Sponsor

Novartis Pharma AG

Generic Drug Name

CAD106

Therapeutic Area of Trial

Alzheimer's Disease (AD)

Approved Indication

Investigational

Protocol Number

CCAD106A2203

Title

A 90-week, multi-center, randomized, double-blind, placebo-controlled study in patients with mild Alzheimer's Disease (AD) to investigate the safety, tolerability and Aβ-specific antibody response following repeated i.m. injections of adjuvanted CAD106.

Study Phase

II

Study Start/End Dates

09-Mar-2010 to 18-Dec-2012

Study Design/Methodology

This 90-week double-blind, placebo-controlled study assessed the safety, tolerability, and antibody response of adjuvanted or non-adjuvanted CAD106 following repeated i.m.

injections of adjuvanted CAD106. A total of 120 patients (105 on CAD106 and 15 on placebo) with AD were planned to be enrolled in two sequential cohorts, called Cohort I (n=80, CAD106 150µg) and Cohort II (n=40, CAD106 450µg). Randomization in a 7:1 ratio of CAD106 vs. Placebo was implemented across the study cohorts. Both cohorts followed the same schedule of injections and assessments during the course of the study.

Cohort I compared the effects of 2 adjuvants (Alum vs. MF59, at 2 different doses each) combined with CAD106 150µg. Based on preliminary data from Cohort I, Alum was selected as adjuvant for use in Cohort II. In Cohort II, the dose of CAD106 450µg was assessed with Alum (at the dose of 450µg) or without adjuvant vs. placebo.

Patients were followed for a total of 90 weeks. They received up to 7 injections over 60 weeks and continued in the study for safety monitoring until Week 90, after a full evaluation was conducted at Week 78. Thereafter, they were contacted by phone on a quarterly basis for serious adverse event (SAE) collection for over 2 years (data reported through the safety database).

Centers

In total 28 investigative sites participated in the study: EU (17), Switzerland (2), Canada (4) and US (5).

Publication

None

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

Seven (7) injections of CAD106 (150µg or 450µg) or placebo and/or adjuvant (Alum or MF59 of dose high / middle / low) were administered at Baseline, Week 6, 12, 24, 36, 48 and 60 by the unblinded study nurse via i.m. route during the study.

CAD106 study medication contained the equivalent of 0.5 mg of CAD106 extractable after reconstitution. Alum ($Al(OH)_3$) or MF59 as adjuvants were provided separately as open-label bulk supplies for mixing with either placebo or the appropriate CAD106 reconstituted solution.

Placebo consisted of dextrose solution for injection, which had similar appearance and viscosity as the reconstituted CAD106 solution.

Dextrose solution (5% and 10%), and water for injection were used for use as placebo and for CAD106 reconstitution.

Statistical Methods

The primary objective of the study was to assess the safety and tolerability and immune response (Aβ-specific IgG antibody titers in serum) for CAD106. These objectives were assessed using the following variables.

- Adverse events (AEs), SAEs, discontinuation due to an AE, deaths and injection related SAEs
- Cerebral safety magnetic resonance imaging (MRI) (including signs of inflammation, microhemorrhages, and other findings)
- Cerebrospinal fluid (CSF) findings related to inflammation (white blood cells, IgG index, oligoclonal bands inblood and CSF)
- All other safety assessments (eg. laboratory tests, ECGs, vital signs)
- Injection-related reactions from the adverse events and the patient's diary such as Bruising (Ecchymosis), Redness, Induration, Swelling, Local pain, Chills, Malaise, Muscle pain (Myalgia), Joint pain (Arthralgia), Headache, Sweating, and Fatigue
- Immune response after repeated up to 7 injections of CAD106 in each treatment arm as measured primarily by the profile of Aβ-specific IgG titers in serum

Secondary objectives also included:

- Amyloid beta (Aβ)-specific and Qβ carrier-specific antibody response to CAD106 (with either adjuvant) in serum and cerebrospinal fluid (CSF)
- Amyloid beta (Aβ)-specific and Qβ carrier-specific T-cell response to CAD106 (with either adjuvant) using peripheral blood mononuclear cells (PBMCs)
- Changes over time of the concentrations of disease related markers (Amyloid beta (Aβ)1-40 and Aβ1-42 in plasma; Aβ1-40, Aβ1-42, total-tau, phospho-tau in cerebrospinal fluid (CSF), or other markers) in patients with mild Alzheimer's Disease (AD) receiving CAD106 (with either adjuvant) compared to placebo

Descriptive summary tables were provided by treatment arm for deaths, AEs, SAEs, discontinuation due to AEs, brain safety MRI (including signs of inflammation, microhemorrhages, and other findings) and CSF findings related to inflammation (white blood cells, IgG index, oligoclonal bands in blood and CSF).

