baseline to year-1. The increase in percent lumbar spine BMD was still seen in Aln10mg and Aln20mg treatment groups from year-1 to year-2 in each study. While Study 037 did not show improvement from year-2 to year-3 in any of the alendronate arms, Aln10mg (mean: 1.74% in Study 035 and 0.56% in Study 037) was shown to still increase percent lumbar spine BMD from year-2 to year-3 in Study 035. When pooled study results were evaluated for comparison between Aln5mg and Aln10mg during the extension (years 4 and 5), percent change from baseline at year 5 was significantly higher with Aln10mg than that with Aln5mg.

- Does alendronate 5 and/or 10mg preserve spine, hip, forearm, and total body BMD from Month-36 to Month-60 ?

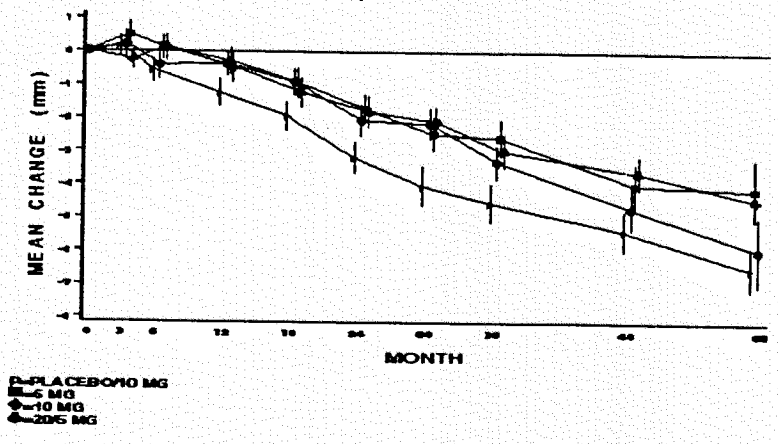
To show that alendronate 5 and/or 10mg preserves or increases spine, femoral neck, trochanter, and total body BMD from Months 36 to 60 in terms of % change, the sponsor tested the conventional superiority hypothesis that alendronate 5 and/or 10mg increases BMD from Month-36 to Month-60. When the hypothesis of no difference between Month-36 and Month-60 cannot be rejected, the sponsor concluded that there was no statistically significant decrease in BMD or no statistically significant BMD loss. However, this did not conclude that the mean percent change is equivalent between Month-36 and Month-60.

To study whether BMD is preserved between Month-36 and Month-60, an equivalence or a noninferiority alternative hypothesis should have been tested with a pre-specified equivalence range. From the pooled study results, lumbar spine BMD in both Aln5mg and Aln10mg and trochanter BMD in Aln10mg group were shown to increase from Month-36 to Month-60. The lower limit of 95% confidence interval for mean % change from Month-36 to Month-60 was less than zero in femoral neck (for Aln5mg and Aln10mg), trochanter (for Aln5mg), and total body BMDs (for Aln5mg and Aln10mg), suggesting that alendronate 5mg and/or 10mg might not preserve the above BMDs from Month-36 to Month-60 in postmenopausal women with continuous use of alendronate for five years, depending on what a pre-specified equivalence range is.

- Stature

Figure 16

Mean Change (±SE) in Stature
(Intention-to-Treat Approach)
(Pooled 035/037)



The sponsor presented mean change (+/- SE) in Stature (mm) by pooling Studies 035 and 037, see Figure 16. The mean change in stature from baseline at Month-60 indicated a significant decrease ($p<=0.05$) of 6.5, 4.1, 6.0, and 4.4mm in the placebo/10mg, 5mg, 10mg, and 20/5mg groups, respectively, see Table 10 of pooled study result (p.21).

This reviewer also summarizes the sponsor's results by study. Statistically significant change from baseline at Month-60 was observed within each study and each treatment arm. Change from Month-36 at Month-60 was also observed within each study and each treatment arm except Aln5mg and Aln20/5mg in Study 037. Mean change from baseline at Month-60 was not significantly different between Aln5mg (-5.58mm) and Aln10mg (- 4.97mm) in Study 035 (US study), but was significantly different between Aln5mg (-2.79mm) and Aln10mg (-6.81mm) in Study 037 (International study). In the international study, patients treated with Aln10mg showed a decrease in stature (mm) more than twofold than patients treated with Aln5mg in Study 037, mean difference and its 95% CI were -4.02 mm and (-7.66mm, -0.38mm). Mean change in stature from Month-36 to Month-60 appeared to be similar in numerical trend, though not statistically significantly different.

- Pooling of studies 035 and 037

Pooling of two studies was considered "the most inferential statistical analysis" in the Data Analysis Plan, which was a revised plan after 3 to 5 months beyond completion of the study.

As evaluated by this reviewer under "the ITT analysis", results from individual studies and combined study were consistent on percent change from baseline to Month-60, see Table 8. However, the analysis of "stature" appeared to show a qualitative interaction between protocols (Table 10). That is, Aln10mg had a larger decrease from baseline to Month-60 in stature than Aln5mg in Study 037, but the opposite was seen in Study 035. Thus, the combined study analysis was not helpful to conclude which of Aln5mg and Aln10mg induced a large decrease in stature.

