Sponsor

Novartis

Generic Drug Name

AAE581

Therapeutic Area of Trial

Postmenopausal Osteoporosis

Approved Indication

Investigational

Study Number

CAAE581A2203E1

Title

A 2-year extension to study 2203, partially randomized, double-blind, placebo-controlled in the first year and open label in the second year, to assess the safety of the dose of AAE581 selected for phase III development in postmenopausal osteoporosis, and the offset of effect on bio-markers and BMD

Phase of Development

Phase IIb

Study Start/End Dates

22-Mar-2005 to 03-May-2006

The study was terminated early by the recommendation of the DSMB after safety concerns resulting from the CAAE581A2203 core study.

Study Design/Methodology

This was to be a 2-year of the extension to study CAAE581A2203, double blind and placebo controlled in the first year, and open label in the second year. At the end of the treatment period in the core study, patients were offered to continue in the extension and then were to be re-randomized as follows: In the first year extension: The patients who received placebo, AAE581 5 mg and 10 mg, all were to receive 50 mg of AAE581 daily. Of the patients who received AAE581 25 mg, half were to receive placebo and half AAE581 50 mg by random. Of the pa-

tients who received AAE581 50 mg, half were to receive placebo, and the other half were to continue AAE581 50 mg by random. The first year extension was double-blinded. In the second year of the extension, all the patients were to receive the dose for phase III in open label fashion on a daily regimen.

The study was terminated early by the recommendation of the DSMB after a maximum treatment period of 5 months following review of the serious skin adverse events and other non-serious skin adverse events in the core study CAAE581A2203.

Centres

38 sites in 10 countries: Austria (2), Canada (3), Czech Republic (3), Spain (4), France (2), Italy (10), Poland (4), Russia (3), Slovakia (2), USA (5)

Publication

Ongoing

Objectives

Primary objective(s)

To obtain 3-year safety data of AAE581

Secondary objective(s)

To assess long-term efficacy of AAE581 on bone mineral density (BMD) by dual-energy X-Ray absorptiometry (DXA) on lumbar spine, total hip, total body, forearm and the effect on biomarkers over the 24 month extension period and over the entire 36 month period of the combined core and extension studies, and to obtain the offset of action over one year on biomarkers and BMD.

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

One 50 mg tablet daily orally in the morning

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

Placebo (daily), matching tablet, orally in the morning.

Criteria for Evaluation

Primary variables

Safety. See below.

Secondary variables

• Offset of action of AAE581 after 12 months treatment over 1 year on bone biomarkers and BMD by DXA.

• Comparisons of the period 12 to 24 months of the placebo versus 50 mg AAE581.

• Offset of action after 1 month (visit 9), 3 months (visit 10) , 6 (visit 11) and 9 months (visit 12) off treatment on biomarkers.

• Long-term efficacy and disease control over the 24 months extension period and over the entire 36 months period of the combined core and extension studies.

Safety and tolerability

Adverse events, ECG, laboratory serum and urine parameters, special focus on skin reactions, with skin biopsies in case of visible skin reactions, and renal safety, including urinary protein/creatinine ratio performed at every visit.

Pharmacology

No pharmacokinetic evaluations were performed.

Other

NA

Statistical Methods

Data obtained were presented for the 7 treatment groups, defined by their treatment assignment in the core and extension studies.

Since at the time of termination of the extension study the maximum duration in the extension study was 5 months, the statistical analysis plan as detailed in the original protocol was adapted to the new situation and descriptive statistics was performed.

Study Population: Inclusion/Exclusion Criteria and Demographics

Any patient who completed the core study, Study 2203, who was compliant in the core study, who demonstrated no major protocol violation in the core study and/or who did not develop any disease mentioned in the exclusion criteria of the core study (see below).

Inclusion criteria for the core study:

• Ambulatory female patients between 50 and 75 years of age, post-menopausal ≥5

years or after natural or surgical menopause with Lumbar-spine (LS) BMD T-score, as measured by DXA, at least 2 and no more than 3.5 SD below the mean BMD for young healthy adult females

Exclusion criteria for the core study:

• Any bone disease other than osteopenia/osteoporosis (including severe osteoporosis (established osteoporosis), Paget's bone disease, osteomalacia, osteogenesis imperfecta)

• Urolithiasis: history or current or diagnosed any time during the study

• Bisphosphonates prior to randomization.