Tolerability was assessed primarily based on injection-related reactions from the AEs and the patient's diary such as bruising (ecchymosis), redness, induration, swelling, local pain, chills, malaise, muscle pain (myalgia), joint pain (arthralgia), headache, sweating, and fatigue.

The primary analysis was performed on the safety analysis set (SAF) and contrasted the originally assigned treatment arms for immune response and tolerability. All other safety reports contrasted the CAD106 dose groups pooled across adjuvant which also included non-adjuvanted treatment arms (grouping by CAD106 dose: CAD106 150µg, CAD106 450µg, CAD106 Total, Placebo Total) or contrasting by adjuvant when appropriate.

Immune response after repeated up to 7 injections of CAD106 in each treatment arm as measured primarily by the profile of Aβ-specific IgG titers in serum. The immune response was assessed primarily based on maximum or peak concentration (C_{max}), time to reach C_{max}

(T_{max}) and the area under the curve (AUC) for different time intervals depending on the purpose of the analysis. The hypothesis that there was no difference in AUC up to Week 20 of Aβ-specific IgG titers in serum between the treatment arms was assessed by means of descriptive summary statistics including confidence intervals and was supported by inferential methods (Analysis of variance and corresponding non-parametric method Wilcoxon rank sum test on a significance level of 5%).

Patients treated with CAD106 were classified as serological responders, strong responders and corresponding non-responders based on Aβ-antibody titers (IgG) in serum. The following definition of serological responders and strong responders was used:

- Responder: patients whose Aβ-specific IgG titer in serum is both greater than 16 units after 2nd injection and greater than 3 times the lower limit of quantification (LLOQ=8.93 units, 3*LLOQ=26.8 units) after the 3rd injection.
- Strong responder: patients whose Aβ IgG titer is above 4 times the lower limit of quantification (LLOQ=8.93 units, 4*LLOQ=35.7 units) after two or more different injections (non-necessarily consecutive) starting from 2nd injection onwards. Of note strong responders are therefore a subset of responders.

Patients on CAD106 who did not fulfill the criteria for responder were classified as non-responders.

The Aβ and Qβ-specific T-cell lymphocyte responses were assessed by the numbers of cells secreting IFN-γ or IL-4 upon stimulation with $Aβ_{1-6}$, $Aβ_{1-42}$ or Qβ, as detected using a qualified enzyme-linked immunosorbent spot (ELISPOT)) assay on PBMC samples.

Other safety variables such as clinically notable and changes from baseline for laboratory values, ECGs, vital signs, and weight were evaluated by presenting descriptive summary tables and were listed with out-of reference range values flagged.

Descriptive statistics of change from baseline by treatment arm was provided for the disease related biomarkers ($Aβ_{1-40}$, $Aβ_{1-42}$ in plasma and CSF, and total-tau, phospho-tau in CSF). Biomarker analyses were primarily conducted for the Full Analysis Set (FAS). In addition, to explore results according to serological response, these analyses were also conducted according to responder status using a mixed-repeated measures model (MMRM).

Study Population: Inclusion/Exclusion Criteria and Demographics

Main inclusion criteria

1. Male and/or female patients below 85 years of age (inclusive)
2. Diagnosis of mild AD
3. Mini-Mental State Examination (MMSE) 20 to 26 (inclusive) at screening, untreated or on stable dose of cholinesterase inhibitor or memantine over the last 4 weeks prior to clinical assessments

Main exclusion criteria

1. Previously participated in an AD vaccine study and received active treatment

2. History or presence of an active autoimmune disease
3. History or presence of seizure disorder
4. Presence of significant coronary heart disease and/or cerebrovascular disease
5. Presence of other neurodegenerative disease and/or psychiatric disorders (with the exception of successfully treated depression)
6. Advanced, severe, progressive or unstable disease that might interfere with the safety, tolerability and pharmacodynamic assessments of the patient

Other protocol-defined inclusion/exclusion criteria may apply.

Participant Flow

Patient disposition by treatment – n (%) of patients (randomized analysis set)