- **Subgroup Analysis on % change from baseline and Month-36 for lumbar spine BMD**

Baseline age of 65 years was the cutoff point for the two age subgroups. According to the sponsor, percent change in lumbar spine BMD from baseline at Month-60 was relatively higher in the subgroup of patients having age 65 ≥years (see sponsor Table 4.35.1). Percent change of lumbar spine BMD from Month-36 at Month-60 indicated no difference between the two subgroups based on age.

4.35.1: (Pooled 035/037)
Age
Subgroup Analysis for Percent Change in Lumbar Spine BMD at Month 60
(Intention-to-Treat Approach)

| Subgroup | Treatment | N | Baseline Mean (g/cm2) | Month 60 Mean (g/cm2) | Percent Change Mean | S.D. | Confidence Interval (95%) |
|---|---|---|---|---|---|---|---|
| Age < 65 Years | | | | | | | |
| | Placebo/10 mg | 144 | 0.77 | 0.81 | 5.72 | 5.39 | ( 4.84 , 6.60) |
| | 5 mg | 61 | 0.76 | 0.81 | 6.37 | 5.59 | ( 4.97 , 7.77) |
| | 10 mg | 92 | 0.76 | 0.82 | 8.46 | 5.51 | ( 7.34 , 9.59) |
| | 20/5 mg | 71 | 0.76 | 0.82 | 7.52 | 5.31 | ( 6.29 , 8.76) |
| Age >= 65 Years | | | | | | | |
| | Placebo/10 mg | 113 | 0.74 | 0.79 | 6.37 | 6.08 | ( 5.25 , 7.49) |
| | 5 mg | 62 | 0.73 | 0.77 | 6.35 | 4.63 | ( 5.19 , 7.50) |
| | 10 mg | 51 | 0.72 | 0.80 | 10.96 | 6.30 | ( 9.23 ,12.69) |
| | 20/5 mg | 51 | 0.73 | 0.80 | 11.33 | 9.24 | ( 8.77 ,13.90) |

## SUMMARY

Based on the protocol defined primary efficacy variable, both Trials 035 and 037 showed statistical evidence that Aln10mg was superior to Aln5mg with respect to mean percent increase in lumbar spine BMD from baseline at Month-60, as per the sponsor's selected ITT (n=644) analysis and this reviewer's ITT (n=724) analysis. Although there was no placebo group as one of the comparison group at the extension phase (years 4 and 5) to ensure that Aln5mg is superior to placebo, the original 3-year study had demonstrated that while patients treated with 5mg, 10mg, or 20/5mg alendronate showed a significant percent increase from baseline at Month-36 on lumbar spine BMD in both studies ($p<=0.001$), a decreasing trend from baseline at Month-36 in placebo arm (-0.64% in Study 035 and -0.31% in Study 037) was found. That is, Aln5mg is superior to placebo in percent change from baseline at month-36 on BMDs. Thus, comparison between Aln10mg and Aln5mg would be reasonable.

BMD related efficacy variables of lumbar spine (Figure 1), femoral neck (Figure 5), trochanter (Figure 10), and total body BMD (Figure 14), see p.13-14, all depicted improved mean percent change from placebo at Month-24, that is, the trend in the first two-year seen in Aln10mg was also seen in years 4 and 5 of patients blindly switched to Aln10mg after three years of placebo treatment. From these Figures, continuous use of alendronate over 5 years seemed to show plateau in the percent increase by year 4 or 5, and might start to decrease after year 4. The largest improvement in terms of percent increase in BMD in patients treated with alendronate was seen during the first year (see Figure R, p.13).

