Sponsor

Novartis Pharma AG

Generic Drug Name

CAD106

Therapeutic Area of Trial

Mild Alzheimer's Disease (AD)

Approved Indication

Investigational

Study Number

CCAD106A2201

Title

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 of CAD106.

Phase of Development

Phase IIA

Study Start/End Dates

15 Jul 2008 (first patient first visit) to 18 Feb 2010 (last patient last visit)

Study Design/Methodology

The present study was a multi-center, randomized, double-blind, placebo-controlled, parallel group study in patients with mild AD. Twenty-seven patients from four centers in Europe received subcutaneous (s.c.) 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 s.c. injections of 150µg CAD106 or placebo were administered to each patient at weeks 0, 6 and 12. Patients participated in the study for a total of 52 weeks.

Centres

There were 4 study centers in 4 countries: France (1), Sweden (1), Switzerland (1), and United Kingdom (1).

Publication

None.

Objectives

Primary objective(s)

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

Secondary objective(s)

- To determine the Aβ-specific (β-amyloid protein) antibody response to CAD106 by means of evaluating titer levels (Immunoglobulin G (IgG) and Immunoglobulin M (IgM)) in serum and in cerebrospinal fluid (CSF); and assessing Qβ-specific antibody response: (IgG and IgM) in serum over the 52 weeks of the study (Qβ = bacteriophage used for the construct of the virus-like particle).
- To characterize Aβ-specific and Qβ-specific T-cell response in peripheral blood mononuclear cells (PBMCs) from patients receiving CAD106 or placebo over the first 14 weeks of the study.

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

Three subcutaneous injections of CAD106 (150µg) were administered at weeks 0, 6 and 12 during the study. Concentration of the vials of CAD106: 1mg/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 variables

There was no efficacy evaluation performed for this study.

Secondary variables

There was no efficacy evaluation performed for this study.

Safety and tolerability

- The primary objective of this study was the assessment of safety 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

- Immunological response:
  - Aβ-antibody and Qβ-antibody response was measured by determination of Aβ-antibody and Qβ-antibody titers using ELISA methods (Enzyme-linked immunosorbent assay). Aβ-antibody and Qβ-antibody titers (IgG and IgM) were determined in serum at each scheduled visit from Screening up to end of study (except at baseline). Aβ-antibody titers (IgG and IgM) were also determined in CSF at Screening and Week 20 on aliquots of the CSF sample.
  - Immunological research studies were planned as a part of this study with the objective of characterizing Aβ- and Qβ-specific proliferation responses of T-cell lymphocytes following treatment with CAD106. To evaluate T-cell response to the $A\beta_{1-6}$ peptide, the $A\beta_{1-40}$ peptide and the Qβ protein, a specific T-cell proliferation assay was performed on PBMC samples.

Statistical Methods

The main purpose of the final analysis was to summarize safety, tolerability, and Aβ 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 (maximal concentration), Tmax (time to maximal concentration), and Area Under Curve (AUC) for Aβ-specific antibody titers and in addition by responder analyses. 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.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria:

- Male and/or female patients between 40 and 85 years of age (both inclusive)
- Diagnosis of mild Alzheimer's Disease (AD)
- Mini-Mental State Examination (MMSE) 20 to 26 at screening, untreated or on stable dose of cholinesterase inhibitor or memantine over the last 6 weeks.

Exclusion Criteria:

- Previously participated in an AD vaccine study and received active treatment.
- History or presence of an active autoimmune and/or with an acute or chronic inflammation, and/or clinically relevant atopic condition.
- History or presence of seizures and/or cerebrovascular disease.
- Presence of other neurodegenerative disease and/or psychiatric disorders (with the exception of successfully treated depression)
- 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 = 22 n (%)	Placebo N = 5 n (%)	Total N = 27 n (%)
Randomized	22 (100)	5 (100)	27 (100)
Exposed to study drug	22 (100)	5 (100)	27 (100)
Completed study	22 (100)	5 (100)	27 (100)
Withdrawal from study	0 (0.0)	0 (0.0)	0 (0.0)

Demographic and Background Characteristics

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

		CAD106 150µg N = 22	Placebo N = 5	Total N = 27
Sex – n (%)	Male	14 (63.6)	3 (60.0)	17 (63.0)
	Female	8 (36.4)	2 (40.0)	10 (37.0)
Age (years)	Mean	65.6	64.4	65.4
	SD	7.05	2.51	6.43
	Median	66.0	63.0	65.0
	Range	53, 79	62, 68	53, 79
Age group – n (%)	< 65 years	10 (45.5)	3 (60.0)	13 (48.1)
	65 – 75 years	10 (45.5)	2 (40.0)	12 (44.4)
	> 75 years	2 (9.1)	0 (0.0)	2 (7.4)
Race – n (%)	Caucasian	22 (100)	5 (100)	27 (100)
	Black	0 (0.0)	0 (0.0)	0 (0.0)
	Oriental	0 (0.0)	0 (0.0)	0 (0.0)
	Other	0 (0.0)	0 (0.0)	0 (0.0)
MHIS** – n (%)	0	12 (54.5)	3 (60.0)	15 (55.6)
	1	4 (18.2)	2 (40.0)	6 (22.2)
	2	5 (22.7)	0 (0.0)	5 (18.5)
	3	1 (4.5)	0 (0.0)	1 (3.7)
	4	0 (0.0)	0 (0.0)	0 (0.0)
	> 4	0 (0.0)	0 (0.0)	0 (0.0)
MMSE	Mean	23.1	24.2	23.3
	SD	2.23	1.64	2.15
	Median	24.0	23.0	24.0
	Range	20, 26	23, 26	20, 26
ApoE4 carriers*	n (%)	11 (55.0)	4 (100)	15 (62.5)

