Additive Effects of Raloxifene and Alendronate on Bone Density and Biochemical Markers of Bone Remodeling in Postmenopausal Women with Osteoporosis

OLOF JOHNELL, WIM H. SCHEELE, YILI LU, JEAN-YVES REGINSTER, ALLAN G. NEED, AND EGO SEEMAN

Department of Orthopaedics (O.J.), Universitetssjukhuset MAS, Malmö, Sweden; Lilly Research Laboratories, Eli Lilly & Co. (W.H.S., Y.L.), Indianapolis, IN; Bone/Cartilage Metabolism Unit, CHU Brull (J.-Y.R.), Liege, Belgium; Department of Clinical Biochemistry, Institute of Medical and Veterinary Science (A.G.N.), Adelaide, Australia; and Department of Endocrinology, Austin and Repatriation Medical Centre Heidelberg (E.S.), Melbourne, Australia

Both raloxifene (RLX) and alendronate (ALN) can treat and prevent new vertebral fractures, increase bone mineral density (BMD), and decrease biochemical markers of bone turnover in postmenopausal women with osteoporosis. This phase 3, randomized, double-blind 1-yr study assessed the effects of combined RLX and ALN in 331 postmenopausal women with osteoporosis (femoral neck BMD T-score, less than −2). Women (aged ≥75 yr; ≥2 yr since their last menstrual period) received placebo, RLX 60 mg/d, ALN 10 mg/d, or RLX 60 mg/d and ALN 10 mg/d combined. At baseline, 6 and 12 months, BMD was measured by dual x-ray absorptiometry. The bone turnover markers serum osteocalcin, bone-specific alkaline phosphatase, and urinary N- and C-telopeptide corrected for creatinine were measured. The effects of RLX and ALN were considered to be independent and additive if the interaction effect was not statistically significant (P > 0.10) in a two-way ANOVA model. All changes in BMD and bone markers at 12 months were different between placebo and each of the active treatment groups, and between the RLX and RLX+ALN groups (P < 0.05). On average, lumbar spine BMD increased by 2.1, 4.3, and 5.3% from baseline with RLX, ALN, and RLX+ALN, respectively. The increase in femoral neck BMD in the RLX+ALN group (3.7%) was greater than the 2.7 and 1.7% increases in the ALN (P = 0.02) and RLX (P < 0.001) groups, respectively. The changes from baseline to 12 months in bone markers ranged from 7.1 to −16.0% with placebo, −23.8 to −46.5% with RLX, −42.3 to −74.2% with ALN, and −54.1 to −81.0% in the RLX+ALN group. RLX and ALN increased lumbar spine and femoral neck BMD, and decreased osteocalcin and C-telopeptide corrected for creatinine in an additive and independent manner, because the interaction effects were not significant. Although the ALN group had changes in BMD and bone markers that were approximately twice the magnitude as in the RLX group, it is not known how well these changes correlate to the clinical outcome of fracture. RLX+ALN reduced bone turnover more than either drug alone, resulting in greater BMD increment, but whether this difference reflects better fracture risk reduction was not assessed in this study.

The antiresorptive agents that are currently approved in the United States for the prevention and treatment of postmenopausal osteoporosis include estrogens alone or combined with progestin in hormone replacement therapy (HRT), the bisphosphonates alendronate (ALN) and risedronate, salmon calcitonin nasal spray, and the selective estrogen receptor modulator (SERM) raloxifene (RLX). Several large, double-blind, placebo-controlled clinical trials of postmenopausal women with established osteoporosis have shown that ALN (3, 4), salmon calcitonin (5), and RLX (6) significantly reduce the risk of vertebral fractures. Each of these therapies increases bone mineral density (BMD) to a different extent.

Previous studies have found that greater skeletal benefits are obtained when two antiresorptive therapies are administered in combination, compared with either agent given alone. Intermittent cyclic etidronate given in combination with HRT increased lumbar spine BMD more than each therapy given alone (7). Other studies found that women treated with ALN combined with either conjugated equine estrogens (8) or HRT (9) had greater BMD increases, compared with women who received estrogen, HRT, or ALN alone. In all of these studies, the number of fractures that were reported in the combination therapy group was lower than that found in the respective individual therapy groups. However, none of these studies had adequate statistical power to establish a greater decrease in fracture risk than found with monotherapy.