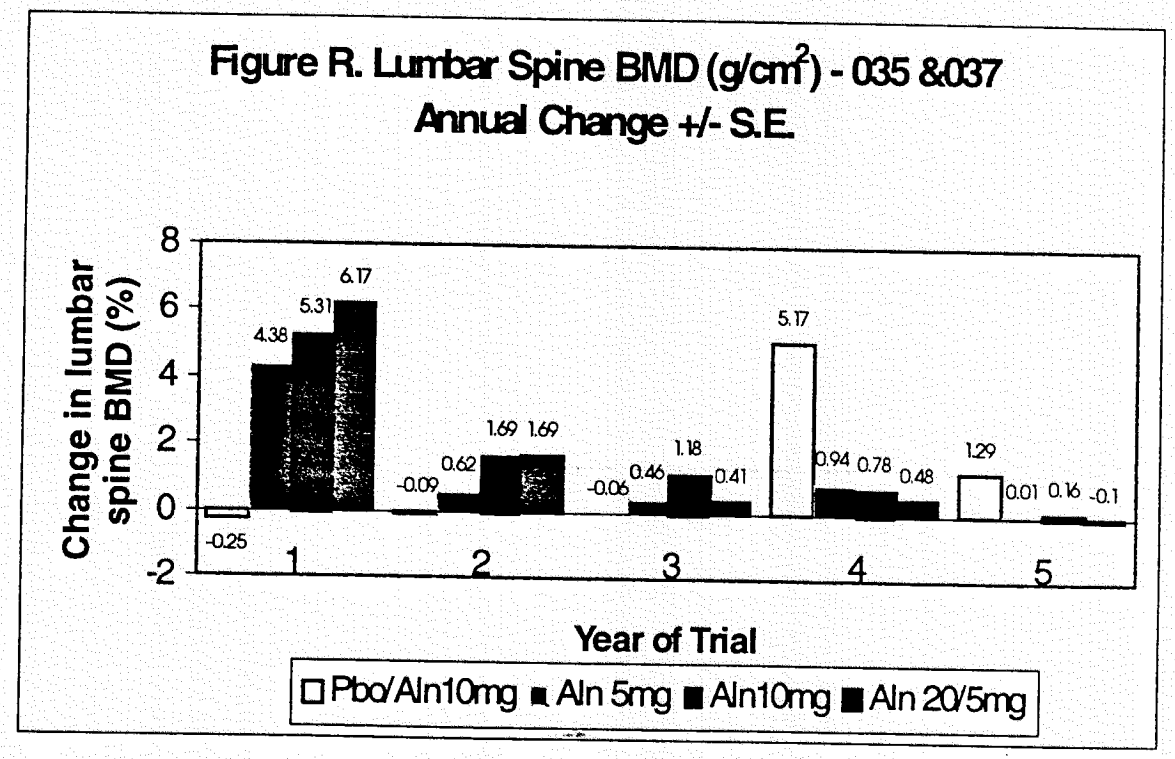
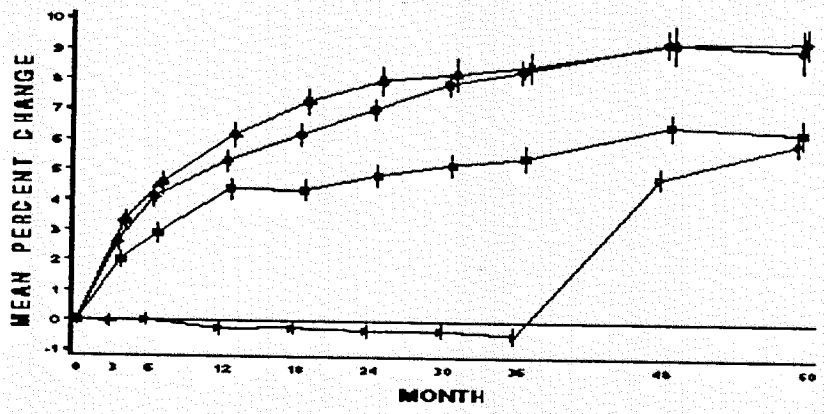


Figure 1

Mean Percent Change (±SE) in Lumbar Spine BMD
(Intention-to-Treat Approach)
(Pooled 035/037)




Data Source: [4.37.5; 4.37.6]

Figure 5

Mean Percent Change (±SE) in Femoral Neck BMD
(Intention-to-Treat Approach)
(Pooled 035/037)

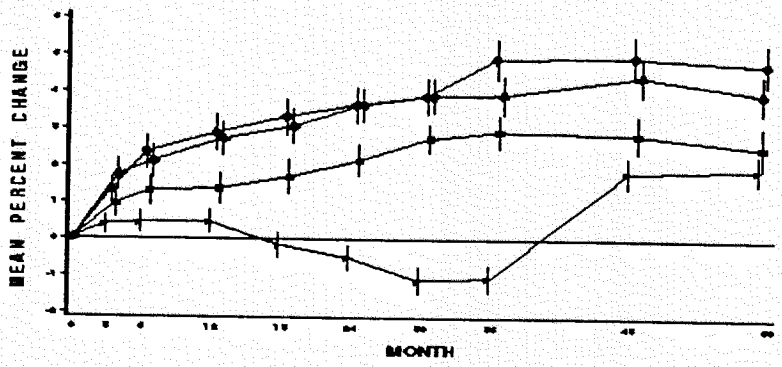


Figure 10

Mean Percent Change (±SE) in Trochanter BMD
(Intention-to-Treat Approach)
(Pooled 035/037)

