Sponsor

Novartis

Generic Drug Name

AAE581

Trial Indication(s)

Post-Menopausal Osteoporosis

Protocol Number

CAAE581A2203E2

Protocol Title

An observational, safety follow-up extension to studies 2203 and 2203E1 to assess the safety of AAE581 in postmenopausal women with osteopenia/osteoporosis

Clinical Trial Phase

Phase IIb

Study Start/End Dates

06 Sep 2007 to 25 Sep 2008

Reason for Termination (If applicable)

The study was terminated based on DMC recommendation due to administrative problems, withdrawal of consent by the patient and abnormal lab values.

Study Design/Methodology

This was an multicenter, multinational, observational safety follow-up second extension (E2) to study AAE581A2203 and to its first extension study AAE581A2203E1.

Centers

33 centers in 10 countries: Austria (2), Canada (2), Czech Republic (3), Spain (2), France (2), Italy (10), Poland (4), Russia (5), Slovakia (1), USA (2)

Objectives:

Primary Objective:

- To identify if any dose group not otherwise treated with anti-osteoporosis therapy since core study participation showed a signal of continued increase of ≥20% in the bone marker serum CTX-I beyond 6 months off treatment from baseline (entry into the core study) and versus the placebo group.

Secondary Objective:

- To identify if any individual showed continued increase of ≥40% in the bone marker serum CTX-I beyond 6 months off treatment versus entry into the core study.
- To identify if any dose group lost BMD at the lumbar spine or total hip more than the placebo group, evaluated by percentage change from baseline (entry into core study) to time of evaluation in the E2 extension study.
- To identify any individuals with a BMD loss of greater than 5% per year at the total hip or 8% per year at the lumbar spine from end of treatment to time of evaluation in the E2 study and with a BMD value lower than the baseline value (entry into core study).

- To evaluate the incidence of adverse events (AEs) in patients who:

1. Had their last visit in the core study and did not enter the extension study.

2. had their last visit in the E1 extension study

With a special focus on respiratory, skin, osteoporosis and OA related events, between treatment groups.

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

No investigational treatment was dispensed. This was an observational, follow-up safety study.

Statistical Methods

Descriptive summary statistics was presented for the absolute values and percentage change from baseline of serum CTX-I and BMD. Between treatment group comparisons for serum CTX-I percentage change from baseline was performed with an analysis of covariance model, adjusting for baseline serum CTX-I as covariate. Percentage change from baseline of BMD lumbar spine and total hip was also analyzed with similar ANCOVA model. These analysis were done mainly on the sensitivity analysis set which was introduced after recommendation from the 1st DMC meeting, as this analysis set had patients with high exposure to the highest (25 mg and 50 mg) AAE581 doses.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria

- All efforts were taken to contact all patients randomized in the CAAE581A2203 core study. But only those patients who had not taken any anti-osteoporosis therapy since study participation were allowed to be enrolled.
- Patients who had signed a written informed consent before any trial procedure is performed
- Patients were allowed to take part in other clinical trials as long as this did not involve taking any prohibited medication. Exclusion criteria.

Exclusion criteria

- Patients who had taken any anti-osteoporosis therapy since study participation (Core or extension E1)

Participant Flow Table

Patient disposition – n (%) of patients (Safety population E2)

Parameter	Group 1 (Placebo) N=15 n (%)	Group 2 (50 mg) N=140 n (%)	Group 3 (5 mg) N=11 n (%)	Group 4 (10 mg) N=16 n (%)	Group 5 (25 mg) N=32 n (%)	All patients N=214 n (%)
Enrolled E2	15	140	11	16	32	214
Completed E2	12 (80.0)	93 (66.4)	9 (81.8)	13 (81.3)	20 (62.5)	147 (68.7)
Discontinued E2	3 (20.0)	47 (33.6)	2 (18.2)	3 (18.8)	12 (37.5)	67 (31.3)
Adverse event(s)	0 (0.0)	1 (0.7)	0 (0.0)	1 (6.3)	0 (0.0)	2 (0.9)
Abnormal laboratory value(s)	0 (0.0)	6 (4.3)	0 (0.0)	0 (0.0)	2 (6.3)	8 (3.7)
Abnormal test procedure result(s)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
Subject withdrew consent	1 (6.7)	13 (9.3)	1 (9.1)	0 (0.0)	2 (6.3)	17 (7.9)
Lost to follow-up	0 (0.0)	3 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.4)
Administrative problems[1]	2 (13.3)	23 (16.4)	1 (9.1)	2 (12.5)	8 (25.0)	36 (16.8)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Protocol Deviation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Grouping of patients based on maximum AAE581 dose received in either core and/or E1.
[1]Administrative problems was recorded as discontinuation reason for all patients still in the study when the E2 extension study was prematurely terminated, following the DMC recommendation.

