Once-weekly dose of 8400 IU vitamin D3 compared with placebo: effects on neuromuscular function and tolerability in older adults with vitamin D insufficiency1–3

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ABSTRACT
Background: Vitamin D insufficiency, which is prevalent in older individuals, is associated with bone and muscle weakness and falls.

Objective: We examined the effects of a weekly dose of 8400 IU vitamin D3 on postural stability, muscle strength, and safety.

Design: In this double-blind trial, subjects aged ≥70 y with serum 25-hydroxyvitamin D [25(OH)D] concentrations ≤20 but ≥6 ng/mL were randomly assigned to receive a weekly dose of 8400 IU vitamin D3 (n = 114) or a placebo (n = 112). Mediolateral body sway with eyes open (assessed with the AccuSwayPLUS platform; Advanced Medical Technology Inc, Watertown, MA) was the primary endpoint. Secondary endpoints included the short physical performance battery (SPPB) and serum 25(OH)D concentrations. An analysis of covariance model was used for treatment comparisons. Safety and tolerability were monitored.

Results: Serum 25(OH)D concentrations rose significantly (from 13.9 to 26.2 ng/mL, P < 0.001) in patients treated with 8400 IU vitamin D3 but not in patients treated with the placebo. After 16 wk, neither mediolateral sway nor SPPB differed significantly between treatment groups. However, in the post hoc analysis of patients subgrouped by baseline sway (≥0.46 compared with <0.46 cm), treatment with 8400 IU vitamin D3 significantly reduced sway compared with treatment with placebo (P = 0.047) in patients with elevated baseline sway but not in patients with normal baseline sway. Adverse experiences and incidences of hypercalcemia, hypercalciuria, and elevated creatinine were similar with both treatments. In patients treated with 8400 IU vitamin D3, but not in placebo-treated patients, parathyroid hormone decreased significantly.

Conclusions: Weekly treatment with 8400 IU vitamin D3 raised 25(OH)D concentrations in elderly, vitamin D–insufficient individuals. Treatment with 8400 IU vitamin D3 did not reduce mediolateral sway significantly compared with treatment with placebo in this population, although in post hoc analysis, treatment with 8400 IU vitamin D3 reduced sway in the subgroup of patients who had elevated sway at baseline. Weekly treatment with 8400 IU vitamin D3 was well tolerated. This trial was registered at clinicaltrials.gov as NCT00242476. Am J Clin Nutr 2010;91:985–91.

INTRODUCTION
Vitamin D insufficiency is prevalent in older individuals (1–5). Among the major problems associated with inadequate vitamin D status are skeletal fragility and neuromuscular dysfunction (2). Vitamin D deficiency leads to bone loss, largely because of secondary hyperparathyroidism aggravated by insufficient calcium intake, whereas adequate vitamin D intake enables normal bone mineralization, in part by stimulating increases in the absorption of calcium and phosphate from the intestine. The nuclear receptor for vitamin D was detected in many cell types, including enterocytes and muscle cells (2, 6, 7). The abundance of vitamin D receptors in muscle declines in older women compared with younger women (8), and hypovitaminosis D has been associated with poorer neuromuscular function in elderly individuals of either sex (9).

Muscle weakness increases the likelihood of falls (10). The association between low–vitamin D concentrations and falls has been shown in epidemiologic studies and randomized clinical trials and is supported by meta-analyses (10, 11). In elderly individuals, especially those with osteoporosis, an elevated risk of falls leads to an elevated risk of fractures (11), which are associated with excess morbidity and mortality (12, 13).

The current randomized, double-blind, placebo-controlled trial was designed to assess whether a once-weekly treatment with 8400 IU vitamin D3 would improve body postural stability and lower-extremity function in elderly people with low–vitamin D status (serum 25-hydroxyvitamin D [25(OH)D] concentrations ≤20 ng/mL) (2). The primary endpoint, mediolateral sway with eyes open as assessed with the AccuSwayPLUS platform (Advanced Medical Technology Inc, Watertown, MA), was shown to be significantly associated with recurrent falling in a subgroup of patients of the Longitudinal Aging Study Amsterdam (LASA) (14). Stel et al (14) showed that increased mediolateral body sway was predictive of having more than one fall during a 12-mo period. They identified 0.46 cm as the value separating individuals who fell multiple times from individuals who did not.