Disposition Reason	CAD106 150µg (N=69)	CAD106 450µg (N=37)	CAD106 Total (N=106)	Placebo Total (N=15)
Randomized	69 (100)	37 (100)	106 (100)	15 (100)
Exposed to study drug	69 (100)	37 (100)	106 (100)	15 (100)
Completed study	40 (58.0)	28 (75.7)	68 (64.2)	7 (46.7)
Completed with all injections	5 (7.2)	0 (0)	5 (4.7)	0 (0)
Completed with less than scheduled injections	35 (50.7)	28 (75.7)	63 (59.4)	7 (46.7)
Withdrawal from study	29 (42.0)	9 (24.3)	38 (35.8)	8 (53.3)
Adverse event(s)	5 (7.2)	1 (2.7)	6 (5.7)	0 (0)
Abnormal laboratory value(s)	0 (0)	0 (0)	0 (0)	0 (0)
Abnormal test procedure result(s)	1 (1.4)	0 (0)	1 (0.9)*	0 (0)
Unsatisfactory therapeutic effect***	15 (21.7)	1 (2.7)	16 (15.1)	3 (20.0)
Subject's condition no longer requires study drug	0 (0)	1 (2.7)	1 (0.9)**	1 (6.7)**
Subject withdrew consent	1 (1.4)	6 (16.2)	7 (6.6)	3 (20.0)
Lost to follow-up	1 (1.4)	0 (0)	1 (0.9)	0 (0)
Administrative problems	3 (4.3)	0 (0)	3 (2.8)	1 (6.7)
Death	1 (1.4)	0 (0)	1 (0.9)	0 (0)
Protocol deviation	2 (2.9)	0 (0)	2 (1.9)	0 (0)

* One patient in the CAD106 Total group listed under abnormal test procedure discontinued the study due to increase in MHs that qualified as an AE.

** Another patient in the CAD106 Total group discontinued from the study due to progression of AD.
One patient in the Placebo group was a case of possible misdiagnosis and was discontinued from the study.

*** Patients who did not meet serological responder criteria were discontinued per protocol with reason for discontinuation captured as “Unsatisfactory therapeutic effect” unless another primary reason was reported. Placebo patients were discontinued in 7:1 ratio to CAD106 patients to preserve the blind.

Baseline Characteristics

Demographic and baseline disease characteristics by treatment (Safety analysis set)

	CAD106 150µg (N=69)	CAD106 450µg (N=37)	CAD106 Total (N=106)	Placebo Total (N=15)
Sex, n (%)				
Female	32 (46.4)	24 (64.9)	56 (52.8)	8 (53.3)
Male	37 (53.6)	13 (35.1)	50 (47.2)	7 (46.7)
Age (years)				
N	69	37	106	15
Mean (SD)	67.7 (9.0)	66.3 (9.4)	67.2 (9.1)	68.0 (8.4)
Median	68.0	68.0	68.0	69.0
Range	(50.0, 84.0)	(36.0, 82.0)	(36.0, 84.0)	(52.0, 81.0)
Age group, n (%)				
<65	26 (37.7)	13 (35.1)	39 (36.8)	5 (33.3)
65-75	27 (39.1)	17 (45.9)	44 (41.5)	6 (40.0)
>75	16 (23.2)	7 (18.9)	23 (21.7)	4 (26.7)
Race, n (%)				
Caucasian	67 (97.1)	37 (100)	104 (98.1)	14 (93.3)
Asian	1 (1.4)	0 (0)	1 (0.9)	1 (6.7)
Other	1 (1.4)	0 (0)	1 (0.9)	0 (0)
Baseline MHIS, n (%)				
0	37 (53.6)	25 (67.6)	62 (58.5)	8 (53.3)
1	25 (36.2)	11 (29.7)	36 (34.0)	6 (40.0)
2	6 (8.7)	0 (0)	6 (5.7)	1 (6.7)
3	1 (1.4)	1 (2.7)	2 (1.9)	0 (0)
Baseline MMSE				
N	69	37	106	15
Mean (SD)	22.8 (2.2)	23.2 (2.2)	22.9 (2.2)	22.9 (1.9)
Median	22.0	23.0	23.0	23.0
Range	(20.0, 26.0)	(20.0, 26.0)	(20.0, 26.0)	(20.0, 26.0)
APO E4 carrier status*, n (%)				
Missing	8 (-)	12 (-)	20 (-)	0 (0)
Non E4	18 (29.5)	8 (32.0)	26 (30.2)	6 (40.0)
One E4 allele	29 (47.5)	15 (60.0)	44 (51.2)	5 (33.3)
Two E4 alleles	14 (23.0)	2 (8.0)	16 (18.6)	4 (26.7)

*= Percentage based on the number of patient genotyped; MHIS = Modified Hachinski Ischemic Score

Outcome Measures

Primary Outcome Result(s)

This was primarily a safety study. Safety results are reported in the safety section.