Patient disposition – n (%) of patients (Sensitivity analysis set E2)

Parameters	Placebo + low exposure to AAE581 N=23 n (%)	High exposure to AAE581 (50 mg) N=38 n (%)	High exposure to AAE581 (25 mg) N=39 n (%)	All patients N=100 n (%)
Enrolled E2	23	38	39	100
Completed E2	19 (82.6)	22 (57.9)	27 (69.2)	68 (68.0)
Discontinued E2	4 (17.4)	16 (42.1)	12 (30.8)	32 (32.0)
Adverse event(s)	0 (0.0)	1 (2.6)	0 (0.0)	1 (1.0)
Abnormal laboratory value(s)	0 (0.0)	4 (10.5)	1 (2.6)	5 (5.0)
Abnormal test procedure result(s)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subject withdrew consent	1 (4.3)	6 (15.8)	1 (2.6)	8 (8.0)
Lost to follow-up	0 (0.0)	2 (5.3)	0 (0.0)	2 (2.0)
Administrative problems[1]	3 (13.0)	3 (7.9)	10 (25.6)	16 (16.0)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Protocol Deviation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Grouping of patients based on AAE581 dose received in core and/or E1 and duration of exposure.
[1]Administrative problems was recorded as discontinuation reason for all patients still in the study when the E2 extension study was prematurely terminated, following the DMC recommendation.

Baseline Characteristics

Demographic summary by treatment group (Safety population E2)

Parameters	Group 1 (Placebo) N=15	Group 2 (50 mg) N=140	Group 3 (5 mg) N=11	Group 4 (10 mg) N=16	Group 5 (25 mg) N=32	All patients N=214
Age group (years) - n (%)						
50 - <60	4 (26.7%)	52 (37.1%)	5 (45.5%)	5 (31.3%)	9 (28.1%)	75 (35.0%)
60 - <70	10 (66.7%)	74 (52.9%)	5 (45.5%)	7 (43.8%)	19 (59.4%)	115 (53.7%)
>=70	1 (6.7%)	14 (10.0%)	1 (9.1%)	4 (25.0%)	4 (12.5%)	24 (11.2%)
Age (years)						
n	15	140	11	16	32	214
Mean (SD)	62.9 (4.89)	62.0 (5.80)	60.6 (7.05)	63.5 (6.97)	63.4 (5.50)	62.3 (5.85)
Median	64.0	62.0	60.0	64.0	64.0	62.0
(Min, Max)	(53, 72)	(50, 74)	(51, 74)	(50, 73)	(53, 75)	(50, 75)
Sex - n (%)						
Male	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Female	15 (100.0%)	140 (100.0%)	11 (100.0%)	16 (100.0%)	32 (100.0%)	214 (100.0%)
Race - n (%)						
Caucasian	15 (100.0%)	139 (99.3%)	11 (100.0%)	16 (100.0%)	31 (96.9%)	212 (99.1%)
Black	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.1%)	1 (0.5%)
Oriental	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Height (cm)						
n	15	140	11	16	32	214
Mean (SD)	158.9 (8.07)	158.7 (5.65)	160.0 (4.60)	157.2 (4.71)	158.9 (6.73)	158.7 (5.87)
Median	161.0	159.0	158.0	157.0	159.5	159.0
(Min, Max)	(142, 171)	(147, 173)	(153, 167)	(151, 166)	(140, 170)	(140, 173)

Parameters	Group 1 (Placebo) N=15	Group 2 (50 mg) N=140	Group 3 (5 mg) N=11	Group 4 (10 mg) N=16	Group 5 (25 mg) N=32	All patients N=214
Weight (kg)						
n	15	140	11	16	32	214
Mean (SD)	70.54 (11.258)	65.00 (11.815)	69.05 (9.124)	66.77 (13.112)	66.19 (10.020)	65.91 (11.519)
Median	69.30	63.15	69.90	62.20	63.25	64.00
(Min, Max)	53.9 (100.2)	38.0 (101.0)	51.0 (81.2)	51.5 (95.0)	52.0 (93.5)	38.0 (101.0)
BMI (kg/m²)						
n	15	140	11	16	32	214
Mean (SD)	27.96 (3.956)	25.82 (4.606)	26.96 (3.255)	27.00 (5.050)	26.24 (3.943)	26.18 (4.452)
Median	26.73	25.10	28.26	25.88	25.71	25.60
(Min, Max)	(22.6, 38.2)	(16.2, 42.9)	(21.8, 30.9)	(21.7, 41.1)	(19.1, 36.3)	(16.2, 42.9)

