These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert in the country of prescription.

Sponsor / Company: sanofi-aventis and Proctor & Gamble **Drug substance(s):** Risedronate (HMR4003)	**Study Identifier:** NCT00358176 **Study code:** EFC6063
Title of the study: A Multicenter, Double-Blind, Randomized, Active-Controlled, Parallel Group, Noninferiority Study Comparing 75 mg Risedronate Dosed on Two Consecutive Days Monthly with 5 mg Daily Risedronate in the Treatment of Postmenopausal Osteoporosis as Assessed over 24 Months.	
Study centers: Multicenter, international study with a total of 61 centers in Argentina, Australia, Canada, the Czech Republic, France, Lebanon, Poland, South Africa, Turkey, the United Kingdom, and the United States.	
Study period: Date first patient enrolled: 12 July 2004 Date last patient completed: 07 Mar 2007	
Phase of development: Phase 3	

Objectives:

Primary objectives:
The primary objective was to determine the efficacy of a 2 consecutive day monthly dosing regimen (75 mg on 2 consecutive days, monthly, 2CDM regimen) of risedronate compared to a daily dosing regimen (5 mg daily, Daily regimen) of risedronate by demonstarting the noninferiority of the 2 consecutive day monthly regimen to the daily regimen assessed by percent change from baseline in lumbar spine bone mineral density (BMD) at 12 months in women with postmenopausal osteoporosis (PMO).

Secondary objectives:
Efficacy
The secondary efficacy objectives were to evaluate the efficacy of the 2CDM regimen of risedronate, compared to the Daily regimen by the following criteria:

- Percent change from baseline in lumbar spine BMD at Months 6 and 24
- Percentage of responders (positive change >0 g/cm^2 in lumbar spine BMD) at Months 12 and 24
- Percent change from baseline in total proximal femur, femoral neck, and trochanter BMD at Months 6, 12, and 24
- Percent change from baseline in bone resorption marker [urine type 1 collagen cross-linked N-telopeptide (NTX)], and bone formation marker [serum bone-specific alkaline phosphatase (BAP)] at Months 3, 6, 12, and 24
- Number of patients with at least 1 new vertebral body fracture at Months 12 and 24
- Change from baseline in patient reported outcomes (overall health status based on the EQ-5D instrument) at Months 12 and 24.

Safety
The secondary safety objectives were to evaluate the safety of the 2CDM regimen of risedronate compared to the Daily regimen by the following criteria: assessment of clinical laboratory values, vital signs, clinical fractures, adverse event (AE) profiles, and bone histomorphometry. Bone biopsies were obtained at Month 24 in study sites with the capacity to perform them.

Methodology:

Global, multicenter, 2-year, Phase III, double-blind, randomized, active-controlled, parallel-group, noninferiority study Patients were randomly assigned 1:1 to the 2CDM regimen or to the Daily regimen.

Number of patients:	Planned: 1068 (534 per arm); Randomized: 1231; Treated: 1229 Evaluated: Efficacy: primary efficacy (Month 12): 524 (2 CDM regimen), 527 (Daily regimen) Lumbar spine BMD population (Month 24): 479 (2CDM regimen), 474 (Daily regimen Safety: Intent-to-treat (ITT): 616 (2CDM regimen), 613 (Daily regimen)

Diagnosis and criteria for inclusion:

Ambulatory female patients, 50 years of age or older, postmenopausal (natural or surgical) for at least 5 years, in generally good health, and with at least 3 evaluable lumbar spine vertebral bodies (L1-L4), ie, without fracture or degenerative disease. Patients had to meet 1 of the following BMD criteria, as determined by dual energy X-ray absorptiometry (DXA): lumbar spine BMD (L1-L4) more than 2.5 standard deviations (SD) below the young adult female mean value, or lumbar spine BMD more than 2.0 SD below the young adult female mean value and at least 1 prevalent vertebral body fracture (T4-L4).

