

1 receive in a 20 microgram dose would do. In that
2 study, eight monkeys received this particular dose.
3 Seven of eight of those monkeys we were able to
4 reproduce the lesion, and one monkey did not develop
5 the lesion.

6 Of those seven monkeys that had the
7 lesions, six of these had no changes in renal function
8 as far as creatinine clearance, urinary concentrating
9 ability, urinary acidification ability.

10 One of those monkeys developed a sustained
11 hypercalcemia. Serum calcium pre-dose, not post dose,
12 but pre-dose serum calcium was up to 14 milligrams per
13 deciliter. That monkey did develop renal failure in
14 association with that hypercalcemia, and that monkey
15 after removal of teriparatide treatment and after the
16 hypercalcemia resolved, renal function returned and
17 the lesions were at least partially reversible.

18 Does that address the question?

19 And in addition, I didn't highlight those
20 are all findings from the toxicology model. Going
21 back, again, to the pharmacology study, this is a
22 study where monkeys were treated for up to 18 months,

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1 and there were 20 monkeys per group. So a more
2 robustly powered study, and we did not see any renal
3 alterations.

4 ACTING CHAIRPERSON MOLITCH: Just to
5 pursue this particular area, in the human studies was
6 urinary concentrating ability looked at?

7 DR. MITLAK: No. In the human studies, we
8 measured creatinine and creatinine clearance.
9 Concentrating ability was not measured.

10 ACTING CHAIRPERSON MOLITCH: I mean,
11 certainly in even the hypercalcemic states and
12 hyperparathyroidism, concentrating ability is probably
13 the earliest thing that's noted. Why wasn't that
14 looked for?

15 DR. MITLAK: What we found in the clinical
16 studies was that urinary calcium changed to a very
17 small degree. Urinary calcium, as was highlighted by
18 Dr. Gaich, changed on average by about 30 milligrams
19 per day.

20 We also saw no difference in the
21 proportion of patients with hypercalcaemia across the
22 treatment groups. So between those changes and the

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1 assessments that we made, we felt we had assessed
2 renal function. We did not measure concentrating
3 capacity.

4 ACTING CHAIRPERSON MOLITCH: And, again,
5 continuing with this line, the patients who were
6 treated with hydrochlorothiazide and furosemide at low
7 dose, plus the PTH, there was no particular change in
8 serum calcium that occurred in those patients; is that
9 correct?

10 You said there was no drug interaction.

11 DR. MITLAK: Dr. Gaich.

12 DR. GAICH: Yes, that is correct. Among
13 the patients treated with thiazide diuretics in our
14 Phase 3 study, we looked at the serum calcium
15 response, and it was similar.

16 In addition, we did a specific clinical
17 pharmacology study to specifically look at the
18 interaction on serum in urine calcium between
19 teriparatide and thiazide diuretics, and likewise
20 there is no interaction there.

21 ACTING CHAIRPERSON MOLITCH: Dr. Gelato.

22 DR. GELATO: Hi. This is just to follow

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1 through with this.

2 In going through your safety data, it was
3 noted that there were a small number of patients who
4 had calciums that exceeded 11, and so what I wasn't
5 clear about was did that -- was that also a transient
6 elevation or did it persist?

7 And were they the same patients who had
8 increases in urinary calcium excretion?

9 And there was a subset, I think that
10 continued with impairment or at least elevated serum
11 creatinines, and I wondered if there was a link
12 between those findings of the elevated calcium,
13 urinary calcium in the creatinine to sort of get at
14 some of these issues.

15 DR. MITLAK: Let me invite Dr. Gaich back
16 to address those questions for you.

17 DR. GAICH: Thank you.

18 Let me start from the bottom and work my
19 way up.

20 First, we did look for a relationship
21 between the increase in serum calcium and effects on
22 serum creatinine or creatinine clearance, and we did

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1 not find one.

2 Second, all of the calcemic effects that
3 were observed were transient. So even the patients
4 that had the highest serum calciums, the baseline
5 serum or the pre-dose serum calcium is back down to
6 normal.

7 And finally -- what was your third
8 question?

9 DR. GELATO: Was there a relationship to
10 those patients because --

11 DR. GAICH: Between serum calcium and
12 urine calcium?

13 DR. GELATO: And the elevation of serum
14 creatinine.

15 DR. GAICH: Okay. There was not a
16 relationship between -- a strong relationship --
17 between the patients who had high serum calcium and
18 high urine calcium, nor was there any relationship
19 between the patients who had high serum calcium
20 transiently and an increase in serum creatinine.

21 DR. TAMBORLANE: Again, on the same, just
22 even from that individual animal experiment, the case,

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1 it seemed to me I was hearing the suggestion that
2 serum calcium did not have to be monitored during
3 therapy, and maybe under the normal circumstances, but
4 it's likely that patients with hyperparathyroidism
5 might be exposed to the drug, and there's very limited
6 data.