Primary immune response results:

A-beta IgG antibody titers in serum by responder status - summary parameters (Safety set)

Parameter	Statistic	CAD106 150µg N=69		CAD106 450µg N=37		CAD106 Total N=106		
		R[1]	SR[2]	R [1]	SR[2]	R [1]	SR [2]	Total
Rate in group	N (%)	48 (69.6%)	37 (53.6%)	31 (83.8%)	28 (75.7%)	79 (74.5%)	65 (61.3%)	106 (100%)
$AUC_{Week\ 20}$ (unit*days)	Mean	5084.97	6086.00	7822.17	8381.37	6159.06	7074.77	5137.64
	SD	3581.733	3482.341	5932.318	5978.759	4803.639	4818.043	4930.236
	Min	283.7	1965.1	1682.5	1682.5	283.7	1682.5	0.0
	Median	4104.28	5195.50	6531.00	7065.83	4871.00	5940.40	3791.18
	Max	16831.9	16831.9	26985.3	26985.3	26985.3	26985.3	26985.3
Cmax (unit)	Mean	91.80	111.03	120.29	128.82	102.98	118.69	86.10
	SD	72.807	72.435	95.876	97.108	83.220	83.716	83.366
	Min	11.0	30.7	23.6	23.6	11.0	23.6	0.0
	Median	80.30	92.50	102.00	107.50	85.00	96.00	61.05
	Max	339.0	339.0	407.0	407.0	407.0	407.0	407.0

[1] R= responder defined as a patient showing an Aβ -specific IgG titer in serum above 16 units after 2nd injection and above 3 times the LLOQ after 3rd injection or injection at the higher dose.

[2] SR = strong responder defined as a patient having Aβ IgG titer in serum above 4 times the LLOQ or their individual baseline level if above the LLOQ for at least after two different injections during the study.

AUC is computed using the trapezoidal method for Week 0 to Week 20. Titer values below the LLOQ were set to 0 for the computation of AUC.

Cmax is the observed maximum post-treatment concentration value up to Week 20. Tmax is not shown in this table.

Placebo not shown as all having titers below LLOQ at all timepoints, so AUC and Cmax = 0 in 15 patients (100%)

In CSF, levels of Aβ-specific IgGs remained below LLOQ.

Dose/adjuvant effect on immune response

A-beta IgG antibody titers in serum - Wilcoxon rank sum test to compare AUC at Week 20 between treatment groups (Safety set)

Treatment X		Treatment Y	Median of X	Median of Y	Difference in medians	p-value
CAD106 150µg + Alum 150µg	vs.	CAD106 150µg + MF59 250µL	1872.4	3943.7	-2071.4	0.0764
CAD106 450µg + Alum 450µg	vs.	CAD106 450µg without adj.	6037.0	5246.8	790.1	0.4526
CAD106 150µg (pooled)	vs.	CAD106 450µg (pooled)	3024.1	5622.6	-2598.5	0.0010

Wilcoxon rank sum test for AUC (at Week 20) between treatment groups using normal approximation.

Secondary Outcome Result(s)

AD related biomarkers

AD biomarkers - model-based change from Baseline (Full Analysis Set)

AD biomarker	CSF Abeta$_{1-40}$		CSF Abeta$_{1-42}$		CSF Phospho-tau		CSF Total-tau		Plasma Abeta$_{1-40}$	
	SR	Controls	SR	Controls	SR	Controls	SR	Controls	SR	Controls
LS Means FAS										
N	20	8	20	8	20	8	20	8	51	15
Week 78	-1755	-1165	248.6	168.8	-3.37	1.76	25.04	60.99	712.2	72.18
Group difference at Week 78										
Estimate	-590		79.75		-5.13		-35.95		640.02	
(95% CI)	(-1733, 553.19)		(-55.79, 215.29)		(-12.25, 1.99)		(-141.6, 69.67)		(230.15, 1049.9)	
p-value	0.3076		0.2451		0.1554		0.5003		0.0025	

N = Number of patients; SR = Strong serological responders; Controls = Non-responders and placebo
Repeated analysis of variance model: Change from baseline = group + week + group*week + baseline + week*baseline

T-cell response by treatment and visit (Safety set)

Parameter	Statistic	CAD106 150µg (N=69)		CAD106 450µg (N=37)		CAD106 Total (N=106)		Placebo Total (N=15)	
		Baseline	Change	Baseline	Change	Baseline	Change	Baseline	Change
Gamma interferon Aβ_{1-42} peptide									
Week 8	n	67		37		104		15	
	Mean	8.31	-0.03	-0.34	-0.17	5.24	-0.08	56.10	-37.04
	Min	-12.9	-76.4	-15.4	-29.8	-15.4	-76.4	-2.7	-313.9
	Median	-0.24	-0.24	-0.82	-0.39	-0.49	-0.32	0.00	-0.67
	Max	327.5	68.5	19.3	45.6	327.5	68.5	315.2	5.6
Gamma interferon Aβ_{1-6} peptide									
Week 8	n	67		37		104		15	
	Mean	-0.30	0.43	6.48	-0.89	2.11	-0.04	0.67	-0.99
	Min	-9.8	-11.9	-12.7	-24.2	-12.7	-24.2	-3.9	-12.3
	Median	-0.24	-0.08	-0.49	0.00	-0.24	-0.07	0.00	0.19
	Max	19.2	27.4	144.9	14.2	144.9	27.4	9.6	4.1
Gamma interferon Qβ peptide pool									
Week 8	n	64		36		100		15	
	Mean	80.42	53.26	63.44	59.15	74.31	55.38	84.27	-15.06
	Min	-2.6	-99.7	-0.7	-127.4	-2.6	-127.4	1.8	-252.1
	Median	36.40	32.67	27.44	40.42	32.11	35.13	38.70	-2.45
	Max	435.1	330.7	334.5	210.2	435.1	330.7	316.0	147.1