Investigational product: Risedronate

Dose: Daily regimen (5 mg daily on each day of the monthly dosing period); 2CDM regimen (75 mg on 2 consecutive days per month)

Administration: Oral

Duration of treatment: 24 months

Duration of observation: Patients were observed from the time of the first dose of investigational product until the patient's last visit for completers. For patients who withdrew prior to completion, patients were observed until 14 days after the last dose of investigational product.

Reference therapy: Placebo

Dose: Not applicable

Administration: Oral

Criteria for evaluation:

Efficacy:

Primary efficacy

The primary efficacy variable was the percent change from baseline to Month 12 in lumbar spine BMD.

Secondary efficacy

The secondary efficacy variables were:

- Percent change from baseline in lumbar spine BMD at Months 6 and 24, and endpoint (the last postbaseline measurement available for a patient during the study)
- Change from baseline to Months 6, 12, and 24, and endpoint in lumbar spine BMD
- Percentage of responders (positive change >0 g/cm^2 in lumbar spine BMD) at Months 12 and 24, and endpoint
- Percent change and change from baseline in total proximal femur, femoral neck, and trochanter BMD at Months 6, 12, and 24, and endpoint
- Percent change in bone resorption marker [urine NTX corrected by urine creatinine and serum type 1 collagen cross-linked C-telopeptide (CTX)], and bone formation marker [serum bone-specific alkaline phosphatase (BAP)] at Months 3, 6, 12, and 24 and endpoint in all patients.
- Number of patients with at least 1 new vertebal body fracture at Months 12 and 24, and endpoint
- Change from baseline in patient reported outcomes [overall health status based on the Euro quality-of-life (EuroQOL) group – 5 dimensions instrument (EQ-5D)] at Months 12 and 24, and endpoint.

Safety:

Safety assessments included clinical laboratory values, vital signs, clinical fractures, AE profiles evaluated in all patients throughout the study, and bone histomorphometry evaluated at Month 24 in a subset of patients at study sites designated to perform bone biopsies.

Statistical methods:

Efficacy

Primary efficacy

The primary efficacy (PE) analysis was to demonstrate that the percent change from baseline in lumbar spine BMD at Month 12 for the 2CDM regimen was noninferior to the Daily regimen using a noninferiority margin of 1.5%. The PE analysis was performed on the PE population, which included all ITT patients with evaluable lumbar spine BMD data at baseline and Month 12. This analysis used an analysis of variance (ANOVA) model with fixed effects for treatment and pooled investigative centers. If the 2-sided 95% upper confidence bound for the treatment difference (defined as Daily regimen – 2CDM regimen) obtained from the model did not exceed the predefined noninferiority margin of 1.5%, then the 2CDM regimen was considered noninferior to the Daily regimen. To test the robustness of the primary analysis, the analysis was repeated using the ITT population (all patients who were randomized and received at least 1 dose of investigational product) with last observation carried forward (LOCF) and the per protocol (PP) population (all patients in the ITT population who had no major protocol violations).

The key efficacy analysis for Year 2 was to demonstrate that the percent change from baseline in lumbar spine BMD at Month 24 for the 2CDM regimen was noninferior compared to that of the Daily regimen using a prespecified noninferiority margin of 2.0%.

The noninferiority analysis was performed in a similar manner by using the same ANOVA model as for the primary analysis. If the upper limit of the 95% 2-sided confidence interval (CI) for the treatment difference obtained from the ANOVA model did not exceed the noninferiority margin of 2%, then the 75 mg 2CDM regimen would be declared noninferior to the 5 mg Daily regimen at Month 24. Patients who were randomized and received at least 1 dose of investigational product and had evaluable baseline and Month 24 lumbar spine BMD values (Month 24 Lumbar spine BMD Population) were included in the noninferiority analysis.

Secondary efficacy

All analyses of secondary efficacy variables and patient reported outcomes were performed using the ITT population with treatment group as randomized.

