The Vitamin D Analogue 2MD Increases Bone Turnover but Not BMD in Postmenopausal Women With Osteopenia: Results of a 1-Year Phase 2 Double-Blind, Placebo-Controlled, Randomized Clinical Trial

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ABSTRACT

Most osteoporosis drugs act by inhibiting bone resorption. A need exists for osteoporosis therapies that stimulate new bone formation. 2-Methylene-19-nor-(20S)-1α,25-dihydroxyvitamin D3 (2MD) is a vitamin D analogue that potently stimulates bone formation activity in vitro and in the ovariectomized rat model. In this randomized, double-blind, placebo-controlled study of osteopenic women, the effect of daily oral treatment with 2MD on bone mineral density (BMD), serum markers of bone turnover, and safety were assessed over 1 year. Volunteers were randomly assigned to three treatment groups: placebo (n = 50), 220 ng of 2MD (n = 54), and 440 ng of 2MD (n = 53). In general, 2MD was well tolerated. Although 2MD caused a marked increase in markers of bone formation, it did not significantly increase BMD. Since 2MD also shows marked activity on bone resorption (as revealed by dose-dependent increases in serum C-telopeptide cross-links of type I collagen in this study), 2MD likely stimulated both bone formation and bone resorption, thereby increasing bone remodeling. © 2011 American Society for Bone and Mineral Research.

KEY WORDS: OSTEOPOROSIS; BONE; VITAMIN D; 2MD; BMD

Introduction

Osteoporosis is a debilitating disease whose prevalence is increasing in an aging population. Osteoporotic fractures in both men and women are associated with significant morbidity and mortality. Nearly 1% of women over the age of 65 years suffer a hip fracture annually, and more than 20% of these women die within a year of the fracture.1) Quite clearly, development of effective therapies that reduce fracture risk in these patients is a major health goal.

The most commonly used osteoporosis therapies are antiresorptive agents, including bisphosphonates and selective estrogen modulators.2) Less effective antiresorptive agents include calcitonin,3) 1α-hydroxyvitamin D3 [1α(OH)D3],4,5) and 1α,25-dihydroxyvitamin D3 [1,25(OH)2D3].6) A new antiresorptive agent currently under development is the RANKL antibody denosumab.7) These drugs inhibit the resorptive component of the bone-remodeling system, thus reducing the resorbed surfaces required for new bone synthesis.8) As a result, new bone synthesis is inhibited within several months of antiresorptive therapy,9) limiting further improvement in bone mass after a year or two of therapy.10)

Only one anabolic osteoporosis drug, teriparatide, is currently available in the United States. Teriparatide use is limited perhaps owing to the delivery method (daily subcutaneous injection), high cost, and labeling for this drug (boxed warning regarding osteosarcoma and limitation of therapy duration to 2 years maximum).11)

As noted earlier, the hormonal forms of vitamin D, 1,25(OH)2D3, and other vitamin D analogues have been studied...
for possible use in the treatment of osteoporosis and in some countries are in use for that purpose. For example, 1α(OH)D₃ and 1,25(OH)₂D₃ have been used in Japan for at least two decades. Clinical evidence of improvements in fracture rates following 1,25(OH)₂D₃ or 1α(OH)D₃ therapy in postmenopausal osteoporosis have been published and debated. Thus far, all vitamin D compounds in use and under development act primarily by suppression of bone resorption rather than as anabolic agents at dose levels that are not hypercalcemic.

A new series of vitamin D analogues that stimulate new bone formation has been discovered. One of these, 2-methylene-19-nor-(20S)-1α,25-dihydroxyvitamin D₃ (2MD or DP001) has been studied extensively in the ovariectomized (OVX) rat model. 2MD acts as a bone anabolic agent in this model and is effective in increasing bone mass without hypercalcemia. Since the OVX rat is an accepted model by regulatory agencies worldwide, it is compelling to consider 2MD as a promising therapy for osteoporosis. This article presents the results of a clinical trial designed to test this hypothesis.