7 Is that your continued suggestion that
8 calcium not be monitored?

9 DR. MITLAK: Let me invite Dr. Gaich again
10 to help address this question.

11 What we are suggesting and what we have
12 observed in the clinical studies is that the
13 incremental change in serum calcium in patients seemed
14 to be independent of the baseline serum calcium, that
15 is, whether somebody is in the low, mid, or upper part
16 of the range, the increment in calcium was fairly
17 consistent with the dosing.

18 Therefore, we recommend that high calcium,
19 hypercalcemia be excluded before patients are
20 considered for treatment, and once that has happened,
21 we found based on the clinical trial results that that
22 is a reasonable course of action.

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1 Let me see if Dr. Gaich has --

2 DR. GAICH: Thank you.

3 Could we look at slide 4455?

4 We actually did look at a number of
5 factors to determine if there were any particular
6 characteristics of patients who would have higher
7 responses of serum calcium, and I will show you what
8 we evaluated.

9 I'm sorry. I need 4455. We need to go
10 one back. There we go.

11 We looked at the relationship between the
12 highest post dose serum calcium and baseline serum
13 calcium, baseline serum, 25 hydroxy Vitamin D, the
14 body mass index, the baseline intact parathyroid
15 hormone 1 to 84, and age.

16 Now if we can go to 4456, please.

17 The only significant relationship or
18 strongly significant relationship was the relationship
19 between baseline serum calcium and the highest post
20 baseline. The correlation coefficient was .45, which
21 was highly statistically significant, and as you can
22 see, based on the graph, the higher the baseline serum

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1 calcium, the higher your post baseline serum calcium.

2 And this was the only strong predictor of
3 baseline -- of post baseline serum calcium.

4 As Dr. Mitlak also mentioned, we also
5 looked at the relationship between baseline serum
6 calcium and the change in serum calcium, and there was
7 not a positive relationship.

8 So patients who started with high baseline
9 serum calciums did not have an exaggerated response.

10 May I have the next slide, please, 4457?

11 Among the other things, there were some
12 weak negative and weak positive correlations. There
13 was a weak positive correlation with 25 hydroxy
14 Vitamin D, the correlation coefficient of .13.

15 Weak negative correlations of particular
16 interest to your question is there was a negative
17 correlation between baseline intact parathyroid
18 hormone and the highest post baseline serum calcium.
19 So patients who started with higher intact PTH at
20 baseline tended to have lower post baseline serum
21 calciums.

22 Nevertheless, we do believe that patients

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1 with hypercalcemia should not be treated with
2 teriparatide.

3 DR. KREISBERG: I have two questions.
4 One is other than a reduction in pain, do you have any
5 other quality of life indicators about these patients?
6 Did they generally feel better, worse or the same?

7 The reason I ask is that in primary
8 hyperparathyroidism, which I'm not suggesting this is
9 comparable to, there are neuropathic and muscular
10 types of symptoms that patients have other than just
11 cramps.

12 DR. MITLAK: Based on assessment of
13 adverse events, those sorts of symptoms were not seen.

14 DR. KREISBERG: Okay. The other question
15 actually relates to the longest duration of therapy
16 that patients have received teriparatide, and I
17 believe in one of Dr. Lindsay's slides, it was up to
18 36 months.

19 Based upon the change in the markers of
20 bone formation and bone resorption, one would predict
21 eventually that that would come into balance and the
22 bone density would plateau. So one of the question

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1 is: is that true?

2 And then a follow-up question is: how
3 long would you intend to use teriparatide for the
4 treatment of osteoporosis? Do you see that as an
5 indefinite exposure to the hormone?

6 Because I think that gets to the issue
7 that is troubling everybody, and that is longer term
8 exposure might, in fact, bring out some side effects
9 that haven't been brought out by short term exposure.

10 DR. MITLAK: Let me answer in part, and
11 then invite Dr. Lindsay up to comment on part of your
12 question.

13 As I laid out in my final comments, I
14 think based on the available data and to maximize the
15 benefit-risk for patients, we would propose to limit
16 duration of treatment for two years until further
17 information is available to help us.

18 DR. LINDSAY: We have treated people for
19 up to three years with parathyroid hormone 1 to 34,
20 and in those studies, the bone mass changes continue
21 for the three years of the study.

22 We subsequently followed those patients

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1 still remaining on hormone replacement therapy, and
2 their bone density plateau has remained stable.

3 During the third year of treatment, it's
4 interesting that the biochemical markers of formation
5 and resorption are returning back to baseline, despite
6 continued treatment with parathyroid hormone, and we
7 think that the increase in bone density that you see
8 during the third year is the phase of secondary
9 mineralization that would follow the synthesis of
10 newborn matrix.

11 And I would agree with you that longer
12 term use is probably going to be associated with a
13 plateauing. We just don't have data out beyond that
14 three years.