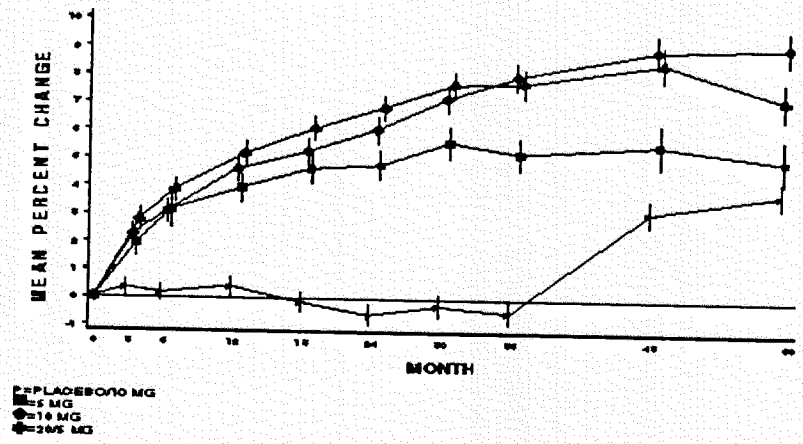
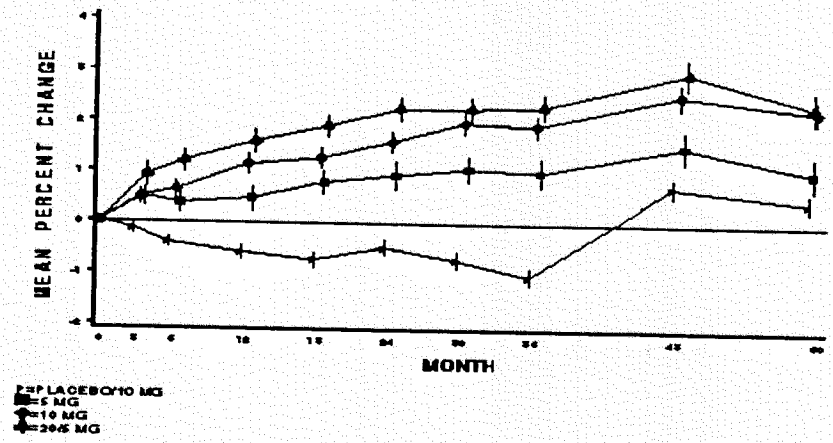



Figure 14

Mean Percent Change (±SE) in Total Body BMD
(Intention-to-Treat Approach)
(Pooled 035/037)



## CONCLUSION

A total of 994 patients were randomized to receive double-blind treatment. Of those patients who entered the double-blind extension phase (years 4 and 5), n=727, there appeared to be no significant difference in the demographic and baseline characteristics except a highly significant difference in body mass index at baseline between alendronate 10mg (23.6 $kg/m^2$) and alendronate 5mg (24.8 $kg/m^2$).

Based on the protocol defined primary efficacy variable, both Trials 035 and 037 showed that the mean percent increase in lumbar spine BMD from baseline to Month-60 in patients treated with Aln10mg was statistically significantly larger than those treated with Aln5mg. However, a decrease in stature appeared to be significantly greater with Aln10mg than with Aln5mg in the International Study. The decrease was not statistically significantly different in US patients. Mean change in stature from Month-36 to Month-60 seemed to show a similarly decreasing pattern, though not statistically significantly different, as the percent change from baseline at Month-60.

The clinical relevance of the alendronate effect on BMD needs to be addressed by the medical review team, because while there is an increase in % change from baseline at Month-60 in lumbar spine BMD (the primary efficacy variable) and similar pattern for femoral neck, trochanter, and total body BMDs, there appeared to be a significant decrease in mean yearly rate of change in mm of stature (a secondary efficacy variable) over the entire five years, especially, in the international study. The US study did not support such a decrease in stature observed in the international study.

/S/ [redacted]
Sue-Jane Wang, Ph.D.
Mathematical Statistician

Concur: Dr. Sahlroot /S/ [redacted] 4/29/99

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This review consists of 21 pages, which includes 11 reviewer summary tables, 1 Reviewer Figure, 8 sponsor figures and 3 Attachments.

Appendix I – Calculation of BMD value (p.18 of sponsor clinical study report)

Dual energy X-ray absorptiometry (DXA) was performed to obtain bone mineral density (BMD). Densitometers from [redacted] companies were used to measure bone mineral content (BMC). BMD was calculated as the ratio of total BMC to corresponding total bone area of the site. Due to differences between areas analyzed by [redacted] versus [redacted] densitometers, the total hip measurements were analyzed only for Hologic.

When the local radiologist diagnosed a fractured vertebra on the lateral spine radiograph, all data from that vertebral body were deleted from the calculations of spine BMD for the entire 5-year period of the study.

All analyses of BMD data reflect correction of these data to account for any change in calibration of DXA instruments over the period of the study. The correction factor for each instrument was determined for each day during the study by the Quality Assurance Center and applied using the following formula:

Corrected BMD value
= patient's BMD in the day range + Phantom correction factor in the day range* (patient's BMD/baseline phantom BMD).

Appendix II – Sponsor's relative day range for efficacy and safety analysis*

| | Relative Day ranges | | | |
|---|---|---|---|---|
| Time Point | BMD | Efficacy Stature | Biochemical | Safety Clinical and Lab |
| Baseline | -100 to 14 | -100 to 14 | -100 to 1 | -100 to 1 |
| Month -1 | - | - | 2 to 59 | 2 to 59 |
| Month -3 | 15 to 134 | 15 to 134 | 60 to 134 | 60 to 134 |
| Month -6 | 135 to 272 | 135 to 224 | 135 to 224 | 135 to 224 |
| Month -9 | - | 225 to 317 | 225 to 317 | 225 to 317 |
| Month -12 | 273 to 454 | 318 to 454 | 318 to 454 | 318 to 454 |
| Month -18 | 455 to 637 | 455 to 637 | 455 to 637 | 455 to 637 |
| Month -24 | 638 to 819 | 638 to 775 | 638 to 775 | 638 to 775 |
| Month -27 | - | 776 to 865 | 776 to 865 | 776 to 865 |
| Month -30 | 820 to 1002 | 866 to 1002 | 866 to 1001 | 866 to 1001 |
| Month -36 | 1003 to 1277 | 1003 to1277 | 1002 to 1199 | 1002 to 1199 |
| Month -48 | 1278 to 1644 | 1278 to 1644 | 1278 to 1644 | 1278 to 1644 |
| Month -60 | 1645 to 2011 | 1645 to 2011 | 1645 to 2011 | 1645 to 2011 |

* Table 19 of sponsor clinical study report.