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not fall or who had fallen once (odds ratio: 2.9; 95% CI: 1.3, 6.8) (14).

In the current study, the dose of vitamin D₃ was selected—on the basis of the pharmacokinetic analysis of Barger-Lux et al (15) —so that patients would achieve serum 25(OH)D concentrations ≈20–33 ng/mL. This range of serum 25(OH)D concentrations corresponds to concentrations shown to be associated with improved neuromuscular function (16, 17), lies well within vitamin D concentrations known to be safe (18, 19), and is consistent with recommendations from the 2005 consensus on optimal vitamin D status (20) and from the World Health Organization (21). During the 16 wk of treatment, physical performance, laboratory measures related to vitamin D status, and safety were monitored.

SUBJECTS AND METHODS

Patients

Patients were men and women aged ≥70 y who were vitamin D insufficient [serum 25(OH)D concentrations ≤20 but ≥6 ng/mL]. All study participants were required to be ambulatory (able to walk 10 ft without a walking aid) and mentally competent [obtaining a score ≥24 on the Folstein’s Mini-Mental State Examination (22)]. If patients had serum 25(OH)D concentrations ≥6 but ≤9 ng/mL, they needed to have 24-h urine calcium concentrations ≥50 mg/d and bone-specific alkaline phosphatase concentrations not higher than the upper limit of normal to be eligible for the study. Exclusion criteria included primary hyperparathyroidism, active thyroid disease, impaired renal function, osteomalacia, neurologic impairment, peripheral neuropathy, myocardial infarction within 6 mo of screening, uncontrolled hypertension, postural hypotension, malabsorption syndrome, alcohol abuse (ie, >2 drinks/d), or cancer. Treatment with oral glucocorticoids, anabolic steroids, or a growth hormone within 12 mo of screening; treatment with >800 IU vitamin D/d or with active metabolites of vitamin D within 6 mo of screening; or treatment with any drug that might affect vitamin D metabolism or interfere with postural stability at screening were also reasons for exclusion. All patients signed an informed consent statement, and the protocol was approved by all institutional review boards [the Hospital Ángeles Integrantes de la Comisión de Ética en Material de Investigación (Mexico City, Mexico); the Quorum Review institutional review board (Seattle, WA); the IUPI and Clarian Institutional Review Boards & Subcommittees Review (Indianapolis, IN); the Creighton University institutional review board (Omaha, NE); the Medisch Ethische Toetsing Commissie Vrije Universiteit Medisch Centrum (Amsterdam, Netherlands); the Ethikkommission der Ärztekammer Niedersachsen (Berlin, Germany); the Ethikkommission der Ärztekammer Hamberg (Hamburg, Germany); and the Institutional Review Board Services (Aurora, Canada)].

Study design

This 16-wk randomized, double-blind, placebo-controlled, multicenter study (protocol number 009) to assess efficacy and safety of weekly 8400 IU vitamin D₃ was conducted between October 2005 and June 2006 at medical centers in North America (9 centers) and Europe (3 centers). The primary end-point was mediolateral body sway (measured with eyes open with the AccuSwayPLUS platform (Advanced Medical Technology Inc) at baseline and after 16 wk of treatment. Secondary endpoints included change in functional status assessed with the short physical performance battery (SPPB) (23, 24) as well as mean serum 25(OH)D, calcium, and phosphate concentrations. Safety and tolerability were also assessed.

After a 2-wk placebo run-in period, participants were randomly assigned 1:1 to receive a once-weekly dose of 8400 IU vitamin D₃ or a placebo. Participants were stratified (2:1) at randomization according to baseline serum 25(OH)D concentration (≤15 ng/mL; >15 ng/mL). Patients were assigned a unique allocation number according to their appropriate stratification block. Investigators were blinded to serum 25(OH)D concentrations and to stratum definitions.

During the treatment period, participants received 3 tablets once per week containing a placebo or 2800 IU vitamin D₃ according to the treatment assignment. For those with a daily dietary calcium intake <1000 mg (as assessed by a questionnaire at screening), daily calcium carbonate containing 500 mg elemental calcium was also prescribed.