T-cell response is defined as MEAN(antigen) - SD(antigen) - MEAN(medium control) - SD(medium control).

Safety Results

Adverse Events by System Organ Class

Number (%) of patients with AEs by primary System organ class and treatment (Safety set)

Primary system organ class (SOC)	CAD106 150µg N=69 n (%) [95% CI]	CAD106 450µg N=37 n (%) [95% CI]	CAD Total N=106 n (%) [95% CI]	Placebo Total N=15 n (%) [95% CI]
Number (%) of patients with AE in any SOC	**58 (84.1) [73.3, 91.8]**	**30 (81.1) [64.8, 92.0]**	**88 (83.0) [74.5, 89.6]**	**12 (80.0) [51.9, 95.7]**
Blood and lymphatic system disorders	3 (4.3) [0.9, 12.2]	2 (5.4) [0.7, 18.2]	5 (4.7) [1.5, 10.7]	0 (0) [0.0, 21.8]
Cardiac disorders	6 (8.7) [3.3, 18.0]	0 (0) [0.0, 9.5]	6 (5.7) [2.1, 11.9]	1 (6.7) [0.2, 31.9]
Congenital, familial and genetic disorders	1 (1.4) [0.0, 7.8]	1 (2.7) [0.1, 14.2]	2 (1.9) [0.2, 6.6]	0 (0) [0.0, 21.8]
Ear and labyrinth disorders	2 (2.9) [0.4, 10.1]	3 (8.1) [1.7, 21.9]	5 (4.7) [1.5, 10.7]	1 (6.7) [0.2, 31.9]
Endocrine disorders	1 (1.4) [0.0, 7.8]	0 (0) [0.0, 9.5]	1 (0.9) [0.0, 5.1]	0 (0) [0.0, 21.8]
Eye disorders	6 (8.7) [3.3, 18.0]	2 (5.4) [0.7, 18.2]	8 (7.5) [3.3, 14.3]	1 (6.7) [0.2, 31.9]
Gastrointestinal disorders	21 (30.4) [19.9, 42.7]	5 (13.5) [4.5, 28.8]	26 (24.5) [16.7, 33.8]	3 (20.0) [4.3, 48.1]
General disorders and administration site conditions	27 (39.1) [27.6, 51.6]	13 (35.1) [20.2, 52.5]	40 (37.7) [28.5, 47.7]	3 (20.0) [4.3, 48.1]
Hepatobiliary disorders	4 (5.8) [1.6, 14.2]	0 (0) [0.0, 9.5]	4 (3.8) [1.0, 9.4]	0 (0) [0.0, 21.8]
Infections and infestations	30 (43.5) [31.6, 56.0]	11 (29.7) [15.9, 47.0]	41 (38.7) [29.4, 48.6]	5 (33.3) [11.8, 61.6]
Injury, poisoning and procedural complications	18 (26.1) [16.3, 38.1]	9 (24.3) [11.8, 41.2]	27 (25.5) [17.5, 34.9]	4 (26.7) [7.8, 55.1]
Investigations	11 (15.9) [8.2, 26.7]	2 (5.4) [0.7, 18.2]	13 (12.3) [6.7, 20.1]	3 (20.0) [4.3, 48.1]
Metabolism and nutrition disorders	3 (4.3) [0.9, 12.2]	4 (10.8) [3.0, 25.4]	7 (6.6) [2.7, 13.1]	1 (6.7) [0.2, 31.9]
Musculoskeletal and connective tissue disorders	22 (31.9) [21.2, 44.2]	9 (24.3) [11.8, 41.2]	31 (29.2) [20.8, 38.9]	2 (13.3) [1.7, 40.5]