* Percentage based on the number of patients genotyped.
**MHIS = Modified Hachinski Ischemic Score

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 responder status - summary parameters (Full analysis set)

		CAD106 150µg	Placebo
	n (%)	22 (100)	5 (100)
AUC (unit*days)	Mean	9680.15	0
	SD	10915.5	0
	Median	5885.43	0
	Range	0.0, 46929.1	0
C_{max} (units)	Mean	93.31	0
	SD	85.1	0
	Median	57.00	0
	Range	0.0, 298.2	0
T_{max} (days)	Mean	84.2	0
	SD	33.5	0
	Median	98.0	0
	Range	15, 139	0

[1] A responder was defined as a patient showing an Abeta-specific IgG titer in serum above 16 units at least at one timepoint 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} is 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 (C_{max}) 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 = 22 n (%)	Placebo N = 5 n (%)
Any primary system organ class	15 (68.2)	3 (60.0)
Cardiac disorders	3 (13.6)	0 (0.0)
Eye disorders	1 (4.5)	0 (0.0)
Gastrointestinal disorders	6 (27.3)	0 (0.0)
General disorders and administration site conditions	6 (27.3)	1 (20.0)
Infections and infestations	8 (36.4)	1 (20.0)
Investigations	4 (18.2)	1 (20.0)
Metabolism and nutrition disorders	1 (4.5)	0 (0.0)
Musculoskeletal and connective tissue disorders	6 (27.3)	0 (0.0)
Nervous system disorders	4 (18.2)	0 (0.0)
Psychiatric disorders	2 (9.1)	1 (20.0)
Renal and urinary disorders	2 (9.1)	1 (20.0)
Reproductive system and breast disorders	2 (9.1)	1 (20.0)
Respiratory, thoracic and mediastinal disorders	1 (4.5)	1 (20.0)
Skin and subcutaneous tissue disorders	0 (0.0)	1 (20.0)
Vascular disorders	2 (9.1)	0 (0.0)

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 AEs 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 = 22 n (%)	Placebo N = 5 n (%)
Diarrhea	3 (13.6)	0 (0.0)
Abdominal pain	2 (9.1)	0 (0.0)
Bronchitis	2 (9.1)	0 (0.0)
Headache	2 (9.1)	0 (0.0)
Myalgia	2 (9.1)	0 (0.0)
Nasopharyngitis	2 (9.1)	0 (0.0)
Benign prostatic hyperplasia	1 (4.5)	1 (20.0)
Pyrexia	1 (4.5)	1 (20.0)
Epistaxis	0 (0.0)	1 (20.0)
Hallucination	0 (0.0)	1 (20.0)
Urinary retention	0 (0.0)	1 (20.0)
Urinary tract infection	0 (0.0)	1 (20.0)
Urticaria	0 (0.0)	1 (20.0)
Weight decreased	0 (0.0)	1 (20.0)

A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category. Preferred terms are sorted in descending order of frequency in the CAD106 150 µg 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)

	CAD106 150µg N = 22 n (%)	Placebo N = 5 n (%)
Serious or other significant events		
Death	0	0
SAE(s)	4 (18.2)	2 (40.0)
Permanently discontinued due to SAE(s)	0	0
AE(s) leading to permanent discontinuation of study drug	0	0

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

Serious adverse events, regardless of study drug relationship, by primary system organ-class, preferred term and treatment (Safety analysis set)

Primary system organ class Preferred term	CAD106 150µg N = 22 n (%)	Placebo N = 5 n (%)
Any primary system organ class	4 (18.2)	2 (40.0)
Cardiac disorders	1 (4.5)	0 (0.0)
Coronary artery stenosis	1 (4.5)	0 (0.0)
Myocardial ischemia	1 (4.5)	0 (0.0)

Infections and infestations	0 (0.0)	1 (20.0)
Urinary tract infection	0 (0.0)	1 (20.0)
Investigations	0 (0.0)	1 (20.0)
Weight decreased	0 (0.0)	1 (20.0)
Metabolism and nutrition disorders	1 (4.5)	0 (0.0)
Dehydration	1 (4.5)	0 (0.0)
Nervous system disorders	2 (9.1)	0 (0.0)
Cerebral hemorrhage	1 (4.5)	0 (0.0)
Presyncope	1 (4.5)	0 (0.0)
Psychiatric disorders	0 (0.0)	1 (20.0)
Hallucination	0 (0.0)	1 (20.0)
Renal and urinary disorders	1 (4.5)	1 (20.0)
Calculus ureteric	1 (4.5)	0 (0.0)
Urinary retention	0 (0.0)	1 (20.0)

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 patient with multiple occurrences of an AE under treatment is counted only once in the AE category for that treatment.
A patient with multiple AEs within a primary system organ class is counted only once in the total row.

Other Relevant Findings

None.

Date of Clinical Trial Report

06-Jan-2011.

Date Inclusion on Novartis Clinical Trial Results Database

14-Feb-2011.

Date of Latest Update

31-Jan-2011.