Each antiresorptive therapy achieves its therapeutic effects on bone through different modes of action. Bisphosphonates bind to hydroxyapatite and inhibit bone resorption by decreasing the number and activity of osteoclasts (10). Although the mechanisms of action of SERMs are not yet fully understood, some factors that contribute to the tissue-specific actions of SERMs include binding to estrogen receptor α and β isoforms, binding of the SERM-estrogen receptor complex to target genes, and modification of gene expression by cellular proteins (11). For example, the tissue-specific actions of RLX have been documented in clinical trials. Increases in BMD and decreases in markers for bone turnover (6, 12) and lipid metabolism (13, 14) are examples

Abbreviations: ALN, Alendronate; BCE, bone collagen equivalent; BMD, bone mineral density; BSAP, bone-specific alkaline phosphatase; Cr, creatinine; CTx, C-telopeptide; DXA, dual x-ray absorptiometry; HRT, hormone replacement therapy; NTx, N-telopeptide; OC, osteocalcin; RLX, raloxifene; SERM, selective estrogen receptor modulator.

Downloaded from jcem.endojournals.org at Bibliothèque de la Faculté de Med - Univ De Liege on July 15, 2009
of the estrogen-agonist effects of RLX. Compared with the stimulation seen with estrogen therapies, RLX did not increase endometrial thickness (15, 16) or breast density (17), demonstrating estrogen-antagonist effects on these tissues. Due to these different mechanisms of action, the present study tests the hypothesis that the addition of ALN would have an independent, additive effect on the changes in BMD and biochemical markers of bone metabolism in postmenopausal women with osteoporosis. Patients and Methods

Patients

Ambulatory women aged up to 75 yr, with their last menstrual period at least 2 yr before study entry, were eligible for the study. Postmenopausal status was verified in women who had not had a hysterectomy by serum E2 levels less than 73 pmol/liter and FSH levels greater than 30 IU/liter. Women with femoral neck BMD greater than 2.0 sp below peak bone mass for healthy premenopausal women were eligible, regardless of the presence of prevalent vertebral fractures. Exclusion criteria for this study included: current bone disorders other than primary osteoporosis, any history of cancer in the previous 5 yr, active venous thromboembolic disease, and endocrine disorders requiring pharmacologic therapy, except type II diabetes. Women who received therapeutic doses of any of the following medications before study entry were excluded: androgen, calcitonin, estrogen and progestin in the past 6 months, systemic corticosteroids for at least 1 month in the past 12 months, bisphosphonates for at least 14 d in the past 18 months, any bisphosphonates in the past 6 months, and fluoride (>20 mg/d) for more than 3 months during the past 2 yr. Women with upper gastrointestinal problems requiring medical treatment within the past 12 months, or who were currently treated with systemic lipid lowering agents, H2 blockers, or proton pump inhibitors were excluded. Women signed a written informed consent document before entering the study. Investigators obtained local Institutional Review Board approval.

Study design

This phase 3, randomized, double-blind study was conducted at 30 study sites in Australia, Belgium, Canada, Italy, Mexico, South Africa, Spain, and Sweden. A total of 331 women were randomly assigned in blocks of four to one of the following groups: placebo, RLX HCl 60 mg/d in tablet form, ALN sodium 10 mg/d in capsule form, or a combination of RLX (60 mg/d) and ALN (10 mg/d). All women received a supplement containing approximately 500 mg/d elemental calcium and vitamin D 400–600 IU/d. Placebo was provided in tablets identical in appearance to RLX and in capsules identical in appearance to ALN (double dummy). Women were instructed to take one capsule and one tablet of the blinded study medication. According to the prescribing information for ALN, the capsule was to be taken upon waking in the morning with a large glass of water, and no food or drink was to be taken for 30 min afterward. The tablet, along with the calcium and vitamin D supplement, was taken at least 30 min after the capsule. The study medication and placebo were packaged in kits numbered according to a random-number table. At randomization, kits were assigned sequentially to each woman, beginning with the lowest number available.

Methods

Lumbar spine and femoral neck BMD were measured by dual x-ray absorptiometry (DXA) at baseline and at 6-month intervals, using either Hologic QDR (Hologic, Inc., Waltham, MA), Lunar DPX (Lunar Corp.)

