Sponsor Novartis Pharmaceuticals
Generic Drug Name QBX258
Therapeutic Area of Trial Mild to moderate asthma
Approved Indication Not applicable
Protocol Number CQBX258X2101

Title

A randomized, double-blind, placebo controlled study to compare the safety, tolerability, and pharmacokinetics of QBX258 (sequential administration of a fixed dose of VAK694 and single ascending doses of QAX576) in patients with well-controlled mild to moderate asthma.

Phase of Development

Phase I

Study Start/End Dates

04-Nov-2010 to 08-Aug-2011

Study Design/Methodology

This was a double-blind, randomized, fixed dose and single ascending dose study in subjects with well controlled, mild to moderate atopic asthma. Subjects received a fixed dose of 3 mg/kg VAK694 or placebo intravenously over a 1 hour period. Cohort 1 only received VAK694 or placebo. In cohorts 2 to 5, subjects were observed for a period of 1 hour while infused with 50 mL normal saline alone (to keep the vein open) followed by a single intravenous administration given over a 2 hour period of ascending doses of 0.3 mg/kg, 1 mg/kg, 3 mg/kg or 6 mg/kg QAX576 or placebo per cohort.

Centres

2 centers in 1 country: USA (2)

Publication

None

Outcome measures

Primary outcome measures(s)

- Safety and tolerability over 100 days
- Pharmacokinetics over 100 days

Secondary outcome measures(s)

- IgE, IgA and IgG measured over 100 days
- Anti-QAX576 antibodies and anti-VAK694 antibodies measured over 100 days

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

QAX576 (lyophilisate in vial) 100mg, QAX576 placebo (lyophilisate in vial), VAK694 (lyophilisate in vial) 150mg andVAK694 placebo (lyophilisate in vial) for intravenous administration.

The treatment arms and cohorts were as follows:

- Cohort 1:
  - 8 subjects received 3 mg/kg VAK694
  - 2 subjects received VAK694 placebo.
- Cohort 2:
  - 8 subjects received 3 mg/kg VAK694 and 0.3 mg/kg QAX576
  - 2 subjects received VAK694 placebo and QAX576 placebo.
- Cohort 3:
  - 8 subjects received 3 mg/kg VAK694 and 1 mg/kg QAX576
  - 2 subjects received VAK694 placebo and QAX576 placebo.
- Cohort 4:
  - 8 subjects received 3 mg/kg VAK694 and 3 mg/kg QAX576
  - 2 subjects received VAK694 placebo and QAX576 placebo.
- Cohort 5:
  - 8 subjects received 3 mg/kg VAK694 and 6 mg/kg QAX576

2 subjects received VAK694 placebo and QAX576 placebo.

Statistical Methods

Safety and pharmacokinetic data were listed and summarized by descriptive statistics. No statistical method to impute missing values was applied.
All subjects who received at least one dose of study drug were included in the safety data analysis set. All subjects who received active treatment and who had no major protocol deviations with impact on PK data were included in the PK data analysis set. All subjects without major protocol deviations with impact on PD data were included in the PD data analysis set. Placebo subjects from the different cohorts were pooled to form one placebo group in summary tables but were listed within the appropriate cohort.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

Subjects must have been aged 18 to 60 years at time of enrollment with a body mass index (BMI) within the range of 18 to 35 kg/m^2. They had to be in good health apart from their asthma (as determined by past medical history, physical examination, vital signs, electrocardiogram, and laboratory tests at screening) with vital signs within a specified range and to be able to communicate well. Asthma had to be under good control. Females were not of child bearing potential, and males had to be using two methods of contraception and refrain from fathering a child in the six months following drug administration. Subjects had to have a positive skin prick test to one or more common airborne allergens.

Exclusion criteria

1. Participation in any clinical investigation or use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives of enrollment.
2. History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes.
3. A history of clinically significant ECG abnormalities, or any of the ECG abnormalities described in the protocol at screening or baseline.
4. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there was evidence of local recurrence or metastases.
5. Smokers (use of tobacco products in the previous 3 months). Individuals with a previous history of smoking (i.e. prior to the previous 3 months) should not have exceeded a 10 pack-year history.
6. Use of prescription drugs other than those required for control and relief of asthma, stable (4 weeks) use of hormone replacement or thyroid replacement within four (4) weeks prior to dosing.
7. Use of any over the counter (OTC) medication (other than non-sedating antihistamines and normal doses of vitamins and nutrients) within forty eight (48) hours prior to dosing.
8. Use of oral steroids within 12 weeks prior to dosing.