Study participants were asked not to alter their diets or exercise regimens during the trial. Direct exposure to the sun was to be limited; participants agreed to apply sunscreen (sun protection factor ≥15) if exposure to direct sunlight for a period of time exceeding 15 min was anticipated. Patients also refrained from consumption of dietary supplements that contain >100 IU vitamin D per day, and they were to abstain from alcoholic beverages for 24 h before a clinic visit.

Assessments

Neuromuscular function

Postural stability was determined by measuring postural body sway, which is the corrective body movement resulting from the control of body position. The primary endpoint was mediolateral body sway, which was measured with eyes open with the AccuSwayPLUS platform (Advanced Medical Technology Inc). This system analyzes input from strain gauges under a force platform and thereby calculates the center of pressure. The extent of the center-of-pressure movement is directly related to the individual’s ability to maintain balance in an upright position. The balance tests were performed in patients with eyes open, standing on the force platform for 30 s with bare feet, and looking straight ahead. Four tests were performed at all study visits; the mean result was used for data analysis.

The lower-extremity performance was measured at all study visits by the SPPB (23, 24), which included an assessment of standing balance, a gait speed test (ie, a timed 4-m walk), and timed rising from a chair and sitting without the use of arms for 5 repetitions. The SPPB was evaluated by using an ordered scale of 0–12 for combined measures of balance, gait speed, and ability to rise from and sit in a chair or as a continuous variable for the gait speed test separately (23).

Laboratory values and adverse experiences

Chemical analysis was conducted at a central laboratory (Global Central Labs at Ppd, Highland Heights, KY). Serum parathyroid hormone (PTH) was detected with a DiaSorin
Liaison chemiluminescence analyzer (DiaSorin, Stillwater, MN). Serum 25(OH)D concentrations were measured by reverse phase HPLC by using methodology previously described (25). The laboratory performing 25(OH)D measurements participates in and meets proficiency standards of the vitamin D External Quality Assessment Scheme. The intraassay CV for this assay ranges from 1.9% at a 25(OH)D concentration of 61.5 ng/mL to 6.3% at a 25(OH)D concentration of 14.3 ng/mL. The interassay CV for this assay is 3.2% at a 25(OH)D concentration of 59.8 ng/mL and 3.9% at a 25(OH)D concentration of 14.3 ng/mL.

Adverse experiences (AEs) were recorded at each study visit and by the voluntary reporting of patients at any time during the study.

Statistical methods

The all-patients-treated population was used for efficacy analyses. Randomized participants who took at least one treatment dose were included in the all-patients-treated analyses, provided that the necessary baseline and at least one post-randomization data point were available. All statistical results were generated with a statistical program (SAS 8.2; SAS Institute Inc, Cary, NC).

A parametric analysis of covariance model with terms for baseline body sway, baseline vitamin D stratum, and treatment group was used to analyze data and estimate the within- and between-treatment differences for the primary endpoint of mediolateral sway after treatment for 16 wk. A prespecified subgroup analysis on the basis of a baseline 25(OH)D concentration (<15 or >15 ng/mL) and a post hoc subgroup analysis on the basis of baseline mediolateral sway with eyes open (≥0.46 or <0.46 cm) were performed for the primary endpoint. For the analysis of urine calcium and serum PTH, a log transformation was used. The least-squares means were back transformed for the presentation of results.

The study was powered at 82% in the overall population and 80% in the low-baseline 25(OH)D stratum to detect between-treatment differences in mediolateral sway with eyes open. The per protocol patient population, in which participants with important protocol deviations were excluded, was also evaluated for efficacy. Safety was assessed in all treated patients.

