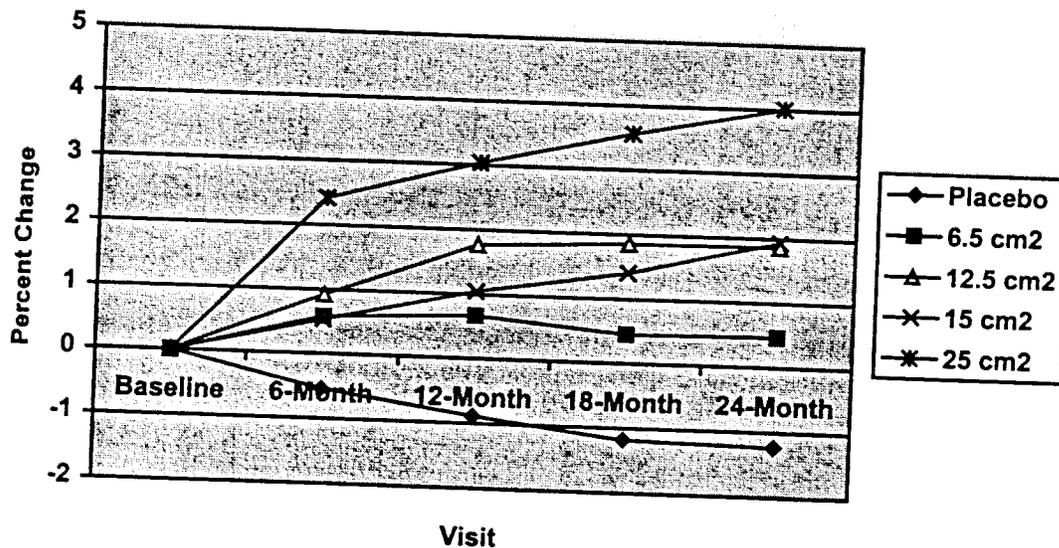


Table 9. ITT1 on Percent Change in BMD of Total Hip					
Mean Percent Change From Baseline in BMD (g/cm ²) of Total Hip by Treatment and Visit					
Treatment Group		6 months	12 months	18 months	24 months
Placebo	N/Mean	46/-0.54	46/-0.89	46/-1.18	46/-1.23
6.5 cm ²	N/Mean	32/0.58	32/0.67	32/0.45	32/0.47
	p-Value	0.010	0.001	0.008	0.009
12.5 cm ²	N/Mean	31/0.92	31/1.77	31/1.86	31/1.87
	p-Value	0.001	<0.0001	<0.0001	<0.0001
15 cm ²	N/Mean	31/0.53	31/1.05	31/1.41	31/1.94
	p-Value	0.016	<0.0001	<0.0001	<0.0001
25 cm ²	N/Mean	35/2.42	35/3.04	35/3.56	35/4.01
	p-Value	0.01	0.0002	<0.0001	<0.0001

P-values are for comparisons of each dose against placebo. All of the p-values remained significant after adjusting for multiple comparisons using the Hochberg method.

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Figure 6. ITT1: Mean Percent Change in BMD of Total Hip



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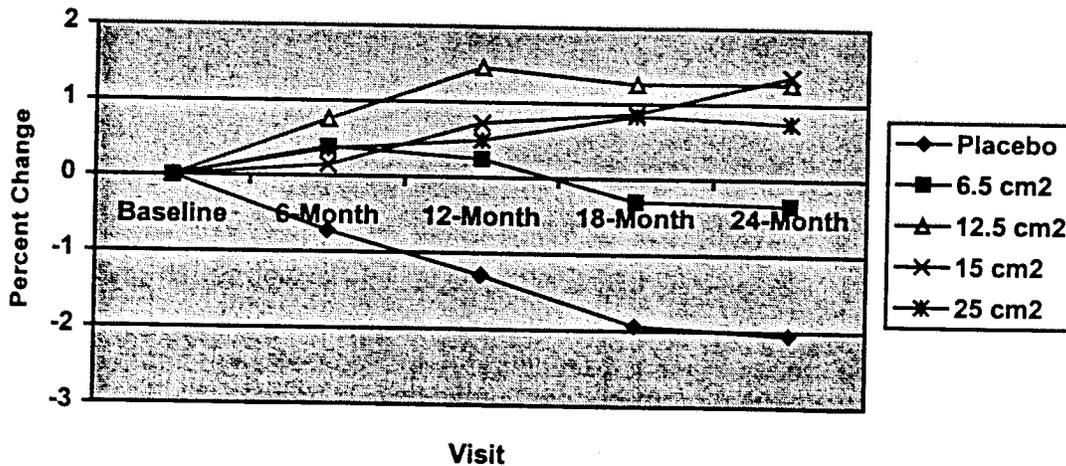
- Approach II (ITT2): dropouts, including those who dropped out before 6 months, were assumed to follow average placebo response.