BMI (Body mass index) (kg/m²) is calculated for a patient as weight in kilograms divided by the square of the height in meters.
Baseline and demographic data are taken from Visit 2 (baseline of Core study), visit 1 for height.
Grouping of patients based on maximum AAE581 dose received in either core and/or E1.

Summary of Efficacy

Primary Outcome Result

Serum CTX-I (ng/mL) at visit 24, sensitivity analysis with only baseline covariate adjustment (Sensitivity analysis set E2)

Parameters		% change				Pairwise comparison: AAE581 versus placebo †	
	n	Mean baseline	Mean V24	From baseline Mean (SD)	From baseline Median	Difference in LS means (95% CI)	P-value*
Serum CTX-I (ng/mL)							
Placebo and low exposure to AAE581	21	0.53	0.60	22.44 (41.498)^	35.03		
High exposure to AAE581 (50 mg)	29	0.50	0.54	40.30 (115.05)^	20.25	13.89 (-28.60, 56.38)	0.5171
High exposure to AAE581 (25 mg)	32	0.47	0.61	43.25 (65.305)^	26.45	12.27 (-29.53, 54.06)	0.5607

n is the number of patients with both a baseline and a Visit 24 (E2) value.
Baseline is last valid pre-treatment value (Baseline retest value used, if available, otherwise original baseline value).
% change from baseline to Visit 24 in serum CTX-I calculated as: 100 x (Visit 24 – baseline)/baseline
Grouping of patients based on AAE581 dose received in core and E1 and duration of exposure.
LS = Least Square; CI = confidence interval.
† Calculated from an analysis of covariance of % change from baseline using baseline serum CTX-I as a covariate.
No adjustment for multiplicity. ^≥ 20% LS mean increase from baseline in treatment group.
* Indicates statistical significance at the 5% level (i.e. p-value < 0.05)

Secondary Outcome Result

Number of patients (%) with increased serum CTX-I values compared to baseline, by treatment group (Sensitivity Analysis Set E2)

Visit	Increase in serum CTX-I values compared to baseline	Placebo + low exposure to AAE581 N=23 n (%)	High exposure to AAE581(50 mg) N=38 n (%)	High exposure to AAE581(25 mg) N=39 n (%)	All patients N=100 n (%)
Increase in serum CTX-I values compared to baseline					
Visit 24	<0%	7 (30.4%)	10 (26.3%)	4 (10.3%)	21 (21.0%)
	≥0-<20%	1 (4.3%)	3 (7.9%)	10 (25.6%)	14 (14.0%)
	≥20-<30%	2 (8.7%)	5 (13.2%)	3 (7.7%)	10 (10.0%)
	≥30-<40%	2 (8.7%)	2 (5.3%)	4 (10.3%)	8 (8.0%)
	≥40%	9 (39.1%)	9 (23.7%)	11 (28.2%)	29 (29.0%)

% change from baseline to post-baseline visit in serum CTX-I calculated as: 100 x (post-baseline - baseline)/baseline.
Baseline is last valid pre-treatment value (Baseline retest value used, if available, otherwise original baseline value).
Only reported and reliable results were considered.
Patients with missing or 'invalid' baseline serum CTX-I data are excluded from the analysis.
Grouping of patients based on AAE581 dose received in core and duration of exposure.

Number of patients with a loss in BMD greater than 8%/year at the lumbar spine or 5%/year at the total hip from end of treatment or a BMD below baseline, by treatment group (Sensitivity analysis set E2)

Visit	Loss in BMD	Placebo + low exposure to AAE581 N=23 n (%)	High exposure to AAE581 (50 mg) N=38 n (%)	High exposure to AAE581 (25mg) N=39 n (%)	All patients N=100 n (%)
23	At LS >8%/year	0	0	0	0
	At LS >8%/year and BMD < BL	0	0	0	0
	BMD < BL at LS	10 (43.5)	12 (31.6)	17 (43.6)	39 (39.0)
	At TH >5%/year	1 (4.3)	1 (2.6)	0	2 (2.0)
	At TH >5%/year and BMD < BL	1 (4.3)	1 (2.6)	0	2 (2.0)
	BMD < BL at TH	16 (69.6)	21 (55.3)	21 (53.8)	58 (58.0)

BL = baseline value (core study), the mean of the two DXA measurements taken at the screening visit. LS = Lumbar Spine, TH = Total Hip
Patients with missing or 'invalid' baseline BMD data are excluded from the table.
Percent change from end of treatment is from last on active treatment value.
Grouping of patients based on AAE581 dose received in core and duration of exposure.