15 ACTING CHAIRPERSON MOLITCH: Dr. Lindsay,
16 while you're still there, you cited the well known
17 data that there's an increase in mortality associated
18 with fracture. I don't think you meant to imply that
19 there are any studies that show the intervention to
20 increase bone mineral density with perhaps decreased
21 fracture as might decrease mortality rates.

22 DR. LINDSAY: No, I did not show data

1 about that.

2 ACTING CHAIRPERSON MOLITCH: Thank you.

3 Dr. Schneider, do you have one?

4 DR. SCHNEIDER: I had one small, beginning
5 technical question. Could you just tell us the
6 multiple comparisons procedure that you used to adjust
7 your p values, given that you were looking at two
8 active doses?

9 I couldn't find that in my briefing
10 document.

11 DR. MITLAK: Dr. Wang, would you please
12 come to the microphone?

13 DR. WANG: My name is Ouhong Wang. I'm
14 the statistician on the teriparatide product team.

15 To answer your question, the study was
16 designed to control for the primary efficacy variable
17 at the .05 level. For the secondary comparisons,
18 everything is reported at the nominal .05 level. It's
19 not adjusted.

20 But, in essence, the protocol is designed
21 in a way that we wouldn't report any secondary
22 efficacy results if the primary efficacy result is not

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1 significant. So it is kind of a gatekeeper strategy.

2 DR. SCHNEIDER: I'm sorry. Could you say
3 again something about the primary efficacy variable?
4 How did you handle multiple comparisons on that?

5 DR. WANG: The primary efficacy actually
6 is the combined -- well, when you look at the
7 particle, it is the combined teriparatide doses, 20
8 and 40 microgram groups compared with placebo. So
9 that's the primary, and to separate the doses we will
10 also look at the separate doses versus placebo.

11 DR. SCHNEIDER: Thank you.

12 The second question I had is in GHAJ the
13 primary efficacy variable was noted as a change in
14 lumbar bone mass density, and you presented the
15 percent change and later indicated that the change was
16 independent of baseline.

17 Do you have data or analysis on just the
18 change from baseline in lumbar BMD?

19 DR. MITLAK: Let me ask our group if we
20 have the slide.

21 I can tell you that the analysis of change
22 rather than percent change was identical. The

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1 statistical inferences were identical, except for that
2 the change at the total hip, which was not significant
3 by percent change was significant for actual change.

4 DR. SCHNEIDER: And the final question I
5 had was in the AC study, did you look at BMI or
6 weight, the effect of that as a covariant in either
7 the adverse experiences or the efficacy variables?
8 And what level of effect did it have?

9 DR. MITLAK: Let me invite our
10 pharmacokineticist, Dr. Satterwhite, to come to the
11 microphone to address your questions.

12 DR. SATTERWHITE: My name is Julie
13 Satterwhite. I am a senior research scientist at
14 Lilly, and I was responsible for the pharmacokinetic
15 and pharmacodynamic analyses.

16 For the pharmacodynamics we looked at --
17 in terms of efficacy, we looked at the biochemical
18 markers and BMD response. We did evaluate body mass
19 index and weight and found that neither one of them
20 was a significant covariant governing response.

21 DR. KREISBERG: This was GHAC.

22 DR. SATTERWHITE: Yes. We saw that in

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1 both AC and AJ, and it was not a significant
2 covariant.

3 DR. KREISBERG: Do you remember what the
4 slope was? Was it positive, negative? In fact, the
5 correlation, even though it wasn't significant?

6 DR. SATTERWHITE: I can get that answer
7 for you.

8 DR. KREISBERG: Thank you.

9 DR. GRADY: I'd like to ask about calcium
10 intake. In this study it was recommended that women
11 take, I think, a gram of calcium per day, and I think
12 one of the things we've perhaps been fairly successful
13 at is getting most post menopausal women to take
14 calcium supplementation.

15 I wonder if you adjusted calcium
16 supplementation during the study and also if you
17 planned to recommend calcium supplementation in
18 addition to the drug during treatment.

19 DR. MITLAK: Let me invite Dr. Gaich up
20 also while I tell you that the mean intake at baseline
21 in the women was in the range of seven to 800
22 milligrams per day so that a 1,000 milligram

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1 supplement resulted in a total of approximately 1,700
2 to 1,800 milligrams of calcium.

3 We expect that going forward, that
4 patients who receive treatment would take calcium
5 supplements. We would recommend that their calcium
6 total intake be adjusted to that recommended for
7 patients with post menopausal osteoporosis or
8 osteoporosis in men.

9 I might ask Dr. Gaich to help comment on
10 any dose adjustments that have occurred in the study.

11 DR. GAICH: Okay. Thank you.

12 First of all, a flat dose of 1,000
13 milligrams a day was prescribed for all of the
14 patients, was recommended for all of the patients. So
15 we did not adjust based on dietary intake to bring up
16 to some level, and again, we think that's fairly more
17 typical of the clinical practice than doing an
18 extensive dietary survey and doing an adjustment.