Table 10. ITT2 on Percent Change in BMD of Total Hip					
Mean Percent Change From Baseline in BMD (g/cm ²) of Total Hip by Treatment and Visit					
Treatment Group		6 months	12 months	18 months	24 months
Placebo	N/Mean	46/-0.72	46/-1.29	46/-1.94	46/-2.05
6.5 cm ²	N/Mean	32/0.39	32/0.25	32/-0.30	32/-0.34
	p-Value	0.013	0.003	0.013	0.015
12.5 cm ²	N/Mean	31/0.76	31/1.46	31/1.26	31/1.27
	p-Value	0.0015	<0.0001	0.0001	<0.0001
15 cm ²	N/Mean	31/0.15	31/0.73	31/0.87	31/1.37
	p-Value	0.019	0.0002	<0.0001	<0.0001
25 cm ²	N/Mean	35/0.36	35/0.50	35/0.84	35/0.75
	p-Value	0.015	0.0004	<0.0001	<0.0001

P-values are for comparisons of each dose against placebo. All of the p-values remained significant after adjusting for multiple comparisons using the Hochberg method.

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Figure 7. ITT2: Mean Percent Change in BMD of Total Hip



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- Serum Osteocalcin

All groups showed significance at time points: 12, 18 and Endpoint.

At 6 months, no group was significantly different from placebo. At 24 months, 6.5 and 25 cm² were significant.

- Urinary deoxypyridinoline/creatinine ratio

Only 12.5 cm² showed significance at 6 months and Endpoint.

- Urinary pyridinoline/creatinine ratio

No significance.

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Conclusions

All analyses, including the sponsor's original analyses and two additional ITT analyses performed by this reviewer, suggest that the active treatment groups (6.5, 12.5, 15, and 25 cm²) were statistically significantly different from the placebo group in the primary efficacy endpoint, i.e., the percent change from the baseline in the BMD of the spine A-P view (L2-L4), at all time points: 6 months, 12 months, 18 months and 24 months. All active treatment groups showed improvement (i.e., positive percent changes from baseline) in the average BMD of the spine from 6 months to 24 months, while the placebo group showed negative percent changes during this time period. Furthermore, consistent evidence also indicated that the dose-response relationship for this variable primarily followed a linear trend at each time point.

The analyses on the secondary efficacy endpoints showed that all active treatment groups were statistically significantly different from the placebo group in the mean percent change in the BMD of the total hip at all time points. All active treatment groups showed improvements (i.e., positive percent changes from baseline) in the average BMD of the total hip from 6 months to 24 months, while the placebo group showed negative percent changes during this time period.

Another secondary efficacy endpoint, the percent change from baseline in serum osteocalcin, also showed statistical significance at 12 and 18 months and at endpoint.

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Z. Jonathan Ma, Ph.D.
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Archival: NDA 20-994

cc:

HFD-715/E. Nevius
HFD-510/R. Hedin
HFD-510/J. Zawadzki
HFD-510/G. Troendle
HFD-510/S. Sobel
HFD-715/T. Sahlroot
HFD-715/J. Ma
HFD-510/division file
HFD-715/division file

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Appendix: Interim Analysis

The original protocol stated that "An interim analysis will be done when about 60% of the targeted sample sizes in the placebo groups and the combined active dose groups complete 18 months of therapy." Later, on May 23, 1996, protocol amendment revised this statement as "An *administrative* interim analysis *without intent to stop the trial* will be done when about 50% of the targeted sample sizes in the placebo groups and the combined active dose groups complete 18 months of therapy." (The italicized words represent the changed parts.) Also, the significance level for each planned comparison at the interim analysis was reduced from 0.0035 to 0.0022.

