Sponsor

Novartis Pharma AG

Generic Drug Name

CAD106

Therapeutic Area of Trial

Mild Alzheimer's Disease (AD)

Approved Indication

Investigational

Study Number

CCAD106A2202

Title

A 52-week, multi-center, randomized, double-blind, placebo-controlled, parallel group study with mild Alzheimer's disease (AD) to investigate the safety and tolerability of repeated subcutaneous injections of CAD106

Phase of Development

IIa

Study Start/End Dates

31-Oct-2008 (first patient first visit) to 22-Nov-2010 (last patient last visit)

Study Design/Methodology

This study was a multi-center, randomized, double-blind, placebo-controlled, parallel group study in patients with mild Alzheimer's disease (AD). Thirty-one patients from 8 centers in USA received up to three subcutaneous (s.c.) or intramuscular (i.m.) injections of CAD106 or placebo. Patients were allocated to the active drug CAD106 or placebo in a 4:1 randomization ratio under double-blind conditions. Three injections of 150µg CAD106 or placebo were administered to each patient at Weeks 0, 2 and 6 either via the s.c. or the i.m. route. Patients participated in the study for a total of 52 weeks.

Centers

There were 8 centers in the United States of America.

Publication

None.

Objectives

Primary objectives

- To evaluate the safety and tolerability of repeated injections of 150µg CAD106 in patients with mild AD over the 52 weeks of the study.

Secondary objectives

- To determine the Aß-specific antibody response to CAD106 by means of evaluating titer levels (IgG and IgM) in serum and in CSF; and assessing Qß-specific antibody response: (IgG and IgM) in serum over the 52 weeks of the study.
- To characterize Aß-specific and explore Qß-specific T-cell response in PBMCs from patients receiving CAD106 or placebo over the first 8 weeks of the study.

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

Three injections of CAD106 (150µg) or placebo were administered at Weeks 0, 2 and 6 either via the s.c. or the i.m. route during the study. Concentration of the vials of CAD106: 1 mg/ml solution.

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

Sucrose (glucose or dextrose) isotonic 5% solution for injection was used as placebo treatment.

Criteria for Evaluation

Primary efficacy variable

There was no efficacy evaluation performed for this study.

Secondary efficacy variables

There was no efficacy evaluation performed for this study.

Safety and tolerability

The primary objective of this study was the assessment of safety and tolerability based on general physical examinations, neurological examinations, 12-lead electrocardiograms (ECGs), vital signs, standard laboratory evaluations (hematology, blood chemistry, urinalysis), special safety laboratory evaluations in blood and CSF, cerebral Magnetic Resonance Imaging (MRIs), as well as adverse event (AE) and serious adverse event (SAE) monitoring.

Pharmacology

Not applicable.

Other - Immunological response

Tolerability and immunogenicity of CAD106 with i.m. versus s.c. route of administration were assessed.

Aß-antibody and Qß-antibody response was measured by determination of Aß-antibody and Qß-antibody titers using ELISA methods (Enzyme-linked immunosorbent assay). Aß-antibody and Qß-antibody titers (IgG and IgM) were determined in serum at each scheduled visit from Screening up to end of study (except at baseline). Aß-antibody titers (IgG and IgM) were also determined in CSF at Screening and Week 14 on aliquots of the CSF sample.

Additional immunological research was planned as a part of this study with the objective of characterizing Aß- and Qß-specific proliferation responses of T-cell lymphocytes following treatment with CAD106. To evaluate T-cell response to the Aß1-6 peptide, the Aß1-40 peptide and the Qß protein, a specific T-cell proliferation assay was performed on PBMC samples.

Statistical Methods

The main purpose of the analysis was to summarize safety and tolerability and Aß IgG titer profiles. An interim analysis of data from the treatment period was performed in order to support future studies.

The immune response was assessed by different parameters like Cmax, Tmax, and AUC for Aß-specific antibody titers and in addition by responder analyses. The safety and tolerability of repeated subcutaneous (s.c.) or intramuscular (i.m.) injections of 150µg CAD106 was assessed by means and frequency 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.

The volumes of five volumetric MRI regions were summarized by treatment group and time (weeks) by means of descriptive statistics. Other exploratory PD data such as clinical scales were summarized by treatment group and time by means of descriptive statistics.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

(1) Male and/or female patients between 40 and 85 years of age (both inclusive).

(2) Female patients were to be without childbearing potential (post-menopausal or surgically sterilized).

- If sterilized, female patients had to have been surgically sterilized at least 6 months prior to screening. Surgical sterilization procedures were to be supported with clinical documentation made available to the Novartis Clinical Research Associate and noted in the Relevant Medical History / Current Medical Conditions section of the Electronic Case Report Form (eCRF) OR
- Postmenopausal women were to have no regular menstrual bleeding for at least 1 year prior to inclusion as documented in the patient's records.

(3) Diagnosis of dementia of the Alzheimer's type according to the DSM-IV criteria (Diagnostic and Statistical Manual of Mental Disorders, 4th edition).

