7348	45.0136	31.3642
		minimum	3.69	1.87	0.59
		median	25.550	9.295	10.000
		maximum	160.00	152.00	112.50
	VISIT19	n	11	11	13
		mean	99.148	79.791	27.982
		SD	161.5150	106.6270	37.2356
		minimum	1.63	4.06	0.48
		median	43.000	42.100	11.200
		maximum	560.00	361.00	129.50
	VISIT22	n	12	11	12
		mean	90.891	71.699	56.953
		SD	113.2192	95.3813	80.2104
		minimum	1.48	4.23	0.47
		median	39.350	39.800	15.950
		maximum	372.00	313.00	221.50
	VISIT24	n	11	11	12
		mean	73.107	62.573	54.864
		SD	70.2459	95.5503	77.8978
		minimum	1.15	2.59	0.87
		median	38.200	27.200	15.900
		maximum	213.00	320.00	246.00
	VISIT25	n	11	11	12
		mean	42.526	33.953	40.147
		SD	42.7901	42.7324	57.6529
		minimum	1.13	1.61	0.50
		median	27.200	16.600	11.615
		maximum	133.00	134.00	188.00
Grass-pollen specific IgG4 (mgA/L)	**BAS**	**n**	**12**	**12**	**13**
		mean	0.160	0.276	0.085
		SD	0.1463	0.5364	0.0947
		minimum	0.02	0.00	0.00
		median	0.115	0.100	0.050
		maximum	0.53	1.91	0.35
	VISIT19	n	11	11	13
		mean	2.772	3.917	0.078
		SD	2.1121	5.4689	0.0917
		minimum	0.03	0.06	0.01
		median	2.440	2.450	0.040
		maximum	6.56	18.60	0.35
	VISIT22	n	12	11	12
		mean	3.498	4.259	0.112
		SD	2.8964	6.6095	0.1616
		minimum	0.08	0.16	0.00

		median	2.585	1.380	0.050
		maximum	8.77	21.70	0.60
	VISIT24	n	11	11	12
		mean	1.679	2.265	0.115
		SD	1.2507	2.7758	0.1716
		minimum	0.03	0.09	0.00
		median	1.320	1.100	0.045
		maximum	3.61	9.54	0.62
	VISIT25	n	11	11	12
		mean	0.589	0.941	0.130
		SD	0.4215	1.3346	0.2527
		minimum	0.02	0.02	0.00
		median	0.410	0.550	0.045
		maximum	1.19	4.67	0.92
IgE-FAB (%)	**BAS**	**n**	**12**	**12**	**13**
		mean	98.538	97.702	94.865
		SD	8.1347	4.0790	6.0933
		minimum	78.63	92.06	78.63
		median	100.350	97.720	95.670
		maximum	107.98	105.02	102.55
	VISIT19	n	11	11	13
		mean	70.977	73.808	94.152
		SD	12.2809	15.9804	8.6425
		minimum	45.08	31.02	69.53
		median	72.720	74.950	96.690
		maximum	87.05	91.56	102.13
	VISIT22	n	12	11	12
		mean	65.641	66.046	94.133
		SD	17.3412	18.2398	7.9369
		minimum	32.25	19.41	70.89
		median	68.020	66.720	95.970
		maximum	95.52	86.55	100.61
	VISIT24	n	11	11	12
		mean	79.870	72.074	91.298
		SD	13.7102	15.8027	14.4091
		minimum	57.23	38.33	46.58
		median	83.710	72.650	95.890
		maximum	96.47	96.21	99.92
	VISIT25	n	11	11	12
		mean	88.046	85.234	92.388
		SD	9.4684	8.0081	9.9877
		minimum	64.83	69.30	62.16
		median	91.380	85.940	95.750
		maximum	97.92	95.78	98.41