As a result, the sponsor calculated the penalty of the significance level at this interim analysis as $0.0022 \times 4 = 0.0088$ (for four pairwise comparisons between active dose and placebo). Thus, the overall significance level used at the final stage was $0.05 - 0.0088 = 0.0412$. If the sponsor had not made this change, the final overall significance level would have been calculated as $0.05 - 0.0035 \times 4 = 0.036$.

Another major change in the amendment was the addition of BMD of Total Hip as one of the secondary endpoints.

The interim data was unblinded on July 20, 1996, which was about one month after the above protocol amendment was submitted. Results including tables and charts from the interim analysis was included in NDA, but no text report was submitted.

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Table A1. Sponsor's Interim Analysis on the Primary Efficacy Parameter						
Mean Percent Change From Baseline in BMD (g/ cm²) of Spine A-P View (L2-L4)						
by Treatment and Visit (Interim Analysis after 50% subjects completed 18 months)						
Treatment Group		6 months	12 months	18 months	24 months	Endpoint
Placebo	N/Mean	34/-0.8	22/-0.9	9/1.5	-/-	34/-1.0
6.5 cm ²	N/Mean	26/1.2	19/2.5	10/2.1	-/-	26/2.5
	p-Value	0.009	0.006	0.62	-	0.0004
12.5 cm ²	N/Mean	24/2.3	19/3.6	8/1.3	1/0.2	24/3.0
	p-Value	<0.0001	0.0002	0.77	-	<0.0001
15 cm ²	N/Mean	24/1.9	22/2.9	7/3.2	-/-	24/3.0
	p-Value	0.001	0.002	0.24	-	0.0002
25 cm ²	N/Mean	28/3.2	21/3.9	8/5.5	1/4.8	28/4.4
	p-Value	<0.0001	0.0001	0.01	-	<0.0001

P-values are for comparisons of each dose against placebo. For all four treatment groups, p-values at 12 months remained significant after adjusting for multiple comparisons using the Hochberg method.

References

Hochberg, Y. (1988). A sharper Bonferroni procedure for multiple tests of significance *Biometrika*, 75, 800-802.

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Statistical Analysis
For internal communications only
NDA 20-994, Climara, Berlex
Statistician: Jonathan Ma
Date: 1/20/99

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Interim Analysis

The original protocol stated that "An interim analysis will be done when about 60% of the targeted sample sizes in the placebo groups and the combined active dose groups complete 18 months of therapy." Later, on May 23, 1996, protocol amendment revised this statement as "An *administrative* interim analysis *without intent to stop the trial* will be done when about 50% of the targeted sample sizes in the placebo groups and the combined active dose groups complete 18 months of therapy." (The italicized words represent the changed parts.) Also, the significance level for each planned comparison at the interim analysis was reduced from 0.0035 to 0.0022.

As the result, the sponsor calculated the penalty of the significance level at this interim analysis as $0.0022 \times 4 = 0.0088$ (for four pairwise comparisons between active dose and placebo). Thus, the significance level used at the final stage was $0.05 - 0.0088 = 0.0412$. If the sponsor had not made this change, the final significance level would have been calculated as $0.05 - 0.0035 \times 4 = 0.036$.

Another major change in the amendment was the addition of BMD of Total Hip as one of the secondary endpoints.

The interim data was unblinded on July 20, 1996, which was about one month after the above protocol amendment was submitted. Results including tables and charts from the interim analysis was included in NDA, but no text report was submitted.