19 The physicians were allowed to change
20 calcium supplements to or to adjust calcium
21 supplements based on side effects, especially GI side
22 effects with some supplements, and also if the

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1 patients had transient increases in serum calcium or
2 urine calcium, which was documented on repeated
3 measurements.

4 And the number of patients who underwent
5 adjustments in the calcium supplements was fairly
6 small.

7 DR. GRADY: What does "fairly small" mean?
8 And was it the same in the two groups?

9 DR. GAICH: I'm sorry. The question was
10 what was fairly small and was it the same in the two
11 groups?

12 Yeah, first of all, let's see. If I can
13 have slide 3373.

14 This slide will show the incidence of the
15 number of patients who had one and more than one
16 increase in serum calcium, as well as the number of
17 patients that had adjustments in calcium or study
18 drug.

19 And this is the line that we're looking
20 at. Among the patients that had an increase in serum
21 calcium, 7.2 percent or 7.2 percent of the patients
22 had a decrease in their calcium intake as a result of

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1 a transient increase in the serum calcium. So that's
2 what I mean by "fairly small." It was lower in the
3 placebo group, and because there were more patients
4 with transient increases in serum calcium in the high
5 dose group, there were more in the high dose group.

6 Thank you.

7 DR. GRADY: I'd also like to ask about
8 uric acid. You know, I know you kind of sort of
9 mentioned, but could you just tell me the percentage
10 of participants who had elevated uric acid in the two
11 groups? Because it does seem that that also is a
12 persistent problem.

13 DR. GAICH: Yes, the increases in uric
14 acid were similar to the order seen by other things,
15 such as thiazides and aspirin therapy, things along
16 those lines.

17 The number of patients with increased uric
18 acid in the 20 microgram group was 2.8 percent, in the
19 40 microgram group was five percent.

20 By study endpoint and six months follow-
21 up, the serum uric acid concentrations were very
22 nearly back down to baseline. The difference between

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1 placebo and the treatment groups was less than two
2 percent, even though that was still statistically
3 significant.

4 And at that time, there was no difference
5 in the number of patients with high uric acid
6 concentrations.

7 DR. GRADY: What did you define as high?

8 DR. GAICH: The upper limit of normal was
9 -- let's see. If we can have my main slide.

10 DR. GRADY: I really just want to know the
11 percent or proportion above whatever you defined as
12 high in the two groups.

13 DR. GAICH: Correct. My main slide 83.

14 It has that on there. I just want to make
15 sure I give you the right number. Yes, it was 9.0
16 milligrams per deciliter, and the reference ranges are
17 based on a large database, over 20,000 clinical trial
18 patients and are adjusted for age and gender as well
19 where appropriate.

20 DR. BONE: Thank you.

21 I have a series of questions as well, and
22 I'll just continue, if I may, with Dr. Grady's line of

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1 questions about the uric acid.

2 There's two issues here. I think one is
3 the number of patients who exceed the fairly high
4 upper limit that you used, and the other is, you know,
5 how the sort of overall curve shifts for "uric
6 acidemia," if I can put it that way.

7 Did you get an idea of the interactive
8 risk of hyper uric acidemia in patients taking other
9 concomitant medications, such thiazides, or any other
10 risk factors for the development of either an overtly
11 elevated uric acid level or an increase in the uric
12 acid level of, let's say, two milligrams per deciliter
13 or so?

14 DR. GAICH: The data that we looked at is
15 we looked at all of the data, including concomitant
16 medications, adverse events, laboratory effects for
17 all the patients that had an increase in the serum
18 uric acid above the upper limit of normal, and in that
19 group there were not patients who -- a lot of patients
20 who were on thiazides. There weren't enough patients
21 who had high uric acid and who had thiazides in our
22 study for us to do a meaningful kind of analysis

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1 looking for the interaction.

2 DR. BONE: We may come back to that
3 question later. Let me ask you some questions about
4 the Vitamin D status of the patients. Obviously the
5 Vitamin D status of patients who would potentially
6 take this medication is of considerable concern
7 because if we accelerate bone turnover at the same
8 time as having insufficient Vitamin D, we may induce
9 a mineralization defect that might not have been
10 apparent in the clinical trials.

11 Can you tell us what the baseline 25
12 hydroxy Vitamin D status was for your patients and
13 also what was the effect on 125 dihydroxy Vitamin D
14 levels in the patients in the treatment groups?

15 DR. MITLAK: Let me ask Dr. Gaich to come
16 to the microphone again.

17 Let me also first show you the slide to
18 answer your second question, which is the 125
19 dihydroxy Vitamin D change during treatment for the
20 three groups.

21 It's slide 4260.

22 What this panel shows is measurement of

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1 125 Vitamin D over the first year of the study, and it
2 shows that with treatment, 125 Vitamin D levels
3 increase.

4 In combination with this, we actually see
5 a slight decrease in 25 Vitamin D levels, which we
6 presume is part of the conversion process.