Summary assessment of association between increase in serum CTX-I and loss in BMD and vice versa (Sensitivity analysis set E2)

	Placebo + low exposure to AAE581 N=23 n (%)	High exposure to AAE581 (50 mg) N=38 n (%)	High exposure to AAE581 (25mg) N=39 n (%)	All patients N=100 n (%)
sCTX-I increase of ≥40% compared to BMD loss at LS or total Hip				
Number of patients with sCTX-I increase of ≥40%(n)	9	9	11	29
simultaneous				
LS BMD loss >8% / year*	0	0	0	0
LS BMD below BL (%of n)	3 (33.2%)	2 (22.2%)	4 (36.4%)	8 (31.0%)
total Hip BMD loss >5%/ year*	0	0	0	0
total Hip BMD below BL (%of n)	8 (88.9%)	4 (44.4%)	6 (54.6%)	18 (62.1%)
BMD loss at LS or total Hip compared to sCTX-I increase				
simultaneous				
LS BMD loss > 8% / year* (n)	0	0	0	0
sCTX-I increase of ≥40% (%of n)	0	0	0	0
LS BMD below BL (n)	10	12	17	39
sCTX-I increase of ≥40% (%of n)	3 (30.0%)	2 (16.7%)	4 (23.5%)	9 (23.1%)
total Hip BMD loss >5%/ year* (n)	1	1	0	2
sCTX-I increase of ≥40% (%of n)	0	0[1]	0	0
total Hip BMD below BL (n)	16	21	21	58
sCTX-I increase of ≥40% (%of n)	8 (50.0%)	4 (19.0%)	6 (28.6%)	18 (31.0%)

*Since end of treatment BL= Baseline
[1] Baseline modeled for respective patient, therefore biomarker not included in this analysis

Summary of Safety

Adverse Events by System Organ Class

Number (%) of patients with adverse events since the previous study participation by SOCs (Sensitivity analysis set E2)

Parameters	Placebo + low exposure to AAE581 N=23 n (%)	High exposure to AAE581 (50 mg) N=38 n (%)	High exposure to AAE581 (25 mg) N=39 n (%)	All patients N=100 n (%)
No. (%) of patients with AE(s)	11 (47.8)	13 (34.2)	15 (38.5)	39 (39.0)
System organ class				
Musculoskeletal and connective tissue disorders	6 (26.1)	7 (18.4)	6 (15.4)	19 (19.0)
Infections and infestations	2 (8.7)	2 (5.3)	7 (17.9)	11 (11.0)
Injury, poisoning and procedural complications	4 (17.4)	3 (7.9)	0 (0.0)	7 (7.0)
Nervous system disorders	2 (8.7)	0 (0.0)	2 (5.1)	4 (4.0)
Skin and subcutaneous tissue disorders	0 (0.0)	1 (2.6)	2 (5.1)	3 (3.0)
Vascular disorders	1 (4.3)	2 (5.3)	0 (0.0)	3 (3.0)
Eye disorders	1 (4.3)	0 (0.0)	1 (2.6)	2 (2.0)
Gastrointestinal disorders	0 (0.0)	0 (0.0)	2 (5.1)	2 (2.0)
General disorders and administration site conditions	1 (4.3)	0 (0.0)	1 (2.6)	2 (2.0)
Respiratory, thoracic and mediastinal disorders	2 (8.7)	0 (0.0)	0 (0.0)	2 (2.0)
Endocrine disorders	0 (0.0)	1 (2.6)	0 (0.0)	1 (1.0)
Reproductive system and breast disorders	0 (0.0)	0 (0.0)	1 (2.6)	1 (1.0)

MedDRA primary system organ classes are sorted by descending frequency in the all patients group.
Grouping of patients based on AAE581 dose received in core and duration of exposure.