-2 years (if used for 48 weeks or longer)

-1 year (if used for greater than 8 weeks but less than 48 weeks)

-6 months (if used for greater than 2 weeks but less than or equal to 8 weeks)

-2 months (if used less than or equal to 2 weeks)

-Any prior use of i.v. bisphosphonate within the last 2 years

• Estrogen replacement therapy (ERT) or hormonal (estrogen/progestogen) replacement therapy (HRT) implantable , injectable , transdermal 6 months and oral 3 months prior to randomization and anytime during the trial.

• Tibolone (Livial), raloxifene, calcitonin, or any other form of use 12 months prior to randomization and during the trial

• Systemic corticosteroid use >2 weeks of > 5 mg prednisone or equivalent /average per day within the past 3 months prior to randomization or during the study period.

• Sodium fluoride for postmenopausal osteoporosis at a dose greater than 1 mg/day for more than 2 weeks at any time.

• Anabolic androgens within six months prior to randomization or during the trial.

• Any prior use of PTH for more than 1 week; if used for < 1 week, washout period for PTH 6 months

Number of Subjects

Treatment group	Core study	Extension study
Group 1	Placebo	AAE581 50 mg
Group 2	AAE581 5 mg	AAE581 50 mg
Group 3	AAE581 10 mg	AAE581 50 mg
Group 4	AAE581 25 mg	AAE581 50 mg
Group 5	AAE581 25 mg	Placebo
Group 6	AAE581 50 mg	AAE581 50 mg
Group 7	AAE581 50 mg	Placebo

Patient disposition (ITT extension)

Core study	Placebo	AAE581 5 mg	AAE581 10 mg	AAE581 25 mg	AAE581 25 mg	AAE581 50 mg	AAE581 50 mg	Total
Extension study	AAE581 50 mg (N=77)	AAE581 50 mg (N=79)	AAE581 50 mg (N=77)	AAE581 50 mg (N=41)	Placebo (N=38)	AAE581 50 mg (N=33)	Placebo (N=30)	(N=375)
Disposition/Reason	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Completed	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Discontinued	77 (100.0)	79 (100.0)	77 (100.0)	41 (100.0)	38 (100.0)	33 (100.0)	30 (100.0)	375 (100.0)
Adverse event(s)*	0 (0.0)	2 (2.5)	3 (3.9)	1 (2.4)	1 (2.6)	0 (0.0)	0 (0.0)	7 (1.9)
Unsatisfactory therapeutic effect	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Subject withdrew consent	1 (1.3)	2 (2.5)	1 (1.3)	2 (4.9)	1 (2.6)	2 (6.1)	1 (3.3)	10 (2.7)
Lost to follow-up	0 (0.0)	0 (0.0)	1 (1.3)	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)
Administrative problems	75 (97.4)	75 (94.9)	72 (93.5)	37 (90.2)	36 (94.7)	30 (90.9)	29 (96.7)	354 (94.4)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.0)	0 (0.0)	1 (0.3)
Follow-up in extension study								
Accepted follow-up	70 (90.9)	67 (84.8)	70 (90.9)	36 (87.8)	34 (89.5)	31 (93.9)	29 (96.7)	337 (89.9)
Completed follow-up period	69 (89.6)	66 (83.5)	67 (87.0)	33 (80.5)	32 (84.2)	30 (90.9)	29 (96.7)	326 (86.9)

