Sponsor

Novartis

Generic Drug Name

CAD106

Therapeutic Area of Trial

Alzheimer's Disease

Approved Indication

Investigational

Study Number

CCAD106A2101

Title

A 52-week, multi-center, randomized, double-blind, placebo-controlled, time-lagged, parallel group study in patients with mild to moderate Alzheimer's Disease (AD) to investigate the safety, tolerability and Aβ-specific antibody response following three subcutaneous injections of CAD106.

Phase of Development

Phase I

Study Start/End Dates

First patient dosed: 02-Aug-2005 / Last patient completed: 11-Mar-2008 (main study)
2 years safety follow up ongoing

Study Design/Methodology

This multicenter, randomized, double-blind, placebo-controlled, time-lagged (partially overlapping), parallel-group study in patients with mild to moderate Alzheimer Disease was conducted in Sweden, investigating two doses of CAD106 (50 and 150 µg CAD106) using placebo as control.

Centres

2 centers in 1 country: Sweden (2)
Specialized PET center: 1 center in 1 country: Sweden (1)

Publication

None

Objectives

Primary objective

To investigate safety and tolerability, time-course and decline, isotype switch from IgM to IgG of the Aβ-specific antibody response in serum following repeated subcutaneous (s.c.) injections of CAD106 or placebo in patients with mild to moderate Alzheimer's Disease (AD).

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

Three subcutaneous injections of CAD106 (50 and 150 µg). Concentration of the vials: 0.1 mg/ 0.2 mL.
Cohort I: 50 µg CAD106 at weeks 0, 6 and 18
Cohort II: 150 µg CAD106 at weeks 0, 2 and 6

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

Matching placebo (Phosphate-buffered saline) vials administered s.c.
Cohort I: 0.1 ml administered at weeks 0, 6 and 18

Cohort II: 0.3 ml administered at weeks 0, 2 and 6

Criteria for Evaluation

Primary variables

Tolerability/ safety assessments: physical/ neurological examinations, ECG, vital signs, standard and special immunological laboratory evaluations, MRIs, EEGs, AE/ SAE monitoring at multiple timepoints including but not limited to screening, baseline and through the end of the study to week 52.

Aβ/Qβ-specific immune response to CAD106/placebo: Antibody titers (IgM and IgM titers against amyloid and carrier protein) at multiple timepoints including but not limited to baseline and through the end of the study to week 52.

Statistical Methods

All subjects who received at least one dose of study drug are included in the analyses.

Patients and treatments

The demographic variables and Mini Mental State Examination (MMSE) total score at baseline are summarized by treatment group.

Safety and tolerability analyses

Adverse events are tabulated by System Organ Class and treatment group; most frequent preferred terms (with incidence of at least 10% in either CAD106 group), serious AEs, deaths, and discontinuation due to AEs are tabulated by treatment group. Other safety assessments (vital signs, ECG, laboratory, standard clinical and immunological laboratory assessments, safety MRI assessed by a central reader and by a local radiologist, and EEG) are summarized.

Immune response (Aβ-specific immune response to CAD106/placebo)

The maximum IgG Aβ antibody titer concentration in serum over the treatment period (C_{max}) is summarized by treatment group; patients are classified as responders or non-responders based on their IgG Aβ antibody response to treatment (serum titers above 16 units at least once during the treatment period for a given patient), and the percentage of responders in each treatment group is calculated, along with its 95% CI.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria:

- Male and/ or females patients between 50 to 80 years of age (both inclusive).
- Female patients must have been without childbearing potential (post-menopausal or surgically sterilized).
- Diagnosis of dementia of the Alzheimer's type according to the DSM-IV criteria (Diagnostic and Statistical Manual of Mental Disorders, 4th edition).
- Mild to moderate AD as confirmed by Mini-Mental State Exam score of 16 to 26 (both inclusive) at screening.
- Has been able to provide written informed consent and had a responsible caregiver that provided written assent prior to study participation.

Exclusion criteria

- Previously participated in an AD vaccine study and received active treatment
- History or presence of an active autoimmune and/or cerebrovascular disease
- History or presence of seizures, with an acute or chronic inflammation
- Clinically relevant atopic condition, who suffered from an other neurodegenerative disease and/or psychiatric disorders (with the exception of successfully treated depression)
- Immunosuppressive treatment including systemic steroids
- Obtained a vaccination (e.g. against influenza) within 4 weeks before the first study drug injection
- Advanced, severe, progressive or unstable disease that might have interfered with the safety of the patient
- Started treatment with psychotropic medication within 3 months (4 weeks for SSRIs and other newer antidepressants without anticholinergic properties) prior to randomization with the exception of mild hypnotic drugs (e.g. zolpidem, zopiclone, oxazepam) and low doses of neuroleptic drugs (e.g. up to 2 mg risperidone). Patients, who had been on stable treatment with cholinesterase-inhibitors (ChEIs) and/or memantine for at least 3 months, and/or with SSRIs and/or other newer antidepressants (without anticholinergic properties) for at least 4 weeks before randomization, were allowed to be included into the study.