Appendix III - Tables 11 and 12 of sponsor clinical study report (baseline and Month-36 clinical efficacy parameters)

Table 11

Summary of Baseline Clinical Efficacy Parameters
(Pooled 035/037)

| BMD Site | Densitometer | Alendronate Treatment | n | Mean | SD | Median | Range |
|---|---|---|---|---|---|---|---|
| Femoral Neck BMD (g/cm²) | Hologic/Norland | All | 410 | 0.61 | 0.08 | 0.60 | 0.39 to 0.92 |
| | | Placebo/10 mg | 155 | 0.61 | 0.08 | 0.61 | 0.42 to 0.89 |
| | | 5 mg | 87 | 0.60 | 0.10 | 0.59 | 0.39 to 0.86 |
| | | 10 mg | 84 | 0.59 | 0.07 | 0.58 | 0.46 to 0.74 |
| | | 20/5 mg | 84 | 0.62 | 0.09 | 0.62 | 0.42 to 0.92 |
| | Lunar | All | 209 | 0.74 | 0.09 | 0.74 | 0.47 to 0.98 |
| | | Placebo/10 mg | 85 | 0.75 | 0.08 | 0.74 | 0.58 to 0.98 |
| | | 5 mg | 40 | 0.76 | 0.10 | 0.78 | 0.59 to 0.95 |
| | | 10 mg | 42 | 0.72 | 0.09 | 0.71 | 0.53 to 0.93 |
| | | 20/5 mg | 42 | 0.72 | 0.08 | 0.73 | 0.47 to 0.89 |
| Lumbar Spine BMD (g/cm²) | Hologic/Norland | All | 425 | 0.71 | 0.08 | 0.72 | 0.38 to 0.93 |
| | | Placebo/10 mg | 165 | 0.71 | 0.08 | 0.72 | 0.38 to 0.84 |
| | | 5 mg | 89 | 0.71 | 0.09 | 0.72 | 0.48 to 0.93 |
| | | 10 mg | 88 | 0.70 | 0.08 | 0.71 | 0.42 to 0.85 |
| | | 20/5 mg | 83 | 0.71 | 0.08 | 0.73 | 0.47 to 0.85 |
| | Lunar | All | 258 | 0.81 | 0.08 | 0.83 | 0.45 to 0.95 |
| | | Placebo/10 mg | 107 | 0.82 | 0.09 | 0.84 | 0.54 to 0.95 |
| | | 5 mg | 47 | 0.82 | 0.08 | 0.83 | 0.62 to 0.95 |
| | | 10 mg | 57 | 0.82 | 0.06 | 0.83 | 0.66 to 0.93 |
| | | 20/5 mg | 47 | 0.80 | 0.10 | 0.82 | 0.45 to 0.93 |

Table 11 (Cont.)

Summary of Baseline Clinical Efficacy Parameters
(Pooled 035/037)

| BMD Site | Densitometer | Alendronate Treatment | n | Mean | SD | Median | Range |
|---|---|---|---|---|---|---|---|
| Total Hip BMD (g/cm²) | Hologic/Norland | All | 410 | 0.69 | 0.09 | 0.70 | 0.42 to 1.00 |
| | | Placebo/10 mg | 155 | 0.71 | 0.09 | 0.72 | 0.42 to 1.00 |
| | | 5 mg | 87 | 0.69 | 0.10 | 0.69 | 0.43 to 0.92 |
| | | 10 mg | 84 | 0.68 | 0.10 | 0.67 | 0.50 to 0.96 |
| | | 20/5 mg | 84 | 0.69 | 0.09 | 0.69 | 0.43 to 0.91 |
| Trochanter BMD (g/cm²) | Hologic/Norland | All | 405 | 0.53 | 0.07 | 0.52 | 0.25 to 0.73 |
| | | Placebo/10 mg | 153 | 0.54 | 0.07 | 0.54 | 0.30 to 0.73 |
| | | 5 mg | 86 | 0.52 | 0.08 | 0.52 | 0.25 to 0.72 |
| | | 10 mg | 83 | 0.52 | 0.08 | 0.51 | 0.36 to 0.71 |
| | | 20/5 mg | 83 | 0.52 | 0.06 | 0.52 | 0.33 to 0.68 |
| | Lunar | All | 209 | 0.63 | 0.09 | 0.62 | 0.42 to 0.94 |
| | | Placebo/10 mg | 85 | 0.63 | 0.09 | 0.63 | 0.42 to 0.86 |
| | | 5 mg | 40 | 0.64 | 0.10 | 0.65 | 0.45 to 0.94 |
| | | 10 mg | 42 | 0.61 | 0.08 | 0.61 | 0.45 to 0.82 |
| | | 20/5 mg | 42 | 0.61 | 0.09 | 0.60 | 0.42 to 0.86 |

Table 11 (Cont.)