Primary system organ class (SOC)	CAD106 150µg N=69 n (%) [95% CI]	CAD106 450µg N=37 n (%) [95% CI]	CAD Total N=106 n (%) [95% CI]	Placebo Total N=15 n (%) [95% CI]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (2.9) [0.4, 10.1]	3 (8.1) [1.7, 21.9]	5 (4.7) [1.5, 10.7]	1 (6.7) [0.2, 31.9]
Nervous system disorders	24 (34.8) [23.7, 47.2]	14 (37.8) [22.5, 55.2]	38 (35.8) [26.8, 45.7]	4 (26.7) [7.8, 55.1]
Psychiatric disorders	20 (29.0) [18.7, 41.2]	12 (32.4) [18.0, 49.8]	32 (30.2) [21.7, 39.9]	4 (26.7) [7.8, 55.1]
Renal and urinary disorders	8 (11.6) [5.1, 21.6]	3 (8.1) [1.7, 21.9]	11 (10.4) [5.3, 17.8]	2 (13.3) [1.7, 40.5]
Reproductive system and breast disorders	5 (7.2) [2.4, 16.1]	0 (0) [0.0, 9.5]	5 (4.7) [1.5, 10.7]	0 (0) [0.0, 21.8]
Respiratory, thoracic and mediastinal disorders	11 (15.9) [8.2, 26.7]	5 (13.5) [4.5, 28.8]	16 (15.1) [8.9, 23.4]	3 (20.0) [4.3, 48.1]
Skin and subcutaneous tissue disorders	13 (18.8) [10.4, 30.1]	5 (13.5) [4.5, 28.8]	18 (17.0) [10.4, 25.5]	4 (26.7) [7.8, 55.1]
Surgical and medical procedures	2 (2.9) [0.4, 10.1]	1 (2.7) [0.1, 14.2]	3 (2.8) [0.6, 8.0]	0 (0) [0.0, 21.8]
Vascular disorders	14 (20.3) [11.6, 31.7]	6 (16.2) [6.2, 32.0]	20 (18.9) [11.9, 27.6]	1 (6.7) [0.2, 31.9]

Primary SOC are presented alphabetically.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
A patient with multiple AEs within a primary SOC is counted only once in the total row.
Exact 95% confidence interval used.

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

Number (%) of patients with common AEs (greater than or equal to 10% in any group) by preferred term and treatment (Safety set)

Preferred term	CAD106 150µg N=69 n (%) [95% CI]	CAD106 450µg N=37 n (%) [95% CI]	CAD Total N=106 n (%) [95% CI]	Placebo Total N=15 n (%) [95% CI]
Headache	10 (14.5) [7.2, 25.0]	7 (18.9) [8.0, 35.2]	17 (16.0) [9.6, 24.4]	1 (6.7) [0.2, 31.9]
Nasopharyngitis	10 (14.5) [7.2, 25.0]	6 (16.2) [6.2, 32.0]	16 (15.1) [8.9, 23.4]	2 (13.3) [1.7, 40.5]
Back pain	7 (10.1)	3 (8.1)	10 (9.4)	0 (0)

Preferred term	CAD106 150µg N=69 n (%) [95% CI]	CAD106 450µg N=37 n (%) [95% CI]	CAD Total N=106 n (%) [95% CI]	Placebo Total N=15 n (%) [95% CI]
	[4.2, 19.8]	[1.7, 21.9]	[4.6, 16.7]	[0.0, 21.8]
Hypertension	7 (10.1) [4.2, 19.8]	4 (10.8) [3.0, 25.4]	11 (10.4) [5.3, 17.8]	0 (0) [0.0, 21.8]
Insomnia	7 (10.1) [4.2, 19.8]	2 (5.4) [0.7, 18.2]	9 (8.5) [4.0, 15.5]	0 (0) [0.0, 21.8]
Osteoarthritis	7 (10.1) [4.2, 19.8]	0 (0) [0.0, 9.5]	7 (6.6) [2.7, 13.1]	0 (0) [0.0, 21.8]
Pyrexia	7 (10.1) [4.2, 19.8]	4 (10.8) [3.0, 25.4]	11 (10.4) [5.3, 17.8]	0 (0) [0.0, 21.8]
Fatigue	6 (8.7) [3.3, 18.0]	2 (5.4) [0.7, 18.2]	8 (7.5) [3.3, 14.3]	2 (13.3) [1.7, 40.5]
Urinary tract infection	6 (8.7) [3.3, 18.0]	3 (8.1) [1.7, 21.9]	9 (8.5) [4.0, 15.5]	2 (13.3) [1.7, 40.5]
Arthralgia	5 (7.2) [2.4, 16.1]	1 (2.7) [0.1, 14.2]	6 (5.7) [2.1, 11.9]	2 (13.3) [1.7, 40.5]
Fall	5 (7.2) [2.4, 16.1]	4 (10.8) [3.0, 25.4]	9 (8.5) [4.0, 15.5]	2 (13.3) [1.7, 40.5]
Aggression	4 (5.8) [1.6, 14.2]	1 (2.7) [0.1, 14.2]	5 (4.7) [1.5, 10.7]	2 (13.3) [1.7, 40.5]
Depression	4 (5.8) [1.6, 14.2]	5 (13.5) [4.5, 28.8]	9 (8.5) [4.0, 15.5]	1 (6.7) [0.2, 31.9]
Cough	3 (4.3) [0.9, 12.2]	2 (5.4) [0.7, 18.2]	5 (4.7) [1.5, 10.7]	2 (13.3) [1.7, 40.5]
Agitation	2 (2.9) [0.4, 10.1]	1 (2.7) [0.1, 14.2]	3 (2.8) [0.6, 8.0]	2 (13.3) [1.7, 40.5]
Anxiety	1 (1.4) [0.0, 7.8]	1 (2.7) [0.1, 14.2]	2 (1.9) [0.2, 6.6]	3 (20.0) [4.3, 48.1]
Weight decreased	1 (1.4) [0.0, 7.8]	0 (0) [0.0, 9.5]	1 (0.9) [0.0, 5.1]	2 (13.3) [1.7, 40.5]