9. FEV1 <80% predicted at screening or baseline.
10. Use of albuterol more than twice a week for relief of asthma (other than with exercise); or nocturnal asthma more than twice a month.
11. Any immunotherapy with systemic biologics as a treatment therapy or during a clinical study within the last 6 months.
12. Any immunotherapy with subcutaneous injections for allergy (allergy shots), within 3 months.
13. Donation or loss of 400 ml or more of blood within eight (8) weeks prior to initial dosing, or longer if required by local regulation.
14. Clinically relevant illness within two (2) weeks prior to initial dosing.
15. Recent (within the last three [3] years) and/or recurrent history of autonomic dysfunction (e.g., recurrent episodes of fainting, palpitations, etc).
16. Patients who suffered from active hay fever at baseline or were likely to require treatment during the study.
17. History of chronic respiratory disease other than asthma or chronic allergic rhinitis.
18. Emergency room visit within 6 weeks of screening due to asthma.
19. Hospitalization for asthma in the last year.
20. History of intubation/assisted ventilation for asthma in the last 5 years.
21. History of autoimmune disease, with the exception of hypothyroidism.
22. History of tuberculosis or history of active bacterial or viral infection.
23. History of anaphylaxis.
24. Administration of live vaccines within the preceding month.
25. History of immunodeficiency diseases, including a positive HIV (ELISA and Western blot) test result.
26. A positive Hepatitis B surface antigen (HBsAg) or Hepatitis C test result.
27. History of drug or alcohol abuse within the 12 months prior to dosing, or evidence of such abuse as indicated by the laboratory assays conducted during screening and baseline.
28. History of clinical schistosomiasis or travel within the preceding 6 months to an area with endemic schistosomiasis, including but not limited to Southeast Asia and Northwest Africa.
29. Positive ELISA for Strongyloides stercoralis
30. Positive stool sample for ova or parasites.
31. If blood absolute eosinophil count at screening ≥450 cells/mm3, subjects could have been included in the study only after active parasitic infection was ruled out as the etiology of eosinophilia.
32. Any prior treatment with IgG (marketed or investigational monoclonal antibody).

Participant Flow

Patients	VAK694 3 mg/kg N=8 (n%)	VAK694 3 mg/kg + QAX576 0.3 mg/kg N=8 (n%)	VAK694 3 mg/kg + QAX576 1 mg/kg N=8 (n%)	VAK694 3 mg/kg + QAX576 3 mg/kg N=8 (n%)	VAK694 3 mg/kg + QAX576 6 mg/kg N=8 (n%)
Randomized	8 (100.0)	8 (100.0)	8 (100.0)	8 (100.0)	8 (100.0)
Completed	8 (100.0)	8 (100.0)	8 (100.0)	8 (100.0)	7 (87.5)
Discontinued					1 (12.5)
Lost to follow up					1 (12.5)

	Placebo (pooled) N=10 (n%)	Total N=50 (n%)
Randomized	10 (100.0)	50 (100.0)
Completed	10 (100.0)	49 (98.0)
Discontinued		1 (2.0)
Lost to follow up		1 (2.0)

Baseline Characteristics

Demographic and baseline data summary (Safety analysis set)