The continuous secondary efficacy variables [BMD and bone turnover marker (BTM)] were analyzed using the same ANOVA model as above. However, 2-sided 95% CIs for the treatment differences were constructed and examinations of noninferiority were not made. Endpoint analyses were based on the last available valid postbaseline measurement during study treatment (that did not necessarily coincide with a value used in 1 of the timepoint-specific analyses). The analyses of treatment group differences in the number of responders to treatment and the number of patients with at least 1 new vertebral body fracture of the thoracic or lumbar spine were conducted using the Fisher's exact test.

Analyses of patient-reported outcomes compared the 2 treatment groups with regard to changes from baseline to Months 12 and 24 in 6 variables (5 categorical, 1 continuous). For the 5 categorical variables, the distribution between groups were compared using the Cochran-Mantel-Haenszel test stratified by pooled center. For the continuous variable [visual analog scale (VAS), 20 cm], the changes from baseline to Months 12 and 24 were compared between the 2 treatment groups using ANOVA with treatment and pooled center as fixed effects. At Month 24, a repeated measurement ANOVA was used to analyze the cumulative data collected at both Month 12 and Month 24.

Safety

For safety assessments, AEs, clinical laboratory values, vital signs, physical examination findings, new clinical fractures, and bone histomorphometry data were summarized by treatment group with descriptive statistics. Safety analyses were performed using the ITT population with treatment group as randomized.

Summary:

Study population:

A total of 3027 patients were screened for the study and 1229 patients were randomized and treated with the investigational product (2CDM: 616; Daily: 613). Evaluation of patient demographic and baseline characteristics showed no statistically significant differences between the treatment groups, except for age at screening in the ITT population. The median age at screening was 64.0 years in the 2CDM regimen and 63.0 years in the Daily regimen.

The samll difference in age was statistically significant in the ITT population but not in the PE or PP population, and was not considered to be clinically meaningful. The vast majority of patients were Caucasian (95.9% overall), and the median number-of years since their last menses was 17.0 years in both groups.

I n addition, there were no statistically significant differences at baseline between the 2 treatment groups in the ITT population in BMD of lumbar spine or proximal femur (total proximal femur, femoral neck and trochanter), or T-scores, prevalent fracture status among patients with 13 evaluable vertebrae, or levels of any of the BTMs. Patient disposition is presented in the table below.

Summary of patient disposition

	Number (%) of patients		
Parameters	**75 mg 2CDM**	**5 mg Daily**	**Overall**
Randomized	618	613	1231
Randomized, not treated	2	0	2
Intent-to-treat population	616 (100.0)	613 (100.0)	1229 (100.0)
Primary efficacy population (Month 12)	524 (85.1)	527 (86.0)	1051 (85.5)
Month 24 lumbar spine BMD population[a]	479 (77.8)	474 (77.3)	953 (77.5)
Per protocol population (Month 24)	441 (71.6)	440 (71.8)	881 (71.7)
Discontinued prior to month 24	142 (23.1)	146 (23.8)	288 (23.4)
Adverse event	80 (13.0)	86 (14.0)	166 (13.5)
Protocol violation	6 (1.0)	2 (0.3)	8 (0.7)
Voluntary withdrawal	43 (7.0)	45 (7.3)	88 (7.2)
Other: investigator recommended	7 (1.1)	7 (1.1)	14 (1.1)
Other: lost to follow-up	6 (1.0)	6 (1.0)	12 (1.0)
Completed Month 24[a]	476 (77.3)	467 (76.2)	943 (76.7)

2CDM=2 consecutive days per month; BMD = bone mineral density

[a]6 patients, 3 in each treatment group, among those completed Month 24 did not have evaluable lumbar spine BMD measurements within the Month 24 visit window, while 16 patients (6 in 75 mg 2CDM, 10 in 5 mg Daily) who withdrew prior to Month 24 had evaluable lumbar spine BMD measurements within the Month 24 visit window. They are included in the Month 24 lumbar spine BMD population.