7 And now if I could ask Dr. Gaich to answer
8 the first part of your question.

9 DR. GAICH: Thank you.

10 All the patients in our clinical trials
11 required to have a 25 hydroxy Vitamin D above the
12 upper limit of normal. Some of them at screening were
13 below the upper limit of normal, but then came into
14 the normal range with supplementation.

15 DR. BONE: I think you misspoke.

16 DR. GAICH: I'm sorry.

17 DR. BONE: You said that all of the
18 patients had to be above the upper limit of normal?

19 DR. GAICH: I'm sorry.

20 DR. BONE: I'm sure you didn't mean that.

21 DR. GAICH: Had to be above the lower
22 limit of normal. Thank you.

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1 DR. BONE: Meaning what?

2 DR. GAICH: We used the standard
3 laboratory reference range, and I'd have to look that
4 up for you.

5 DR. BONE: Well, as you know, most of the
6 standard laboratory reference ranges are considered to
7 be -- in most of the standard laboratory reference
8 ranges what is presented as the lower limit of the
9 reference range is widely regarded by clinicians in
10 this field as consistent with Vitamin D insufficiency.

11 So I think it's a specific question we'd
12 like a specific answer to as to what the distribution
13 of 25 hydroxy Vitamin D levels actually was in the
14 trial, and we may want to give some further thought to
15 whether we can really account -- I think in the
16 briefing document you said there was about a 25
17 percent decrease in mean 25 hydroxy Vitamin D levels,
18 and this was explained or supposedly explained by the
19 conversion to 125 dihydroxy Vitamin D, but since the
20 ratio of the actual mass of 25 hydroxy to 125
21 dihydroxy Vitamin D is a ration of nanograms to
22 picograms, I think that we will have to invoke some

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1 additional explanation for that phenomenon, and
2 perhaps you will be able to comment on that after
3 lunch.

4 One or two additional questions. One of
5 the striking findings in your results was the failure
6 to protect height. The usual result in trials where
7 there's a substantial reduction in the rate of
8 vertebral fracture, such as you have very nicely
9 described, is that there is also a measurable
10 difference between the height loss in the treatment
11 groups and the height loss in the placebo groups.

12 And I'm wondering what you've done to try
13 to identify a basis for that phenomenon. For example,
14 since you have the radiographs, was an attempt made to
15 assess the effect on actual vertebral heights to
16 determine whether the height loss in the patients in
17 the different groups could be explained in that way?
18 Did people look at disk spaces? What was done to try
19 to figure out why there was a discrepancy between your
20 very impressive reduction in fracture rate and the
21 lack of any apparent effect on height?

22 DR. MITLAK: We actually don't think that

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1 there is a discrepancy. I think because height
2 changes likely occur in patients with fractures, and
3 most patients in the treatment groups did not have
4 fractures, it was not surprising to us that we didn't
5 see overall differences.

6 But to answer your question about what we
7 did to try and address this, let me ask for slide
8 4246.

9 What we did in this analysis is to take
10 all of the patients in the study regardless of
11 treatment assignment and stratify them by the most
12 severe fracture grade. In other words, we took
13 patients who did not have a fracture, those who had a
14 mild fracture, a moderate fracture, or a severe
15 fracture, and based on these grades looked at change
16 in height.

17 And just as you might expect, patients
18 with more severe type of fractures actually did lose
19 height. We believe, again, because most patients did
20 not have fractures in this study that it was not
21 possible to see this effect if we looked at all of the
22 patients together.

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1 DR. KREISBERG: Did you use a stadiometer
2 to measure height? How did you measure height in this
3 study?

4 DR. MITLAK: Yes, stadiometers were used.

5 DR. BONE: To continue, one of the
6 questions that we're concerned with is the duration of
7 treatment, and it's clear from your data that most of
8 the increase in height occurs in the first year or --
9 excuse me -- most of the increase in bone density
10 occurs in the first year on treatment with a smaller,
11 much smaller increase in the second year, and
12 Professor Lindsay has described the phenomenon in the
13 third year of increased density despite declining
14 turnover.

15 This suggests that somewhere between the
16 end of the first year and the end of the second year
17 you start having more of a phenomenon of filling holes
18 than you do of actually laying down more matrix.

19 Some of your patients completed about two
20 years on treatment, and many only completed about a
21 year. Did you look at what happened to -- since we
22 know that there was not much of an increase in the

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1 second year in bone density compared with that in the
2 first year, an interesting question is what happened
3 to the relative risk of fracture in the patients whose
4 second year of observation was off drug compared with
5 those whose second year of observation was on drug.

6 In other words, was there a protective
7 effect of being on drug in the second year or was the
8 protective effect against fracture mostly carried over
9 from the main gain in bone mass in the first year?

10 DR. MITLAK: There's several parts to that
11 question. Let me try and address them, and then I'm
12 going to invite Dr. Neer up to make a comment also.