Summary of Baseline Clinical Efficacy Parameters
(Pooled 035/037)

| BMD Site | Densitometer | Alendronate Treatment | n | Mean | SD | Median | Range |
|---|---|---|---|---|---|---|---|
| One-third Forearm (Radius+Ulna) BMD (g/cm²) | Hologic/Norland | All | 367 | 0.54 | 0.07 | 0.54 | 0.35 to 0.75 |
| | | Placebo/10 mg | 138 | 0.55 | 0.07 | 0.55 | 0.36 to 0.75 |
| | | 5 mg | 78 | 0.54 | 0.08 | 0.53 | 0.35 to 0.75 |
| | | 10 mg | 76 | 0.53 | 0.06 | 0.53 | 0.40 to 0.68 |
| | | 20/5 mg | 75 | 0.53 | 0.08 | 0.53 | 0.35 to 0.66 |
| Total Body BMD (g/cm²) | Hologic/Norland | All | 241 | 0.92 | 0.07 | 0.93 | 0.68 to 1.14 |
| | | Placebo/10 mg | 83 | 0.94 | 0.06 | 0.93 | 0.77 to 1.14 |
| | | 5 mg | 55 | 0.91 | 0.09 | 0.92 | 0.68 to 1.11 |
| | | 10 mg | 54 | 0.93 | 0.07 | 0.92 | 0.80 to 1.12 |
| | | 20/5 mg | 49 | 0.91 | 0.07 | 0.91 | 0.75 to 1.06 |
| | Lunar | All | 207 | 0.95 | 0.07 | 0.96 | 0.73 to 1.15 |
| | | Placebo/10 mg | 85 | 0.96 | 0.07 | 0.96 | 0.73 to 1.09 |
| | | 5 mg | 36 | 0.97 | 0.08 | 0.96 | 0.82 to 1.12 |
| | | 10 mg | 45 | 0.94 | 0.07 | 0.96 | 0.81 to 1.11 |
| | | 20/5 mg | 41 | 0.94 | 0.08 | 0.95 | 0.74 to 1.15 |

Table 11 (Cont.)

Summary of Baseline Clinical Efficacy Parameters
(Pooled 035/037)

| BMD Site | Densitometer | Alendronate Treatment | n | Mean | SD | Median | Range |
|---|---|---|---|---|---|---|---|
| Ultra-Distal Forearm (Radius+Ulna) BMD (g/cm²) | Hologic/Norland | All | 367 | 0.31 | 0.05 | 0.31 | 0.12 to 0.45 |
| | | Placebo/10 mg | 138 | 0.32 | 0.05 | 0.32 | 0.12 to 0.45 |
| | | 5 mg | 78 | 0.31 | 0.06 | 0.31 | 0.18 to 0.44 |
| | | 10 mg | 76 | 0.30 | 0.05 | 0.31 | 0.21 to 0.42 |
| | | 20/5 mg | 75 | 0.30 | 0.05 | 0.30 | 0.17 to 0.39 |
| Ward's Triangle BMD (g/cm²) | Hologic/Norland | All | 405 | 0.42 | 0.09 | 0.42 | 0.12 to 0.81 |
| | | Placebo/10 mg | 153 | 0.43 | 0.09 | 0.43 | 0.20 to 0.81 |
| | | 5 mg | 86 | 0.41 | 0.09 | 0.41 | 0.12 to 0.67 |
| | | 10 mg | 82 | 0.40 | 0.08 | 0.38 | 0.25 to 0.60 |
| | | 20/5 mg | 84 | 0.42 | 0.08 | 0.42 | 0.24 to 0.60 |
| | Lunar | All | 209 | 0.60 | 0.11 | 0.59 | 0.25 to 0.92 |
| | | Placebo/10 mg | 85 | 0.60 | 0.10 | 0.58 | 0.40 to 0.90 |
| | | 5 mg | 40 | 0.63 | 0.11 | 0.64 | 0.39 to 0.83 |
| | | 10 mg | 42 | 0.58 | 0.10 | 0.56 | 0.42 to 0.92 |
| | | 20/5 mg | 42 | 0.57 | 0.11 | 0.56 | 0.25 to 0.81 |

Data Source: [4.37.5; 4.37.6]

Table 12

Summary of Month 36 Clinical Efficacy Parameters
(Pooled 035/037)