Summary statistics for PBMC IL-4, IL-10

Parameter	Visit		VAK694 + SCIT N=12	SCIT N=12	Placebo N=13
Elispot (Frequency of IL-4+IL-10+ cells)	**BAS**	**n**	**12**	**12**	**13**

		mean	5.875	8.563	7.032
		SD	4.0655	6.0473	5.9684
		minimum	1.75	0.25	1.25
		median	4.750	8.125	5.500
		maximum	14.75	18.50	20.00
	VISIT 22	n	12	11	12
		mean	11.354	19.977	6.854
		SD	9.4667	11.5788	7.9082
		minimum	0.00	1.00	0.75
		median	8.750	19.500	3.000
		maximum	29.25	44.25	26.50
	VISIT 25 (CE)	n	11	11	12
		mean	2.455	5.205	2.000
		SD	2.0119	4.0401	1.6272
		minimum	0.00	0.50	0.00
		median	2.250	5.000	2.250
		maximum	6.00	15.00	4.25
Elispot (Frequency of IL-10+ cells) (1)	**BAS**	**n**	**12**	**12**	**13**
		mean	109.729	118.646	80.885
		SD	116.5367	138.5381	96.1773
		minimum	6.75	4.75	7.00
		median	75.000	66.625	24.000
		maximum	437.50	386.25	295.00
	VISIT 22	n	12	11	12
		mean	26.333	42.750	17.146
		SD	21.5500	28.8691	18.2254
		minimum	3.75	5.75	0.25
		median	16.875	42.750	8.500
		maximum	68.25	104.50	58.00
	VISIT 25 (CE)	n	11	11	12
		mean	5.909	12.591	7.813
		SD	4.2046	8.9102	7.5680
		minimum	0.00	4.25	0.00
		median	7.250	12.000	6.375
		maximum	12.50	32.50	26.25
Elispot (Frequency of IL-4+ cells) (1)	**BAS**	**n**	**12**	**12**	**13**
		mean	207.958	203.167	171.462
		SD	93.0718	134.3146	78.7082
		minimum	41.25	0.00	26.25
		median	206.625	172.625	179.000
		maximum	353.25	461.25	279.75
	VISIT 22	n	12	11	12
		mean	135.438	298.636	182.375
		SD	109.8451	151.2753	135.3163
		minimum	9.00	55.50	0.00
		median	113.000	295.250	186.250

		maximum	353.00	591.75	435.75
	VISIT 25 (CE)	n	11	11	12
		mean	86.932	164.886	100.375
		SD	46.5468	123.1790	37.2347
		minimum	4.75	35.75	41.25
		median	87.250	155.000	103.875
		maximum	170.50	468.50	183.00

Summary statistics for PBMC T helper cell phenotyping

Parameter	**Visit**		**VAK694 + SCIT N=12**	**SCIT N=12**	**Placebo N=13**
CD4+CD127 low cells[1] (%)	**BAS**	**n**	**12**	**12**	**13**
		mean	2.017	2.100	2.246
		SD	0.5441	0.5117	0.8293
		minimum	1.10	1.10	0.70
		median	1.950	2.100	2.000
		maximum	2.90	3.00	3.90
	VISIT 22	n	12	11	12
		mean	2.442	2.500	2.592
		SD	1.0370	0.6885	0.7549
		minimum	1.20	1.30	1.50
		median	2.150	2.500	2.550
		maximum	4.40	3.60	4.40
	VISIT 25 (CE)	n	11	11	12
		mean	2.036	2.282	2.317
		SD	1.0736	0.6047	0.5408
		minimum	1.10	1.50	1.50
		median	1.700	2.000	2.300
		maximum	4.70	3.30	3.20
CD4+CD25high+CD127 low cells[2] (%)	**BAS**	**n**	**12**	**12**	**13**
		mean	79.692	84.942	79.831
		SD	12.3854	9.0747	13.5913
		minimum	58.10	68.90	51.20
		median	80.050	85.150	81.800
		maximum	94.50	97.70	98.70
	VISIT 22	**n**	12	11	12
		mean	89.525	90.018	91.908
		SD	7.2428	7.7307	4.2124
		minimum	71.00	77.50	84.40
		median	91.200	91.200	92.900
		maximum	97.80	99.10	96.40
	VISIT 25 (CE)	n	11	11	12
		mean	90.755	90.955	93.692
		SD	5.4193	2.1649	2.8273
		minimum	78.60	87.30	88.90
		median	90.500	90.900	92.850