13 I think that as we look at the data from
14 these studies, we certainly agree that the rate of
15 change in bone density in the spine becomes less over
16 time.

17 However, and I think importantly, if we
18 look at the rate of change in bone density at the hip
19 or the total body, it's more of a linear change, and
20 that is that patients do have proportionate increases
21 in those two important measurements over time.

22 I think to your question about looking at

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1 fracture risk at an earlier time point or for those
2 who were treated for a shorter amount of time, we
3 cannot do that in this study for spine fractures
4 because spine fractures were only assessed by
5 baseline and endpoint radiographs.

6 We can do it for nonvertebral fractures,
7 and I think the data show that for the fractures that
8 we track, that after nine months there was a
9 progressive reduction in the risk of fractures, and
10 that as we followed patients out off of treatment, the
11 risk of fracture did not increase, and I think that's
12 the answer that I have.

13 And let me ask if Dr. Neer would like to
14 comment further.

15 DR. NEER: I'd like to make a comment.
16 I'm Robert Neer. I was involves in helping to design
17 and conduct the trial GHAC.

18 I'd like to make a comment in response to
19 Dr. Bone's question about height. Approximately 14 or
20 15 percent of the women in the study GHAC had a
21 fracture. That means that 85 percent did not, and as
22 in prior trials of, for example, alendronate, it is

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1 very difficult to demonstrate effects on height if
2 one dilutes the therapeutic effect by including large
3 numbers of people who don't have an adverse endpoint.

4 So, for example, as in trials of
5 alendronate, if one analyzes the entire patient
6 population, there's no change in height as a
7 consequence of treatment. That is, treatment doesn't
8 protect against height loss.

9 But as with alendronate, if one restricts
10 the analysis to people who had an incident fracture,
11 then there's a very clear effect on protecting against
12 height loss. The treatment in those patients is
13 clearly associated with less height loss.

14 As we reported in the paper in the New
15 England Journal of Medicine, there was a statistically
16 significant height loss in women in GHAC in the
17 placebo treatment group, but there was no
18 statistically significant height loss in either of the
19 PTH treatment groups, and the difference between the
20 PTH treatment groups and the placebo group was also
21 statistically significant.

22 So it depends upon trying -- if you want

1 to see an effect on height loss in studies of such
2 patient populations regardless of the drug being
3 evaluated, you need to restrict the analysis to people
4 who had had a new incident fracture.

5 DR. BONE: I expect you have the data to
6 answer the question I posed a little more
7 specifically, but I'm not sure you conducted the
8 analysis, and that was to look at the patients who
9 completed one year on therapy, and then you followed
10 this out.

11 You said you had the nonvertebral fracture
12 data because those are spontaneous reports of clinical
13 fractures. You didn't do vertebral height measurement
14 or didn't do spine films after the interruption of the
15 trial?

16 DR. MITLAK: Yes, we did. We did.

17 DR. BONE: Well, if you have the films --

18 DR. MITLAK: Yes.

19 DR. BONE: -- for the spine films, then
20 I'm not completely clear why you can't look at
21 incident vertebral fractures in the group that got a
22 year of treatment and then were followed compared with

1 the group that got two years of treatment.

2 Maybe I'm missing something here.

3 DR. MITLAK: Let me try and answer again.

4 What we have done is to collect
5 radiographs in the follow-up phase after all of the
6 patients had discontinued treatment with drug. I do
7 not have data to show you for patients who may have
8 discontinued treatment during the study and then were
9 followed in the study to the endpoint visit.

10 If you wish, I can show you the data that
11 we had collected systematically after all of the
12 patients had been asked to stop treatment, if that
13 would address your question.

14 DR. BONE: Well, that's what I'm talking
15 about.

16 DR. MITLAK: I'm sorry. then I
17 misunderstood.

18 DR. BONE: Do you have the patients -- if
19 I'm not mistaken, you have patients who completed
20 about a year and then were stopped, right?

21 DR. MITLAK: In the -- I think the point
22 of misunderstanding -- in the study in women, the

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1 median duration of treatment was 19 months.

2 DR. BONE: Right.

3 DR. MITLAK: Okay, and what we've done is
4 to have follow-up radiographs done now about 18 months
5 after the time that they stopped treatment.

6 DR. BONE: So some of those patients, the
7 ones who were about a year, have about an 18-month
8 follow-up after one year of therapy, and those who got
9 closer to two years would have 18-month -- would have
10 a period of observation of about two years.

11 Does this just mean that the analysis I
12 asked for -- I'm not expecting you to have done every
13 single conceivable analysis. I'm just asking if you
14 have that information.

15 What I'm trying to find out is whether the
16 fracture risk reduction is mainly the result of the
17 first year treatment or whether there's an incremental
18 effect on fracture risk that's due to the ongoing
19 application of the drug.

20 DR. MITLAK: We don't have data to answer
21 that question for you.

22 DR. BONE: You haven't analyzed the

1 follow-up data for that purpose?