(4) Mild AD as confirmed by a MMSE score of 20 to 26 (both inclusive) at screening, and either untreated or on stable dose of cholinesterase inhibitor and/or other AD treatment over the last 6 weeks.

(5) Patients who satisfied the criteria for a clinical diagnosis of probable AD established by a Work Group of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA).

Exclusion criteria

The exclusion criteria included criteria related to CNS, criteria related to other medical conditions, criteria related to other therapies/substances and criteria related to study procedures:

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

(2) History or presence of an active autoimmune and/or with an acute or chronic inflammation, and/or clinically relevant atopic condition.

(3) History or presence of seizures and/or cerebrovascular disease.

(4) Presence of other neurodegenerative disease and/or psychiatric disorders (with the exception of successfully treated depression)

(5) Advanced, severe, progressive or unstable disease that might interfere with the safety of the patient.

Number of Subjects

Patient disposition by treatment - n (%) of patients (Randomized analysis set)

	CAD106 150µg N=25 n (%)	Placebo N=6 n (%)	Total N=31 n (%)
Randomized	25 (100)	6 (100)	31 (100)
Exposed to stud rug	25 (100)	6 (100)	31 (100)
Completed study	24 (96.0)	6 (100)	30 (96.8)
Withdrawal from study	1 (4.0)	0 (0.0)	1 (3.2)
Primary reason for withdrawal from study Subject withdrew consent	1 (4.0)	0 (0.0)	1 (3.2)

Demographic and Background Characteristics

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

		CAD106 150µg N=25	Placebo N=6	Total N=31
Sex - n (%)	Male	15 (60.0)	3 (50.0)	18 (58.1)
	Female	10 (40.0)	3 (50.0)	13 (41.9)
Age (Years)	Mean	70.5	67.8	70.0
	SD	8.68	9.13	8.68
	Median	73.0	66.0	71.0
	Range	53, 83	58, 84	53, 84
Age group - n (%)	< 65 years	6 (24.0)	3 (50.0)	9 (29.0)
	65 to 75 years	9 (36.0)	2 (33.3)	11 (35.5)
	> 75 years	10 (40.0)	1 (16.7)	11 (35.5)
Race - n (%)	Black	1 (4.0)	0 (0.0)	1 (3.2)
	Caucasian	24 (96.0)	5 (83.3)	29 (93.5)
	Oriental	0 (0.0)	0 (0.0)	0 (0.0)
	Other	0 (0.0)	1 (16.7)	1 (3.2)
MHIS - n (%)	0	17 (68.0)	5 (83.3)	22 (71.0)
	1	5 (20.0)	1 (16.7)	6 (19.4)
	2	3 (12.0)	0 (0.0)	3 (9.7)
	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	Mean	21.9	21.7	21.8
	SD	1.88	2.25	1.92
	Median	21.0	20.5	21.0
	Range	20, 26	20, 25	20, 26
ApoE4 carriers *	n (%)	20 (86.9)	5 (83.3)	25 (86.2)

MHIS = Modified Hachinski Ischemic Score, MMSE = Mini Mental State Examination

* Percentage based on the number of patient genotyped.

Primary Objective Result(s)

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

Secondary Objective Result(s)

Abeta IgG antibody titers in serum by route of administration – summary parameters (Full analysis set)

		CAD106 150µg		
		s.c.	i.m.	Total
		N=9	N=16	N=25
AUC (units*days)	n	9	15	24
	Mean	4743.57	11107.13	8720.80
	SD	3292.176	12955.956	10763.235
	Median	4612.5	77 4 5	6356.7
	Range	752.7, 10514.4	0.0, 51652.3	0.0, 51652.3
C_{max} (units)	n	9	15	24
	Mean	65. 3	114.89	96.53
	SD	49.951	152.135	124.669
	Median	58.5	70.7	69.2
	Range	21.9, 181.0	0.0, 627.0	0.0, 627.0
T_{max} (days)	n	9	14	23
	Mean	60.0	59.8	59.9
	SD	5.77	8.24	7.23
	Median	57.0	57.0	57.0
	Range	55, 70	51, 84	51, 84

[1] A responder was defined as a patient showing an Abeta-specific IgG titer in serum above 16 units at least at one time-point during the study.

[2] A strong responder was defined as a patient having at least two Abeta IgG titers in serum above 4 times the LLOQ or their individual baseline level if above the LLOQ for at least two points in time during the study.

AUC was computed using the trapezoidal method for Week 0 to Week 52. Titer values below the LLOQ were set to 0 for the computation of AUC. C_{max} was the observed maximum post-treatment concentration value up to Week 52. T_{max} was calculated as the time in study days in which the maximum concentration (Cmax) occurred up to Week 52.