### TABLE 1. Summary of baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N = 82)</th>
<th>RLX 60 mg/d (N = 82)</th>
<th>ALN 10 mg/d (N = 83)</th>
<th>RLX + ALN (N = 84)</th>
<th>Between group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>63.8 ± 5.3</td>
<td>63.4 ± 6.3</td>
<td>63.7 ± 6.0</td>
<td>63.8 ± 6.3</td>
<td>0.97</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.3 ± 3.9</td>
<td>24.8 ± 3.8</td>
<td>24.8 ± 3.8</td>
<td>25.0 ± 3.8</td>
<td>0.71</td>
</tr>
<tr>
<td>Years postmenopausal</td>
<td>17.6 ± 8.2</td>
<td>15.6 ± 7.7</td>
<td>16.5 ± 7.7</td>
<td>17.1 ± 9.0</td>
<td>0.44</td>
</tr>
<tr>
<td>Previous use of HRT</td>
<td>41%</td>
<td>32%</td>
<td>36%</td>
<td>24%</td>
<td>0.12</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>28.0%</td>
<td>24.7%</td>
<td>28.9%</td>
<td>19.0%</td>
<td>0.45</td>
</tr>
<tr>
<td>Estimated dietary calcium intake (mg/d)</td>
<td>740 ± 485</td>
<td>675 ± 425</td>
<td>830 ± 480</td>
<td>770 ± 410</td>
<td>0.17</td>
</tr>
<tr>
<td>Femoral neck BMD (g/cm²)</td>
<td>0.76 ± 0.13</td>
<td>0.77 ± 0.12</td>
<td>0.78 ± 0.14</td>
<td>0.76 ± 0.12</td>
<td>0.59</td>
</tr>
<tr>
<td>Femoral neck BMD (g/cm²)</td>
<td>0.62 ± 0.09</td>
<td>0.62 ± 0.07</td>
<td>0.62 ± 0.08</td>
<td>0.61 ± 0.08</td>
<td>0.39</td>
</tr>
<tr>
<td>OC (µg/liter)</td>
<td>23.6 ± 8.6</td>
<td>25.9 ± 11.7</td>
<td>25.9 ± 11.6</td>
<td>24.7 ± 10.6</td>
<td>0.58</td>
</tr>
<tr>
<td>BSAP (µg/liter)</td>
<td>14.6 ± 6.0</td>
<td>14.6 ± 6.0</td>
<td>14.5 ± 6.4</td>
<td>14.5 ± 6.5</td>
<td>0.77</td>
</tr>
<tr>
<td>CTx/BSAP (µg/mmol)</td>
<td>277.6 ± 149.6</td>
<td>299.8 ± 147.1</td>
<td>288.9 ± 140.2</td>
<td>258.6 ± 136.3</td>
<td>0.27</td>
</tr>
<tr>
<td>NTx/BSAP (µmol/mmol)</td>
<td>70.6 ± 25.9</td>
<td>53.2 ± 24.2</td>
<td>54.3 ± 31.4</td>
<td>52.8 ± 29.5</td>
<td>0.89</td>
</tr>
</tbody>
</table>

BMI, Body mass index; NTx, cross-linked N-telopeptide of type I collagen; CTx, cross-linked C-telopeptide of type I collagen (Crosslaps). a Values obtained at randomization were expressed as mean ± SD. N represents number of women randomized, except for BMD measurements where n = 77 in each group.