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Primary Efficacy Analyses

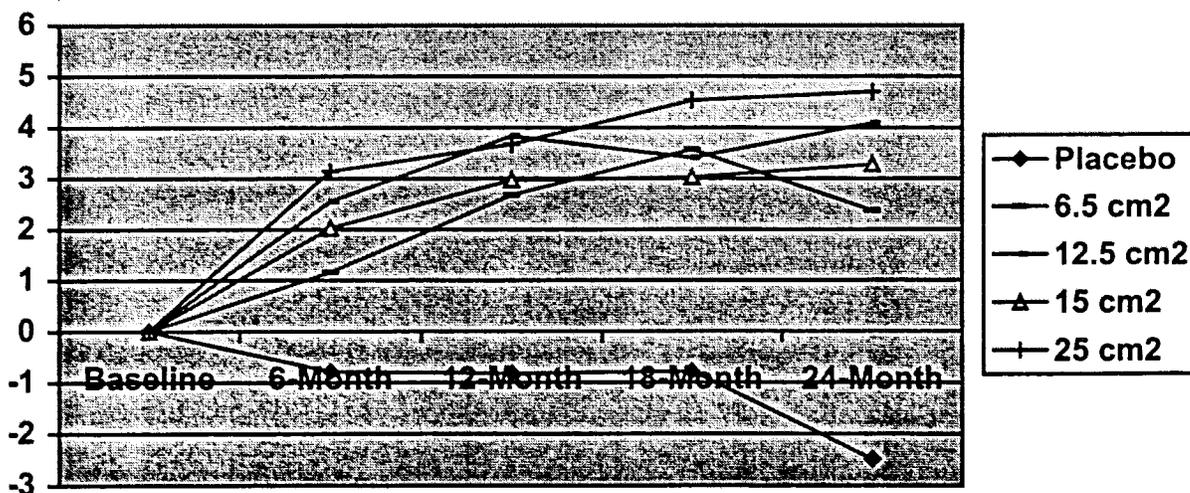
Primary efficacy parameter: Mean percent change from baseline in bone mineral density of spine A-P view (L2-L4)

1. Sponsor's Primary Efficacy Analysis (ITT: only include those who had 6-month observations.)

Mean Percent Change From Baseline in BMD (g/cm ²) of Spine A-P View (L2-L4) by Treatment and Visit (Sponsor's ITT Analysis)						
Treatment Group		6 months	12 months	18 months	24 months	Endpoint
Placebo	N/Mean	34/-0.78	26/-0.82	22/-0.78	21/-2.49	34/-2.33
6.5 cm ²	N/Mean	25/1.16	20/2.67	17/3.57	16/2.37	25/2.32
	p-Value	0.009	0.003	0.0009	0.0008	<0.0001
12.5	N/Mean	23/2.54	21/3.84	18/3.41	18/4.09	23/3.74
	p-Value	<0.0001	<0.0001	0.0001	<0.0001	<0.0001
15	N/Mean	24/2.02	24/2.97	22/3.02	20/3.28	25/3.45
	p-Value	0.0003	0.001	0.002	<0.0001	<0.0001
25	N/Mean	27/3.14	24/3.68	23/4.53	21/4.70	27/5.20
	p-Value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

P-values are for comparisons of each dose against placebo. All of the p-values remained significant after adjusting for multiple comparisons using the Hochberg method.

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Sponsor's Interim Analysis on the Primary Efficacy Variable

Mean Percent Change From Baseline in BMD (g/cm²) of Spine A-P View (L2-L4) by Treatment and Visit (Interim Analysis after 50% subjects completed 18 months)

Treatment Group		6 months	12 months	18 months	24 months	Endpoint
Placebo	N/Mean	34/-0.8	22/-0.9	9/1.5	-/-	34/-1.0
6.5 cm ²	N/Mean	26/1.2	19/2.5	10/2.1	-/-	26/2.5
	p-Value	0.009	0.006	0.62	-	0.0004
12.5	N/Mean	24/2.3	19/3.6	8/1.3	1/0.2	24/3.0
	p-Value	<0.0001	0.0002	0.77	-	<0.0001
15	N/Mean	24/1.9	22/2.9	7/3.2	-/-	24/3.0
	p-Value	0.001	0.002	0.24	-	0.0002
25	N/Mean	28/3.2	21/3.9	8/5.5	1/4.8	28/4.4
	p-Value	<0.0001	0.0001	0.01	-	<0.0001

P-values are for comparisons of each dose against placebo. For all four treatment groups, p-values at 12 months remained significant after adjusting for multiple comparisons using the Hochberg method.

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2. Revised Intent-to-treat Analysis

Under the request and instructions of this reviewer, the sponsor did a revised ITT analysis which included all randomized subjects.