Adverse Events by preferred term

Number (%) of patients with adverse events since the previous study participation by preferred term, (greater than 3% for any group) (Sensitivity analysis set E2)

	Placebo + low exposure to AAE581 N=23 n (%)	High exposure to AAE581 (50 mg) N=38 n (%)	High exposure to AAE581 (25 mg) N=39 n (%)	All patients N=100 n (%)
No. (%) of patients with AE(s)	11 (47.8)	13 (34.2)	15 (38.5)	39 (39.0)
AE preferred term				
Back pain	1 (4.3)	2 (5.3)	4 (10.3)	7 (7.0)
Osteoarthritis	3 (13.0)	1 (2.6)	1 (2.6)	5 (5.0)
Bronchitis	0 (0.0)	1 (2.6)	2 (5.1)	3 (3.0)
Asthenia	1 (4.3)	0 (0.0)	1 (2.6)	2 (2.0)
Influenza	1 (4.3)	0 (0.0)	1 (2.6)	2 (2.0)
Upper limb fracture	1 (4.3)	1 (2.6)	0 (0.0)	2 (2.0)
Urinary tract infection	1 (4.3)	0 (0.0)	1 (2.6)	2 (2.0)
Bronchitis chronic	1 (4.3)	0 (0.0)	0 (0.0)	1 (1.0)
Contusion	1 (4.3)	0 (0.0)	0 (0.0)	1 (1.0)
Costochondritis	1 (4.3)	0 (0.0)	0 (0.0)	1 (1.0)
Dizziness	1 (4.3)	0 (0.0)	0 (0.0)	1 (1.0)
Fall	1 (4.3)	0 (0.0)	0 (0.0)	1 (1.0)
Periarthritis	1 (4.3)	0 (0.0)	0 (0.0)	1 (1.0)
Pyrexia	1 (4.3)	0 (0.0)	0 (0.0)	1 (1.0)
Respiratory tract congestion	1 (4.3)	0 (0.0)	0 (0.0)	1 (1.0)
Retinal dystrophy	1 (4.3)	0 (0.0)	0 (0.0)	1 (1.0)
Sciatica	1 (4.3)	0 (0.0)	0 (0.0)	1 (1.0)
Spinal compression fracture	1 (4.3)	0 (0.0)	0 (0.0)	1 (1.0)
Ulna fracture	1 (4.3)	0 (0.0)	0 (0.0)	1 (1.0)
Upper respiratory tract congestion	1 (4.3)	0 (0.0)	0 (0.0)	1 (1.0)
Venous insufficiency	1 (4.3)	0 (0.0)	0 (0.0)	1 (1.0)

MedDRA preferred terms are sorted by descending frequency in the all patients group.
Grouping of patients based on AAE581 dose received in core and duration of exposure.

Serious Adverse Events and Deaths

Number (%) of patients with deaths, other serious or clinically significant AEs or related discontinuations since the previous study participation (Safety population E2)

Parameter	Group 1 (Placebo) (N=15) n(%)	Group 2 (50 mg) (N=140) n(%)	Group 3 (5 mg) (N=11) n(%)	Group 4 (10 mg) (N=16) n(%)	Group 5 (25 mg) (N=32) n(%)	All patients (N=214) n(%)
Death	0 (0.0)	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
SAE	0 (0.0)	3 (2.1)	0 (0.0)	0 (0.0)	1 (3.1)	4 (1.9)
AEs leading to discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AEs requiring additional therapy	5 (33.3)	38 (27.1)	4 (36.4)	4 (25.0)	11(34.4)	62 (29.0)

The categories are not mutually exclusive.
A patient with multiple occurrences of an event under one treatment is count only once in the event category for that treatment. Grouping of patients based on maximum AAE581 dose received in either core and/or E1.

Deaths, other serious or related discontinuations adverse events since the previous study participation – n (%) of patients (Sensitivity analysis set E2)

Parameter	Placebo + low exposure to AAE581 N = 23 n (%)	High exposure to AAE581 (50 mg) N = 38 n (%)	High exposure to AAE581 (25 mg) N = 39 n (%)	All patients N = 100 n (%)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
SAE	0 (0.0)	1 (2.6)	1 (2.6)	2 (2.0)
AEs leading to discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AEs requiring additional therapy	9 (39.1)	9 (39.1)	14 (35.8)	32 (32)

The categories are not mutually exclusive.
A patient with multiple occurrences of an event under one treatment is counted only once in the event category for that treatment.

Other Relevant Findings

Not Applicable

Date of Clinical Trial Report.

02 Sep 2009