Demographic and Background Characteristics

Core study	Placebo AAE581	AAE581 5 mg AAE581	AAE581 10 mg AAE581	AAE581 25 mg AAE581	AAE581 25 mg	AAE581 50 mg AAE581	AAE581 50 mg	Total
Extension study	50 mg (N=77)	50 mg (N=79)	50 mg (N=77)	50 mg (N=41)	Placebo (N=38)	50 mg (N=33)	Placebo (N=30)	(N=375)
Demographic variable	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Age (years)								
Mean	62.5	62.7	61.8	62	64.3	59.8	61.3	62.2
SD	5.89	5.87	6.22	6.34	5.96	5.28	5.82	6
Race								
Caucasian	76(98.7%)	79(100.0%)	76(98.7%)	41(100.0%)	38(100.0%)	33(100.0%)	30(100.0%)	373(99.5%)
Oriental	1(1.3%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	1(0.3%)
Other	0(0.0%)	0(0.0%)	1(1.3%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	1(0.3%)

Primary Objective Result(s)

The primary objective, 3-year safety data of AAE581 was not achieved as the study was terminated early.

Secondary Objective Result(s)

The secondary objectives, long-term efficacy over the planned 2-year extension period, and the offset of action after 12 months were not achieved as the study was terminated early.

Safety Results

Adverse Events by System Organ Class

Core study treatment group Extension study treatment group System organ class, n (%)	Placebo AAE581 50 mg (N=77)	AAE581 5 mg AAE581 50 mg (N=79)	AAE581 10 mg AAE581 50 mg (N=77)	AAE581 25 mg AAE581 50 mg (N=41)	AAE581 25 mg Placebo (N=38)	AAE581 50 mg AAE581 50 mg (N=32)	AAE581 50 mg Placebo (N=30)	Total (N=374)
Any system organ class	30(39.0)	35(44.3)	29(37.7)	15(36.6)	15(39.5)	16(50.0)	15(50.0)	155(41.4)
Musculoskeletal and connective tissue disorders	10(13.0)	10(12.7)	9(11.7)	4(9.8)	5(13.2)	9(28.1)	4(13.3)	51(13.6)
Infections and infestations	7(9.1)	12(15.2)	9(11.7)	5(12.2)	4(10.5)	4(12.5)	5(16.7)	46(12.3)
Skin and subcutaneous tissue disorder	11(14.3)	14(17.7)	7(9.1)	5(12.2)	6(15.8)	1(3.1)	1(3.3)	45(12.0)
Gastrointestinal disorder	7(9.1)	4(5.1)	5(6.5)	2(4.9)	2(5.3)	3(9.4)	1(3.3)	24(6.4)
Nervous system disorders	2(2.6)	6(7.6)	5(6.5)	3(7.3)	0(0.0)	2(6.3)	1(3.3)	19(5.1)
Injury, poisoning and procedural complications	2(2.6)	3(3.8)	2(2.6)	1(2.4)	1(2.6)	1(3.1)	1(3.3)	11(2.9)
Psychiatric disorders	1(1.3)	1(1.3)	2(2.6)	2(4.9)	1(2.6)	2(6.3)	0(0.0)	9(2.4)
Respiratory, thoracic and mediastinal disorders	2(2.6)	1(1.3)	4(5.2)	1(2.4)	0(0.0)	1(3.1)	0(0.0)	9(2.4)
General disorders/ administration site conditions	1(1.3)	3(3.8)	1(1.3)	1(2.4)	0(0.0)	2(6.3)	0(0.0)	8(2.1)
Eye disorders	2(2.6)	0(0.0)	2(2.6)	0(0.0)	1(2.6)	1(3.1)	1(3.3)	7(1.9)
Investigations	0(0.0)	0(0.0)	2(2.6)	0(0.0)	4(10.5)	0(0.0)	1(3.3)	7(1.9)
Metabolism and nutrition disorders	1(1.3)	2(2.5)	2(2.6)	0(0.0)	0(0.0)	1(3.1)	1(3.3)	7(1.9)
Renal and urinary disordes	2(2.6)	1(1.3)	1(1.3)	0(0.0)	3(7.9)	0(0.0)	0(0.0)	7(1.9)
Cardiac disorders	1(1.3)	1(1.3)	1(1.3)	0(0.0)	1(2.6)	1(3.1)	1(3.3)	6(1.6)
Vascular disorders	2(2.6)	2(2.5)	0(0.0)	0(0.0)	1(2.6)	0(0.0)	0(0.0)	5(1.3)
Reproductive system and breast disorders	1(1.3)	0(0.0)	1(1.3)	0(0.0)	0(0.0)	2(6.3)	0(0.0)	4(1.1)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0(0.0)	0(0.0)	1(1.3)	1(2.4)	1(2.6)	0(0.0)	0(0.0)	3(0.8)
Blood and lymphatic system disorders	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(3.1)	1(3.3)	2(0.5)
Ear and labyrinth disorders	0(0.0)	0(0.0)	2(2.6)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	2(0.5)
Hepatobiliary disorders	1(1.3)	0(0.0)	1(1.3)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	2(0.5)
Endocrine disorders	0(0.0)	0(0.0)	1(1.3)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.3)
Immune system disorders	0(0.0)	0(0.0)	1(1.3)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.3)

