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		Study Code:	HMR4003B_4034
Generic drug name:	Risedronate sodium	**Date:**	02/April/ 2008

Title

Open-Label Study to Determine How Prior Therapy with Alendronate or Risedronate in Postmenopausal Women with Osteoporosis Influences the Clinical Effectiveness of Teriparatide (OPTAMISE Study)

Investigator(s), study site(s)

Multicenter study with multiple investigators, 54 sites

Study duration and dates	**Phase**
Duration Per Subject (planned): 12 months First Subject First Visit: 15 March 2004 Last Subject Last Visit: 17 January 2007	IV

Objectives

The *primary* objective of the study was to compare the teriparatide (human, recombinant PTH[1-34]) (TPTD)-associated change from baseline in N-terminal propeptide of type I collagen (P1NP), after 3 months of treatment, between subjects previously treated with risedronate (RIS) and those previously treated with alendronate (ALN).

Secondary objectives of the study were:

- To compare the TPTD-associated change from baseline in P1NP, at 0.5, 1, 2, 4, 5, 6, and 12 months, between subjects previously treated with RIS and those previously treated with ALN.
- To compare the TPTD-associated change from baseline in bone-specific alkaline phosphatase [BSAP], osteocalcin [OC]), urinary N-telopeptide cross links [uNTX] and serum type I collagen C-telopeptide [sCTX] at 0.5, 1, 2, 3, 4, 5, 6, and 12 months, between subjects previously treated with RIS and those previously treated with ALN.
- To compare the TPTD-associated percent change from baseline in lumbar spine (LS), total hip and forearm bone mineral density (BMD) as assessed by dual energy X-ray absorptiometry (DXA), after 6 and 12 months of treatment, between subjects previously treated with RIS and those previously treated with ALN.

Tertiary objectives of the study were:

- To compare the TPTD-associated changes from baseline in cortical moment of inertia and other determinants of bone quality as assessed by central quantitative computed tomography (QCT) measurements of spine and hip, after 12 months of treatment, between subjects previously treated with RIS and those previously treated with ALN.
- To compare the TPTD-associated changes from baseline for the microfinite element analysis variables, eg, trabecular bone area fraction, as assessed by magnetic resonance imaging (MRI) of the distal radius for a subset of subjects at select study sites, after 12 months of treatment, between subjects previously treated with RIS and those previously treated with ALN.
- To compare the TPTD-associated changes from baseline in osteoprotegerin (OPG) and RANK ligand (RANKL) proteins at 0.5, 1, 2, 3, 4, 5, 6, and 12 months, between subjects previously treated with RIS and those previously treated with ALN.
- To compare the TPTD-associated impact on area under the curve (AUC) and time to maximal concentration (C_{max}) determined for each bone marker (P1NP, BSAP, OC, uNTX, and sCTX) and measures of OPG and RANKL between subjects previously treated with RIS and those previously treated with ALN.
- To compare changes from baseline in histomorphometry and dynamic measurements of bone (synchrotron scanning, Fourier Transform Infrared Spectroscopic Imaging [FTIRI], backscatter, nanoindentation, µ-CT) for a subset of subjects at select study sites, after 12 months of TPTD therapy, between subjects previously treated with RIS and those previously treated with ALN, as determined from bone biopsy samples.

Study design

This was a 12-month, multi-center, open-label study in which postmenopausal women previously treated with either RIS or ALN for at least 24 months were treated with TPTD, 20 µg subcutaneously (SC) daily, for 12 months. This study was also called the OPTAMISE (Open-label study to determine how Prior Therapy with Alendronate or risedronate in postmenopausal women with osteoporosis Influences the clinical effectiveness of teriparatidE) trial. The number of subjects previously treated with RIS and ALN were balanced within each of 2 strata, and were further subdivided by the duration of previous bisphosphonates treatment by 6-month periods. Subjects treated with RIS or ALN for >48 months at screening were allowed to participate on a paired basis if a matching subject, based on duration of previous RIS or ALN therapy, was also enrolled.