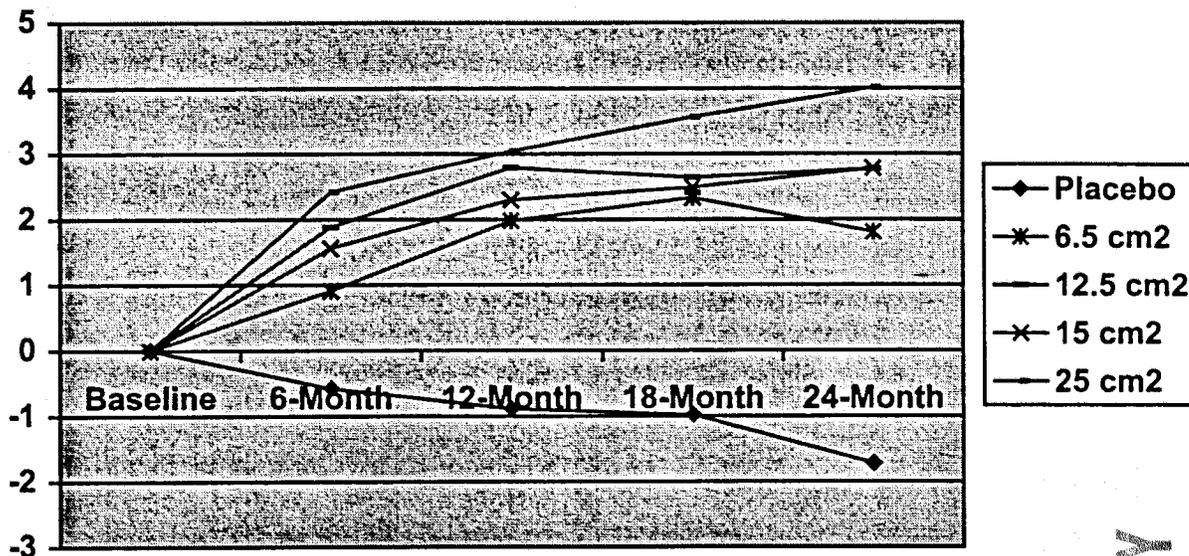
i) Approach I: Last Observation Carried Forward method was used to impute dropouts. For subjects who dropped out before 6 months, baseline values were used as the LOCF.

Mean Percent Change From Baseline in BMD (g/cm²) of Spine A-P View (L2-L4) by Treatment and Visit (Revised ITT Analysis, Approach I)

Treatment Group		6 months	12 months	18 months	24 months
Placebo	N/Mean	46/-0.58	46/-0.89	46/-0.98	46/-1.72
6.5 cm ²	N/Mean	32/0.91	32/1.98	32/2.33	32/1.81
	p-Value	0.020	0.0005	0.0002	0.0001
12.5 cm ²	N/Mean	31/1.88	31/2.79	31/2.64	31/2.77
	p-Value	<0.0001	<0.0001	0.0001	<0.0001
15 cm ²	N/Mean	31/1.56	31/2.30	31/2.49	31/2.78
	p-Value	0.0005	0.0001	<0.0001	<0.0001
25 cm ²	N/Mean	35/2.42	35/3.04	35/3.56	35/4.01
	p-Value	<0.0001	<0.0001	<0.0001	<0.0001

P-values are for comparisons of each dose against placebo. All of the p-values remained significant after adjusting for multiple comparisons using the Hochberg method.

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ii) Approach II: dropouts assumed to follow average placebo response.