RESULTS

Men and women (n = 226) with a low vitamin D status [serum 25(OH)D concentrations ≤20 but ≥6 ng/mL] were randomly assigned to receive weekly vitamin D3 8400 or a placebo for 16 wk. Participant inclusion and reasons for discontinuation in the trial are shown in Figure 1. In general, the vitamin D and

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n = 112)</th>
<th>Vitamin D3 (n = 114)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>77.6 ± 6.6²</td>
<td>78.5 ± 6.2</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>161.9 ± 10.3</td>
<td>162.3 ± 10.7</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>73.8 ± 17.0</td>
<td>72.3 ± 15.2</td>
</tr>
<tr>
<td>Mediolateral sway with eyes open (cm) All patients</td>
<td>0.349 ± 0.150</td>
<td>0.306 ± 0.123</td>
</tr>
<tr>
<td>Mediolateral sway with eyes open (cm) Subgroups by baseline 25(OH)D concentration ≤15 ng/mL</td>
<td>0.355 [68]</td>
<td>0.303 [75]</td>
</tr>
<tr>
<td>Mediolateral sway with eyes open (cm) Subgroups by baseline 25(OH)D concentration &gt;15 ng/mL</td>
<td>0.340 [43]</td>
<td>0.313 [38]</td>
</tr>
<tr>
<td>Serum 25(OH)D concentration (ng/mL) All patients</td>
<td>14.1 ± 5.5</td>
<td>13.7 ± 4.4</td>
</tr>
<tr>
<td>Serum 25(OH)D concentration (ng/mL) Subgroups by baseline mediolateral sway &lt;0.46 cm</td>
<td>14.2 [78]</td>
<td>13.8 [91]</td>
</tr>
<tr>
<td>Serum 25(OH)D concentration (ng/mL) Subgroups by baseline mediolateral sway ≥0.46 cm</td>
<td>13.9 [22]</td>
<td>12.3 [9]</td>
</tr>
<tr>
<td>Serum calcium (mg/dL)</td>
<td>9.4 ± 0.4</td>
<td>9.4 ± 0.4</td>
</tr>
<tr>
<td>24-h urine calcium (mg/d)</td>
<td>123.7 ± 70.2</td>
<td>108.9 ± 83.9</td>
</tr>
<tr>
<td>Serum phosphate (mg/dL)</td>
<td>3.5 ± 0.5</td>
<td>3.5 ± 0.4</td>
</tr>
<tr>
<td>Serum parathyroid hormone (pg/mL)</td>
<td>59.1 ± 29.1</td>
<td>58.8 ± 28.6</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>1.0 ± 0.2</td>
<td>1.0 ± 0.2</td>
</tr>
<tr>
<td>SPPB summary performance score</td>
<td>8.9 ± 2.2</td>
<td>8.9 ± 2.4</td>
</tr>
<tr>
<td>Use of walking device [n (%)]</td>
<td>17 (15.2)</td>
<td>16 (14.0)</td>
</tr>
<tr>
<td>Use of corrective lenses [n (%)]</td>
<td>95 (84.8)</td>
<td>105 (92.1)</td>
</tr>
<tr>
<td>Residence in nursing home [n (%)]</td>
<td>16 (14.3)</td>
<td>16 (14.0)</td>
</tr>
</tbody>
</table>

² Mean ± SD (all such values).
³ Mean; number of patients in brackets (all such values).
placebo groups were similar at baseline (Table 1). Participants were, on average, 78 y of age, 15% of participants used walking devices, 14% of participants resided in nursing homes, and the mean 25(OH)D concentration at baseline was 13.9 ng/mL. All patients who completed the trial were adherent to treatment, which was defined as taking ≥13 of the 16 total doses prescribed.

**Neuromuscular function**

**Mediolateral sway**

Mediolateral sway at 16 wk did not change from baseline in either placebo-treated or vitamin D₃–treated participants, and there was no between-group difference (Figure 2A). Although a between-group difference in the serum 25(OH)D concentration did occur at 8 wk and continued throughout the 16-wk trial (with a final 1.86-fold increase in vitamin D₃–treated participants compared with a slight decrease in placebo-treated participants, *P < 0.001*; Figure 3), no significant treatment differences in mediolateral sway were seen in either of the 2 prespecified subgroups on the basis of the baseline 25(OH)D concentration (≤15 or >15 ng/mL).