SOC are sorted in descending frequency, as reported in the Total Column.
All subjects with adverse events starting at or after first dose in extension study are counted.
A subject with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment

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

Number (%) of patients with 10most frequent AEs (extension study) by preferred term (Safety extension)

Core study Extension study	Placebo AAE581 50 mg (N=77) n (%)	AAE581 5 mg AAE581 50 mg (N=79) n (%)	AAE581 10 mg AAE581 50 mg (N=77) n (%)	AAE581 25 mg AAE581 50 mg (N=41) n (%)	AAE581 25 mg Placebo (N=38) n (%)	AAE581 50 mg AAE581 50 mg (N=32) n (%)	AAE581 50 mg Placebo (N=30) n (%)	Total (N=374) n (%)
No. (%) of patients with AE(s)	30(39.0)	35(44.3)	29(37.7)	15(36.6)	15(39.5)	16(50.0)	15(50.0)	155(41.4)
Pruritus	7(9.1)	10(12.7)	5(6.5)	3(7.3)	5(13.2)	1(3.1)	0(0.0)	31 (8.3)
Urinary tract infection	3(3.9)	3(3.8)	5(6.5)	0(0.0)	0(0.0)	0(0.0)	2(6.7)	13 (3.5)
Arthralgia	2(2.6)	2(2.5)	1(1.3)	0(0.0)	0(0.0)	2(6.3)	1(3.3)	8 (2.1)
Back pain	3(3.9)	2(2.5)	1(1.3)	0(0.0)	1(2.6)	0(0.0)	0(0.0)	7 (1.9)
Osteoarthritis	0(0.0)	1(1.3)	1(1.3)	0(0.0)	1(2.6)	3(9.4)	1(3.3)	7 (1.9)
Pain in extremity	0(0.0)	2(2.5)	2(2.6)	2(4.9)	0(0.0)	0(0.0)	0(0.0)	6 (1.6)
Bone pain	2(2.6)	1(1.3)	1(1.3)	1(2.4)	0(0.0)	0(0.0)	0(0.0)	5 (1.3)
Bronchitis	0(0.0)	0(0.0)	1(1.3)	3(7.3)	1(2.6)	0(0.0)	0(0.0)	5 (1.3)
Nasopharyngitis	1(1.3)	1(1.3)	1(1.3)	0(0.0)	1(2.6)	0(0.0)	1(3.3)	5 (1.3)
Headache	0(0.0)	3(3.8)	1(1.3)	0(0.0)	0(0.0)	1(3.1)	0(0.0)	5(1.3)
Depression	1(1.3)	0(0.0)	1(1.3)	2(4.9)	0(0.0)	1(3.1)	0(0.0)	5 (1.3)
Cough	2(2.6)	1(1.3)	2(2.6)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	5 (1.3)

Preferred terms are sorted in descending frequency, as reported in the Total Column.

All subjects with adverse events starting at or after first dose in extension study are counted.
A subject with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.