		Active treatment in cohort number					Placebo (pooled)
		1 N=8	2 N=8	3 N=8	4 N=8	5 N=8	N=10
Age (years)	Mean (SD)	36 (11.2)	33 (16.1)	35 (9.7)	34 (11.8)	36 (18.2)	31 (9.6)
	Range	22-53	21-59	22-48	22-56	21-60	18-50
Gender n (%)	Male	7 (87.5%)	7 (87.5%)	7 (87.5%)	7 (87.5%)	7 (87.5%)	8 (80%)
	Female	1 (12.5%)	1 (12.5%)	1 (12.5%)	1 (12.5%)	1 (12.5%)	2 (20%)
Weight (kg)	Mean(SD)	83 (10.4)	86 (14.2)	84 (19.6)	76 (12.5)	83 (15.6)	80 (9.6)
	Range	67.2-96.8	69.5-110.0	65.1-115.5	55.8-90.5	66.1-116	60.6-95.7
Height (cm)	Mean(SD)	177 (4.9)	176 (7.6)	177 (9.6)	174 (9.9)	179 (6.5)	171 (9.0)
	Range	168-182	165-186	161-192	151-181	170-187	157-183
Race n (%)	Caucasian	5 (62.5%)	5 (62.5%)	7 (87.5%)	5 (62.5%)	7 (87.5%)	5 (50%)
	Black	3 (37.5%)	3 (37.5%)	1 (12.5%)	3 (37.5%)	0	3 (30%)
	Other	0	0	0		1 (12.5%)	2 (20%)[a]
BMI (kg/m^2)	Mean (SD)	26 (2.6)	28 (3.2)	27 (4.8)	25 (2.3)	26 (3.9)	28 (3.4)
	Range	21.3-29.2	24.1-31.8	21.8-36.1	22.2-28.4	20.1-33.8	20.9-32.1
Baseline FEV_1 (L)	Mean (SD)	3.7 (0.74)	3.7 (0.77)	4.1 (0.82)	3.7 (0.93)	4.0 (0.94)	3.5 (0.78)
	Range	2.0-4.2	2.1-4.9	2.6-5.5	1.7-4.8	2.7-5.2	1.9-4.4

[a] includes one Pacific Islander. Active treatments in each cohort: 1 = VAK694 3 mg/kg, 2 = VAK694 3 mg/kg + QAX576 0.3 mg/kg, 3 = VAK694 3 mg/kg + QAX576 1 mg/kg, 4 = VAK694 3 mg/kg + QAX576 3 mg/kg, 5 = VAK694 3 mg/kg + QAX576 6 mg/kg,

Outcome measures

Primary Outcome Result(s)

Safety and tolerability over 100 days

See safety section below

QAX 576 Pharmacokinetics over 100 days

Summary statistics of QAX576 PK parameters (PK analysis set).

		VAK694 3 mg/kg plus QAX576 dose at:			
		0.3 mg/kg N=8	1 mg/kg N=8	3 mg/kg N=8	6 mg/kg N=8
Tmax (day)	Median	0.17	0.31	0.17	0.17
	Range	0.17, 0.46	0.17, 1.00	0.17, 0.46	0.17, 1.00
	CV%	55.9	81.3	55.4	95.7
Cmax (µg/mL)	Mean (SD)	6.79 (1.22)	18.6 (3.61)	60.9 (6.83)	128 (22.6)
	CV%	18.0	19.4	11.2	17.6
AUClast (day* µg/mL)	Mean (SD)	106 (8.69)	322 (106)	963 (106)	2043 (434)
	CV%	8.24	32.9	11.0	21.2
AUCinf (day* µg/mL)	Mean (SD)	111 (9.33)	351 (127)	1017 (122)	2161 (501)
	CV%	8.41	36.1	12.0	23.2
CL (mL/day/kg)	Mean (SD)	2.72 (0.231)	3.42 (2.00)	2.98 (0.348)	2.91 (0.659)
	CV%	8.50	58.5	11.7	22.6
Vss (mL/kg)	Mean (SD)	77.6 (12.6)	91.4 (14.9)	92.2 (15.3)	80.3 (15.0)
	CV%	16.2	16.3	16.6	18.6
T1/2 (day)	Mean (SD)	21.7 (3.28)	24.8 (7.93)	23.0 (4.83)	21.7 (5.49)
	CV%	15.1	32.0	21.0	25.3

VAK694 pharmacokinetics over 100 days

Summary statistics for VAK694 PK parameters (PK analysis set).