| BMD Site | Machine | Alendronate Treatment | n | Mean | SD | Median | Range |
|---|---|---|---|---|---|---|---|
| Femoral Neck BMD (g/cm²) | Hologic/Norland | All | 397 | 0.62 | 0.09 | 0.62 | 0.39 to 0.98 |
| | | Placebo/10 | 151 | 0.61 | 0.08 | 0.61 | 0.39 to 0.87 |
| | | 5 | 85 | 0.62 | 0.10 | 0.62 | 0.45 to 0.89 |
| | | 10 | 81 | 0.62 | 0.07 | 0.62 | 0.47 to 0.78 |
| | | 20/5 | 80 | 0.64 | 0.09 | 0.63 | 0.44 to 0.98 |
| | Lunar | All | 205 | 0.74 | 0.09 | 0.74 | 0.52 to 1.02 |
| | | Placebo/10 | 82 | 0.73 | 0.09 | 0.72 | 0.57 to 1.02 |
| | | 5 | 40 | 0.77 | 0.10 | 0.77 | 0.54 to 0.99 |
| | | 10 | 42 | 0.74 | 0.09 | 0.73 | 0.54 to 0.93 |
| | | 20/5 | 41 | 0.73 | 0.09 | 0.74 | 0.52 to 0.91 |
| Lumbar Spine BMD (g/cm²) | Hologic/Norland | All | 419 | 0.74 | 0.09 | 0.75 | 0.36 to 0.97 |
| | | Placebo/10 | 165 | 0.71 | 0.08 | 0.73 | 0.36 to 0.90 |
| | | 5 | 87 | 0.75 | 0.10 | 0.76 | 0.50 to 0.97 |
| | | 10 | 87 | 0.77 | 0.09 | 0.78 | 0.50 to 0.92 |
| | | 20/5 | 80 | 0.77 | 0.08 | 0.77 | 0.53 to 0.92 |
| | Lunar | All | 257 | 0.84 | 0.09 | 0.85 | 0.44 to 1.04 |
| | | Placebo/10 | 106 | 0.81 | 0.09 | 0.83 | 0.44 to 0.98 |
| | | 5 | 47 | 0.86 | 0.09 | 0.86 | 0.61 to 1.04 |
| | | 10 | 57 | 0.87 | 0.08 | 0.89 | 0.65 to 1.02 |
| | | 20/5 | 47 | 0.86 | 0.08 | 0.87 | 0.62 to 1.00 |

Table 12 (Cont.)

Summary of Month 36 Clinical Efficacy Parameters
(Pooled 035/037)

| BMD Site | Machine | Alendronate Treatment | n | Mean | SD | Median | Range |
|---|---|---|---|---|---|---|---|
| Trochanter BMD (g/cm²) | Hologic/Norland | All | 389 | 0.55 | 0.08 | 0.55 | 0.35 to 0.76 |
| | | Placebo/10 | 147 | 0.55 | 0.07 | 0.55 | 0.36 to 0.72 |
| | | 5 | 83 | 0.56 | 0.09 | 0.55 | 0.35 to 0.79 |
| | | 10 | 80 | 0.56 | 0.07 | 0.55 | 0.43 to 0.76 |
| | | 20/5 | 79 | 0.56 | 0.07 | 0.56 | 0.36 to 0.75 |
| | Lunar | All | 205 | 0.65 | 0.10 | 0.65 | 0.43 to 0.96 |
| | | Placebo/10 | 82 | 0.63 | 0.09 | 0.63 | 0.43 to 0.85 |
| | | 5 | 40 | 0.68 | 0.11 | 0.68 | 0.48 to 0.96 |
| | | 10 | 42 | 0.66 | 0.09 | 0.66 | 0.47 to 0.87 |
| | | 20/5 | 41 | 0.65 | 0.10 | 0.65 | 0.46 to 0.91 |
| Ultra-Distal Forearm (Radius+Ulna) BMD (g/cm²) | Hologic/Norland | All | 368 | 0.31 | 0.05 | 0.31 | 0.18 to 0.48 |
| | | Placebo/10 | 138 | 0.31 | 0.05 | 0.31 | 0.20 to 0.45 |
| | | 5 | 75 | 0.31 | 0.06 | 0.31 | 0.20 to 0.45 |
| | | 10 | 70 | 0.31 | 0.05 | 0.30 | 0.22 to 0.48 |
| | | 20/5 | 70 | 0.31 | 0.05 | 0.31 | 0.18 to 0.41 |
| Ward's Triangle BMD (g/cm²) | Hologic/Norland | All | 389 | 0.44 | 0.09 | 0.44 | 0.18 to 0.79 |
| | | Placebo/10 | 147 | 0.44 | 0.09 | 0.44 | 0.25 to 0.79 |
| | | 5 | 83 | 0.44 | 0.09 | 0.44 | 0.18 to 0.68 |
| | | 10 | 79 | 0.44 | 0.09 | 0.42 | 0.29 to 0.70 |
| | | 20/5 | 80 | 0.45 | 0.08 | 0.46 | 0.27 to 0.68 |

Table 12 (Cont.)

Summary of Month 36 Clinical Efficacy Parameters
(Pooled 035/037)