A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category.
Preferred terms are presented in descending order of frequency in the CAD106 150µg group.
Exact 95% CI used.

Serious Adverse Events and Deaths

Deaths, SAEs and AEs leading to discontinuation of study drug – n (%) of patients (Safety set)

Serious or other significant events	CAD106 150µg N=69 n (%) [95% CI]	CAD106 450µg N=37 n (%) [95% CI]	CAD Total N=106 n (%) [95% CI]	Placebo Total N=15 n (%) [95% CI]
Death	1 (1.4) [0.0, 7.8]	1 (2.7) [0.1, 14.2]	2 (1.9) [0.2, 6.6]	0 (0.0) [0.0, 21.8]
SAEs	18 (26.1) [16.3, 38.1]	8 (21.6) [9.8, 38.2]	26 (24.5) [16.7, 33.8]	1 (6.7) [0.2, 31.9]
SAEs leading to permanent discontinuation of study drug	3 (4.3) [0.9, 12.2]	2 (5.4) [0.7, 18.2]	5 (4.7) [1.5, 10.7]	0 (0.0) [0.0, 21.8]
AEs leading to permanent discontinuation of study drug	6 (8.7) [3.3, 18.0]	2 (5.4) [0.7, 18.2]	8 (7.5) [3.3, 14.3]	0 (0.0) [0.0, 21.8]

Information about deaths stems from the Study Completion page. Information about AEs and SAEs stem from the AEs page.

Exact 95% confidence interval used.

Information about deaths stems from the study completion page:

Only 2 patients were recorded as such on this page. However, another patient died just after premature withdrawal from the study and death is only recorded on the AE panel.

Information about AEs and SAEs stem from the AEs page:

The 8 patients with AEs leading to discontinuation of study drug do not include the following 2 patients:

One patient was to discontinue the study due to MRI finding of new MHs, but withdrawal of informed consent was recorded as the main reason for study discontinuation.

One patient discontinued the study drug due to SUSAR of allergic reaction but was discontinued from study due to MRI finding of new MHs, recorded under the category “Abnormal test procedure”.

Other Relevant Findings

Oligoclonal bands and White blood cell (WBC) count in cerebrospinal fluid (CSF)

Newly occurring CNS inflammation tests abnormalities by treatment – n (%) of patients (Safety set)

Criteria	CAD106 150µg (N=69)	CAD106 450µg (N=37)	CAD Total (N=106)	Placebo Total (N=15)
	n / Tot (%) [95% CI]	n / Tot (%) [95% CI]	n / Tot (%) [95% CI]	n / Tot (%) [95% CI]
Oligoclonal bands in CSF only	5/51 (9.8) [3.3, 21.4]	3/19 (15.8) [3.4, 39.6]	8/70 (11.4) [5.1, 21.3]	0/8 (0) [0.0, 36.9]
White blood cell count in CSF >5/µl	1/54 (1.9) [0.0, 9.9]	1/31 (3.2) [0.1, 16.7]	2/85 (2.4) [0.3, 8.2]	1/9 (11.1) [0.3, 48.2]

n: Number of patients with the finding.

Tot: Number of patients who had at least one observation both at BL and post-BL.

Exact 95% confidence interval used.

'Newly occurring White blood cell count in CSF >5 /µl' is defined as any post-baseline assessment of white blood cell count in CSF which is >5 /µl.

'Newly occurring oligoclonal bands' is defined as any change from 'negative' or 'equivocal' to 'positive' at any post-baseline assessment in comparison to baseline.

