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Novartis CTRD Results Template

Sponsor

Novartis Pharma AG

Generic Drug Name

CAD106

Therapeutic Area of Trial

Alzheimer's Disease

Approved Indication

Investigational

Protocol Number

CCAD106A2202E1

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 injections of CAD106

Study Phase

IIa

Study Start/End Dates

21-Dec-2009 (first patient first visit) to 27-Feb-2012 (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 2202) were considered for participation.

Patients received 4 intramuscular (i.m.) injections with CAD106 (150 µg).

Centres

There were 8 centers in the United States of America

Publication

None.

Outcome measures

Primary outcome measures(s)

- 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)

- To evaluate the antibody response of 4 repeated injections of CAD106 as measured by the titers level of Aβ-specific IgM, Aβ-specific IgG subtype 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 0, 2, 6 weeks in the core study and 4 initial CAD106 injections given 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.

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

Four injections of open-label CAD106 (150 µg) were administered i.m. 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 intramuscularly (i.m.) 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 (CAD106A2202). Local and systemic injection related reactions were summarized by injections and across injections.

Descriptive overall summary tables were provided for antibody response based on all data collected during the 66 weeks of the Extension study. The analysis of Aβ IgG in serum was based on different summary parameters like concentration maximum (Cmax), time to concentration maximum (Tmax) area under curve (AUC) and responder status. The latter

two parameters were derived from core baseline and from extension baseline and were presented by treatment group of Core study to evaluate the antibody response of the different regimen.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

The inclusion criteria for patients entering into the study 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 primary caregiver.
- 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 was performed.

Exclusion criteria

- 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 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.
- Other protocol defined exclusion criteria were applicable.

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Participant Flow

Patient disposition by treatment – n (%) of patients- Extension study

	CAD/CAD N=25 n (%)	Placebo/CAD N=6 n (%)	Total (CAD) N=31 n (%)
Total number of patients	25 (100)	6 (100)	31 (100)
Completed Core Study	24 (96.0)	6 (100)	30 (96.8)
Entered Extension Study	20 (80.0)	4 (66.7)	24 (77.4)
In Safety Analysis Set	20 (100)	4 (100)	24 (100)
Completed Extension Study	15 (75.0)	3 (75.0)	18 (75.0)
Withdrawal from Extension study	5 (25.0)	1 (25.0)	6 (25.0)
Subject withdrew consent	4 (80.0)	1 (100)	5 (83.3)
Death	1 (20.0)	0 (0.0)	1 (16.7)

Safety analysis set consists of all patients who received at least one study medication and had at least one post-injection safety assessment.

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

Upon their final visit (either in the Core or Extension study), all patients were to enter a 2-year Safety Follow-up.

Baseline Characteristics

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

		CAD/CAD N=20	Placebo/CAD N=4	Total (CAD) N=24
Sex - n (%)	Male	13 (65.0)	2 (50.0)	
	Female	7 (35.0)	2 (50.0)	
Age (Years)	Mean	68.9	63.0	
	SD	8.85	4.16	
	Median	71.0	63.0	
	Range	53, 83	58, 68	
Age group - n (%)	< 65 years	6 (30.0)	3 (75.0)	
	65 to 75 years	7 (35.0)	1 (25.0)	
	> 75 years	7 (35.0)	0 (0.0)	
Race - n (%)	Black	1 (5.0)	0 (0.0)	

	Caucasian	19 (95.0)	4 (100)	23 (95.8)
	Oriental	0 (0.0)	0 (0.0)	0 (0.0)
	Other	0 (0.0)	0 (0.0)	0 (0.0)
MHIS - n (%)	0	13 (65.0)	4 (100)	17 (70.8)
	1	5 (25.0)	0 (0.0)	5 (20.8)
	2	2 (10.0)	0 (0.0)	2 (8.3)
	3	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)
	>4	0 (0.0)	0 (0.0)	0 (0.0)
MMSE at Baseline Core Study	Mean	21.9	22.3	21.9
	SD	1.81	2.63	1.91
	Median	21.5	22.0	21.5
	Range	20, 26	20, 25	20, 26
MMSE at Baseline Extension Study	Mean	18.8	21.5	19.2
	SD	4.80	4.73	4.80
	Median	19.0	20.0	19.0
	Range	10, 26	18, 28	10, 28
ApoE4 carriers*	n (%)	17 (94.4)	4 (100)	21 (95.5)

* Percentage based on the number of patients genotyped.

- Age, MHIS, and APO-E4 summarized at core study baseline, which is defined as the assessment on or before date of first injection in the Core study.

- MMSE summarized at core and extension baseline, which 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).

Overall exposure to study medication – n (%) of patients (Safety analysis set)

Patient with injections in extension study	CAD/CAD N=20	Placebo/CAD N=4	Total (CAD) N=24
At least one injection - n (%)	20 (100)	4 (100)	24 (100)
At least two injections - n (%)	20 (100)	4 (100)	24 (100)
At least three injections - n (%)	18 (90.0)	3 (75.0)	21 (87.5)
At least four injections - n (%)	11 (55.0)	2 (50.0)	13 (54.2)

Subjects with more than one injection are counted in multiple categories.

Outcome measures

The primary objectives were safety, tolerability and antibody response (Abeta-specific IgG titers in serum). Safety results are reported in the safety section.