Number of subjects planned

290

Inclusion criteria

- Women who used RIS or ALN continuously for 24 to 48 months prior to enrollment into study.
- Women who were at least 10 years post menopause (ie, 10 years had elapsed since the last menstrual period).
- 55-85 years of age (inclusive), if natural menopause, or 60-85 years of age (inclusive), if surgical menopause.
- Lumbar spine or total hip BMD T-score $\leq$ -2.0 and $\geq$1 prevalent osteoporotic fracture, or LS or total hip BMD T-score $\leq$ -2.5 for US and Australian sites. LS or total hip BMD T-score <-2.5 and $\geq$1 prevalent osteoporotic fracture for sites in Belgium, Canada, France, Netherlands, Germany, and the UK. The qualifying values must have been documented prior to enrollment.
- Vitamin D replete (25-hydroxyvitamin D $\geq$16 ng/ml and $\leq$80 ng/ml).
- Urinary NTX <50 nmol/mmol creatinine (creat) (to assure treatment compliance and bone turnover was well into the pre-menopausal range).
- At least 2 measurable LS vertebrae (ie, without fracture or sufficient degenerative disease) in which bone density assessment could be made without interference.
- In general good health as determined by medical history, physical examination, and laboratory tests.
- Willing to have maintained, after baseline, intake of calcium from all sources (diet and supplements) of at least 1000 mg per day, based on the assessment of the investigator using, the Block Dietary Questionnaire (US, Canada, and Australia), the Fardellone Dietary Questionnaire (France and Canada), or the Montomoli Questionnaire (UK, Netherlands, Germany, and Belgium).
- Willing and able to have provided written informed consent and, when required by the local governing authority, authorized release of prior relevant medical records (eg, a release was required for subjects at all US sites, according to the Health Insurance Portability and Accountability Act [HIPAA]).
- Willing to have complied with instructions for the use of TPTD.

Treatments

TPTD, 20 µg SC daily, for 12 months

Efficacy data

This report of Month 12 data represents the final analysis of efficacy for the OPTAMISE study and includes all bone turnover marker (BTM) data from the entire 12 months of the study.
Primary variable: change from baseline at 3 months for P1NP.
Secondary variables included:

- Change from baseline at 0.5, 1, 2, 3, 4, 5, 6 and 12 months for P1NP (excluding 3 months), BSAP, OC, uNTX, sCTX.
- Change from baseline at 6 and 12 months for spine, hip, and forearm BMD.

Tertiary variables included:

- Change from baseline at Month 12 for spine and hip QCT variables.
- Change from baseline at Month 12 for distal radius MRI determinations.
- Change from baseline at 0.5, 1, 2, 3, 4, 5, 6 and 12 months for OPG and RANKL.
- Changes in AUC and C_{max} for P1NP, BSAP, OC, uNTX, sCTX, OPG, and RANKL.
- Changes from baseline at Month 12 for histomorphometry measurements.

Safety data

Safety data were evaluated using the following parameters:

- Reported adverse events (AEs)
- Laboratory values, including serum calcium
- Physical examination, including vital signs

Statistical procedures

Efficacy: The Completer Population (CMP), all enrolled and treated subjects with both a baseline and an on-treatment Month 3 value for P1NP, was the primary analysis population. The Intent-to-Treat Population (ITT), used to corroborate the findings in the CMP, included all enrolled and treated subjects with both a baseline and a post-baseline value for P1NP.
Efficacy data were evaluated using BTM data collected during the expanded day range for the full 12 months of TPTD therapy (ie, up to Day 410).
The primary efficacy variable was the mean absolute change from baseline at 3 months in P1NP. Absolute mean changes from baseline were analyzed by prior bisphosphonates group (RIS or ALN) using an analysis of covariance (ANCOVA) with treatment, enrollment stratum, and pooled site as class effects and the corresponding baseline value as the covariate. Descriptive statistics, ranked data using ANCOVA, log-transformed analysis with ANCOVA, and repeated measures analysis were conducted to evaluate consistency of effect observed with the primary analysis.
Analysis of secondary efficacy variables were the same as described for the primary efficacy variable.
Safety: Safety data collected during the expanded day range for the full 12 months of TPTD therapy (ie, up to Day 410) were evaluated. The safety population included all enrolled and treated subjects. Incidence tables were provided for this population for AEs for all and possibly-related treatment-emergent AEs (TEAEs), by system organ class (SOC), frequency, intensity, and type of event (eg, serious adverse events [SAEs] and withdrawals).

