Inhaled corticosteroids (ICS) in dosages above 1,000 µg/d may influence parameters of bone metabolism. Fluticasone propionate (FP) is a new ICS with a higher clinical potency than beclomethasone dipropionate (BDP) combined with negligible oral bioavailability. The aim of this study was to evaluate the effects of FP and BDP in clinically equipotent dosages on indices of bone metabolism and morning cortisol. FP 750 µg/d and BDP 1,500 µg/d were compared in a randomized, double-blind, crossover study consisting of two 6-wk treatment periods, each preceded by a 3-wk single-blind placebo period. Twenty-one nonsmoking asthmatics completed the study. FP had the same effect on FEV\(_1\) and peak expiratory flow as the double dose of BDP. Both treatments did not change morning cortisol. BDP decreased both osteocalcin and procollagen type 1 carboxyterminal propeptide, indices of bone formation, significantly by 18.5 and 21.9%, respectively. In contrast, FP did not change any variable of bone formation. FP and BDP did not increase type 1 collagen carboxyterminal telopeptide and deoxyypirdinoline crosslinks, both markers of bone resorption. If changes in parameters of bone metabolism indicate adverse effects on bone quality in the long term, FP may offer an advantage over BDP.

**METHODS**

**Patients**

Thirty nonsmoking patients with asthma 18 to 55 yr of age (mean, 30.3 yr) were recruited from the out-patient department. Their characteristics are summarized in Table 1. All women were premenopausal. No patient had used OCS as maintenance treatment, i.e., continuously for more than 3 mo, but 13 patients had needed short courses of OCS in the preceding 3 yr or had reported spontaneous fractures at all. All patients had been receiving regular treatment with BDP or budesonide for an average of 5.4 yr (range, 0.3 to 16 yr) with an average daily dose of 790 µg (range, 400 to 1,600 µg). None had used OCS as maintenance treatment, i.e., continuously for more than 3 mo, but 13 patients had needed short courses of OCS in the past to treat exacerbations. No patient had used OCS in the preceding 6 mo. The study was approved by the Nijmegen University medical ethics committee. All study subjects gave written informed consent before entry into the study.

**Protocol**

The study was a randomized, crossover trial consisting of a 3-wk single-blind washout (placebo) period before each of the two 6-wk double-blind active treatment periods (flow-chart in Figure 1). Treatment randomization was performed prior to the first placebo period, but at the
end of this first 3-wk placebo (run-in) period, patients needed to have asthma symptoms and a FEV1 of ≥ 50% of predicted. Hence, not all randomized patients entered the first treatment period because of non-treatment-related baseline inclusion criteria. Measurements performed after the two placebo periods were used as baseline values prior to active treatment. Patients inhaled 375 µg FP or 750 µg BDP or placebo by metered-dose inhaler (MDI) twice daily. They used salbutamol 100 µg MDI as rescue medication. No other pulmonary medication was allowed. Patients were instructed how to use their MDI correctly. Before and after each active treatment period (Measurements 1 to 4 in Figure 1), lung function tests were performed, and blood and urine samples were taken. Subjects were not allowed to use rescue and study medication for at least 3 days before each visit.

Clinical efficacy. To assess basal lung function, flow-volume curves were performed and recorded on a heated pneumotachograph (Spiro Analyzer ST-250®; Fukuda Sangyo Co., Tokyo). FEV1 was recorded as the best of three reproducible values (within 5%). During the last 3 wk of each period was used for statistical analysis. Extracts were dried under nitrogen and chromatographed (intra-assay CV was 4.1 to 6.5% at levels of 2.3 to 4.2 nmol/L). P1CP and ICTP were measured using a radioimmunoassay kit (Orion Diagnostica, Espoo, Finland); for P1CP intra-assay CV was 2.1 to 2.7% and interassay CV was 4.1 to 6.6% at levels of 0.22 to 4.26 nmol/L. ICS and ICTP were measured using a radioimmunoassay kit (Cis, Gif sur Yvette, France); intra-assay coefficient of variation (CV) was 3.0 to 3.6% and interassay CV was 5.5 to 6.6% at levels of 0.22 to 4.26 nmol/L. UF ICS and ICTP were measured using a radioimmunoassay kit (Hitachi 747 automatic analyzer (Boehringer, Mannheim, Germany)), lung function tests were performed, and blood and urine samples were taken. Subjects were not allowed to use rescue and study medication for at least 3 days before each visit.