| BMD Site | Machine | Alendronate Treatment | n | Mean | SD | Median | Range |
|---|---|---|---|---|---|---|---|
| One-Third Forearm (Radius+Ulna) BMD (g/cm²) | Hologic/Norland | All | 348 | 0.54 | 0.07 | 0.54 | 0.34 to 0.77 |
| | | Placebo/10 | 135 | 0.54 | 0.07 | 0.54 | 0.39 to 0.76 |
| | | 5 | 75 | 0.54 | 0.08 | 0.54 | 0.36 to 0.77 |
| | | 10 | 70 | 0.54 | 0.06 | 0.54 | 0.40 to 0.67 |
| | | 20/5 | 70 | 0.53 | 0.07 | 0.54 | 0.34 to 0.66 |
| Total Body BMD (g/cm²) | Hologic/Norland | All | 225 | 0.93 | 0.07 | 0.94 | 0.71 to 1.14 |
| | | Placebo/10 | 78 | 0.93 | 0.06 | 0.94 | 0.78 to 1.11 |
| | | 5 | 49 | 0.92 | 0.09 | 0.93 | 0.71 to 1.11 |
| | | 10 | 49 | 0.95 | 0.07 | 0.95 | 0.81 to 1.14 |
| | | 20/5 | 49 | 0.93 | 0.08 | 0.95 | 0.75 to 1.08 |
| | Lunar | All | 189 | 0.93 | 0.07 | 0.96 | 0.73 to 1.15 |
| | | Placebo/10 | 79 | 0.94 | 0.07 | 0.94 | 0.73 to 1.08 |
| | | 5 | 31 | 0.96 | 0.07 | 0.97 | 0.83 to 1.10 |
| | | 10 | 41 | 0.96 | 0.06 | 0.97 | 0.85 to 1.11 |
| | | 20/5 | 38 | 0.96 | 0.08 | 0.96 | 0.76 to 1.15 |
| Total Hip BMD (g/cm²) | Hologic/Norland | All | 397 | 0.71 | 0.10 | 0.71 | 0.38 to 1.01 |
| | | Placebo/10 | 151 | 0.70 | 0.09 | 0.70 | 0.38 to 0.97 |
| | | 5 | 85 | 0.71 | 0.10 | 0.72 | 0.49 to 0.98 |
| | | 10 | 81 | 0.71 | 0.10 | 0.70 | 0.52 to 1.01 |
| | | 20/5 | 80 | 0.73 | 0.09 | 0.72 | 0.46 to 0.96 |

Table 12 (Cont.)

Summary of Month 36 Clinical Efficacy Parameters
(Pooled 035/037)

| BMD Site | Machine | Alendronate Treatment | n | Mean | SD | Median | Range |
|---|---|---|---|---|---|---|---|
| Ward's Triangle BMD (g/cm²) | Lunar | All | 205 | 0.60 | 0.11 | 0.59 | 0.30 to 0.96 |
| | | Placebo/10 | 82 | 0.59 | 0.10 | 0.57 | 0.37 to 0.96 |
| | | 5 | 40 | 0.64 | 0.12 | 0.63 | 0.38 to 0.87 |
| | | 10 | 42 | 0.60 | 0.10 | 0.61 | 0.45 to 0.91 |
| | | 20/5 | 41 | 0.58 | 0.11 | 0.58 | 0.30 to 0.79 |

Data Source: [4.37.5; 4.37.6]

Table 10. Analysis of change in Stature (mm) from baseline by protocol and pooled*

| Study 035 | N | Baseline | Month-36 | Month-60 | **Change from baseline** (LSD) | **Change from Month-36** (LSD) |
|---|---|---|---|---|---|---|
| Pbo/Aln10mg | 129 | 1601 | 1596 | 1594 | -6.72 (-7.35, -5.30) | -1.76 (-2.61, -0.42) |
| Aln5mg | 62 | 1593 | 1589 | 1587 | **-5.58** (-6.42, -3.50) | **-2.00** (-3.40, -0.27) |
| **Aln10mg** | 64 | 1600 | 1597 | 1595 | **-4.97** (-5.98, -3.12) | **-1.54** (-3.23, -0.16) |
| Aln20/5mg | 63 | 1605 | 1602 | 1600 | -5.08 (-6.63, -3.74) | -2.05 (-3.41, -0.32) |
| Study 037 | | | | | | |
| Pbo/Aln10mg | 146 | 1567 | 1563 | 1561 | -6.33 (-7.66, -4.99) | -2.38 (-3.90, -0.96) |
| Aln5mg | 67 | 1554 | 1553 | 1551 | **-2.79** (-4.74, -0.89) | **-1.47** (-3.49, 0.75)** |
| **Aln10mg** | 77 | 1563 | 1560 | 1556 | **-6.81** (-8.46, -4.88) | **-3.06** (-5.18, -1.24) |
| Aln20/5mg | 72 | 1569 | 1566 | 1565 | -3.88 (-5.70, -1.99) | -1.33 (-3.33, 0.74)** |
| Studies 035 & 037 | | | | | | |
| Pbo/Aln10mg | 275 | 1583 | 1579 | 1577 | -6.52 (-7.33, -5.63) | -2.09 (-2.79, -1.06) |
| Aln5mg | 129 | 1573 | 1570 | 1569 | **-4.13** (-5.24, -2.80) | **-1.72** (-2.91, -0.25) |
| Aln10mg | 141 | 1580 | 1576 | 1574 | **-5.97** (-7.09, -4.77) | **-2.37** (-3.74, -1.21) |
| Aln20/5mg | 135 | 1586 | 1583 | 1581 | -4.44 (-5.91, -3.53) | -1.67 (-2.80, -0.20) |

* extracted from sponsor Tables 48, 49, 4.18.2, 4.18.3, 4.18.6, 4.18.7; stature data from investigator #035002, #035005, #035018 and month-3 data from investigator #035013 was excluded.

** not significantly different from zero