Primary Outcome Result(s)

Aβ IgG antibody titers in serum by treatment – summary parameters (Safety analysis set)

		CAD s.c/CAD N=9	CAD i.m/CAD N=11	Placebo/CAD N=4	Total (CAD) N=24
Calculated from Baseline Core Study					
AUC (unit*days)	Mean	23944.08	47327.75		
	SD	18328.243	47657.410		
	Median	21256.65	26956.85		
	Range	5095.5, 65827.1	5339.8, 129644.6		
Cmax (units)	Mean	94.24	113.64		
	SD	56.793	130.269		
	Median	84.50	90.30		
	Range	21.9, 181.0	0.0, 453.0		
Tmax (days)	Mean	313.78	318.80		
	SD	246.604	289.014		
	Median	410.00	214.00		
	Range	57.0, 577.0	51.0, 688.0		
Calculated from Baseline Extension Study					
AUC (unit*days)	Mean	18657.63	38101.66	12723.58	25230.19
	SD	17382.905	39809.827	9832.118	28483.214
	Median	16005.33	22932.15	15736.70	16926.93
	Range	483.0, 58815.1	3694.9, 107886.0	1737.5, 20696.6	483.0, 107886.0
Cmax (units)	Mean	68.69	99.53	73.83	83.68
	SD	53.388	135.200	39.120	96.764
	Median	54.40	39.40	89.20	56.45
	Range	11.5, 177.0	0.0, 453.0	15.9, 101.0	0.0, 453.0
Tmax (days)	Mean	131.00	146.40	139.50	139.17
	SD	80.492	120.758	106.497	99.595
	Median	99.00	180.50	142.00	180.00
	Range	14.0, 275.0	15.0, 309.0	15.0, 259.0	14.0, 309.0

AUC is computed using the trapezoidal method from core or extension baseline up to extension Week 66. Titer values below the LLOQ were set to 0 for the computation of AUC.

C_{max} is the observed maximum post-treatment concentration value up to extension Week 66.

T_{max} is calculated as the time in study days in which the maximum concentration (C_{max}) occurred up to extension Week 66. If (C_{max}) =0 then T_{max} 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

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

Primary system organ class	Total (CAD) N=24 n (%)
Any Primary System organ class	19 (79.2)
Cardiac disorders	4 (16.7)
Eye disorders	3 (12.5)
Gastrointestinal disorders	9 (37.5)
General disorders and administration site conditions	6 (25.0)
Hepatobiliary disorders	2 (8.3)
Infections and infestations	7 (29.2)
Injury, poisoning and procedural complications	7 (29.2)
Investigations	2 (8.3)
Metabolism and nutrition disorders	2 (8.3)
Musculoskeletal and connective tissue disorders	6 (25.0)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (4.2)
Nervous system disorders	9 (37.5)
Psychiatric disorders	11 (45.8)
Renal and urinary disorders	2 (8.3)
Respiratory, thoracic and mediastinal disorders	3 (12.5)
Skin and subcutaneous tissue disorders	6 (25.0)
Vascular disorders	1 (4.2)

Primary system organ classes 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 adverse events within a primary system organ class is counted only once in the total row.

Only AE's occurring during the extension study (i.e. ongoing at start of extension or newly occurring during extension study) are presented in this table.

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

Preferred term	Total (CAD) N=24 n (%)
Headache	5 (20.8)
Agitation	4 (16.7)
Depression	4 (16.7)
Fatigue	4 (16.7)
Confusional state	3 (12.5)

Fall	3 (12.5)
Hallucination	3 (12.5)
Anxiety	3 (12.5)
Diarrhoea	3 (12.5)
Nausea	3 (12.5)

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 frequency in the Total (CAD) group.

Only AEs occurring during the extension study (i.e. ongoing at start of extension or newly occurring during the extension study) are presented in this table.

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=24n (%)**
Death	1 (4.2)*
SAE(s)*	3 (12.5)**
Permanently discontinued study drug due to SAE(s)	1 (4.2)*
AE(s) leading to permanent discontinuation of study drug	1 (4.2)*

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

* The same patient A2202E1-0509-00010 was counted in the different categories. For this patient, discontinuation of study medication was reported due to the SAE (COPD). He died a few days later due to respiratory failure further to SAE “chronic obstructive pulmonary disease”.

** The three SAEs were: 1/ cholecystitis along with progression of Alzheimer’s dementia), 2/ convulsion and 3/ worsening of chronic obstructive pulmonary disease. None were suspected to be related to study drug.

Newly occurring specific safety assessments abnormalities by treatment – n (%) (Safety analysis set)

	Total (CAD) N=24 n/Total (%)
White blood cell count in CSF > 5 / µl	0/7 (0.0)

Collection of CSF at week 40 and/or 66 was optional for extension study and percentage is based on only those patients with test results.

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

	Total (CAD) N=24 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	0 (0.0)
Any other type of hemorrhage	0 (0.0)
Any stroke	1 (4.2)
Any significant cerebrovascular disease worsening	4 (16.7)
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	0 (0.0)
Any other type of hemorrhage	0 (0.0)
Any stroke	0 (0.0)
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 include 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 the specified 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).

Other Relevant Findings

None.

Date of Clinical Trial Report

06-Dec-2012

Date Inclusion on Novartis Clinical Trial Results Database

24-Feb-2013