Statistical Analysis
A first- and second-order carryover effect can be distinguished, of which only the latter may interfere with the treatment effect. Therefore, a p value > 0.01 was taken for the second-order carryover effect to supposedly exclude any influence on treatment effects. The first-order carryover effect was tested by comparing the differences of Measurements 3 and 1 between treatment-order groups. The second-order carryover effect was tested by comparing the sum of two differences (i.e., 2 minus 1 and 4 minus 3) between treatment-order groups. In this way a necessary adjustment was made for the unbalance present in several variables at Measurement 1 in order to prevent this unbalance from interfering with the carryover effects. Provided there was no second-order carryover effect, the difference in treatment effect between FP and BDP was tested next by comparing the difference of Measurements 2 and 4 between treatment-order groups; (the mean difference in effects between FP and BDP can be calculated as [(FP-BDP) - (BDP-FP)]/2 (19). The treatment effects of both ICS (A-effect) were also expressed by taking the difference between real baseline values and the corresponding values after treatment. FEV1, and PEFR data are shown as absolute values. The mean of all values of PEFR recorded during the last 2 wk of each period was used for statistical analysis. Wilcoxon's signed rank test or the paired t-test were used for analysis when appropriate; p values less than 0.05 were considered significant. Results are reported as means ± SEM.

RESULTS
Thirty patients entered the first placebo (run-in) period. Seven patients dropped out in the run-in period because of an exacerbation of their asthma. At the end of this period, two other patients did not meet the final inclusion criteria because they experienced no asthma symptoms. The remaining 21 patients all completed the study. Their characteristics are summarized in Ta-
TABLE 2
CARRYOVER AND DIRECT-TREATMENT-EFFECT COMPARISON OF THE TWO ICS ANALYZED ACCORDING TO TREATMENT-ORDER GROUP*

<table>
<thead>
<tr>
<th>Calcium metabolism</th>
<th>First-Order Carryover Effect</th>
<th>Second-Order Carryover Effect</th>
<th>Differences in Treatment Effect FP-BDP (mean ± SEM)</th>
<th>(95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca</td>
<td>p = 0.81</td>
<td>p = 0.41</td>
<td>-0.04 ± 0.02</td>
<td>-0.09 to 0.003</td>
<td>p = 0.06</td>
</tr>
<tr>
<td>P</td>
<td>p = 0.63</td>
<td>p = 0.80</td>
<td>0.02 ± 0.04</td>
<td>-0.07 to 0.11</td>
<td>p = 0.61</td>
</tr>
<tr>
<td>PTH</td>
<td>p = 0.10</td>
<td>p = 0.12</td>
<td>0.11 ± 0.19</td>
<td>-0.28 to 0.51</td>
<td>p = 0.53</td>
</tr>
<tr>
<td>1,25(OH)2D3</td>
<td>p = 0.88</td>
<td>p = 0.97</td>
<td>11.8 ± 11.0</td>
<td>-11.3 to 34.9</td>
<td>p = 0.27</td>
</tr>
<tr>
<td>Bone formation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AP</td>
<td>p = 0.84</td>
<td>p = 0.79</td>
<td>1.29 ± 1.4</td>
<td>-1.61 to 4.18</td>
<td>p = 0.36</td>
</tr>
<tr>
<td>OC</td>
<td>p = 0.67</td>
<td>p = 0.99</td>
<td>0.29 ± 0.11</td>
<td>0.06 to 0.52</td>
<td>p = 0.02</td>
</tr>
<tr>
<td>PICP</td>
<td>p = 0.78</td>
<td>p = 0.93</td>
<td>23.7 ± 8.0</td>
<td>6.88 to 40.5</td>
<td>p = 0.008</td>
</tr>
<tr>
<td>Bone Resorption</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1CTP</td>
<td>p = 0.12</td>
<td>p = 0.19</td>
<td>0.04 ± 0.04</td>
<td>-0.05 to 0.12</td>
<td>p = 0.24</td>
</tr>
<tr>
<td>U Ca/Cr</td>
<td>p = 0.48</td>
<td>p = 0.26</td>
<td>0.02 ± 0.03</td>
<td>-0.05 to 0.10</td>
<td>p = 0.57</td>
</tr>
<tr>
<td>U H/P/Cr</td>
<td>p = 0.28</td>
<td>p = 0.07</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>U Dpd/Cr</td>
<td>p = 0.38</td>
<td>p = 0.48</td>
<td>0.10 ± 0.80</td>
<td>-1.58 to 1.79</td>
<td>p = 1.00</td>
</tr>
<tr>
<td>Adrenal function</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortisol</td>
<td>p = 0.09</td>
<td>p = 0.35</td>
<td>0.04 ± 0.04</td>
<td>-0.05 to 0.12</td>
<td>p = 0.36</td>
</tr>
</tbody>
</table>

