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Sponsor Novartis Pharma AG
Generic Drug Name CAD106
Therapeutic Area of Trial Mild Alzheimer's Disease (AD)
Approved Indication Investigational
Protocol Number Protocol no. CCAD106A2201E1
Title An open-label extension to a 52-week, multi-center, randomized, double-blind, placebo-controlled, parallel group study in patients with mild Alzheimer's Disease (AD) to investigate the safety and tolerability of repeated subcutaneous injections to CAD106.
Phase of Development Phase IIA
Study Start/End Dates 08-Sep-2009 (first patient first visit) to 21-Jun-2011 (last patient last visit)
Study Design/Methodology This study consisted of a 66-week open-label extension study with CAD106. Only patients with AD who completed the core 52-week, randomized, double-blind, placebo-controlled, parallel group study (Study 2201) may have participated. Patients received 4 subcutaneous (s.c.) injections with CAD106 (150 µg).
Centres 4 centers (same as in the core study CCAD106A2201): 1 in France, 1 in Sweden, 1 in Switzerland, and 1 in United Kingdom.
Publication None.

Outcome measures

Primary outcome measures(s)

The primary objectives of the open label extension were:

- To evaluate the safety and tolerability of repeated injections of 150µg CAD106 in AD patients over the 66 weeks of the extension study
- To evaluate the antibody response of repeated injections of CAD106 as measured by the titers levels of Aβ-specific IgG in serum in AD patients over the 66 weeks of the extension study.

Secondary outcome measures(s)

The secondary objectives were as follows:

- To evaluate the antibody response of repeated injections of CAD106 as measured by the titers levels of Aβ-specific IgM, Aβ-specific IgG subtypes and Qβ-specific IgG and IgM in serum over the 66 weeks of the extension study.
- To compare the antibody response (Aβ-specific IgG in serum) between the 3 initial CAD106 injections given at 6-week intervals in the core study and 4 initial CAD106 injections given at 12-week intervals in the extension study in patients initially treated with placebo in the core study.
- To evaluate the antibody response (Aβ-specific IgG in serum) after 4 additional injections in the extension study in patients initially treated with CAD106 in the core study.

As CSF collection was optional, the following objectives were analyzed only if sufficient number of CSF samples were collected:

- To evaluate the immunogenicity of repeated injections of 150µg CAD106 as measured by Aβ-specific IgG, IgM in CSF in patients with mild AD over the 66 weeks of the extension study.
- To evaluate the effect of CAD106 on the concentrations of disease-related markers in CSF ($A\beta_{1-40}$, $A\beta_{1-42}$, total-tau, and phospho-tau) up to extension Week 44 in patients with mild AD.

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

Four injections of open-label CAD106 (150 µg) were administered s.c. at Weeks 0, 12, 24, and 36. Concentration of the vials of CAD106 was 1mg/mL solution.

Statistical Methods

The main purpose of the final analysis was to summarize safety, tolerability, and immune response (Aβ-specific IgG titer).
The safety and tolerability of repeated subcutaneous (s.c.) injections of 150µg CAD106 was assessed by descriptive summaries of adverse events, injection-related local and systemic reactions, cerebral safety MRI and CSF findings based on the Safety analysis set. No inferential statistical analyses were performed. Safety and tolerability parameters were summarized by treatment group of the Core study (CCAD106A2201). Local and systemic injection-related reactions were summarized by injection and across injections.
The immune response was assessed by different parameters like Cmax (maximal concentration), Tmax (time to maximal concentration), and Area Under Curve (AUC) for Aβ-specific antibody titers. Descriptive overall summary tables were provided for antibody response based on all data collected during the 66 weeks of the Extension study.

Study Population: Inclusion/Exclusion Criteria and Demographics

The study population consisted of mild AD patients who completed the core study with no major safety concerns.

The inclusion criteria were as follows:

- Patients who have completed the core study with no significant safety concerns.
- Cooperative, willing to complete all aspects of the open-label extension and capable of doing so, either alone or with the aid of a responsible caregiver.
- Residing with someone in the community throughout the open-label extension or, if living alone, who have daily contact with a primary caregiver.
- Primary caregiver willing to accept responsibility for assessing the condition of the patient throughout the open-label extension, and for providing input to safety and tolerability assessments in accordance with all protocol requirements.
- Able to provide written informed consent and having a responsible caregiver that can provide written assent prior to participation in the open-label extension. Written informed consent must be obtained before any assessment is performed.

The main exclusion criteria were as follows:

- Diagnosis of other neurodegenerative disease and/or psychiatric disorders (with the exception of successfully treated depression).
- Any medical or neurological condition, other than AD, that contributes significantly to the patient's dementia (e.g., abnormal thyroid function tests, Vitamin B12 or folate deficiency, post-traumatic conditions, Huntington's disease, Parkinson's disease, Lyme's disease, syphilis), including any CSF and/or cerebral MRI findings.
- CNS inflammation as indicated by (1) MRI findings indicative of either meningoencephalitis or of another adverse immune reaction (according to central reader evaluation); or (2) signs of inflammation in CSF as defined by clinical judgment and according to ranges from the laboratory used.
  In most cases in a CSF sample not contaminated by blood, this will be shown by >5 leukocytes/ l, and protein above the age-defined normal range of the laboratory used (e.g. abnormal IgG index, IgG oligoclonal bands).