In a post hoc analysis, we examined mediolateral sway in subgroups on the basis of sway at baseline (Figure 2, B and C). A baseline mediolateral sway of 0.46 cm was selected as the cutoff for subgroup analysis on the basis of work of Stel et al (14). The post hoc analysis revealed a treatment difference in sway between patients with baseline sway ≥0.46 cm (Figure 2B). In this cohort (*n* = 31), mediolateral sway was reduced in the vitamin D₃ group compared with the placebo group (at week 16, the mean difference was −0.161 cm; *P = 0.047*). In the cohort with low baseline sway (<0.46 cm, *n* = 179), there was no difference between groups (Figure 2C).

**SPPB**

There was no significant difference in the change in SPPB scores between patients receiving vitamin D₃ and patients receiving the placebo (Table 2).

**Laboratory assessments**

Serum 25(OH)D concentrations rose (*P < 0.001*) in the vitamin D₃–treated participants from ≈14 to ≈26 ng/mL during Figure 2. Mean (±SE) mediolateral sway with eyes open. A: All treated patients. B: Subset of patients with baseline mediolateral sway ≥0.46 cm. C: Subset of patients with baseline mediolateral sway <0.46 cm. *P = 0.047* at 16 wk, with no correction for multiplicity. Data were analyzed by an ANCOVA model with terms for baseline body sway, baseline vitamin D stratum, and treatment group. The interaction term between baseline sway and treatment effect was significant (*P = 0.0004*). However, the analysis of interaction was limited by the small sample sizes in the subgroup analysis, and the larger changes in sway among only a few patients drove the interaction.

Figure 3. Mean (±SE) concentrations of 25-hydroxyvitamin D [25 (OH) Vitamin D]. *P < 0.001* at 16 wk. Data were analyzed by an ANCOVA model, with terms for the baseline 25-hydroxyvitamin D concentration, baseline vitamin D stratum, and treatment group.
### TABLE 2
Change from baseline in short physical performance battery (SPPB)

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 104)</th>
<th>Vitamin D₃ (n = 109)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPPB summary score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>9.07 ± 2.0³</td>
<td>9.00 ± 2.3</td>
<td></td>
</tr>
<tr>
<td>Change from baseline</td>
<td>0.601</td>
<td>0.355</td>
<td>0.162</td>
</tr>
<tr>
<td>(0.351, 0.852)⁵</td>
<td>(0.108, 0.601)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| SPPB gait test speed (cm/s) |                   |                      |         |
| Baseline                   | 88.7 ± 25.9       | 93.7 ± 31.5          |         |
| Change from baseline       | 3.94              | 3.10                 | 0.717   |
| (0.567, 7.38)              | (−0.252, 6.458)   |                      |         |

¹ Data were analyzed by using an ANCOVA model with terms for baseline value, baseline vitamin D stratum, and treatment group. Treatment groups were not significantly different at baseline.

² Mean ± SD (all such values).

³ Week 16 least-squares mean change from baseline; 95% CI in parentheses (all such values).

### DISCUSSION
In this randomized, double-blind, placebo-controlled study in ambulatory, vitamin D–insufficient [serum 25(OH)D concentration ≤20 ng/mL] older adults, a once-weekly treatment with 8400 IU vitamin D₃ for 16 wk significantly increased serum 25(OH)D concentrations. Despite this, vitamin D treatment did not affect mediolateral body sway or alter neuromuscular function as measured by the SPPB. However, in post hoc analysis, among those participants with greater baseline mediolateral sway (≥0.46 cm), weekly 8400 IU vitamin D₃ reduced mediolateral sway. In the cohort with normal baseline sway, vitamin D₃ had no effect on mediolateral sway.

A once-weekly dose of 8400 IU vitamin D₃ increased the serum 25(OH)D concentration in participants by ~12 ng/mL, an increment consistent with a prior report (15). The study was conducted during the winter and spring, and there could have been a seasonal influence on 25(OH)D concentrations. However, the change in 25(OH)D concentrations in the placebo-treated group was only marginal, which indicates that the seasonal influence was not substantial. Treatment with 8400 IU vitamin D₃ also led to a reduction in serum PTH. The significant decrease in PTH (<5%) was smaller than might have been expected. We might have observed a larger decrease if the baseline 25(OH)D concentrations had been lower and the 25(OH)D concentrations had risen from ~5 to 15 ng/mL instead of ~15 to 25 ng/mL (26). Finally, a trend toward increased urinary calcium excretion was observed with vitamin D₃ treatment, as could be expected in patients with a low vitamin D status (27).