		maximum	97.30	94.50	98.00
CD3+CD4+CRTH2+ cells[1] (%)	**BAS**	**n**	12	12	13
		mean	1.575	1.217	1.146
		SD	0.8203	0.5424	0.9623
		minimum	0.30	0.60	0.30
		median	1.500	1.100	0.800
		maximum	3.30	2.30	3.40
	VISIT 22	n	12	11	12
		mean	3.267	1.355	2.200
		SD	3.6323	0.5973	2.7772
		minimum	0.70	0.30	0.50
		median	1.850	1.500	1.100
		maximum	12.30	2.10	10.20
	VISIT 25 (CE)	**n**	11	11	12
		mean	2.545	1.373	1.950
		SD	2.4841	0.7268	1.7911
		minimum	0.50	0.30	0.60
		median	1.300	1.300	1.500
		maximum	8.30	2.30	7.10
CD3+CD4+CRTH2+CD124+ cells[3] (%)	**BAS**	**n**	**12**	**12**	**13**
		mean	16.433	15.667	11.623
		SD	13.1503	10.5771	7.1452
		minimum	5.30	3.80	2.70
		median	10.600	11.400	10.600
		maximum	51.50	40.40	25.80
	VISIT 22	n	12	11	12
		mean	9.192	5.782	9.150
		SD	7.5014	4.2720	9.3065
		minimum	0.70	1.70	2.10
		median	7.700	4.900	5.400
		maximum	23.80	17.10	30.50
	VISIT 25 (CE)	**n**	11	11	12
		mean	14.755	12.936	14.975
		SD	7.0807	8.7015	5.5831
		minimum	5.70	2.60	3.30
		median	14.300	14.400	14.650
		maximum	26.70	33.90	23.10
CD4+FoxP3+ cells[1] (%)	**BAS**	**n**	**12**	**12**	**13**
		mean	2.992	3.092	2.954
		SD	1.7021	1.5270	1.1609
		minimum	0.50	1.00	1.30
		median	2.500	2.900	2.800
		maximum	6.30	6.30	5.90
	VISIT 22	n	12	11	12
		mean	2.567	2.955	2.692
		SD	1.3296	0.9933	1.0892
		minimum	0.70	1.80	0.80

		median	2.600	3.000	2.850
		maximum	4.70	4.40	4.50
	VISIT 25 (CE)	**n**	11	11	12
		mean	5.318	5.273	6.100
		SD	1.4127	2.0274	1.8954
		minimum	3.30	0.70	3.30
		median	5.500	4.900	6.200
		maximum	7.50	8.10	9.70
CD4+CD25high+FoxP3+ cells[4] (%)	**BAS**	**n**	**12**	**12**	**13**
		mean	67.133	70.358	74.831
		SD	17.7528	14.1989	15.4334
		minimum	25.90	44.40	39.40
		median	69.600	68.750	76.200
		maximum	94.40	89.70	94.50
	VISIT 22	n	12	11	12
		mean	67.017	74.509	68.600
		SD	21.5934	12.3213	22.0277
		minimum	26.50	44.60	21.30
		median	75.850	76.800	73.000
		maximum	88.90	84.90	91.80
	VISIT 25 (CE)	**n**	11	11	12
		mean	88.418	82.336	89.917
		SD	4.7975	18.2709	8.4847
		minimum	82.70	31.20	70.70
		median	87.100	90.500	92.900
		maximum	95.50	94.70	97.50

1 As a percentage of CD4+ cells

2 As a percentage of CD4+CD127 low cells

3 As a percentage of CD3+CD4+CRTH2+ cells

4 As a percentage of CD4+FoxP3+ cells

Safety Results

Adverse events overall and frequently affected system organ classes - n (%) of subjects

	VAK694 + SCIT N=12 n (%)	**SCIT N=12 n (%)**	**Placebo N=13 n (%)**	**Total N=37 n (%)**
Patients with AE(s)	12 (100.0)	11 (91.7)	13 (100.0)	36 (97.3)
System organ class				
General disorders and administration site conditions	12 (100.0)	11 (91.7)	6 (46.2)	29 (78.4)
Infections and infestations	8 (66.7)	5 (41.7)	10 (76.9)	23 (62.2)
Respiratory, thoracic and mediastinal disorders	7 (58.3)	6 (50.0)	7 (53.8)	20 (54.1)
Nervous system disorders	5 (41.7)	3 (25.0)	6 (46.2)	14 (37.8)
Skin and subcutaneous tissue disorders	7 (58.3)	4 (33.3)	2 (15.4)	13 (35.1)
Gastrointestinal disorders	3 (25.0)	3 (25.0)	3 (23.1)	9 (24.3)
Injury, poisoning and procedural complications	4 (33.3)	3 (25.0)	2 (15.4)	9 (24.3)