### TABLE 2. Percentage changes in BMD and biochemical markers from baseline to 1 yr

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Placebo</th>
<th>RLX</th>
<th>ALN</th>
<th>RLX + ALN</th>
<th>Between group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumbar spine BMD</td>
<td>-0.004 ± 0.3</td>
<td>2.1 ± 0.4</td>
<td>4.3 ± 0.4</td>
<td>5.3 ± 0.4</td>
<td>0.04</td>
</tr>
<tr>
<td>Femoral neck BMD</td>
<td>0.2 ± 0.4</td>
<td>1.7 ± 0.4</td>
<td>2.7 ± 0.5</td>
<td>3.7 ± 0.5</td>
<td>0.04</td>
</tr>
<tr>
<td>OC</td>
<td>-1.2</td>
<td>-25.7</td>
<td>-42.3</td>
<td>-54.3</td>
<td>0.04</td>
</tr>
<tr>
<td>BSAP</td>
<td>-11.8b</td>
<td>-32.2</td>
<td>-52.1</td>
<td>-54.1</td>
<td>0.04</td>
</tr>
<tr>
<td>CTx/OC</td>
<td>-16.0</td>
<td>-46.5</td>
<td>-74.2</td>
<td>-81.0</td>
<td>0.04</td>
</tr>
<tr>
<td>NTx/OC</td>
<td>7.1b</td>
<td>-23.8</td>
<td>-58.4</td>
<td>-63.3</td>
<td>0.04</td>
</tr>
</tbody>
</table>

a BMD values are mean percentage change ± SEM. Values for the biochemical markers of bone turnover are median percentage change.

b Statistically significantly different from baseline.

c Statistically significantly different from placebo.

d Statistically significantly different from ALN.

e Statistically significantly different from RLX + ALN.
Radiation, Madison, WI), or Norland (Norland Medical Systems, Inc., White Plains, NY) densitometers. For each study site and DXA device, a Hologic, Inc. anthropomorphic spine phantom was used as daily quality control, and phantom cross-calibration data were used to correct in vivo values and to standardize all BMD measurements. Each DXA scan was reviewed and evaluated by a central laboratory (Synarc, Portland, OR). If any differences existed among the DXA machines or due to longitudinal drifting of densitometers over time, the central laboratory adjusted for these differences by use of correction factors. Biochemical markers of bone metabolism were measured at baseline and at 1, 6, and 12 months. The markers included serum osteocalcin (OC) (ELSA-IRMA, CIS Biointernational, Gif-sur-Yvette, France), serum bone-specific alkaline phosphatase (BSAP) (Ostase IRMA, Hybritech, San Diego, CA), urinary N-telopeptide (NTx) (Ostex International, Inc., Seattle, WA), and C-telopeptide (CTx) (Crosslaps, Os-}

![Image](https://example.com/image.png)

**Fig. 1.** Mean percentage changes ± SEM in lumbar spine and femoral neck BMD after 6 and 12 months of treatment with placebo (PL, circles), RLX 60 mg/d (squares), ALN 10 mg/d (triangles), or combined RLX and ALN (diamonds). Asterisks (*) indicate statistically significant changes from baseline ($P < 0.05$).


...continued above...

At each clinic visit, women were questioned about the occurrence and nature of adverse events. All adverse events reported at each postbaseline visit were recorded. Hot flashes associated with RLX therapy may be reported as vasodilatation or sweating. Esophageal or gastric irritation associated with ALN therapy may be reported as substernal chest or abdominal pain.
Statistical analyses

All data analyses were performed on an intent-to-treat basis in women who had at least one follow-up visit. For continuous data, such as BMD and biochemical markers of bone turnover, the percentage change from baseline to endpoint within each group was analyzed using *t* test. The ANOVA model, with fixed effects for therapy and investigator, evaluated the differences between treatment groups. Pair-wise comparisons were performed using contrast statements in the ANOVA model. For categorical data such as adverse events, Pearson’s χ² test was used to test treatment group differences. Statistical inferences were made on the basis of two-sided, significance level of *P* < 0.05.

To test for possible additive effects of RLX and ALN, a two-way ANOVA model with RLX treatment, ALN treatment, and the interaction of the two treatments was used to evaluate the percentage changes in BMD and biochemical markers. Treatment additivity, defined as the sum of the interaction between the two treatments, was tested at the significance level of *P* = 0.10. When the interaction was not statistically significant (*P* > 0.10), the effects of RLX and ALN were considered to be independent of each other, and the effects of RLX and ALN were additive when given in combination.

Results

The women had a mean age of 63.6 yr, an average of 16.7 yr after their final menstrual period, and a mean body mass index of 24.7 kg/m². Ninety-five percent of the women were
white. There were no differences in baseline characteristics among the groups (Table 1). Of the 331 women enrolled, 274 (82.8%) completed the study. There were no differences among the groups in the overall discontinuation rate or in any specific reason for discontinuation.