Number of Subjects

	Cohort I		Cohort II	
	CAD106 (50 µg)	**Placebo**	**CAD106 (150 µg)**	**Placebo**
Planned N	30		30	
Randomized n	24	7	22	5
Intent-to-treat population (ITT) n (%)	24 (100.0%)	7 (100.0%)	22 (100.0%)	5 (100.0%)
Completed n (%)	24 (100.0%)	7 (100.0%)	21 (95.5%)	5 (100.0%)
Withdrawn n (%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
Withdrawn due to adverse events n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Withdrawn due to lack of efficacy n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Withdrawn for other reasons n (%)	0 (0.0%)	0 (0.0%)	1 (4.5%)	0 (0.0%)

Demographic and Background Characteristics

	Cohort I		Cohort II	
	CAD106 (50 µg)	**Placebo**	**CAD106 (150 µg)**	**Placebo**
N (ITT)	24	7	22	5
Females : males	8 : 16	4 : 3	13 : 9	3 : 2
Mean age, years (SD)	68.9 (8.03)	70.6 (7.61)	68.2 (7.83)	67.0 (9.46)
Mean weight, kg (SD)	72.03 (10.98)	64.91 (15.77)	67.45 (9.49)	72.86 (10.52)
Race Caucasian n (%) Black n (%) Asian n (%) Other n (%)	 24 (100.0%) 0 (0.0%) 0 (0.0%) 0 (0.0%)	 7 (100.0%) 0 (0.0%) 0 (0.0%) 0 (0.0%)	 22 (100.0%) 0 (0.0%) 0 (0.0%) 0 (0.0%)	 5 (100.0%) 0 (0.0%) 0 (0.0%) 0 (0.0%)
Characteristics relevant to study population: Mean MMSE scores (SD)	 21.1 (3.59)	 21.1 (3.29)	 21.3 (2.60)	 23.4 (2.51)

Safety Results

Adverse Events by System Organ Class n (%)

	Cohort I		Cohort II	
	CAD106 (50 µg)	**Placebo**	**CAD106 (150 µg)**	**Placebo**
	N=24	**N=7**	**N=22**	**N=5**
Any Body System	23 (95.8%)	6 (85.7%)	22 (100.0%)	5 (100.0%)
Cardiac disorders	2 (8.3%)	1 (14.3%)	0 (0.0%)	0 (0.0%)
Ear and labyrinth disorders	1 (4.2%)	0 (0.0%)	0 (0.0%)	1 (20.0%)
Eye disorder	2 (8.3%)	1 (14.3%)	2 (9.1%)	0 (0.0%)
Gastrointestinal disorders	12 (50.0%)	3 (42.9%)	8 (36.4%)	2 (40.0%)
General disorders and Administration site condition	14 (58.3%)	1 (14.3%)	18 (81.8%)	2 (40.0%)
Immune system disorders	0 (0.0%)	0 (0.0%)	1 (4.5%)	0 (0.0%)
Infections and infestations	12 (50.0%)	2 (28.6%)	7 (31.8%)	2 (40.0%)
Injury, poisoning and procedural complications	4 (16.7%)	1 (14.3%)	5 (22.7%)	1 (20.0%)
Investigations	3 (12.5%)	1 (14.3%)	2 (9.1%)	0 (0.0%)
Musculoskeletal and connective tissue disorders	10 (41.7%)	2 (28.6%)	6 (27.3%)	0 (0.0%)
Nervous system disorders	10 (41.7%)	3 (42.9%)	8 (36.4%)	2 (40.0%)
Psychiatric disorders	3 (12.5%)	2 (28.6%)	3 (13.6%)	3 (60.0%)
Renal and urinary disorders	1 (4.2%)	1 (14.3%)	0 (0.0%)	0 (0.0%)
Reproductive system and breast disorders	0 (0.0%)	1 (14.3%)	0 (0.0%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders	3 (12.5%)	0 (0.0%)	3 (13.6%)	0 (0.0%)
Skin and subcutaneous tissue disorders	3 (12.5%)	1 (14.3%)	2 (9.1%)	0 (0.0%)
Vascular disorders	5 (20.8%)	0 (0.0%)	1 (4.5%)	0 (0.0%)