A once-weekly dose of 8400 IU vitamin D₃ was well tolerated. The incidence of hypercalcemia, hypercalciuria, or kidney stones did not differ between groups. Vitamin D₃ treatment was not associated with other laboratory, clinical, or serious AEs.

These results of neuromuscular function do not confirm the results of a number of studies (10, 16, 28–35) that showed higher serum 25(OH)D concentrations to be associated with better physical performance. One possible reason for this discrepancy is that those with severe vitamin D deficiency (serum 25(OH)D concentration <6 ng/mL) were excluded from the current study. Perhaps those with severe vitamin D deficiency experience the greatest physical performance benefit. In LASA, an epidemiologic study where patients with severe vitamin D deficiency were not excluded, the main improvement in physical performance occurred when serum 25(OH)D concentrations increased from 2 to 14 ng/mL (17). Another possible explanation for the
The discrepancy is that so many patients in the current trial had low mediolateral sway at baseline, perhaps reflecting overall good health. In fact, mean baseline mediolateral sway in this study (0.33 cm) was similar to that of individuals who did not fall or who had fallen once in LASA using the same apparatus (0.34 cm), whereas the mean mediolateral sway of individuals who fell repeatedly in LASA was higher (0.43 cm) (14). Furthermore, the baseline SPPB score of 9.1 in the current study was relatively high in the scale of 1–12, in which elderly patients with scores of 10–12 are considered the healthiest (24). Thus, the results of the current study may represent a ceiling effect. Improvements in neuromuscular function as assessed by mediolateral sway may not occur above a ceiling or maximum level. In the current study, many patients were at or near this maximum level of neuromuscular function at baseline. In a post hoc subgroup analysis, the patients who were not near the ceiling level of neuromuscular function at baseline did experience an average improvement in mediolateral sway with treatment with 8400 IU vitamin D₃.

The subgroup analysis that was prespecified in the study protocol—change in sway between patients with lower 25(OH)D concentrations compared with patients with higher 25(OH)D concentrations—did not yield a significant difference. Several observations may explain this unexpected result: the number of patients with lower 25(OH)D concentrations may have been too small to detect a statistically significant difference between the 2 subgroups; the study population was one of overall good health; and the baseline sway, even in the patients with lower 25(OH)D concentrations, was quite low.

The main limitation of this study was that a substantial number of participants had mediolateral sway values at baseline that were consistent with participants who did not fall, suggesting that their balance as measured by sway was adequate. In these patients, there may have been little room for improvement of sway and physical performance with treatment. Another limitation of the trial was its small size. In our estimation, the primary endpoint did not provide a clear answer because of the unusually healthy condition of the elderly patients enrolled in this trial and perhaps to the low number of patients enrolled. Neuromuscular efficacy was only observed by post hoc analysis in a subset with greater mediolateral sway at baseline.

In conclusion, in the current investigation of elderly men and women, 16 wk of treatment with 8400 IU vitamin D₃ once weekly did not alter mediolateral sway as measured with the AccuSwayPLUS platform (Advanced Medical Technology Inc) or physical performance as measured by the SPPB. In the small subgroup of participants with elevated sway at baseline who were examined in a post hoc analysis, improvements in sway occurred with vitamin D₃ treatment compared with the placebo treatment. The weekly dose of 8400 IU vitamin D₃, a dose well above currently recommended intakes (20, 21), was well tolerated.

The authors’ responsibilities were as follows—PL, NB, MP, RR, and DAP: study design and protocol development, data acquisition, data analysis, and writing of the paper; SS and ER: data analysis and writing of the paper; DAC: protocol development, data acquisition, and writing of the paper; and JC: study design and protocol development and writing of the paper. PL, NB, MP, and RR received research grants from the sponsor of the study, Merck & Co Inc. SS, DAC, JC, ER, and DAP are employed by Merck & Co Inc and may potentially own stock options in the company.

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