2 DR. MITLAK: That's correct. We have --

3 DR. BONE: Thank you.

4 DR. GAICH: We just have the data that Dr.
5 Bone asked, and very few patients had a year or less
6 of treatment prior to the study closeout. It was only
7 between ten and 15 percent in each treatment group.
8 so not really enough to do an adequate vertebral
9 fracture analysis.

10 DR. BONE: How many had between 12 and 18
11 months, in other words, below the median?

12 DR. GAICH: I'm sorry. You found it?

13 DR. BONE: I guess it would be about half.

14 (Laughter.)

15 ACTING CHAIRPERSON MOLITCH: We'll take a
16 last question before the break from Dr. Tamborlane.

17 DR. TAMBORLANE: I think you showed the
18 post -- sort of the follow-up data after the study was
19 stopped as far as fracture rate, but in regard to sort
20 of follow-up of Dr. Kreisberg's question, do you have
21 the -- because it relates to duration of treatment --
22 do you have the bone marrow density data post

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1 discontinuation of the trial?

2 DR. MITLAK: yes.

3 DR. TAMBORLANE: Over time?

4 DR. MITLAK: yes.

5 DR. TAMBORLANE: Because that would say
6 whether the density then goes back. I think those
7 data -- I don't believe we saw those data.

8 DR. MITLAK: Let me ask you to put slide
9 4304 up, please.

10 Let me also explain as a preface, as Dr.
11 Gaich had highlighted, approximately 80 percent of the
12 patients who had previously been enrolled in the prior
13 study elected to continue into the follow-up study,
14 the follow-up study was an observational study. After
15 the primary study database was locked, patients were
16 unblinded to treatment assignment, and in the follow-
17 up phase, patients could take other treatments for
18 osteoporosis.

19 About half of the patients by 18 months
20 out had begun to take some other treatment for
21 osteoporosis, but the use of these treatments, whether
22 it was any specific treatment or the use of any

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1 treatment was statistically similar across groups. So
2 we have these data shown with that piece of background
3 information.

4 What this slide shows for the spine is
5 that in the first -- the data shown are for the
6 endpoint of the prior study, the first visit for the
7 follow-up study, and the second visit for the follow-
8 up study. This is six months and then an additional
9 12 months.

10 It shows that the bone density decreases
11 from the endpoint visit, but remains statistically
12 significant for the next 18 months and is different
13 from placebo even 18 months after treatment.

14 Let me ask also for you to show the next
15 slide 4305, which is the same type of analysis at the
16 hip.

17 All right. Thank you.

18 ACTING CHAIRPERSON MOLITCH: I think at
19 this juncture we will take a break. We will be able
20 to ask the sponsor additional questions after the FDA
21 presentation.

22 It is now 10:32. We'll resume at 10:47.

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1 (Whereupon, the foregoing matter went off
2 the record at 10:34 a.m. and went back on
3 the record at 10:55 a.m.)

4 ACTING CHAIRPERSON MOLITCH: We will now
5 continue with the FDA presentation. The first person
6 to present will be Dr. Kuijpers, who will be
7 discussing the preclinical studies.

8 DR. KUIJPERS: Thank you, Mr. Chairman,
9 ladies and gentlemen.

10 My name is Gemma Kuijpers. I'm a
11 pharmacology reviewer in the Division of Metabolic and
12 Endocrine Drug Products.

13 I thank you for giving me the opportunity
14 to talk today about the preclinical safety of
15 teriparatide. After my presentation, Dr. Bruce
16 Schneider will address clinical efficacy, and Dr.
17 Bruce Stadel will talk clinical safety of teriparatide
18 injection.

19 In this presentation, I will focus on the
20 main preclinical safety issue that emerged during the
21 development program of teriparatide, namely, that
22 teriparatide injection causes bone neoplasms in the

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1 rat.

2 First, I will briefly describe the purpose
3 and design of carcinogenicity studies. Then I will
4 address the data obtained in the two-year study, and
5 finally, I will discuss the clinical relevance of the
6 tumor findings.

7 For most new drugs for long-term use, the
8 FDA recommends testing for carcinogenic potential.
9 The most elaborate and stringent test for
10 carcinogenicity is the in vivo rodent bioassay. This
11 bioassay is usually done in both the rat and the
12 mouse. It's carried out over a large part of the
13 animal's life span, usually one and a half to two
14 years, and with multiple dose groups, including a
15 maximum tolerated dose to maximize the potential for
16 detecting tumorigenicity.

17 Animals are sacrificed at the end of the
18 study. Old tissues are examined histologically, and
19 the statistical analysis is carried out to determine
20 the significance of the tumor findings.

21 Finally, an attempt is made to evaluate
22 the clinical relevance of the findings using all the

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1 data that are available on the pharmacologic and
2 toxicologic effects of the drug.