At 1 yr, lumbar spine and femoral neck BMD in the active treatment groups significantly increased from baseline (Fig. 1), and these increases were also significantly greater than placebo (Table 2). The increase in lumbar spine BMD at 1 yr in the combination group did not differ from that in the ALN group ($P = 0.10$). The 4.3% increase in lumbar spine BMD with ALN was different from the 2.1% increase in the RLX group ($P <$
The increase in femoral neck BMD in the combination group at 1 yr was greater than the increases in both the ALN (\(P < 0.001\)) and RLX (\(P < 0.001\)) groups. The 2.7% increase in femoral neck BMD with ALN was different from the 1.7% increase in the RLX group (\(P < 0.03\)). BMD at the trochanter, intertrochanter, and Ward’s triangle increased by 3.9, 2.3, and 4.4%, respectively, in the ALN group. The combination group had increases of 3.9, 2.4, and 4.6% in the trochanter, intertrochanter, and Ward’s triangle, respectively, at 1 yr. These increases were not different between the ALN and combination groups, but were statistically significantly different from the changes in the placebo and RLX groups.

The biochemical markers of bone turnover, OC, BSAP, CTx/Cr, and NTx/Cr in all treatment groups decreased from baseline (Fig. 2) and differed from placebo (Table 2). The decreases in OC, BSAP, and CTx/Cr were approximately 1.6-fold greater in the ALN group, compared with the RLX group (\(P < 0.02\)). The decrease in NTx/Cr was 2.5-fold greater in the ALN group than in the RLX group (\(P < 0.001\)). None of the decreases in bone markers differed between the ALN and combination groups, but both had greater decreases than the RLX group (Table 2). The percentage of women with postbaseline CTx/Cr values below the lower limit of the premenopausal range (5.0 nm BCE/mmol), and the between-group difference was not statistically significant.

To determine whether the effects of RLX and ALN were independent and additive in combination, the groups with RLX (alone and combined with ALN) and without RLX (placebo and ALN) were compared. A visual assessment for additive effects showed no intersection of the lines connecting the groups with RLX and those without RLX (Fig. 3), suggesting that RLX and ALN act independently on BMD and the effects were additive. A two-way ANOVA model supported these observations, where the interaction of the two treatments was not significant (\(P > 0.10\)). Combined RLX and ALN have independent and additive effects on the changes in lumbar spine and femoral neck BMD, OC and CTx/Cr (Table 3), but not on changes in BSAP and NTx/Cr because the interaction terms were significant (\(P < 0.10\)).

There were no statistically significant differences among the groups in the incidences of any of the adverse events that may be associated with either RLX or ALN therapy (Table 4). The differences in discontinuation rates were not statistically significant among the groups.

Discussion

RLX and ALN, alone or in combination, increased lumbar spine and femoral neck BMD and decreased all biochemical markers of bone turnover, compared with baseline and placebo in healthy postmenopausal women with osteoporosis. The effects of ALN alone and in combination with RLX on
TABLE 4. The incidence of adverse events that may be associated with RLX or ALN therapya

<table>
<thead>
<tr>
<th>Event</th>
<th>PL (N = 82)</th>
<th>RLX (N = 82)</th>
<th>ALN (N = 83)</th>
<th>RLX + ALN (N = 84)</th>
<th>P valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasodilatation</td>
<td>4.9%</td>
<td>4.9%</td>
<td>4.8%</td>
<td>4.8%</td>
<td>1.00</td>
</tr>
<tr>
<td>Sweating</td>
<td>2.4%</td>
<td>1.2%</td>
<td>2.4%</td>
<td>0%</td>
<td>0.52</td>
</tr>
<tr>
<td>Chest pain substernal</td>
<td>2.4%</td>
<td>4.9%</td>
<td>7.2%</td>
<td>3.6%</td>
<td>0.49</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>6.1%</td>
<td>7.3%</td>
<td>10.8%</td>
<td>6.0%</td>
<td>0.60</td>
</tr>
<tr>
<td>Discontinuations due to adverse event</td>
<td>4.9%</td>
<td>8.5%</td>
<td>9.6%</td>
<td>6.0%</td>
<td>0.61</td>
</tr>
</tbody>
</table>

PL, placebo.

a Hot flashes associated with RLX therapy may be reported as vasodilatation or sweating. Esophageal or gastric irritation associated with ALN therapy may be reported as substernal chest or abdominal pain.

b Overall P value among all treatment groups as calculated by Pearson’s χ² test.