Efficacy results:

The following table summarizes the efficacy analyses for the primary efficacy variable, for the PE populations at Month 12 and the Month 24 lumbar spine BMD population (all ITT patients with analyzable lumbar spine BMD data at baseline and Month 24).

Mean percent change from baseline in lumbar spine bone mineral density

Analysis population	75 mg 2CDM N	75 mg 2CDM LS mean	5 mg daily N	5 mg daily LS mean	LS mean difference[a] (95% CI) 5 mg daily - 75 mg 2CDM
Primary efficacy[b]					
Baseline BMD (g/cm^2)	524	0.744	527	0.745	
Percent change from baseline					
Month 12	524	3.386[c]	527	3.600[c]	0.214 (-0.189; 0.618)
Month 24 lumbar spine BMD					
Baseline BMD (g/cm^2)	479	0.745	474	0.745	
Percent change from baseline					
Month 24	479	4.181[c]	474	4.348[c]	0.167 (-0.345; 0.679)

BMD = bone mineral density; LS = least squares; N = Number of patients in the indicated population with values at baseline and the relevant visit, i.e., Month 12 and Month 24, respectively; 95% CI = 95% two-sided CI.

[a] Adjusted means, mean difference, and CIs are from an ANOVA model containing Treatment and Pooled Investigative Center.

[b] The primary efficacy population is based on the Year-1 database used in the Year 1 study report. The primary efficacy results reported in the Year 1 study report are considered final and are presented for Month 12 in this table.

[c] Indicates a statistically significant difference from baseline determined from a 95% confidence interval unadjusted for multiple comparisons.

- The 2CDM regimen was shown to be noninferior (95% 2-sided upper confidence bound <1.5%) to the Daily regimen for the primary efficacy variable of percent change from baseline to Month 12 in lumbar spine BMD.
- The 2CDM regimen was shown to be noninferior (95% 2-sided upper confidence bound <2.0%) to the Daily regimen for the key secondary efficacy variable of percent change from baseline to Month 24 in lumbar spine BMD.
- Both treatment groups showed statistically significant percent increases from baseline to Month 6, Month 12, Month 24, and Endpoint in lumbar spine BMD. The mean percent increases from baseline at Month 6, Month 12, Month 24, and Endpoint were similar in both treatment groups. At Month 24, the mean percent changes from baseline were as follows, 2CDM: 4.181%; Daily: 4.348%.
- The percentage of responders (BMD change >0 g/cm^2) was consistently high throughout the 2-year study and comparable between the 2 groups with approximately 85%, 86%, and 86% of responders at Month 12, Month 24, and Endpoint respectively, in the 2CDM regimen and 86% of responders at Month 12, Month 24, and Endpoint in the Daily regimen.
- Both treatment groups showed statistically significant percent increases from baseline to Months 6, 12, and 24, and to Endpoint in total proximal femur, femoral neck, and femoral trochanter BMD. The mean percent increases in total proximal femur, femoral neck, and trochanter BMD in the 2CDM regimen were comparable to those in the Daily regimen at each of these timepoints. At Month 24, the percent changes from baseline were as follows: total proximal femur (2CDM: 2.549%; Daily: 2.307%); femoral neck (2CDM: 1.981%; Daily: 1.677%); trochanter (2CDM: 3.957%; Daily: 3.870%).
- At Months 3, 6, 12, 24, and Endpoint, there were statistically significant within-group mean percent decreases from baseline in the levels of the bone resorption markers, urine NTX/creatinine and serum CTX, and the bone formation marker serum BAP, in both treatment groups. For serum BAP at all timepoints and urine NTX/creatinine at Month 12, Month 24 and Endpoint, the percent decreases from baseline were similar between groups. For urine NTX/creatinine at Months 3 and 6 and for serum CTX at all timepoints, small differences between groups were observed, with the Daily regimen having a greater mean percent decrease from baseline than the 2CDM regimen. It is unlikely that these differences are clinically relevant. The percent changes from baseline to Month 24 were as follows: urine NTX/creatinine (2CDM: -48.34%; Daily: -51.77%), serum CTX (2CDM: -30.58%; Daily: -39.51%) and serum BAP (2CDM: -29.71%; Daily: -30.20 %).
- The numbers of patients with new vertebral (radiographically determined) fractures at Months 12 and 24, and Endpoint were similar in the 2CDM regimen and the Daily regimen. In the 2CDM regimen, at least 1 new fractured vertebra occurred in 7 (1.33%), 16 (3.34%), and 16 (2.88%) patients at Months 12 and 24, and Endpoint, respectively. In the Daily regimen, at least 1 new fractured vertebra occurred in 7 (1.33%), 13 (2.79%) and 15 (2.72%) patients at Months 12 and 24, and Endpoint, respectively. At Month 12, approximately 99% of patients in either group had no new fractured vertebrae and at Month 24, 97% in either regimen had not sustained a new vertebral fracture.