Serious Adverse Events and Deaths

Number (%) of patients who died, had other serious or clinically significant AEs (extension study) or discontinued because of them (Safety extension)

Treatment Group Core study Treatment Group Extension study	Placebo AAE581 50 mg (N=77) n (%)	AAE581 5 mg AAE581 50 mg (N=79) n (%)	AAE581 10 mg AAE581 50 mg (N=77) n (%)	AAE581 25 mg AAE581 50 mg (N=41) n (%)	AAE581 25 mg Placebo (N=38) n (%)	AAE581 50 mg AAE581 50 mg (N=32) n (%)	AAE581 50 mg Placebo (N=30) n (%)	Total (N=374) n (%)
No. (%) of patients with AE(s)	30(39.0)	35(44.3)	29(37.7)	15(36.6)	15(39.5)	16(50.0)	15(50.0)	155(41.4)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	1 (0.3)
SAE (fatal and non-fatal)	0 (0.0)	1 (1.3)	3 (3.9)	1 (2.4)	0 (0.0)	2 (6.3)	0 (0.0)	7 (1.9)
AEs leading to discontinuation	0 (0.0)	2 (2.5)	3 (3.9)	1 (2.4)	1 (2.6)	1 (3.1)	0 (0.0)	8 (2.1)
SAEs leading to discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	1 (3.1)	0 (0.0)	2 (0.5)
Total skin related AEs	12 (15.6)	14 (17.7)	9 (11.7)	7 (17.1)	6 (15.8)	2 (6.3)	1 (3.3)	51 (13.6)
Invisible skin related AEs	8 (10.4)	7 (8.9)	7 (9.1)	3 (7.3)	4 (10.5)	0 (0.0)	0 (0.0)	29 (7.8)
Visible skin related AEs	4 (5.2)	8 (10.1)	3 (3.9)	4 (9.8)	3 (7.9)	2 (6.3)	1 (3.3)	25 (6.7)
Cardiovascular AEs	3 (3.9)	3 (3.8)	1 (1.3)	0 (0.0)	4 (10.5)	1 (3.1)	1 (3.3)	13 (3.5)
Fractures reported as AEs	1 (1.3)	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	0 (0.0)	1 (3.3)	3 (0.8)
Oedema	0 (0.0)	2 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)
AEs related* to pulmonary disease/lung fibrosis	2 (2.6)	1 (1.3)	3 (3.9)	3 (7.3)	3 (7.9)	1 (3.1)	0 (0.0)	13 (3.5)
AEs related* to hypersensitivity: respiratory	5 (6.5)	5 (6.3)	4 (5.2)	4 (9.8)	3 (7.9)	2 (6.3)	2 (6.7)	25 (6.7)
AEs related* to hypersensitivity: musculoskeletal	4 (5.2)	6 (7.6)	3 (3.9)	3 (7.3)	2 (5.3)	5 (15.6)	3 (10.0)	26 (7.0)

The categories are not mutually exclusive. All subjects with adverse events starting at or after first dose in extension study are counted.
A patient with multiple occurrences of an event under one treatment is counted only once in the event category for that treatment.
* possibly related to

Listing of patients with serious adverse events during the core + extension study (Safety extension)

	Preferred term	Start day	Duration (days)	Sev-erity	Relationship to study drug
AAE581 5 mg/AAE581 50 mg	Foreign body trauma	75	62	Sev	Not suspected
	Intestinal obstruc-tion	128	33	Sev	Not suspected
AAE581 10 mg/AAE581 50 mg	Back pain	89	22	Mod	Not suspected
	Morphoea	209		Sev	Suspected
	Uterovaginal prolapse	74	4	Sev	Not suspected
AAE581 25 mg/AAE581 50 mg	Scleroderma	34		Mod	Suspected
AAE581 50 mg/AAE581 50 mg	Inguinal hernia	96	2	Mod	Not suspected
	Impaired healing	114	33	Mild	Not suspected
	Metabolic encepha-lopathy	36	9	Sev	Not suspected
	Lung infection pseu-domonal	36	9	Sev	Not suspected

Preferred Terms listed; Severity: Mild=Mild, Mod=Moderate, Sev=Severe; Day is relative to date of visit 8 of extension study (Day 1). Duration=end date-start date+1; Duration for continuing events is missing.

Other Relevant Findings

None

Date of Clinical Trial Report

20 Dec 2006

Date Inclusion on Novartis Clinical Trial Results Database

02 May 2007

Date of Latest Update

02 May 2007