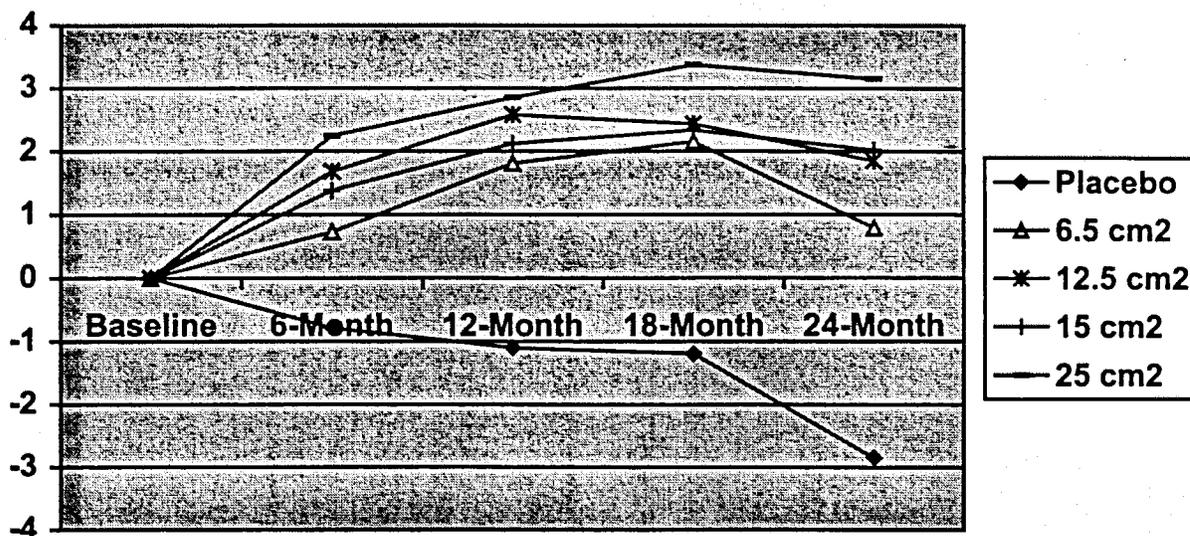
Mean Percent Change From Baseline in BMD (g/cm ²) of Spine A-P View (L2-L4) by Treatment and Visit (Revised ITT Analysis, Approach II)					
Treatment Group		6 months	12 months	18 months	24 months
Placebo	N/Mean	46/-0.79	46/-1.10	46/-1.19	46/-2.85
6.5 cm ²	N/Mean	32/0.73	32/1.81	32/2.15	32/0.79
	p-Value	0.02	0.0006	0.0002	0.0002
12.5 cm ²	N/Mean	31/1.68	31/2.58	31/2.43	31/1.85
	p-Value	<0.0001	<0.0001	0.0001	<0.0001
15 cm ²	N/Mean	31/1.38	31/2.12	31/2.33	31/2.02
	p-Value	0.0008	0.0002	<0.0001	<0.0001
25 cm ²	N/Mean	35/2.24	35/2.85	35/3.37	35/3.15
	p-Value	<0.0001	<0.0001	<0.0001	<0.0001

P-values are for comparisons of each dose against placebo. All of the p-values remained significant after adjusting for multiple comparisons using the Hochberg method.

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Secondary Analyses

P-values are for pairwise comparisons between each treatment group and placebo in terms of Mean Percent Change from Baseline.

- BMD of nondominant radius (midshaft)

Only the 25 cm2 group showed marginal significance at 18 and 24 months.

- BMD of femoral neck (same side as radius)

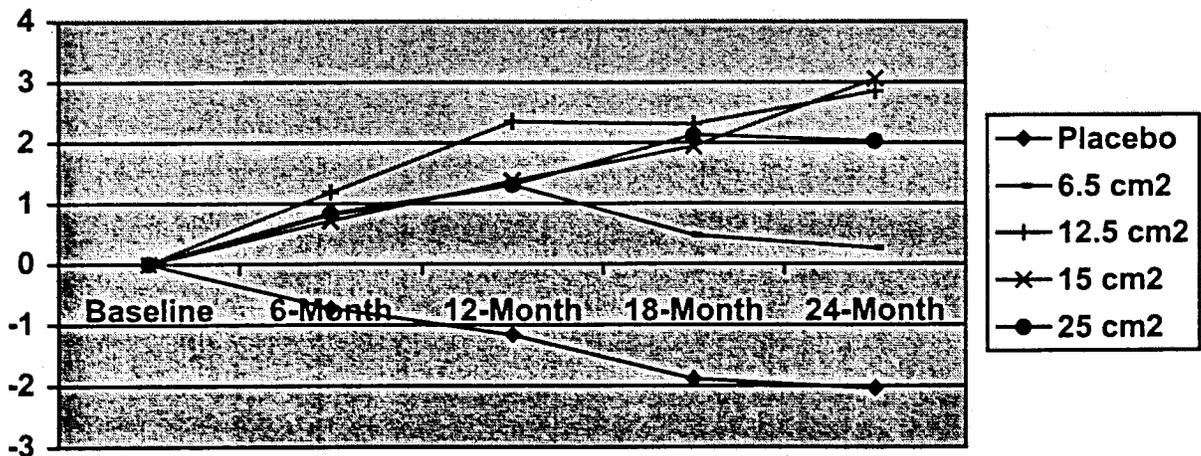
No group showed significance at any time points.