Participant Flow

Patient disposition by Core treatment (CAD or Placebo) - Extension study

n (%) of patients	CAD/CAD N = 22 n (%)	Placebo/CAD N = 5 n (%)	Total (CAD) N = 27 n (%)
Completed core study	22 (100)	5 (100)	27 (100)
Entered OL treatment extension study	18 (90.0)	3 (75.0)	21 (87.5)
Withdrawal from extension study	4 (20.0)	0 (0.0)	4 (16.7)
Adverse event(s)	3 (75.0)	0 (0.0)	3 (75.0)
Protocol deviation	1 (25.0)	0 (0.0)	1 (25.0)

Reason for withdrawal stems from the Study Completion page for patients who withdrew early after entry into the Extension study.

Baseline Characteristics

Demographic and baseline characteristics by treatment (Safety analysis set)

n (%) of patients		CAD/CAD N = 18	Placebo/CAD N = 3	Total (CAD) N = 21
Sex – n (%)	Male	13 (72.2)	2 (66.7)	15 (71.4)
	Female	5 (27.8)	1 (33.3)	6 (28.6)
Age (years)	Mean	65.7	65.7	65.7
	SD	6.60	2.52	6.13
	Median	66.0	66.0	66.0
	Range	53, 77	63, 68	53, 77
Age group – n (%)	< 65 years	8 (44.4)	1 (33.3)	9 (42.9)
	65 to 75 years	9 (50.0)	2 (66.7)	11 (52.4)
	> 75 years	1(5.6)	0 (0.0)	1 (4.8)
Race - n (%)	Black	0 (0.0)	0 (0.0)	0 (0.0)
	Caucasian	18 (100)	3 (100)	21 (100)
	Oriental	0 (0.0)	0 (0.0)	0 (0.0)
	Other	0 (0.0)	0 (0.0)	0 (0.0)
MHIS – n (%)	0	10 (55.6)	2 (66.7)	12 (57.1)
	1	4 (22.2)	1 (33.3)	5 (23.8)
	2	3 (16.7)	0 (0.0)	3 (14.3)
	3	1 (5.6)	0 (0.0)	1 (4.8)
	4	0 (0.0)	0 (0.0)	0 (0.0)
	> 4	0 (0.0)	0 (0.0)	0 (0.0)
MMSE	Mean	21.5	25.7	22.1
	SD	5.50	1.15	5.30
	Median	22.0	25.0	23.0
	Range	11, 29	25, 27	11, 29
ApoE4 carriers*	n (%)	10 (62.5)	2 (100)	12 (66.7)

* Percentage based on the number of patient genotyped.
- MMSE summarized at extension study baseline. Age, MHIS, and APO-E4 summarized at core study baseline.
- Core study baseline is defined as the assessment on or before date of first injection of the core study.
- Extension study baseline is defined as last assessment prior to the first injection of the extension study (either Week 52 from core study or an unscheduled visit from extension just prior to the first injection).

Outcome measures

Primary Outcome Result(s)

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

Secondary Outcome Result(s)

Abeta-specific IgG antibody titers in serum by treatment - summary parameters (Safety analysis set)

		CAD/CAD N = 14*	Placebo/CAD N = 3	Total (CAD) N = 21
Calculation from Week 0 (core baseline)				
AUC (unit*days)	n	14		
	Mean	25865.30		
	SD	20084.895		
	Median	24394.14		
	Range	0.0, 69177.1		
Cmax (units)	n	14		
	Mean	103.06		
	SD	78.445		
	Median	98.35		
	Range	0.0, 277.8		
Tmax (days)	n	13		
	Mean	286.69		
	SD	275.827		
	Median	114.00		
	Range	15.0, 687.0		
Calculation from Week 52 (extension baseline)				
AUC (unit*days)	n	14	3	17
	Mean	18684.16	8448.19	16877.82
	SD	16067.844	4182.636	15104.073
	Median	13510.79	10407.75	12420.15
	Range	0.0, 50336.5	3645.5, 11291.3	0.0, 50336.5
Cmax (units)	n	14	3	17
	Mean	67.62	42.20	63.14
	SD	57.777	20.003	53.498
	Median	50.40	50.40	50.40
	Range	0.0, 187.0	19.4, 56.8	0.0, 187.0
Tmax (days)	n	13	3	16
	Mean	218.62	305.67	234.94
	SD	120.962	16.258	113.895
	Median	218.00	309.00	253.00
	Range	49.0, 491.0	288.0, 320.0	49.0, 491.0

* Out of 18 patients enrolled in CAD/CAD treatment group, 4 patients withdrew and did not provide week 66 Antibody titers.
AUC is computed using the trapezoidal method for week 0 (core and extension) to week 66. 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 66.
Tmax is calculated as the time in study days from the corresponding baseline (Day 0) in which the maximum concentration (Cmax) occurred up to extension Week 66. If (Cmax)=0 then Tmax is set to missing.
Core study baseline is defined as the assessment on or before date of first injection of the core study.
Extension study baseline is defined as last assessment prior to the first injection of the extension study (either Week 52 from core study or an unscheduled visit from extension just prior to the first injection).