* The treatment effects of FP and BDP are directly compared by analyzing the difference of the treatment effects between treatment-order groups [(FP-BDP) - (BDP-FP)]/2.

Definition of abbreviations: FP ~ fluticasone propionate; BDP = beclomethasone dipropionate; Ca = calcium; P = phosphate; PTH = parathyroid hormone; 1,25(OH)2D3 = 1,25-dihydroxy-vitamin D3; AP = alkaline phosphatase; OC = osteocalcin; PICP = carboxyterminal propeptide of type 1 procollagen; 1CTP = carboxyterminal cross-linked telopeptide of type 1 collagen; U Ca/Cr = urinary calcium/creatinine ratio; U H/P/Cr = urinary hydroxyproline/creatinine ratio; U Dpd/Cr = urinary deoxypyridinoline/creatinine ratio.

Clinical Efficacy
Both FP and BDP caused a significant increase in FEV1, and morning and evening PEFR. With FP the Δ-effect on FEV1 was 0.45 ± 0.12 L, and with BDP it was 0.34 ± 0.09 L (both p < 0.01). Compared with baseline, morning PEFR increased by 51.4 ± 10.4 and 46.4 ± 9.6 L/min, and evening PEFR increased by 39.8 ± 8.2 and 29.2 ± 9.4 L/min after FP and BDP, respectively (all p < 0.01). The diurnal variation in PEFR decreased significantly after FP (Δ-effect, -10.8 ± 4.3 L/min; p < 0.01), but not after BDP (Δ-effect, -10.7 ± 6.0 L/min; p = 0.14). A direct comparison of the treatment effects showed no significant differences between the two baseline values (Measurements 1 and 3).

Bone Formation
AP did not change after FP and BDP (Table 3). OC and PICP, however, were significantly decreased after BDP, but not after FP. OC decreased by 18.5 ± 3.9% after BDP (p < 0.001) and by 5.5 ± 3.6% after FP (p = 0.16). PICP decreased by 21.9 ± 6.8% after BDP (p < 0.01), but not after FP (mean increase, 3.5 ± 5.1%) (Table 3 and Figure 2). The levels of OC and PICP after 6 wk of treatment with BDP returned to baseline values after withdrawal of BDP (Table 4). Direct treatment-effect comparison between FP and BDP showed to be significantly different in effects on OC and PICP (Table 2).

Bone Resorption
1ICTP decreased after BDP (-11.5 ± 8.2%; p < 0.05), but not after FP (-3.8 ± 3.8%; p = 0.18) (Table 3). Urinary Ca/Cr and Dpd/Cr did not change after treatment. For all variables of bone resorption, no differences in treatment effects between FP and BDP were found (Table 2).

Adrenal Function
Mean cortisol values changed from 0.64 ± 0.06 to 0.61 ± 0.06 μmol/L after FP (p = 0.42) and from 0.60 ± 0.06 to 0.59 ± 0.06 μmol/L after BDP (p = 0.68). In none of the patients did the cortisol level fall below the lower limit of normal in our laboratory (0.19 μmol/L). There were no significant differences in cortisol changes in both treatment effects between FP and BDP (Table 2).

DISCUSSION
This crossover study in asthmatic patients shows that BDP 1,500 μg daily for 6 wk caused a significant depression of OC and PICP, both markers of bone formation. In contrast, FP did not change any variable of bone formation. Both FP and BDP did not affect indices of bone resorption, calcium metabolism, or cortisol. With regard to clinical efficacy, FP 750 μg daily was as effective as the double dose of BDP on FEV1, and PEFR.