- BMD of the total hip

1. Sponsor's ITT Analysis

Mean Percent Change From Baseline in BMD (g/cm ²) of Total Hip by Treatment and Visit (Sponsor's ITT)						
Treatment Group		6 months	12 months	18 months	24 months	Endpoint
Placebo	N/Mean	34/-0.73	26/-1.17	22/-1.89	21/-2.04	34/-1.66
6.5 cm ²	N/Mean	23/0.81	18/1.31	16/0.47	14/0.26	23/0.65
	p-Value	0.014	0.001	0.011	0.020	0.004
12.5	N/Mean	24/1.19	22/2.35	18/2.31	18/2.85	24/2.41
	p-Value	0.002	<0.0001	<0.0001	<0.0001	<0.0001
15	N/Mean	23/0.71	22/1.38	21/1.94	20/3.05	23/2.61
	p-Value	0.018	0.0003	<0.0001	<0.0001	<0.0001
25	N/Mean	24/0.84	22/1.31	22/2.13	21/2.03	25/1.98
	p-Value	0.013	0.0003	<0.0001	<0.0001	<0.0001

P-values are for comparisons of each dose against placebo. All of the p-values remained significant after adjusting for multiple comparisons using the Hochberg method. All groups showed significance at all time points (6, 12, 18, 24 and Endpoint).



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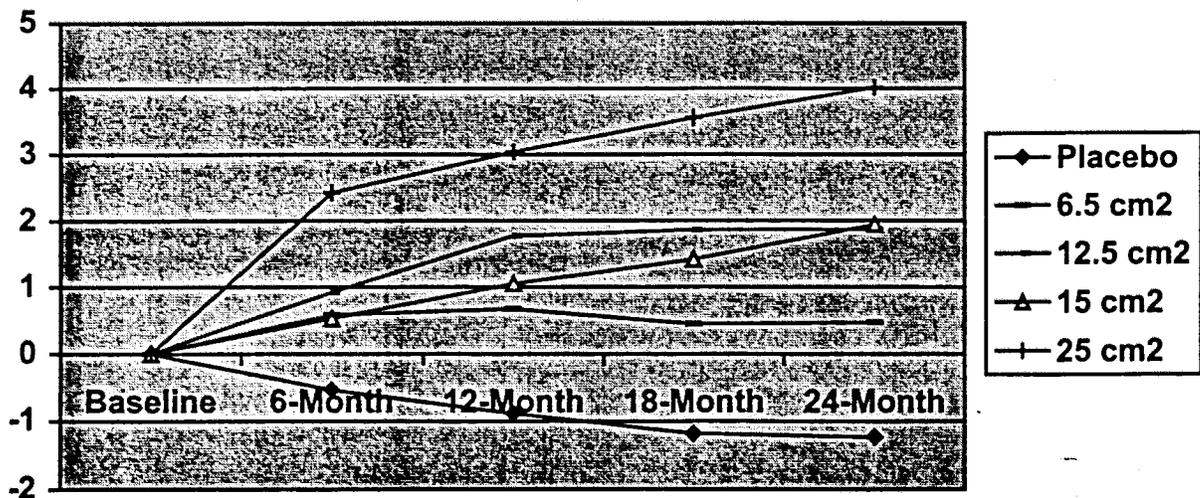
2. Revised Intent-to-treat Analysis

Under the request and instructions of this reviewer, the sponsor did a revised ITT analysis which included all randomized subjects.

i) Approach I: Last Observation Carried Forward method was used to impute dropouts. For subjects who dropped out before 6 months, baseline values were used as the LOCF.