- At Months 12 and 24, and Endpoint, there were no statistically significant differences between the 2CDM regimen and the Daily regimen for change from baseline in any of the 5 categorical health status measures or for health status measured by the VAS of EQ-5D.

Safety results:

- Overall, the frequency of treatment emergent adverse events (TEAEs) was similar in the 2 treatment groups (2CDM, 91.1%; Daily, 89.9%). The 3 most frequently reported TEAEs were arthralgia, back pain, and dyspepsia (14.0%, 12.7%, and 9.9%, respectively) in the 2CDM regimen and (14.0%, 14.2%, and 9.5%, respectively) in the Daily regimen.
- Nine deaths occurred during the 24 months of the study (3 in the 2CDM regimen and 6 in the Daily regimen). All of the deaths were considered to be doubtfully related to the investigational product by the Investigator.
- A total of 14.4% of patients in the 2CDM regimen and 10.8% of patients in the Daily regimen experienced serious TEAEs during the study. Eleven patients reported serious TEAEs that were considered by the Investigator to be possibly or probably related to the investigational product (2CDM: 7 [1.1 %]; Daily: 4 [0.7 %]). After 24 months, the overall higher frequency of patients in the 2CDM regimen reporting serious TEAEs relative to patients in the Daily regimen was primarily due to a difference in patients reporting serious TEAEs in the following 2 system organ classes (SOCs): Injury, poisoning and procedural complications and gastrointestinal disorders. Serious TEAEs in the SOC Injury, poisoning and procedural complications were higher in the 2CDM regimen compared with the Daily regimen after 24 months of treatment. The most commonly occurring events in both treatment groups were clinical fractures requiring hospitalization and disproportionately involving the axial skeleton (pelvis, sacrum) and femur when compared to non-serious TEAE fractures for the SOC Injury, poisoning and procedural complications.
- Unlike the similarity in occurrence of upper gastrointestinal TEAEs between treatment regimens (as detailed below), the overall occurrence of serious gastrointestinal TEAEs at 24 months was higher in the 2CDM regimen (14 patients, 2.3%) compared with the Daily regimen (5 patients, 0.8%). Tthe occurrence of serious upper gastrointestinal TEAEs was also higher in the 2CDM regimen (2CDM: 8 patients; Daily: 4 patients). The frequency of these events was low. The number of serious upper gastrointestinal TEAEs rated by the Investigators as severe was the same in both regimens (2 each), and the number of patients who withdrew due to a serious upper gastrointestinal TEAE was similar (3 patients in the 2CDM regimen and 2 in the Daily regimen).
- The percentage of patients who withdrew from the study due to a TEAE was similar between the 2 treatment groups (2CDM: 12.8%; Daily: 13.9%). The most frequent TEAEs leading to withdrawal were in the gastrointestinal disorders SOC (2CDM: 7.8%; Daily: 7.5%). The most frequent TEAEs leading to withdrawal by preferred term in the 2 treatment groups were as follows for the 2CDM regimen and the Daily regimen, respectively: dyspepsia, 9 patients (1.5%) and 6 patients 1.0%), nausea 6 patients (1.0%) and 7 patients (1.1%), and upper abdominal pain, 3 patients (0.5%) and 15 patients (2.4%).
- A similar percentage of patients reported upper gastrointestinal TEAEs in the 2 treatment groups (2CDM: 26.3%; Daily: 27.6%). The most frequent upper gastrointestinal TEAEs in both treatment groups, by preferred term were as follows for the 2CDM regimen and the Daily regimen, respectively: dyspepsia, 61 patients (9.9%] and 58 patients (9.5%), upper abdominal pain, 44 patients (7.1%) and 55 patients (9.0%), abdominal pain, 23 patients (3.7%) and 31 patients (5.1%), and gastroesophageal reflux disease, 21 patients (3.4%) and 18 patients (2.9%). The majority of the upper gastrointestinal TEAEs in both treatment groups were considered to be mild in severity. The percentages of patients with moderate-to-severe upper gastrointestinal TEAEs were similar in the 2 treatment groups. A total of 9.6% of patients in the 2CDM regimen and 8.6% of patients in the Daily regimen reported moderate-to-severe upper gastrointestinal TEAEs.
- Esophageal endoscopic findings were similar across the 2 treatment groups. In general, gastroduodenal findings were also similar across treatment groups. There were 7 patients in the 2CDM regimen and 2 patients in the Daily regimen who had endoscopy findings of esophageal, gastric, and/or duodenal ulcers. Five patients in the 2CDM group with endoscopy findings of ulcers continued in the study on anti-ulcer medications and did well; 1 patient with a duodenal ulcer and 1 patient with both a duodenal and a gastric ulcer in the 2CDM group withdrew from the study. In the Daily group, both patients with gastric ulcers withdrew from the study, 1 of these withdrawals was attributed to a concomitant abdominal postsurgical lower gastrointestinal complication (colonic polyp).