		VAK694 3 mg/kg plus QAX576 dose at:				
		No QAX576 N=8	0.3 mg/kg N=8	1 mg/kg N=8	3 mg/kg N=8	6 mg/kg N=8
Tmax (day)	Median	0.08	0.08	0.08	0.08	0.13
	Range	0.04, 0.46	0.04, 0.46	0.04, 0.08	0.04, 0.17	0.08, 0.17
	CV%	105	109	26.2	60.0	38.5
Cmax (µg/mL)	Mean (SD)	91.2 (16.0)	54.0 (9.97)	56.8 (9.97)	55.4 (5.40)	65.9 (13.0)
	CV%	17.5	18.5	17.6	9.74	19.7
AUClast (day* µg/mL)	Mean (SD)	888 (165)	633 (85.9)	745 (148)	642 (102)	734 (100)
	CV%	18.6	13.6	19.9	15.9	13.7
AUCinf (day* µg/mL)	Mean (SD)	937 (215)	664 (97.6)	802 (179)	677 (119)	779 (143)
	CV%	23.0	14.7	22.3	17.6	18.3
CL (mL/day/kg)	Mean (SD)	3.34 (0.691)	4.61 (0.703)	3.89 (0.781)	4.54 (0.725)	3.96 (0.682)
	CV%	20.7	15.3	20.1	16.0	17.2
Vss (mL/kg)	Mean (SD)	84.2 (11.9)	120 (18.5)	121 (15.0)	126 (18.3)	104 (24.6)
	CV%	14.1	15.5	12.4	14.5	23.7
T1/2 (day)	Mean (SD)	21.9 (6.11)	21.9 (3.90)	25.2 (4.12)	23.8 (4.12)	22.9 (8.54)
	CV%	27.9	17.8	16.4	17.3	37.3

Secondary Outcome Result(s)

Summary of total IgE IgA and IgG (PD analysis set)

Cohort	Day	N=8*	IgE (IU/mL)	IgA (mg/dL)	IgG (mg/dL)
1	1	Mean (SD)	240.6 (234.1)	252.5 (83.0)	1144.3 (418.6)
		range	12 – 649	145 - 381	805 - 2139
VAK694 3 mg/kg	29	Mean (SD)	235.4 (244.6)	260.6 (88.9)	1157.5 (357.0)
		range	11-687	161 – 415	877 - 1995
	57	Mean (SD)	269.5 (378.5)	261.6 (75.4)	1218.0 (380.7)
		range	9 – 1151	159 - 366	806 - 1868
	100	Mean (SD)	218.9 (238.4)	249.9 (69.0)	1100.7 (90.2)
		range	10 – 688	160 – 344	1014 - 1194
2	1*	Mean (SD)	343.2 (514.66 - 12626)	212.8 (50.6)	1009.4 (214.3)
		range		160 – 273	859 - 1387
VAK694 3 mg/kg	8*	Mean (SD)	308.7 (350.0)	229.0 (37.0)	1100.7 (90.2)
		range	75- 711	192 – 266	1014 - 1194
QAX576 0.3 mg/kg	29	Mean (SD)	278.5 (357.8)	217.0 (36.1)	1047.1 (167.7)
		range	49 – 1042	180 – 271	900 - 1431
	57	Mean (SD)	292.0 (383.4)	223.3 (43.6)	1065.6 (211.0)
		range	52 – 1121	186 – 281	889 - 1557
	100	Mean (SD)	251.1 (281.6)	224.9 (49.9)	1057.4 (217.8)
		range	51 – 848	161 -297	873 -1557
3	1	Mean (SD)	144.6 (142.90)	181.8 (73.5)	955.0 (184.9)
		range	23 – 473	93 – 294	699 - 1231
VAK694 3 mg/kg	29	Mean (SD)	116.5 (93.0)	178.5 (72.3)	974.8 (167.7)
		range	22 – 309	89 – 299	765 - 1216
QAX576 1 mg/kg	57	Mean (SD)	129.4 (108.92)	174.6 (67.7)	929.1 (181.25)
		range	34 - 363	93 - 290	700 - 1177
	100	Mean (SD)	122.9 (103.2)	176.6 (74.11)	918.1 (169.9)
		range	34 - 331	85 – 301	666 - 1129
4	1	Mean (SD)	444.9 (754.6)	202.0 (57.9)	984.9 (195.24)
		range	78 – 2304	144 – 300	653 - 1262
VAK694 3 mg/kg	29	Mean (SD)	167.0 (66.7)	204.1 (60.4)	966.8 (170.90)
		range	70 - 254	147 - 319	667 - 1266
QAX576 3 mg/kg	57	Mean (SD)	161.1 (74.4)	203.3 (64.4)	953.6 (181.9)
		range	61 – 249	147 - 321	658 - 1194
	100	Mean (SD)	393.1 (649.5)	202.3 (65.3)	949.0 (181.2)
		range	71 – 1993	152 – 328	617 - 1235
5	1	Mean (SD)	324.9 (485.9)	176.5 (76.12)	989.6 (235.1)
		range	33 – 1498	53 – 274	672 - 1326
VAK694 3 mg/kg	29	Mean (SD)	390.9 (650.7)	194.5 (73.4)	1040.9 (253.0)
		range	29 – 1977	71 – 298	716 - 1410
QAX576 6 mg/kg	57	Mean (SD)	292.0 (399.38)	196.9 (80.4)	1031.0 (244.11)
		range	35 – 1257	62 – 294	750 - 1396
	100	Mean (SD)	140.3 (90.7)	201.9 (112.7)	1018.7 (247.3)
		range	29 – 279	58 – 385	731 - 1422
Placebo	1	Mean (SD)	185.3 (198.9)	263.1 (104.7)	1058.3 (148.6)
		range	4 - 634	130 - 453	847-1243
(Pooled)	29	Mean (SD)	187.9 (215.4)	271.9 (115.6)	1085.0 (163.4)