**Materials and Methods**

**Study subjects**

Postmenopausal women were screened for study enrollment at nine clinical sites within the United States (Madison, WI, Indianapolis, IN, Omaha, NE, Mineola, NY, West Havenstraw, NY, Dunsvansville, PA, Albuquerque, NM, Upland, CA, and Bethesda, MD). Included participants were osteopenic women who were amenorheic for at least 5 years and between the ages of 55 and 80 years (inclusive). Osteopenia was defined as a lumbar spine (L₁–L₄) bone mineral density (BMD) value of 0.937 to 0.772 g/cm² on Hologic densitometer (Hologic, Inc., Waltham, MA, USA) or 1.060 to 0.880 g/cm² on GE Healthcare Lunar densitometer (GE Healthcare, Madison, WI, USA). Other inclusion criteria included having a body mass index (BMI) of approximately 18 to 35 kg/m², being generally healthy, and being willing and able to comply with the study visits and procedures.

Key exclusion criteria included history of acute or unstable chronic hematologic, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, psychiatric, or neurologic diseases and current treatment with medications that affect vitamin D metabolism or absorption or medications affecting calcium balance or bone turnover (including calcitomin, any prior intravenous bisphosphonate use, or any past oral bisphosphonate treatment for more than 3 months or any time in the previous year). Women also were excluded if they had a QTc value greater than 450 ms, creatinine clearance ≤ 50 mL/min, urinary calcium > 300 mg/24 h, serum 25(OH)D level < 10 ng/mL, dietary calcium intake > 1000 mg/day, vitamin D intake > 2000 IU/day, or were currently using any illicit drug or had history of alcohol abuse (Table 1).

The study protocol was approved by institutional review boards affiliated with the sites or by a central institutional review board, and all subjects provided written informed consent before participating in the study. The clinical study was conducted in accordance with the Declaration of Helsinki. An independent data safety monitoring board (DSMB) met at regular intervals during the study and reviewed safety and BMD data from the study. The study was registered with ClinicalTrials.gov (identifier number NCT00715676).

**Study drug**

2MD was formulated in soft gel capsules, and the placebo was formulated identically, except for the absence of 2MD. A vitamin D₃ supplement (600 IU/day) also was provided to each subject. Both study drug capsules and vitamin D₃ supplement were analyzed for content and stability prior to and during the study. Placebo or 2MD (220 or 440 ng total daily dose) was taken orally once daily.

**Study design and data collection**

The study was a randomized, double-blind, placebo-controlled, parallel-group study with drug treatment lasting 1 year. The study enrolled 157 postmenopausal women with osteopenia between March 2007 and December 2007. Subjects were randomized in a 1:1:1 ratio to three treatment groups: placebo, 220 ng of 2MD, or 440 ng of 2MD. Study drug and placebo were prepackaged in identical subject-specific kits by Columbia University Medical Center Research Pharmacy (CUMCRP, New York, NY, USA), which also provided the computer-generated randomization schedule but had no clinical involvement in the trial. All study participants, the sponsor and data collectors, and all clinical investigators and support staff were blinded to treatment assignments throughout the study until after the study database was locked.

The subjects came to the investigative sites for study evaluations during weeks −6 to −2 (first screening visit), weeks −4 to −1 (second screening visit), on day 1 (baseline), and during weeks 2, 4, 8, 13, 20, 26, 33, 39, 46, and 52. Per protocol, the trial ended when the last remaining subject had completed her final visit.

**Study procedures**

BMD assessments were based on duplicate dual-energy X-ray absorptiometry (DXA) scans at the spine and hip at screening visit 2, baseline, week 26, and week 52. No analysis of postscreening DXA scans was performed at the sites; all DXA scans were sent to Bio-Imaging Technologies (Newtown, PA, USA) for quality control and BMD analyses.