Mean Percent Change From Baseline in BMD (g/cm ²) of Total Hip by Treatment and Visit (Revised ITT Analysis, Approach I)					
Treatment Group		6 months	12 months	18 months	24 months
Placebo	N/Mean	46/-0.54	46/-0.89	46/-1.18	46/-1.23
6.5 cm ²	N/Mean	32/0.58	32/0.67	32/0.45	32/0.47
	p-Value	0.010	0.001	0.008	0.009
12.5 cm ²	N/Mean	31/0.92	31/1.77	31/1.86	31/1.87
	p-Value	0.001	<0.0001	<0.0001	<0.0001
15 cm ²	N/Mean	31/0.53	31/1.05	31/1.41	31/1.94
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	p-Value	0.01	0.0002	<0.0001	<0.0001

P-values are for comparisons of each dose against placebo. All of the p-values remained significant after adjusting for multiple comparisons using the Hochberg method.

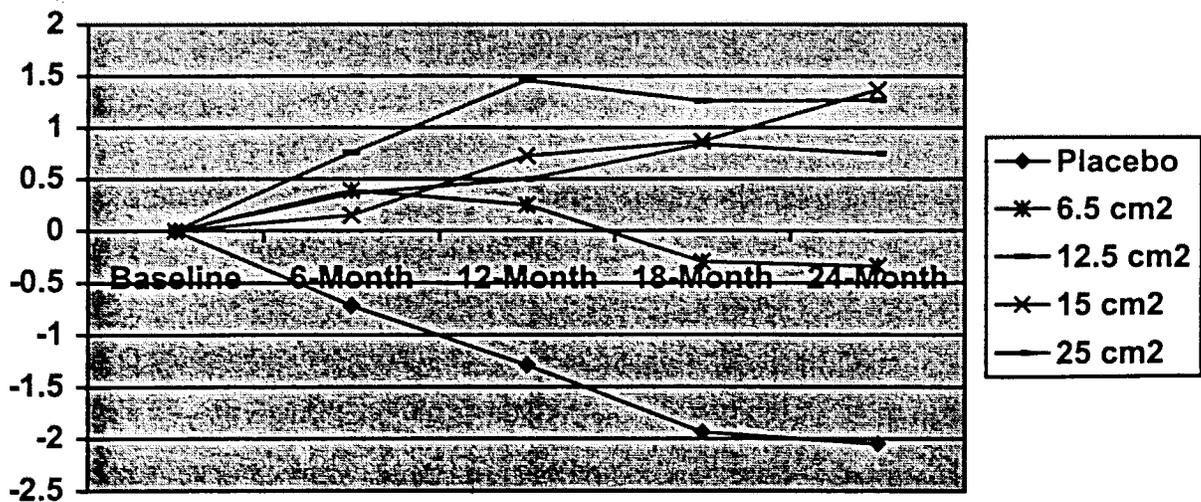


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ii) Approach II: dropouts assumed to follow average placebo response.

Mean Percent Change From Baseline in BMD (g/cm ²) of Total Hip by Treatment and Visit (Revised ITT Analysis, Approach II)					
Treatment Group		6 months	12 months	18 months	24 months
Placebo	N/Mean	46/-0.72	46/-1.29	46/-1.94	46/-2.05
6.5 cm ²	N/Mean	32/0.39	32/0.25	32/-0.30	32/-0.34
	p-Value	0.013	0.003	0.013	0.015
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	p-Value	0.0015	<0.0001	0.0001	<0.0001
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	p-Value	0.019	0.0002	<0.0001	<0.0001
25 cm ²	N/Mean	35/0.36	35/0.50	35/0.84	35/0.75
	p-Value	0.015	0.0004	<0.0001	<0.0001

P-values are for comparisons of each dose against placebo. All of the p-values remained significant after adjusting for multiple comparisons using the Hochberg method.



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- Serum osteocalcin

All groups showed significance at time points: 12, 18 and Endpoints.
At 6 months, no group was significant. At 24 months, 6.5 and 25 cm² were significant.

- Urinary deoxypyridinoline/creatinine ratio

Only 12.5 cm² showed significance at 6 months and Endpoint.

- Urinary pyridinoline/creatinine ratio

No significance.

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