- The incidences of nonvertebral fracture and vertebral fracture TEAEs were similar in the 2 treatment groups. A total of 5.7% of patients in the 2CDM regimen and 5.1% of patients in the Daily regimen reported nonvertebral fracture TEAEs. Overall, 3.4% of patients in the 2CDM regimen and 2.1% of patients in the Daily regimen reported osteoporosis-related nonvertebral fracture TEAEs. The incidences of vertebral fractures reported as TEAEs (clinical fractures) were also similar in the 2 treatment groups (2CDM: 1.0%; Daily: 0.8%).
- Four patients in the 2CDM regimen and none in the Daily regimen reported fever or influenza-like illness as TEAEs occurring within the first 5 days of treatment. These TEAEs were all mild or moderate in severity.
- Clinical laboratory tests, including mean changes from baseline, the number of patients with shifts outside the normal range for each laboratory analyte, and the number of patients with markedly abnormal laboratory values of potential clinical significance were similar between the 2 treatment groups.
- Clinical laboratory tests, including mean changes from baseline, the number of patients with shifts outside the normal range for each laboratory analyte, and the number of patients with markedly abnormal laboratory values of potential clinical significance were similar between the 2 treatment groups.
- There were no clinically meaningful differences in the changes in vital signs between the treatment groups.
- Bone biopsy results were available for 9 patients in the Daily regimen and 4 in the 2CDM regimen. Bone tetracycline label was observed in all samples, indicating continued mineralization of newly deposited bone matrix. No pathological findings (eg, osteomalacia, marrow fibrosis, woven bone, abnormal osteoid, cortical trabecularization) were observed in any of the samples.

Issue date: 18-Jul-2008