As one of the important side effects of corticosteroids may be osteoporosis, we measured in this study effects of FP and BDP on biochemical markers of bone metabolism. OC is a very sensitive marker of osteoblast activity, as most serum OC originates from new cellular synthesis (17). OC is a specific marker of bone formation in processes with uncoupled bone formation and resorption, as is the case in glucocorticoid-induced osteoporosis.
(15). PICP specifically measures collagen type 1 synthesis, the major collagen product produced by osteoblasts. It is cleaved from collagen type 1 during its processing to fibrils (one liberated propeptide for every formed collagen molecule: 1:1). It reflects the changes in whole bone tissue. PICP decreases in therapies that slow the metabolic rate of bone as glucocorticoids (15, 16). Markers of bone resorption included ICTP and Dpd crosslinks (15, 16). ICTP measures the degradation of mature type I collagen (containing pyridinoline crosslinks). ICTP increases in diseases that degrade the surface (cortical part) of bone tissue (e.g., rheumatoid arthritis, bone metastasis), but it changes only a little when trabecular bone is affected as is the case with glucocorticoid therapy (15). Changes in trabecular bone are better reflected in the concentration of crosslinks, and Dpd is more specific for osseous tissue than are pyridinoline crosslinks (16). As ICTP does not change to the same extent as PICP in situations in which the metabolic rate of trabecular bone is affected, as is the case with glucocorticoids, a net formation of type I collagen (PICP/ICTP) cannot be calculated.

Biochemical markers do, however, possess some potential pitfalls. Osteocalcin is regulated at the gene level by 1,25-vitamin D; therefore, osteocalcin may be elevated in patients with abnormal serum 1,25-vitamin D levels. Osteocalcin is cleared by the kidneys, so patients with renal failure can exhibit increased levels of osteocalcin without a concomitant increase in bone formation. Moreover, osteocalcin exhibits a marked diurnal varia-

![Diagram A](image1)

**Figure 2.** Mean ± SEM baseline values and corresponding values of (A) osteocalcin and (B) procollagen type 1 carboxyterminal propeptide (PICP) after 6 wk of treatment with 1,500 μg BDP daily (open bars) and 750 μg FP daily (hatched bars). NS = not significant; *p < 0.05; **p < 0.01; ***p < 0.001.
tion, and the serum antigen loses its immunologic activity at room temperature or by repeatedly freezing and thawing (15, 16). PICP also exhibits diurnal variation (15, 16). Dpd is now considered the best available method for bone resorption, although the concentration of crosslinks is not invariant in bone, which could influence urinary concentration. In addition, Dpd has a marked diurnal variation (16). In the present study, all samples were immediately determined or frozen and processed at once to exclude any influence of laboratory handling. Urinary samples were taken after an overnight fast to correct for dietary sources of hydroxyproline and corrected for creatinine. Finally, to correct for diurnal variation, samples were always taken at the same moment in individual subjects.

Osteoporosis may affect as much as 40% of patients receiving maintenance treatment with OCS (20). OCS inhibit the intestinal absorption of Ca and P, and they may increase urinary Ca excretion. The resulting decrease in serum Ca evokes secondary hyperparathyroidism, reflected in increased serum PTH (21). Furthermore, OCS decrease bone formation (reflected in a decrease in AP, OC, and PICP) (13, 21–23) and possibly also increase bone resorption (reflected in an increase in Ca/Cr and HP/Cr) (21, 23). These changes lead to secondary osteoporosis and a rise in (nontraumatic) fracture incidence (20, 21, 24). OCS in doses of 7.5 mg/d or more cause significant loss of trabecular bone in most patients, but lower doses of OCS may also have adverse effects (25). Furthermore, data suggest that bone loss is most pronounced in the early weeks of OCS therapy, with subsequent slowing during prolonged treatment (25).

ICS interact with the same glucocorticoid receptors, and they would therefore be expected to act in a similar way after systemic absorption. Several short-term studies with ICS, both in healthy subjects and in patients, have shown a decrease in OC levels after treatment, indicating effects of ICS on bone formation (11–14, 21). Other studies, however, have shown no significant changes in OC levels after treatment with ICS (26), and a number of studies have reported increased OC and PICP after treatment with ICS (27, 28). The present study shows a different sensitivity for ICS.