Musculoskeletal and connective tissue disorders	5 (41.7)	2 (16.7)	2 (15.4)	9 (24.3)
Eye disorders	2 (16.7)	1 (8.3)	4 (30.8)	7 (18.9)
Immune system disorders	1 (8.3)	1 (8.3)	3 (23.1)	5 (13.5)
Ear and labyrinth disorders	1 (8.3)	2 (16.7)	1 (7.7)	4 (10.8)
Vascular disorders	0 (0.0)	0 (0.0)	3 (23.1)	3 (8.1)
Reproductive system and breast disorders	0 (0.0)	0 (0.0)	2 (15.4)	2 (5.4)
Blood and lymphatic system disorders	1 (8.3)	0 (0.0)	0 (0.0)	1 (2.7)
Investigations	1 (8.3)	0 (0.0)	0 (0.0)	1 (2.7)
Metabolism and nutrition disorders	0 (0.0)	0 (0.0)	1 (7.7)	1 (2.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.0)	0 (0.0)	1 (7.7)	1 (2.7)
Psychiatric disorders	1 (8.3)	0 (0.0)	0 (0.0)	1 (2.7)

AEs arranged in descending order of frequency

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

	VAK694 + SCIT N=12 n (%)	**SCIT N=12 n (%)**	**Placebo N=13 n (%)**	**Total N=37 n (%)**
Patients with AE(s)	12 (100.0)	11 (91.7)	13 (100.0)	36 (97.3)
Preferred term				
Injection site pruritus	10 (83.3)	10 (83.3)	1 (7.7)	21 (56.8)
Injection site mass	10 (83.3)	10 (83.3)	0 (0.0)	20 (54.1)
Nasopharyngitis	6 (50.0)	4 (33.3)	10 (76.9)	20 (54.1)
Injection site erythema	5 (41.7)	7 (58.3)	0 (0.0)	12 (32.4)
Injection site swelling	4 (33.3)	8 (66.7)	0 (0.0)	12 (32.4)
Headache	3 (25.0)	2 (16.7)	5 (38.5)	10 (27.0)
Cough	3 (25.0)	3 (25.0)	3 (23.1)	9 (24.3)
Rhinorrhoea	1 (8.3)	2 (16.7)	3 (23.1)	6 (16.2)
Epistaxis	3 (25.0)	0 (0.0)	2 (15.4)	5 (13.5)
Injection site urticaria	3 (25.0)	2 (16.7)	0 (0.0)	5 (13.5)
Oropharyngeal pain	1 (8.3)	2 (16.7)	2 (15.4)	5 (13.5)
Urticaria	2 (16.7)	2 (16.7)	1 (7.7)	5 (13.5)

10 most frequent AEs arranged in descending order in total column

Serious Adverse Events and Deaths

No deaths, Serious Adverse Events (SAEs) and Adverse Event discontinuations (AEDs) were reported in the study

	VAK694 + SCIT N=12 n (%)	**SCIT N=12 n (%)**	**Placebo N=13 n (%)**	**Total N=37 n (%)**
No. (%) of subjects studied	12 (100.0)	12 (100)	13 (100.0)	37 (100)
No. (%) of subjects with AE(s)	12 (100.0)	11 (91.7)	13 (100.0)	36 (97.3)
Number (%) of subjects with serious or other significant events	n (%)	n (%)	n (%)	n (%)
Death	0	0	0	0
SAE(s)	0	0	0	0
Discontinued due to SAE(s)	0	0	0	0

Other Relevant Findings

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

Parameter		Dose 1 (n=11)	Dose 4 (n=11)
Cmax (µg/mL)	Mean (SD)	70.7 (8.32)	85.7 (8.33)
	Range	58.6 – 82.1	74.9 – 99.2
	CV (%)	11.8	9.73
Tmax (hr)	Median	1.05	1.05
	Range	0.983 – 1.28	1.00 – 1.10
	CV (%)	8.19	3.22
Cmax ratio ^	Mean (SD)	N.C.	1.24 (0.163)
	Range	N.C.	0.999 – 1.46
	CV (%)	N.C.	13.1

^ n = 10
N.C. = not calculated

Date of Clinical Trial Report
16 Oct 2012

Date Inclusion on Novartis Clinical Trial Results Database
13 Feb 2013

Date of Latest Update