Although histomorphometry shows normal bone quality at the cellular level, severe reductions in bone turnover produced by antiresorptive therapies may indirectly lead to an increased risk of fractures (26). Normal mechanical loading results in microarchitectural deformities, which are repaired during the bone remodeling process. If these deformities are not repaired in so-called frozen bone, which has a very low bone remodeling rate, the accumulation of deformities can theoretically contribute to bone fragility and possibly fracture (26). The present evidence to support this theory is not conclusive and has only been demonstrated in dogs treated with doses of bisphosphonates several times higher than those used clinically (27–29). In the present study, combined RLX and ALN reduced bone turnover markers 54–81%, a range of effects similar to those produced by administering estrogen in combination with ALN (8). Although over 50% of women in the ALN and combination therapy groups had postbaseline CTx/Cr values below the lower limit of the normal premenopausal range, the clinical relevance of this observation is not known. It is not known whether the levels of suppression of bone remodeling observed with combined antiresorptive therapy in women can produce an accumulation of microarchitectural deformities, which can lead to an increased risk of fracture.

None of the published studies of combined antiresorptive therapies had adequate statistical power to demonstrate a greater decrease in fracture risk with combination therapy, compared with either therapy alone. For example, the incidence of fractures in the combined conjugated equine estrogens and ALN group (5.7%) was similar to that observed in the groups with estrogens (6.9%) or ALN (5.4%) alone (8). The incidence of fractures was 7.0% in women who received ALN along with existing HRT and 4.2% in women who received HRT alone (9). The incidence of new vertebral fractures in the combined risedronate and HRT group (1.8%) was not statistically different from the 2.6% observed in the group treated with HRT alone (23). The present study also did not have adequate statistical power to determine antifracture efficacy of combined RLX and ALN.

Some women do not respond and lose BMD when given one antiresorptive agent (30), so it is tempting to consider a combination of antiresorptive therapies. Although there are possible BMD benefits of combined therapy, fracture efficacy data are lacking. Other factors that should be considered include the extraskeletal benefits associated with each therapy and the patient’s concomitant illnesses or risk factors for other disorders.
prohibitive for some patients. The patient and physician should carefully weigh the risks and benefits of combined antiresorptive therapy before deciding on such a regimen.

In summary, RLX and ALN alone and in combination increased lumbar spine and femoral neck BMD and decreased all biochemical markers of bone turnover. The combination of ALN and RLX produced a greater increase in femoral neck BMD compared with either agent alone. Although the increases in lumbar spine BMD and changes in bone turnover markers with ALN alone and in combination therapy were similar and greater than that observed with RLX alone, the effects of combined RLX and ALN on BMD were independent and additive. The effect of combined RLX and ALN on fracture risk is unknown. The long-term clinical safety of combination therapy on the risk of fracture remains to be determined.

Acknowledgments

We are grateful for the assistance of Mark Lakshmanan, M.D., for participation in study design and Mayme Wong, Ph.D., for contributions on manuscript content and critical review of the manuscript.

Other investigators participating in this study were: Kong Wah Ng, Michael J. Hooper, and Philip Sambrook, of Australia; Jean-Marc Kaufman and Anne Perez, Belgium; Jonathan D. Adachi, Jacques P. Brown, John P. Wade, Kerry G. Siminoski, Chui K. Yuen, Aliya A. Khan, and A. Lussier, Canada; Carlo Gennari, Silvano Adami, P.G. Cossignani, Mario Vignali, and Lucia Zichella, Italy; Ricardo Correa-Rotter, Mexico; B.H. Ascott-Evans; F. Stephen Hough, and G.C. Ellis, South Africa; Javier Del Pino and Nuria Guanabens, Spain; and Goran Toss and Maria Saaf, Sweden.

Received March 27, 2001. Accepted December 4, 2001.

Address all correspondence and requests for reprints to: Wim H. Schelle, M.D., Lilly Research Laboratories, Drop Code 2248, Eli Lilly & Co., Indianapolis, Indiana 46285. E-mail: schelle_wim@lilly.com.

This work was supported by Eli Lilly & Co.

References