Laboratory assessments were performed by a central laboratory (Quest Diagnostics Clinical Trials, Valencia, CA, USA) except bone marker and postscreening intact parathyroid hormone (iPTH) analyses, which were performed by the study sponsor. Serum calcium analysis was performed at all study visits except for screening visit 2. Twenty-four-hour urinary calcium measurements were performed for screening visit 2 and the visits at baseline and weeks 2, 4, 8, 13, 26, 39, and 52.

Bone marker and postscreening iPTH samples were stored at −70 or −80°C until the end of the study. Three bone markers were tested: serum C-terminal cross-linked telopeptide of type I collagen (s-CTX), osteocalcin, and procollagen I N-terminal extension peptide (PINP). Bone marker and iPTH analyses were conducted by Deltanoid Pharmaceuticals (Madison, WI, USA) on...
Table 1. Summary of Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n = 49)</th>
<th>220 ng 2MD (n = 54)</th>
<th>440 ng 2MD (n = 53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>39 (80)</td>
<td>44 (82)</td>
<td>42 (79)</td>
</tr>
<tr>
<td>Black</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>9 (18)</td>
<td>8 (15)</td>
<td>9 (17)</td>
</tr>
<tr>
<td>Asian</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Age (years)</td>
<td>61.1 ± 6.5</td>
<td>61.6 ± 5.5</td>
<td>61.9 ± 5.3</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>159.6 ± 6.7</td>
<td>161.1 ± 6.6</td>
<td>160.4 ± 7.1</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>69.0 ± 11.0</td>
<td>66.2 ± 11.0</td>
<td>69.8 ± 12.8</td>
</tr>
<tr>
<td>Lumbar spine BMD (g/cm²)</td>
<td>0.889 ± 0.073</td>
<td>0.894 ± 0.078</td>
<td>0.899 ± 0.089</td>
</tr>
<tr>
<td>Femoral neck BMD (g/cm²)</td>
<td>0.718 ± 0.097</td>
<td>0.726 ± 0.105</td>
<td>0.738 ± 0.094</td>
</tr>
<tr>
<td>Total proximal femur BMD (g/cm²)</td>
<td>0.835 ± 0.069</td>
<td>0.825 ± 0.079</td>
<td>0.852 ± 0.088</td>
</tr>
<tr>
<td>Trochanter BMD (g/cm²)</td>
<td>0.634 ± 0.075</td>
<td>0.617 ± 0.067</td>
<td>0.647 ± 0.080</td>
</tr>
<tr>
<td>Serum 25(OH)D (ng/mL)</td>
<td>29 ± 10</td>
<td>30 ± 10</td>
<td>32 ± 12</td>
</tr>
<tr>
<td>Serum iPTH (pg/mL)b</td>
<td>33 ± 13</td>
<td>34 ± 11</td>
<td>38 ± 16</td>
</tr>
<tr>
<td>Mean dietary calcium intake at screening (mg/day)</td>
<td>642 ± 240</td>
<td>709 ± 299</td>
<td>633 ± 294</td>
</tr>
<tr>
<td>Serum calcium (mg/dL)</td>
<td>9.42 ± 5.9</td>
<td>9.46 ± 3.1</td>
<td>9.38 ± 3.6</td>
</tr>
<tr>
<td>24-Hour urinary calcium (mg/24 h)</td>
<td>153 ± 90</td>
<td>175 ± 73</td>
<td>176 ± 62</td>
</tr>
<tr>
<td>Mean vitamin D intake (IU/day)</td>
<td>114 ± 105</td>
<td>132 ± 139</td>
<td>104 ± 101</td>
</tr>
<tr>
<td>Years postmenopausal</td>
<td>13.2 ± 7.9</td>
<td>12.5 ± 6.1</td>
<td>13.3 ± 6.4</td>
</tr>
</tbody>
</table>

aValues for racial characteristics represent the number of subjects and the percent of subjects within that group. All other values in the table represent the mean value ± SD.