Interim analysis

Baseline data, to determine the relationship of treatment practices and underlying risk factors of osteoporosis, were analyzed during 2006 in an abstract presented at American Society for Bone and Mineral Research (ASBMR) and in posters presented at the European Congress on Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ECCEO) and European Calcified Tissue Society (ECTS) meetings.

Results - Study subjects and conduct

A total of 669 subjects were screened at 54 sites (42 sites from the US and 12 sites from outside the US). Of these, 338 subjects were screening failures and 331 subjects were enrolled into the study (161 subjects previously treated with RIS and 170 subjects previously treated with ALN).
Four major analysis populations were defined in this study. The safety population was defined as enrolled subjects who received at least one dose of TPTD study drug. Because 7 subjects of the 331 enrolled subjects were not treated with TPTD study medication, the safety population consisted of 324 subjects (158 subjects previously treated with RIS and 166 subjects previously treated with ALN). The ITT population consisted of 317 subjects with both a baseline and a post-baseline value for P1NP and included 157 prior RIS subjects and 160 prior ALN subjects. The CMP population, the primary population for efficacy analysis, included all enrolled treated subjects with a baseline P1NP and an on-treatment Month 3 value for P1NP (Days 77-107, inclusive). The CMP population was made up of 146 subjects in each previous bisphosphonates treatment group, for a total of 292 subjects.
The Per-Protocol (PP) population included all efficacy evaluable subjects without major protocol deviations.

The demographic characteristics of the CMP population are summarized as follows (n=292). The overall mean age was 68.5 years (range, 51-85 years).

Baseline characteristics related to osteoporosis in the CMP population are summarized as follows. The mean number of years subjects were postmenopausal was 22.5 (range, 4.7-54.4 years). Most subjects (281/292 or 96.2%) were on weekly bisphosphonates therapy and had been on bisphosphonates therapy for a mean of 37.6 months (range, 24-78 months). Minimum T-score was -3.1 (range, -5.3 to -2.1). Fewer than half of the subjects (130/292 or 44.5%) had a prevalent vertebral fracture based on spinal radiographs read centrally and fewer than half (138/292 or 47.3%) had osteoporotic fractures per medical history. The mean vitamin D level was 32 ng/mL (range, 16-80 ng/mL). Key baseline characteristics, including those related to osteoporosis, in the CMP population did not differ between previous bisphosphonates treatment groups.

Results – Efficacy

The primary endpoint of the OPTAMISE study was the TPTD-associated absolute change from baseline in P1NP, after 3 months of treatment in CMP subjects. The baseline absolute mean ± standard error (SE) P1NP in 146 CMP subjects previously treated with RIS was 31.71 ± 1.516 ng/mL and in 146 CMP subjects previously treated with ALN was 24.62 ± 1.436 ng/mL (p=0.0002). After 3 months of treatment with TPTD, subjects previously treated with RIS experienced a significantly greater increase in P1NP from baseline compared to subjects previously treated with ALN (85.97 ± 5.547 ng/mL versus 61.18 ± 5.273; absolute mean difference=24.78 ± 7.044; p=0.0005; 95% confidence interval [CI] [10.92, 38.65]). Analysis of the primary endpoint by log-transformed data with ANCOVA demonstrated that after 3 months of TPTD therapy, subjects previously treated with RIS experienced a more than 4-fold increase (4.36 or 436%) in P1NP, compared to subjects previously treated with ALN who experienced a more than 3-fold increase (3.51 or 351%) in P1NP. Additional statistical testing was consistent with the primary analysis of the primary efficacy endpoint for an increase in P1NP for prior RIS-treated subjects relative to prior ALN-treated subjects.