Mjw t e ü lA - • I . f

Contrast, a clinically equipotent dose of FP did not change these below 800 to 1,000 µg BDP daily (3). Kiviranta and Tlirpeinen started BDP, cross over to FP, n = 14

<table>
<thead>
<tr>
<th>Measurement (ordered in time)</th>
<th>Placebo</th>
<th>BDP</th>
<th>Placebo</th>
<th>FP</th>
</tr>
</thead>
<tbody>
<tr>
<td>OC, nmol/L</td>
<td>1.96 ± 0.13</td>
<td>1.65 ± 0.15</td>
<td>1.99 ± 0.11</td>
<td>1.83 ± 0.15</td>
</tr>
<tr>
<td>PICP, µg/L</td>
<td>144.9 ± 11.8</td>
<td>124.7 ± 12.9</td>
<td>150.4 ± 14.6</td>
<td>149.3 ± 14.2</td>
</tr>
<tr>
<td>Start FP†, cross over to FP, n = 7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OC, nmol/L</td>
<td>1.60 ± 0.12</td>
<td>1.58 ± 0.13</td>
<td>1.54 ± 0.20</td>
<td>1.17 ± 0.17</td>
</tr>
<tr>
<td>PICP, µg/L</td>
<td>120.4 ± 7.0</td>
<td>125 ± 8.5</td>
<td>125.7 ± 8.8</td>
<td>102.2 ± 7.0</td>
</tr>
</tbody>
</table>

For definition of abbreviations, see Tables 1 and 2.

* Values are mean ± SEM.
† 1,500 µg daily.
‡ 750 µg daily.

No increase in parameters of bone resorption were found in the present study. This is in line with the findings in most studies on ICS (9, 12, 13, 26, 27). Only Ali and coworkers (10) showed an increase in Ca/Cr and HP/Cr ratios after treatment with 2,000 µg BDP/d. The statistical analysis in their open study in eight healthy subjects, however, raises questions about its interpretation. In the present study, ICTP decreased after treatment with BDP (−11.5%, p < 0.05). No differences in direct treatment comparison between FP and BDP were present. Sorva and coworkers (28) also showed in 14 children a decrease in ICTP after 1 mo of treatment with budesonide 800 µg/m²/d. Deoxyxypyrinoline crosslinks in urine, however, did not change. These results are in line with the data from a recent cross-sectional study, showing no differences in (deoxy)pyridinoline crosslinks between asthmatic patients without ICS and patients treated with ICS and occasionally OCS (27). Altogether, these findings indicate that in general ICS do not increase bone resorption.

Changes in Ca, P, PTH, or 1,25(OH)2D3 did not occur. Previous short-term studies with ICS did not show adverse effects on Ca or P in adults either, even with doses of 2.4 and 3.2 mg/d (9, 12).

Morning cortisol, used as a marker of adrenal suppression, did not change. From dosages of 1,000 µg/d ICS on, a dose-dependent decrease in morning cortisol levels has been reported, but at daily doses of approximately 1,500 µg (as in the present study), the majority of studies, as recently reviewed by Barnes and Pedersen (3), still did not show significant changes. Most studies (including ours) did, however, measure only morning serum cortisol, an insensitive method of detecting changes in HPA-axis. The study by Nicolaiikiz and coworkers (29) showed that at 8:00 A.M. cortisol did not change with ICS, but 24-h urinary cortisol levels were significantly depressed. Furthermore, our study lasted for only 6 wk, and patients inhaled ICS without a spacer. This also may have resulted in our inability to detect any changes. Nevertheless, two large studies, both with more than 150 patients, did report significant differences between FP and BDP on HPA-axis, showing an increase in cortisol after 200 and 1,000 µg FP daily for 4 and 6 wk, respectively, in contrast to a (nonsignificant) decrease after 400 and 2,000 µg BDP (5, 6).

Changes in adrenal function are not necessarily related to changes in indices of bone formation. Changes in bone metabolism can be detected from 400 µg BDP daily on (14), in contrast to an absence of significant changes in cortisol levels at doses below 800 to 1,000 µg BDP daily (3). Kiviranta and Turpeinen (30) also reported effects on carbohydrate metabolism without any significant effect on the HPA-axis after treatment with 2,000 µg BDP daily for 5 mo. Apparently, the organs involved may have a different sensitivity for ICS.