bThe iPTH values reported here were screening values reported by the central laboratory.

coded serum samples collected from fasting subjects between 8 and 11 a.m. at baseline and week 26 visits. Assays were performed using reagent kits (N-MID Osteocalcin ELISA, UniQ PIP RIA, Serum CrossLaps ELISA, and Intact PTH ELISA) supplied by Immunodiagnostics Systems, Ltd. (Scottsdale, AZ, USA) following the manufacturer’s instructions. Baseline and week 26 samples were tested at the same time.

Procedures for managing serum or urinary calcium elevations

Because of the potential for any vitamin D compound to cause hypercalcemia and hypercalciuria, subjects had laboratory assessments for serum calcium and 24-hour urinary calcium performed at each study visit. In addition, criteria and procedures for dietary modification and/or dose reduction in the case of confirmed (two consecutive) elevations in serum calcium (>10.6 mg/dL) or 24-hour urinary calcium (>450 mg/24 h) were defined in the protocol. The time between initial elevations and retests varied but usually was greater than 48 hours for serum calcium elevations and greater than 7 days for urinary calcium elevations. Dietary modification involved consultation between a dietitian and the patient to reduce dietary calcium intake by approximately 400 mg/day, if possible, without reducing dietary calcium below a total of 400 mg/day. Dose reduction for specific subjects with hypercalcemia or hypercalciuria did not break the study blind and involved exchange of study drug bottles to lower the 440-ng dose to 330 ng and the 220-ng dose to 110 ng.

After approximately 52% of subjects had completed or discontinued the study, all subjects remaining at the 440-ng dose level (12 of 53 subjects) had their dose adjusted to 330 ng per recommendation by the DSMB. All dose adjustments were done in a blinded manner (Fig. 1).
analyzed using the SAS mixed-model procedure with Dunnett’s adjustment (SAS Institute, Inc., Cary, NC, USA). Serum and urinary calcium levels were analyzed as repeated measures, and missing values were not imputed.

Results

BMD results

The primary endpoint in this study was the percent change from baseline to week 52 in lumbar spine BMD relative to placebo. There was no significant change in lumbar spine BMD following 1 year of treatment with 2MD, as shown in Fig. 2A.

No significant changes in BMD were seen at other anatomic locations (Fig. 2A), at an earlier time point (week 26; data not shown), or for subjects who completed the study through week 52 (Fig. 2B).

Markers of bone turnover

Serum CTX and osteocalcin showed a dose-dependent increase (p < .05 for the 440-ng dose group) at week 26 relative to baseline (Fig. 3A). Serum PINP also showed a trend toward an increase by week 26 at both 2MD doses relative to baseline; however, this increase was not statistically significant. These results suggest overall that bone turnover increased at 26 weeks of treatment with 2MD.

No statistically significant changes in bone mineral content or area were noted at week 26 or week 52 for any treatment group at any anatomic site (ie, lumbar spine, total proximal femur, femoral neck, or trochanter; data not shown).

Parathyroid hormone results

iPTH showed a dose-dependent decrease at week 26 (Fig. 3B) relative to baseline levels. This decrease in PTH level occurred in parallel with biochemical evidence of increased bone turnover.
Safety

2MD generally was well tolerated, especially at the 220-ng level. Table 2 presents an overview of the adverse events and notable laboratory abnormalities that occurred during the study. The only adverse events consistently judged by investigators to be related to study drug administration were serum and urinary calcium elevations in the 440-ng dose group.

Mean serum calcium levels for all dose groups were within the normal range (Fig. 4A); however, 7 (14%) subjects in the 440-ng dose group and 2 (4%) subjects in the 220-ng dose group had confirmed (repeated) serum calcium values greater than 10.6 mg/dL. Once all subjects in the 440-ng group had been dose-reduced to 330 ng, no more confirmed incidents of serum calcium levels above the upper limit of normal were reported. All serum calcium elevations resolved following dose reduction or discontinuation of study drug.