		range	5 – 729	144 – 487	764 - 1386
	57	Mean (SD)	200.9 (252.4)	273.9 (113.9)	1071.1 (143.3)
		range	6 - 832	144 - 487	796 - 1304
	100	Mean (SD)	173.7 (207.3)	265.6 (107.0)	1057.2 (164.0)
		range	5 - 694	129 - 456	754 - 1229

* Cohort 2 - Day 1 (n=5) and Day 8 (n=3)

Summary of Spirometry

Cohort	Day	N=8	Actual FEV1 as a % of predicted	Actual FVC (L)	FEV1/FVC (%)
1	1	Mean (SD)	87.6 (15.0)	4.7 (0.8)	72.3 (10.2)
		range	72-113	2.75-5.28	53-86
VAK694 3 mg/kg	8	Mean (SD)	87.5 (12.2)	4.6 (0.8)	73.3 (9.2)
		range	72-110	2.8-5.4	61-88
	15	Mean (SD)	90.9 (12.2)	4.7 (0.9)	75.9 (8.9)
		range	78-111	2.7-5.3	60-90
	29	Mean (SD)	90.6 (14.1)	4.6 (0.8)	76.4 (8.9)
		range	74-115	2.7-5.2	60-90
	57	Mean (SD)	90.3 (17.2)	4.7 (0.9)	73.8 (11.1)
		range	69-115	2.8-5.6	57-90
	100	Mean (SD)	87.4 (17.5)	4.6 (0.8)	73.6 (11.3)
		range	66-115	2.7-5.2	55-88
2	1	Mean (SD)	93.9 (10.4)	4.7 (1.1)	79.6 (8.2)
		range	79-108	3.2-6.3	66-94
VAK694 3 mg/kg	8	Mean (SD)	94.9 (12.8)	4.7 (0.9)	78.5 (6.6)
		range	75-113	3.3-6.0	68-88
QAX576 0.3 mg/kg	15	Mean (SD)	93.0 (12.1)	4.6 (1.0)	78.8 (5.9)
		range	77-113	3.1-6.0	68-87
	29	Mean (SD)	95.5 (11.8)	4.8 (1.1)	78.4 (5.5)
		range	78-116	3.0-6.2	71-86
	57	Mean (SD)	92.4 (12.8)	4.6 (1.0)	78.4 (6.3)
		range	74-110	3.0-6.0	68-86
	100	Mean (SD)	93.6 (13.5)	4.6 (1.0)	81.5 (7.8)
		range	77-115	3.2-6.1	68-92
3	1	Mean (SD)	96.1 (10.8)	5.2 (0.9)	74.3 (7.9)
		range	80-113	3.5-6.6	61-84
VAK694 3 mg/kg	8	Mean (SD)	98.9 (6.5)	5.2 (0.9)	76.3 (6.8)
		range	86-108	3.6-6.4	68-87
QAX576 1 mg/kg	15	Mean (SD)	97.0 (10.0)	5.2 (0.8)	75.6 (8.2)
		range	74-106	3.6-6.2	62-87
	29	Mean (SD)	98.5 (9.7)	5.2 (0.8)	76.6 (7.2)
		range	76-107	3.7-6.0	64-85
	57	Mean (SD)	97.5 (10.9)	5.1 (0.9)	76.5 (7.8)
		range	75-113	3.4-6.2	63-88
	100	Mean (SD)	95.1 (9.2)	5.0 (1.1)	76.9 (5.8)
		range	78-105	3.1-6.7	69-85
4	1	Mean (SD)	93.5 (7.4)	4.9 (1.2)	73.9 (7.7)