The present investigation was performed using a crossover design, which has the potential disadvantage of a carryover effect. A carryover effect is statistically detectable only with low power. Therefore, a p > 0.1 was taken for the second-order carryover effect to exclude any influence on treatment effects. Furthermore, after the second washout period (Measurement 3), all but urinary hydroxyproline/creatinine ratio returned to pretreatment levels (Measurement 1) (see Table 4). Therefore, carryover effects are not likely to have affected the outcome in the present study both from a statistical point of view and in terms of clinical relevance.

Another point of discussion is that our patients did not use a spacer device to inhale their ICS. The use of a spacer may increase lung deposition, and the fraction deposited in the intrapulmonary airways is likely to be absorbed in active form into the systemic circulation (3). There is no evidence for local metabolism of FP in the lung. Therefore, the majority will reach the bloodstream after absorption from the lungs. It is possible that
the use of a spacer could have given different systemic effects. Nevertheless, the present study compared directly two types of ICS, using the same method of administration, making direct comparison possible. All patients were fully skilled in using a MDI device, and their technique was checked at every visit. All patients improved clinically to a great extent. The use of a spacer is not likely to have changed the observed differences between the two drugs.

Finally, the relevance of effects of ICS on bone metabolism are debatable. Kerstjens and colleagues (26) reported that long-term treatment with ICS did not affect biochemical markers of bone metabolism. PICP and ICTP remained unchanged after 2.5 yr of treatment with 800 μg BDP daily. Long-term studies with higher dosages of ICS have not been reported to our knowledge. The clinical diagnosis of osteoporosis requires the presence of at least one relatively atraumatic fracture (31). Until now no rise in fracture incidence has been reported in patients receiving long-term ICS treatment. The risk of fracture may be assessed by in vivo measurements of bone density. In a prospective study for 1 yr in 63 women who had undergone bilateral oophorectomy, there were high correlations between biochemical markers (bone-specific AP and urinary HP) and the change in cortical area per year (32). Furthermore, in a cross-sectional study of 214 women who had undergone bilateral oophorectomy up to 12 yr previously, changes in bone balance as estimated by differences in biochemical markers of bone formation (bone-specific AP) and bone resorption (urinary HP) paralleled up to 12 yr, the measured changes in bone density (31), confirming the validity of biochemical markers of bone metabolism.

Decreases in bone density have been suggested after treatment with ICS (27, 33). Packe and coworkers (27), measuring density of the lumbar spine by quantitative single energy computed tomography, showed a mean bone density of 160.4 mg/ml in a group of asthmatics treated without ICS compared with 127.5 mg/ml in a matched group treated with > 1,000 μg BDP and courses of OCS for at least 1 yr. In a group of patients treated with ICS for at least 3 mo, Ip and colleagues (33) showed with dual energy X-ray absorptiometry that bone mineral density was decreased at the hip and the lumbar area of the spine in comparison with a matched group of healthy subjects. In these studies it is impossible to quantify the contribution of previous OCS treatment to loss of bone density. This, however, may be the most important factor influencing bone density among other factors such as increased age, inactivity, smoking, malnutrition, menopausal status, and genetic predisposition. In order to avoid these potential sources of bias with respect to biochemical markers of bone turnover, the present study was performed in a crossover design in, besides their asthma, healthy premenopausal nonsmoking subjects.

With regard to the higher dosages, advocated by the guidelines on the management of asthma (1, 2), it cannot be excluded that they have adverse effects on bone in the long term. In this respect, the lack of short-term effects on bone metabolism by FP 750 μg/d, in contrast to a clinically equipotent dose of BDP 1,500 μg/d, may be of potential interest in the long term.

Acknowledgment: The writers would like to thank Dr. H. A. P. Pols and Dr. J. P. T. M. van Leeuwen for measuring urinary deoxypyridinoline crosslinks in the Laboratory of Clinical Endocrinology, Erasmus University Rotterdam, the Netherlands. They would also like to thank Glaxo Research and Development, UK, for kindly supplying the medications.

References