The 24-hour urinary calcium levels did increase for both the 220- and 440-ng dose groups during the study (Fig. 4B), as expected for a vitamin D compound. In the 220-ng dose group, 7 subjects (13%) had confirmed urinary calcium elevations over 450 mg/24 hours, whereas 21 subjects (40%) in the 440-ng dose group had confirmed urinary calcium elevations greater than 450 mg/24 hours. Urinary calcium elevations were asymptomatic and resolved following dose reduction or discontinuation of study drug.

Serum and urinary calcium elevations were not limited to time points early or late in the study but occurred at various times during the study. Some of the subjects with confirmed serum calcium elevations had prior unconfirmed urinary calcium elevations, but others did not. Only one subject, who was in the 440-ng dose group, had both a confirmed urinary calcium elevation and a confirmed serum calcium elevation greater than 11.2 mg/dL.

Discussion

In this study, 1 year of treatment with 2MD did not increase BMD in osteopenic postmenopausal women. This result is in stark contrast to 2MD’s effects in the OVX rat, where dramatic increases in BMD were observed.\(^{(20,21)}\) The rat skeleton differs

![Figure 3](https://example.com/figure3)

**Fig. 3.** (A) Percent change from baseline in bone marker results at week 26. Serum samples for all subjects completing visits at baseline and week 26 were tested for the bone markers s-CTX, osteocalcin, and P1NP. All serum samples were obtained from fasted subjects between the hours of 8 and 11 a.m. Baseline and week 26 samples were tested at the same time on the same immunoassay plate. Data are presented as the mean with error bars representing SEM. \(^*p < .05\) versus placebo. (B) Percent change from baseline in iPTH results at week 26. Serum samples for all subjects completing visits at baseline and week 26 were tested for iPTH. All serum samples were obtained from fasted subjects between the hours of 8 and 11 a.m. Baseline and week 26 samples were tested at the same time on the same immunoassay plate. Data are presented as the mean with error bars representing SEM. \(^*p < .05\) versus placebo.

**Table 2. Summary of Safety Assessments**

<table>
<thead>
<tr>
<th>Result</th>
<th>Placebo (n = 49)</th>
<th>220 ng 2MD (n = 54)</th>
<th>440 ng 2MD (n = 53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of adverse events (AEs)</td>
<td>189</td>
<td>162</td>
<td>234</td>
</tr>
<tr>
<td>Number of subjects with AEs</td>
<td>41 (83.7)</td>
<td>45 (83.3)</td>
<td>46 (86.8)</td>
</tr>
<tr>
<td>Number of related AEs</td>
<td>14</td>
<td>27</td>
<td>75</td>
</tr>
<tr>
<td>Number of subjects with related AEs</td>
<td>5 (10.2)</td>
<td>16 (29.6)</td>
<td>28 (52.8)</td>
</tr>
<tr>
<td>Number of subjects with AEs leading to discontinuation</td>
<td>3 (6.1)</td>
<td>5 (9.3)</td>
<td>21 (39.6)</td>
</tr>
<tr>
<td>Number of subjects with confirmed serum calcium elevations (where at least one value is &gt;10.6 and ≤11.2 mg/dL and the other &gt;10.6 mg/dL)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>4 (7.5)</td>
</tr>
<tr>
<td>Number of subjects with confirmed serum calcium elevations (&gt;11.2 mg/dL)</td>
<td>0 (0)</td>
<td>2 (3.7)</td>
<td>3 (5.7)</td>
</tr>
<tr>
<td>Number of subjects with confirmed urinary calcium elevations (&gt;450 mg/24 h)</td>
<td>0 (0)</td>
<td>7 (13.0)</td>
<td>21 (40.0)</td>
</tr>
</tbody>
</table>