Most frequent AEs - preferred terms with incidence of at least 10% in either CAD106 group n (%)

	Cohort I		Cohort II	
	CAD106 (50 µg)	**Placebo**	**CAD106 (150 µg)**	**Placebo**
	N=24	**N=7**	**N=22**	**N=5**
Gastrointestinal disorders				
Diarrhoea	3 (12.5%)	1 (14.3%)	0 (0.0%)	1 (20.0%)
Nausea	4 (16.7%)	2 (28.6%)	3 (13.6%)	0 (0.0%)
Vomiting	2 (8.3%)	1 (14.3%)	3 (13.6%)	1 (20.0%)
General disorders and administration site conditions				
Chills	1 (4.2%)	0 (0.0%)	6 (27.3%)	0 (0.0%)
Fatigue	7 (29.2%)	0 (0.0%)	4 (18.2%)	1 (20.0%)
Injection site erythema	1 (4.2%)	1 (14.3%)	14 (63.6%)	0 (0.0%)
Injection site pain	0 (0.0%)	0 (0.0%)	4 (18.2%)	0 (0.0%)
Pyrexia	1 (4.2%)	0 (0.0%)	4 (18.2%)	0 (0.0%)
Infections and infestations				
Nasopharyngitis	10 (41.7%)	2 (28.6%)	3 (13.6%)	0 (0.0%)
Rhinitis	3 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Injury, poisoning and procedural complications				
Fall	3 (12.5%)	1 (14.3%)	1 (4.5%)	0 (0.0%)
Musculoskeletal and connective tissue disorders				
Back pain	3 (12.5%)	0 (0.0%)	3 (13.6%)	0 (0.0%)
Myalgia	4 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Nervous system disorders				
Headache	5 (20.8%)	0 (0.0%)	4 (18.2%)	1 (20.0%)

Serious Adverse Events and Deaths

	Cohort I		Cohort II	
	CAD106 (50 µg)	**Placebo**	**CAD106 (150 µg)**	**Placebo**
	N=24	**N=7**	**N=22**	**N=5**
Number (%) of subjects with serious or other significant events				
Death	0 (0%)	0 (0%)	0 (0%)	0 (0%)
SAE(s)[1]	4 (16.7%)	1 (14.3%)	4 (18.2%)	0 (0%)
Discontinued due to SAE(s)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

[1] Description of the SAE's:

- Cohort I (treated with 50 µg CAD106, four (4) patients): Hospitalization for one (1) head trauma, one (1) aortic stenosis and vasovagal syncope, one (1) loss of consciousness and (1) non-cardiac chest pain.
- Cohort I (treated with placebo, one (1) patient): Hospitalization for one (1) sick sinus syndrome/ bradycardia.
- Cohort II (treated with 150 µg CAD106, four (4) patients): Hospitalization for one (1) hip fracture, one (1) headache, one (1) gastrointestinal pain and one (1) syncope and (1) chest pain.

None of these SAEs were considered by the Investigator to be related to the study medication.

Primary Objective Result(s)

Summary statistics for the Aβ IgG antibody C_{max} [units]

	Cohort I		Cohort II	
	CAD106 (50 µg) N=24	**Placebo N=7**	**CAD106 (150 µg) N=22**	**Placebo N=5**
Mean	31.95	4.39	44.07	0.00
SD	31.189	7.681	33.608	0.000

Summary of Aβ IgG antibody responders

	Cohort I		Cohort II	
	CAD106 (50 µg) N=24	**Placebo N=7**	**CAD106 (150 µg) N=22**	**Placebo N=5**
Responders n (%) 95% CI	16 (66.67%) 44.7%, 84.4%	1 (14.29%) 0.4%, 57.9%	18 (81.82%) 59.7%, 94.8%	0 (0.00%) 0.0%, 52.2%

Other Relevant Findings

Analysis of safety MR brain scans and cerebrospinal fluid did not reveal any clinically relevant findings indicative of CNS inflammation. Changes in vital signs, ECG, hematology, blood chemistry, urinalysis and safety EEG parameters were inconspicuous during the observation period. No changes became obvious which could be considered as trend over time and which might be influenced by any dose of CAD106.

Date of Clinical Trial Report

CTR not yet released

Date Inclusion on Novartis Clinical Trial Results Database

30 April 2009

Date of Latest Update

24 April 2009