Secondary endpoints evaluated after 12 months of TPTD therapy included mean absolute changes in P1NP after 0.5, 1, 2, 4, 5, 6, and 12 Months and in BSAP, OC, uNTX, and sCTX after 0.5, 1, 2, 3, 4, 5, 6, and 12 months.

Two weeks (0.5 months) after stopping RIS or ALN and initiating TPTD treatment and continuing for 12 months of TPTD study drug, mean absolute changes from baseline in P1NP were greater in subjects with a history of RIS treatment than in subjects with a history of ALN treatment, an effect that became significant at Month 1 and remained significantly different for the first 5 months (p = 0.0038).

After 3 months of treatment with TPTD, subjects previously treated with RIS experienced a significantly greater increase in BSAP, sCTX, and OC from baseline compared to subjects previously treated with ALN. Similar to the analysis of P1NP, 1 month after stopping RIS or ALN and initiating therapy with TPTD and continuing for the first 6 months of TPTD study drug, mean absolute changes from baseline in all BTMs measured above were greater in subjects with a history of RIS treatment than in subjects with a history of ALN treatment, an effect that became significant at Month 1 and remained significantly different for the first 5 months. uNTX was shifted to the right by one month in terms of significance; becoming significant at Month 2 and remaining significantly different in patients with a history of Ris treatment than in patients with a history of Aln treatment through Month 6 (p=0.0194).

Subset analysis of mean change from baseline to Month 3 in P1NP, BSAP, OC, uNTX, and sCTX demonstrated consistency across strata. In every stratum, subjects previously treated with RIS produced a greater increase in all of these BTMs after the first 3 months of TPTD therapy compared to subjects previously treated with ALN.

After 12 months of TPTD therapy, the percent increase from baseline in total LS BMD in prior RIS subjects was significantly greater than in prior ALN subjects (5.066 ± 0.4930% versus 3.554 ± 0.4556%; mean difference 1.512 ± 0.5993%; 95% CI [0.331, 2.692]; p=0.0123. Mean BMD of the hip decreased significantly from baseline in both prior bisphosphonates treatment groups after 6months (p=0.0001) and after 12 months (p = 0.0051) of TPTD study drug. Previous treatment with RIS resulted in a significantly smaller percent decrease from baseline after 12 months of TPTD therapy (-0.278 ± 0.4215%) than previous treatment with ALN (-1.705 ± 0.3918%; 95% CI [0.416, 2.438]; p=0.0059).

A potential correlation between BTMs and BMD via DXA was evaluated. For the first 3 months of TPTD study drug therapy, absolute changes in bone formation as measured by P1NP and in bone resorption as measured by uNTX and sCTX, at each time point measured, were correlated with percent changes in BMD of the spine in subjects previously treated with RIS; in contrast, similar correlations were found only after the 2 week time point in subjects previously treated with ALN.

The demographics, background variables, fracture history, and BTMs at baseline in the QCT-CMP subjects were not different from the entire CMP population at baseline. Twelve months after stopping RIS or ALN and initiating therapy with TPTD, previous treatment with RIS was associated with significantly larger percent increases from baseline in vertebral integral and trabecular bone density via QCT (6.0952 ± 0.85979% and 24.0815 ± 3.66762%, respectively) compared to previous treatment with ALN (3.5032 ± 0.78009% and 13.6654 ± 3.31634%; p= 0.0194). Twelve months after stopping RIS or ALN and initiating therapy with TPTD, prior RIS was associated with larger mean percent increases from baseline for BMD of the hip. No statistically significant differences were observed