		range	83-106	2.2-6.3	59-84
VAK694 3 mg/kg	8	Mean (SD)	93.6 (13.0)	4.9 (1.3)	74.6 (5.5)
		range	76-116	2.2-6.6	64-82
QAX576 3 mg/kg	15	Mean (SD)	93.0 (9.9)	5.0 (1.3)	73.3 (7.3)
		range	81-110	2.2-6.7	59-81
	29	Mean (SD)	93.9 (10.8)	4.9 (1.2)	73.8 (7.5)
		range	79-111	2.3-6.3	60-85
	57	Mean (SD)	92.5 (13.7)	4.8 (1.2)	73.9 (7.4)
		range	73-110	2.2-6.4	59-82
	100	Mean (SD)	91.5 (9.9)	4.7 (1.3)	73.0 (7.1)
		range	78-103	1.9-6.3	59-80
5	1	Mean (SD)	91.6 (7.4)	5.0 (1.0)	76.5 (6.3)
		range	81-105	3.3-6.3	66-84
VAK694 3 mg/kg	8	Mean (SD)	93.8 (9.0)	5.1 (1.0)	76.6 (6.7)
		range	81-105	3.5-6.3	67-85
QAX576 6 mg/kg	15	Mean (SD)	92.4 (9.2)	5.0 (1.0)	77.1 (6.2)
		range	76-104	3.3-6.1	67-83
	29	Mean (SD)	94.3 (12.8)	5.2 (1.3)	76.9 (6.7)
		range	77-115	3.2-7.3	66-84
	57	Mean (SD)	91.3 (9.4)	5.0 (1.0)	75.8 (7.1)
		range	76-104	3.4-6.5	66-84
	100	Mean (SD)	93.7 (10.3)	5.1 (1.2)	77.3 (5.8)
		range	74-106	3.3-6.4	67-83
Placebo	1	Mean (SD)	89.8 (11.2)	4.7 (1.2)	74.5 (9.3)
		range	73-113	2.5-6.1	60-93
(Pooled)	8	Mean (SD)	89.1 (13.5)	4.6 (1.2)	75.1 (6.9)
		range	70-117	2.6-5.8	64-86
	15	Mean (SD)	88.9 (14.1)	4.6 (1.3)	74.8 (7.6)
		range	69-114	2.4-5.9	61-87
	29	Mean (SD)	87.9 (11.9)	4.6 (1.2)	74.2 (6.8)
		range	75-115	2.5-6.0	65-86
	57	Mean (SD)	89.7 (13.2)	4.6 (1.2)	75.7 (7.7)
		range	75-114	2.5-5.9	65-88
	100	Mean (SD)	88.8 (14.6)	4.5 (1.3)	76.0 (7.4)
		range	68-113	2.4-5.9	68-87

Immunogenicity:

	Active treatment Cohort					Total
	1	**2**	**3**	**4**	**5**	
	N=8	**N=8**	**N=8**	**N=8**	**N=8**	**N=40**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Number of pts with detectable Antibodies to VAK694 before treatment	0	0	0	0	0	0
Number of pts with detectable Antibodies to VAK694 after treatment	0	0	0	0	0	0

Number of pts with detectable Antibodies to QAX756 before treatment	N/A	0	0	2	0	2	
Number of pts with detectable Antibodies to QAX756 after treatment	N/A	0	1	1	0	2	

Active treatments in each cohort: 1 = VAK694 3 mg/kg, 2 = VAK694 3 mg/kg + QAX576 0.3 mg/kg, 3 = VAK694 3 mg/kg + QAX576 1 mg/kg, 4 = VAK694 3 mg/kg + QAX576 3 mg/kg, 5 = VAK694 3 mg/kg + QAX576 6 mg/kg,