Safety Results

Adverse Events by System Organ Class

Number (%) of patients with adverse events by primary system organ class and treatment (Safety analysis set)

Primary system organ class	Total (CAD) N = 21
Any primary system organ class	18 (85.7)
Cardiac disorders	3 (14.3)
Ear and labyrinth disorders	2 (9.5)
Gastrointestinal disorders	6 (28.6)
General disorders and administration site conditions	3 (14.3)
Infections and infestations	9 (42.9)
Injury, poisoning and procedural complications	2 (9.5)
Investigations	2 (9.5)
Metabolism and nutrition disorders	1 (4.8)
Musculoskeletal and connective tissue disorders	3 (14.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (14.3)
Nervous system disorders	2 (9.5)
Psychiatric disorders	4 (19.0)
Renal and urinary disorders	2 (9.5)
Reproductive system and breast disorders	4 (19.0)
Respiratory, thoracic and mediastinal disorders	1 (4.8)
Skin and subcutaneous tissue disorders	1 (4.8)
Vascular disorders	3 (14.3)

Primary system organ classes are presented alphabetically.
A patient with multiple adverse events within a primary system organ class is counted only once.

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

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

Preferred term	Total (CAD) N = 21
Nasopharyngitis	4 (19.0)
Diarrhea	3 (14.3)
Benign prostatic hyperplasia	3 (14.3)
Constipation	2 (9.5)
Depressive symptom	2 (9.5)
Fatigue	2 (9.5)
Hypertension	2 (9.5)
Urinary tract infection	2 (9.5)
Depression	2 (9.5)
Ear infection	1 (4.8)
Joint sprain	1 (4.8)
Nausea	1 (4.8)
Prostatic adenoma	1 (4.8)

A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
Preferred terms are presented in descending frequency in the Total (CAD) group.

Serious Adverse Events and Deaths

Deaths, other serious adverse events and adverse events leading to discontinuation of study drug - n (%) of patients (Safety analysis set)

Serious or other significant events	Total (CAD) N = 21 n (%)
Death	0 (0.0)
SAE(s) (all not suspected to be related to study medication): 1. Rectal Neoplasm 2. Hepatic Neoplasm Malignancy 3. Minor Stroke	3 (14.3)
Permanently discontinued study drug due to SAE(s): 1. Minor Stroke	1 (4.8)
Non-serious AEs leading to permanent discontinuation of study drug	0 (0.0)

Information about deaths stems from the Treatment Period or Study Completion page. Information about AEs and SAEs stem from the Adverse Events page.

Other Relevant Findings

Newly occurring specific safety assessments abnormalities by treatment - n (%) of patients (Safety analysis set)	Total (CAD) N = 9 n (%)
White blood cell count in CSF > 5/µL	0 (0.0)

Lumbar Punctures were optional in this Open-Label Extension

Newly occurring MRI abnormalities during the study by treatment - n (%) of patients (Safety analysis set)	Total (CAD) N = 21 n (%)
Newly occurring abnormalities compared to core study baseline	
Contrast enhancement in the absence of hemorrhage or stroke	0 (0.0)
Hyperintense T2 lesion in the absence of hemorrhage or stroke	0 (0.0)
At least two new microhemorrhages	2 (9.5)
Any other type of hemorrhage	1 (4.8)
Any stroke	1 (4.8)
Any significant cerebrovascular disease worsening	2 (9.5)
Newly occurring abnormalities compared to extension study baseline	
Contrast enhancement in the absence of hemorrhage or stroke	0 (0.0)
Hyperintense T2 lesion in the absence of hemorrhage or stroke	0 (0.0)
At least two new microhemorrhages	2 (9.5)
Any other type of hemorrhage	1 (4.8)
Any stroke	1 (4.8)
Any significant cerebrovascular disease worsening	0 (0.0)

Contrast enhancement includes "CSF staining" and "Contrast enhancement of brain tissue/dura or leptomeningeal enhancement"
Hyperintense T2 lesion is defined as "New hyperintense T2 lesion suggestive of oedema formation".
Stroke is defined as any territorial or lacunar strokes.
Hemorrhage includes intracranial hemorrhage, intraparenchymal hematoma, hemorrhagic transformation, subdural hematoma, epidural hematoma, subarachnoid hemorrhage, and hemosiderosis from past hemorrhage.
All criteria must be fulfilled at the same scan. "Newly occurring" is referring to baseline for all post-baseline assessments.
Core study baseline is defined as the assessment on or before date of first injection of the core study.
Extension study baseline is defined as last assessment prior to the first injection of the extension study (either Week 52 from core study or an unscheduled visit from extension just prior to the first injection).

Date of Clinical Trial Report

19-Apr-2012

Date Inclusion on Novartis Clinical Trial Results Database

08 June 2012

Date of Latest Update

No updates.