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	CAD106 150µg N=25 n (%)	Placebo N=6 n (%)
Any primary system organ class	20 (80.0)	4 (66.7)
Blood and lymphatic system disorders	2 (8.0)	0 (0.0)
Cardiac disorders	3 (12.0)	0 (0.0)
Congenital, familial and genetic disorders	1 (4.0)	0 (0.0)
Ear and labyrinth disorders	2 (8.0)	0 (0.0)
Eye disorders	0 (0.0)	1 (16.7)
Gastrointestinal disorders	2 (8.0)	2 (33.3)
General disorders and administration site conditions	8 (32.0)	1 (16.7)
Hepatobiliary disorders	2 (8.0)	0 (0.0)
Infections and infestations	3 (12.0)	2 (33.3)
Injury, poisoning and procedural complications	5 (20.0)	2 (33.3)
Investigations	2 (8.0)	1 (16.7)
Metabolism and nutrition disorders	1 (4.0)	0 (0.0)
Musculoskeletal and connective tissue disorders	3 (12.0)	1 (16.7)
Nervous system disorders	6 (24.0)	2 (33.3)
Psychiatric disorders	6 (24.0)	3 (50.0)
Renal and urinary disorders	4 (16.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	1 (4.0)	0 (0.0)
Skin and subcutaneous tissue disorders	6 (24.0)	0 (0.0)
Vascular disorders	2 (8.0)	0 (0.0)

Primary system organ classes are presented alphabetically.

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

A subject with multiple adverse events within a primary system organ class is counted only once in the total row.

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

Preferred term	CAD106 150µg N=25 n (%)	Placebo N=6 n (%)
Headache	4 (16.0)	0 (0.0)
Back pain	3 (12.0)	0 (0.0)
Confusional state	3 (12.0)	0 (0.0)
Fall	3 (12.0)	1 (16.7)
Pyrexia	3 (12.0)	0 (0.0)
Anxiety	2 (8.0)	1 (16.7)
Fatigue	2 (8.0)	1 (16.7)
Excoriation	1 (4.0)	1 (16.7)
Oedema peripheral	1 (4.0)	1 (16.7)
Syncope	1 (4.0)	1 (16.7)
Urinary tract infection	1 (4.0)	1 (16.7)
Abdominal pain upper	0 (0.0)	1 (16.7)
Altered visual depth perception	0 (0.0)	1 (16.7)
Arthralgia	0 (0.0)	1 (16.7)
Constipation	0 (0.0)	1 (16.7)
Disorientation	0 (0.0)	1 (16.7)
Dizziness	0 (0.0)	1 (16.7)
Dysarthria	0 (0.0)	1 (16.7)
Insomnia	0 (0.0)	2 (33.3)
Joint sprain	0 (0.0)	1 (16.7)
Lymph node palpable	0 (0.0)	1 (16.7)
Periodic limb movement disorder	0 (0.0)	1 (16.7)
Upper respiratory tract infection	0 (0.0)	1 (16.7)
Weight decreased	0 (0.0)	1 (16.7)

A subject 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.

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	CAD106 150µg N=25 n (%)	Placebo N=6 n (%)
Death*	0	0
SAE(s)	5 (20.0)	2 (33.3)
Permanently discontinued study drug due to SAE(s)	0	0
AE(s) leading to permanent discontinuation of study drug	0	0

* One patient (Patient A2202-0511-00001) died after having withdrawn consent to continue the study.
Information about deaths stems from the Treatment Period or Study Completion page. Information about AEs and SAEs stem from the Adverse Events page.

Number (%) of patients with serious adverse events regardless of study drug relationship by primary system organ class, preferred term and treatment (Safety analysis set)

Serious adverse events	CAD106 150µg N=25 n (%)	Placebo N=6 n (%)
Any primary system organ class	5 (20.0)	2 (33.3)
Cardiac disorders	1 (4.0)	0 (0.0)
Atrioventricular block complete	1 (4.0)	0 (0.0)
Gastrointestinal disorders	1 (4.0)	0 (0.0)
Gastrointestinal hemorrhage	1 (4.0)	0 (0.0)
Hepatobiliary disorders	1 (4.0)	0 (0.0)
Cholecystitis	1 (4.0)	0 (0.0)
Infections and infestations	0 (0.0)	1 (16.7)
Urinary tract infection	0 (0.0)	1 (16.7)
Injury, poisoning and procedural complications	2 (8.0)	0 (0.0)
Femur fracture	1 (4.0)	0 (0.0)
Skin laceration	1 (4.0)	0 (0.0)
Nervous system disorders	1 (4.0)	1 (16.7)
Convulsion	1 (4.0)	0 (0.0)
Syncope	0 (0.0)	1 (16.7)

Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class by descending frequency, as reported in the CAD106 150 µg group.
A subject with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
A subject with multiple adverse events within a primary system organ class is counted only once in the total row.

Other Relevant Findings

None.

Date of Clinical Trial Report

26-Sep-2011

Date Inclusion on Novartis Clinical Trial Results Database

14-Nov-2011

Date of Latest Update

No updates.