Safety Results

Subjects with adverse events by body system and preferred term

	Active treatment in Cohort					Placebo	Total
	1	2	3	4	5	(pooled)	
	N=8	N=8	N=8	N=8	N=8	N=10	N=50
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patients with at least one AE	4 (50)	4 (50)	5 (63)	4 (50)	4 (50)	4 (40)	25 (50)
Primary system organ class and preferred term							
Nervous system disorders	0	1(12.5)	4(50)	2(25)	2(25)	2(20)	11(22)
- Headache	0	1(12.5)	4(50)	1(12.5)	2(25)	2(25)	10(20)
- Presyncope	0	0	0	1(12.5)	0	0	0
Infections & infestations	3(37.5)	1(12.5)	1(12.5)	1(12.5)	2(25)	2(20)	10(20)
- Candidiasis	0	0	0	0	1(12.5)	0	1(2)
- Influenza	1(12.5)	0	1(12.5)	0	0	0	2(4)
- Nasopharyngitis	1(12.5)	1(12.5)	0	1(12.5)	1(12.5)	1(10)	5(10)
- Upper respiratory tract infection	1(12.5)	0	0	0	0	0	1(2)
- Urinary tract infection	0	0	0	0	0	1(10)	1(2)
Gastrointestinal disorders	0	1(12.5)	1(12.5)	2 (25)	1(12.5)	0	5(10)
- Abdominal discomfort	0	0	0	1(12.5)	0	0	1(2)
- Aphthous discomfort	0	0	1(12.5)	0	0	0	1(2)
- Dry mouth	0	1(12.5)	0	0	0	0	1(2)
- Nausea	0	0	0	1(12.5)	1(12.5)	0	2(4)
Injury, poisoning & procedural complications	0	0	1(12.5)	0	1(12.5)	1(10)	3(6)
- Contusion	0	0	0	0	0	1(10)	1(2)
- Skeletal injury	0	0	1(12.5)	0	0	0	1(2)
- Snake bite	0	0	0	0	1(12.5)	0	1(2)
Respiratory, thoracic & mediastinal disorders	1(12.5)	0	0	1(12.5)	0	1(10)	3(6)
- Asthma	1(12.5)	0	0	0	0	0	1(2)
- Pleurisy	0	0	0	0	0	1(10)	1(2)
- Rhinorrhoea	0	0	0	1(12.5)	0	0	1(2)
Skin & subcutaneous tissue disorders	1(12.5)	0	0	0	1(12.5)	0	2(4)
- Pruritis	1(12.5)	0	0	0	0	0	1(2)
- Rash erythematous	0	0	0	0	1(12.5)	0	1(2)
General disorders & administration site conditions	0	1(12.5)	0	0	0	0	1(2)
- Catheter site pain	0	1(12.5)	0	0	0	0	1(2)
Immune system disorders	0	0	0	0	1(12.5)	0	1(2)
- Allergy to plants	0	0	0	0	1(12.5)	0	1(2)
Investigations	0	1(12.5)	0	0	0	0	1(2)
- Blood creatinine phosphokinase increased	0	1(12.5)	0	0	0	0	1(2)

Metabolism & nutrition disorders	1(12.5)	0	0	0	0	0	1(2)
- Increased appetite	1(12.5)	0	0	0	0	0	1(2)
Musculoskeletal & connective tissue disorders	0	0	1(12.5)	0	0	0	1(2)
- Plantar fascitis	0	0	1(12.5)	0	0	0	1(2)
Vascular disorders	0	0	0	1(12.5)	0	0	1(2)
- Hypertension	0	0	0	1(12.5)	0	0	1(2)

AEs by SOC are presented in descending order of frequency in total group.

Active treatments in each cohort: 1 = VAK694 3 mg/kg, 2 = VAK694 3 mg/kg + QAX576 0.3 mg/kg, 3 = VAK694 3 mg/kg + QAX576 1 mg/kg, 4 = VAK694 3 mg/kg + QAX576 3 mg/kg, 5 = VAK694 3 mg/kg + QAX576 6 mg/kg,

Serious Adverse Events and Deaths

	Active treatment in Cohort					Placebo
	1	2	3	4	5	(pooled)
	N=8	N=8	N=8	N=8	N=8	N=10
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Death	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
SAE	0 (0)	0 (0)	0 (0)	0 (0)	1 (12.5)*	0 (0)
Discontinued due to an AE	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Active treatments in each cohort: 1 = VAK694 3 mg/kg, 2 = VAK694 3 mg/kg + QAX576 0.3 mg/kg, 3 = VAK694 3 mg/kg + QAX576 1 mg/kg, 4 = VAK694 3 mg/kg + QAX576 3 mg/kg, 5 = VAK694 3 mg/kg + QAX576 6 mg/kg,

*SAE was hospitalization due to snake bite and not considered related to study treatment

Other Relevant Findings

None

Date of Clinical Trial Report

03 August 2012

Date Inclusion on Novartis Clinical Trial Results Database

03 August 2012

Date of Latest Update