Safety MRI

Newly occurring MRI abnormalities during the study by treatment – n (%) of patients (Safety set)

Newly occurring / worsening of MRI	CAD106 150µg (N=69)	CAD106 450µg (N=37)	CAD Total (N=106)	Placebo Total (N=15)
	n / Total (%) [95% CI]	n / Total (%) [95% CI]	n / Total (%) [95% CI]	n / Total (%) [95% CI]
Findings suggestive of an adverse reaction *	5/69 (7.2) [2.4, 16.1]	2/37 (5.4) [0.7, 18.2]	7/106 (6.6) [2.7, 13.1]	0/14 (0) [0.0, 23.2]
At least 2 new microhemorrhages	3/69 (4.3) [0.9, 12.2]	0/37 (0) [0.0, 9.5]	3/106 (2.8) [0.6, 8.0]	0/14 (0) [0.0, 23.2]
Any other types of hemorrhages **	1/69 (1.4) [0.0, 7.8]	2/37 (5.4) [0.7, 18.2]	3/106 (2.8) [0.6, 8.0]	0/14 (0) [0.0, 23.2]
Ischemic stroke	1/69 (1.4) [0.0, 7.8]	0/37 (0) [0.0, 9.5]	1/106 (0.9) [0.0, 5.1]	0/14 (0) [0.0, 23.2]
White matter disease worsening	2/69 (2.9) [0.4, 10.1]	0/37 (0) [0.0, 9.5]	2/106 (1.9) [0.2, 6.6]	0/14 (0) [0.0, 23.2]

Newly occurring / worsening of MRI	CAD106 150µg (N=69)	CAD106 450µg (N=37)	CAD Total (N=106)	Placebo Total (N=15)
	n / Total (%) [95% CI]	n / Total (%) [95% CI]	n / Total (%) [95% CI]	n / Total (%) [95% CI]

n: Number of patients with the finding.

Tot: Number of patients who had at least one MRI parameter assessed both at BL and post-BL.

Exact 95% confidence interval used.

All criteria must be fulfilled at the same scan. "Newly occurring" is referring to baseline for all post-baseline assessments.

* including findings of hyper- and hypo-intensities on T1, T2 or FLAIR, or other lesions

** including intracerebral hemorrhage (ICH), subdural hematoma (SDH), subarachnoid hemorrhage (SAH)

Effect of adjuvant on tolerability

Local and systemic reactions by treatment – n (%) of patients (Safety set)

		CAD106 150µg (N=69)	CAD106 450µg without adj. (N=16)	CAD106 450µg + Alum 450µg (N=21)	Placebo Total (N=15)
		n (%)	n (%)	n (%)	n (%)
Any injection (n)		69 (100)	16 (100)	21 (100)	15 (100)
	Any (local or systemic)	61 (88.4)	16 (100)	19 (90.5)	11 (73.3)
	Any local reaction	56 (81.2)	14 (87.5)	18 (85.7)	6 (40.0)
	Any systemic reaction	54 (78.3)	15 (93.8)	18 (85.7)	8 (53.3)
	Both local and systemic	49 (71.0)	13 (81.3)	17 (81.0)	3 (20.0)
	Local				
	Bruising (Ecchymosis)	21 (30.4)	6 (37.5)	4 (19.0)	1 (6.7)
	Redness	38 (55.1)	10 (62.5)	10 (47.6)	3 (20.0)
	Induration	30 (43.5)	10 (62.5)	11 (52.4)	4 (26.7)
	Swelling	39 (56.5)	9 (56.3)	10 (47.6)	3 (20.0)
	Pain	49 (71.0)	13 (81.3)	17 (81.0)	4 (26.7)
	Systemic				
	Chills	27 (39.1)	11 (68.8)	7 (33.3)	1 (6.7)
	Malaise	30 (43.5)	11 (68.8)	12 (57.1)	2 (13.3)
	Muscle pain (Myalgia)	35 (50.7)	13 (81.3)	12 (57.1)	1 (6.7)
	Joint pain (Arthralgia)	24 (34.8)	7 (43.8)	7 (33.3)	1 (6.7)
	Headache	29 (42.0)	8 (50.0)	14 (66.7)	6 (40.0)
	Sweating	19 (27.5)	4 (25.0)	9 (42.9)	1 (6.7)
	Fatigue	36 (52.2)	13 (81.3)	11 (52.4)	5 (33.3)
	Fever	12 (17.4)	4 (25.0)	1 (4.8)	0 (0)

Injection site reactions are collected through patient diaries for up to 8 days post-injection.

Systemic reactions are reactions related to the whole body including fever which is defined as body temperature ≥ 38.0º C. For body temperature, post-injection data from vital signs pages is also included.

A subject with multiple occurrences of a reaction under one treatment is counted only once in the reaction category for that treatment.

A subject with multiple reactions within either the local/systemic classification is counted only once in the total row (Any reaction).

Date of Clinical Trial Report

18-Nov-2013

Date Inclusion on Novartis Clinical Trial Results Database

14 Dec 2013

Date of Latest Update

1-Dec-2013