between prior bisphosphonate treatment groups for the percent changes from baseline for integral or trabecular total hip or trochanteric hip variables.
A potential correlation between BTMs and BMD via QCT was evaluated. Beginning after 2 weeks of TPTD study drug therapy and continuing for the first 6 months of the study, absolute changes in bone formation as measured by P1NP and in bone resorption as measured by uNTX and sCTX were correlated with percent changes in bone density of the trabecular spine in subjects previously treated with RIS and in subjects previously treated with ALN.
Magnetic resonance imaging determinations were made in a subset of subjects at centers equipped to perform MRIs. No statistically significant differences were observed between prior bisphosphonate treatment groups for changes from baseline after 12 months of TPTD study drug therapy for any of the MRI variables.

Results – Safety

Treatment with TPTD was well tolerated, regardless of prior bisphosphonate therapy (RIS or ALN). During the study, at least 1TEAE assessed by the investigator as being possibly-related to TPTD therapy was reported by 139/324 (42.9%) of subjects in the safety population (69/158 or 43.7% of prior RIS subjects and 70/166 or 42.2% of prior ALN subjects). The most frequently reported possibly-related TEAEs while on TPTD therapy were hypercalcemia (23/158 or 14.6% of prior RIS subjects and 23/166 or 13.9% of prior ALN subjects), muscle spasms (predominantly leg cramps) (14/158 or 8.9% of prior RIS subjects and 18/166 or 10.8% of prior ALN subjects), nausea (11/158 or 7.0% of prior RIS subjects and 14/166 or 8.4% of prior ALN subjects), and dizziness (10/158 or 6.3% of prior RIS subjects and 10/166 or 6.0% of prior ALN subjects).
During the OPTAMISE study, 14 subjects (9 prior RIS and 5 prior ALN; p=0.2813) experienced 15 fractures at a site of interest as a TEAE. These subjects included 6subjects with fractures of upper limbs, 4subjects with wrist fractures, 2 subjects with finger fractures, and 1 subject each with compression fractures of the spine, hip, and rib.
No reports of death, osteosarcoma, or overdose were received while a subject was taking study drug.
All subjects were required to be postmenopausal for at least 10 years prior to study entry and no subjects became pregnant during the study.
Overall, 27 subjects experienced serious TEAEs while being treated with TPTD, 14 from the prior RIS group and 13 from the prior ALN group. Three of these SAEs (pericardial effusion in a prior RIS subject, liver metastases in a prior ALN subject, and stone in the right ureter in a prior ALN subject) were assessed by the investigator as being possibly related to TPTD therapy.
Adverse events resulted in premature withdrawal from study participation in 38 subjects. Of these subjects, 20 subjects had events assessed by the investigator as possibly-related to TPTD therapy (10 subjects from each prior bisphosphonate group). Possibly-related TEAEs leading to withdrawal were primarily in the Gastrointestinal and Nervous system disorders system organ SOCs.
Serum calcium levels were evaluated at each visit during the study. Six subjects developed a predefined change abnormal (PCA) for increased calcium (=3 mmol/L [or =1.2 mg/dL]) at their last observation (3 prior RIS subjects and 3prior ALN subjects). Increases in serum calcium for individual subjects were poorly correlated with best improvements from baseline in P1NP.

An assessment of vital signs demonstrated statistically significant changes from baseline at various time points in temperature, heart rate, and systolic blood pressure in subjects previously treated with RIS and in respiratory rate and systolic and diastolic blood pressures in subjects previously treated with ALN. Changes in vital signs resulted in TEAEs in 6prior RIS subjects (weight decreased and elevated temperature in 2subjects each and elevated blood pressure and heart rate increased in 1 subject each) and in 5 prior ALN subjects (weight decreased in 3 subjects and elevated blood pressure and heart rate increased in 1 subject each).

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