\(^{a}\)Values represent number of events or subjects, with numbers in parentheses representing the percentage of subjects within that treatment group.
It is plausible that increased markers.

increase bone remodeling is supported in this study by the
postmenopausal women. The idea that 2MD might markedly
increase BMD in an adult remodeling system such as
synthesis in human subjects, which could explain the failure of
bone resorption may equal or exceed its activity on bone
formation, may improve bone quality and reduce fracture rate
without an appreciable increase in bone mass. Unfortunately,
this hypothesis cannot be tested easily because fracture studies
require large numbers of patients and substantial resources. It is
interesting that no fractures occurred in the 2MD-treated groups,
whereas two did occur in the placebo group.

At 440 ng/day, a significant incidence of hypercalcuria/
hypercalcemia occurred that required a reduction of dose to
330 ng/day. This then raises the question of whether the doses
used were too high, causing more bone resorption than at lower
doses. However, preliminary work revealed that 100 ng/day for
6 months did not increase bone mass in postmenopausal women with osteopenia (unpublished results).

Our results carry an important message in regard to preclinical studies of osteoporosis. The data from our laboratory, \(26,27\) as well as Pfizer’s \(28\) demonstrated quite clearly that 2MD is effective in increasing bone mass in both young and old OVX rats. However, in postmenopausal women, 2MD produced no significant increase in bone mass. This demonstrates an inadequacy of the rat as a model of human osteoporosis. On the other hand, positive results in this model have been obtained for teriparatide \(33\) the only currently available anabolic therapeutic in this area. Further, the rat model has been successful in almost all cases involving bone-resorption inhibitors \(36,37\) including other vitamin D compounds. \(37\) If our hypothesis is correct, that is, that 2MD increases bone synthesis and resorption equally, then because the rat has much less resorative activity than formation activity, bone mass data in the rat can be misleading.

The use of vitamin D compounds for the treatment of osteoporosis is not universally accepted. Large doses of vitamin D3 or vitamin D2 had no significant effect on osteoporotic patients in several recent trials \(38,39\) whereas meta-analyses of vitamin D osteoporosis studies have reached conflicting conclusions. \(40–43\) In Japan and other countries where modest calcium intakes are common (and hypercalcemia and hypercalcia therefore less of a concern), 1,25(OH)2D3 or 1α(OH)D3 are used to treat osteoporosis with some success. \(44\) Chugai’s investigational vitamin D analogue ED-71 [1α,25-(OH)2D3] was successful in increasing bone mass in postmenopausal women but occasionally produced hypercalcemia \(45\). In contrast to 2MD, ED-71 and other vitamin D compounds demonstrate significant suppression of bone resorption. \(17,45\)

Increasing bone turnover might be useful in some conditions. Patients with higher baseline bone turnover respond better to bisphosphonates. \(46\) Patients who discontinue bisphosphonate have decreased bone turnover, blunting the subsequent response to other therapies such as PTH \(47\) and strontium ranelate. \(48\) Treatment during bisphosphonate drug holidays with a drug that would increase bone turnover while preserving bone mass for a few months may improve subsequent therapy. Similarly, fracture healing occurs more slowly when bone turnover is low, \(49\) and drugs that increase bone turnover have been shown to improve the rate of fracture healing. \(50\)

In conclusion, 1 year of treatment with 2MD did not improve bone mass in postmenopausal women with osteopenia, although it did increase markers of both bone formation and bone resorption. These results were not expected given the striking anabolic activity noted in the OVX rat model. The discrepancy could be due to the differences in bone metabolism in rats and humans, highlighting a limitation of the OVX rat model when developing novel osteoporosis therapies.

**Disclosures**

HFD, WB, MCD, and LP are officers and own stock in Deltanoid Pharmaceuticals. NB, JCG, MB, MP, and JA served as consultants for or received support from Deltanoid Pharmaceuticals for conducting the clinical trial.
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