3 To assess the carcinogenic potential of
4 teriparatide, the sponsor carried out a
5 carcinogenicity study in one rodent species, the
6 Fisher 344 rat. The animals were treated for two
7 years by subcutaneous injection. There were four dose
8 groups: control, low, mid, and high dose group. And
9 the drug was given to 60 animals per sex per group.

10 All tissues were examined of all animals
11 in the study. Histologic evaluation took place after
12 the animal was sacrificed per protocol at the end of
13 the study or after the animal had died prematurely due
14 to any cause. No interim sacrifices were done.

15 The bone sites examined were the femur,
16 tibia and sternum in all animals, the vertebrae in
17 most animals, and all gross palpable lesions at other
18 skeletal sites.

19 As mentioned by the sponsor, teriparatide
20 caused a number of different types of bone neoplasms
21 in the rat, the majority of which were malignant
22 osteogenic sarcomas. This graph shows the incidence

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1 of animals with any bone neoplasm in the four
2 different dose groups. The incidence is expressed as
3 percent of animals affected.

4 There were no tumors in the controls, and
5 in the treated groups, the incidence varied between
6 about five percent and 60 percent in the males and
7 between about seven percent and 40 percent in the
8 females. The effect was clearly dose dependent.

9 The bone tumors that were observed
10 originated from cells in the osteoblast lineage and
11 are very rare tumors in the rat. They were often seen
12 before the end of the study as grossly palpable bone
13 lesions. Several of them were malignant osteosarcomas
14 that were fatal and metastasized to soft tissue sites.

15 Teriparatide did not cause a significant
16 increase in the incidence of any other type of tumor.

17 This slide shows the systemic exposure to
18 teriparatide and the human exposure multiples
19 associated with the three different doses used in the
20 two-year study. In the low dose group, systemic
21 exposure was equivalent to approximately three times
22 the human exposure at a clinical dose of 20 micrograms

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1 per day, while in the higher dose groups the AEC
2 multiples went up to about 60 times in the high dose
3 group.

4 This graph shows the relationship between
5 the systemic exposure to teriparatide and the
6 osteosarcoma incidence. Note that the exposure on the
7 X axis is expressed as multiple of human exposure,
8 again, at the 20 microgram clinical dose. The graph
9 shows a clear relationship between systemic exposure
10 and tumor incidence.

11 Osteosarcomas were detected at several
12 sites throughout the skeleton as summarized in this
13 slide. In males, the most frequently affected site
14 was the tibia and after that the femur, and in females
15 the most frequently affected site was the vertebra.

16 This graph shows the time of death of all
17 animals in the male groups that were diagnosed with
18 osteosarcoma. Note here that death occurred either
19 due to scheduled sacrifice at the end of the study,
20 around 730 days, or prematurely at some point before
21 the end of the study.

22 For most, but not all of the animals that

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1 died prematurely, death was due to the osteosarcoma
2 being fatal. Overall there was no increase of
3 mortality with dose.

4 The conclusion from this graph is that in
5 addition to an increased incidence, the osteosarcomas
6 were detected earlier in the higher dose groups. The
7 earliest tumor that occurred in the high dose male
8 group was a vertebral osteosarcoma that was detected
9 microscopically in an animal that died as a result of
10 the tumor being fatal after 13 months of treatment.

11 A similar graph depicting time of death of
12 females with osteosarcoma is shown in this slide.
13 Although less pronounced than in the males, the same
14 pattern can be seen, namely, osteosarcomas being
15 detected earlier in the higher dose groups. The
16 earliest tumor in the female high dose group was a
17 fatal tumor in the skull bone in an animal that died
18 at approximately 20 months.

19 As the sponsor has shown with QCT scans,
20 teriparatide has a marked effect on bone mass in the
21 rat. In this graph the relationship between bone
22 mineral content of the vertebra in female rats is

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1 plotted against duration of treatment on the X axis
2 for the different dose groups included in control.

3 Although most of the osteosarcomas in the
4 two-year study were detected in the later time period
5 of the study, it is not known when the tumors were
6 actually first present in the animals.

7 The following slide shows the incidence of
8 osteosarcoma in control Fisher 344 rats. In the
9 current study with teriparatide, there were no tumors
10 in either male or female rats in the control groups,
11 and the incidence was zero percent.

12 Historical control data on osteosarcoma
13 incidence in Fisher rats are also shown. These data
14 are from control experiments carried out previously in
15 the sponsor's research lab or from an historical
16 control database of the National Toxicology Program.
17 The data show that the spontaneous incidence of
18 osteosarcoma in Fisher rats is extremely low and
19 amounts to approximately 0.2 to 0.4 percent.

20 Since there were no osteosarcomas in the
21 current teriparatide study, in the control animals of
22 the current study, we used the average historical

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1 control incidence of 0.2 percent to calculate the
2 relative risk of osteosarcoma in the teriparatide
3 treated rats. The relative risk is shown in this
4 line.

5 And note that even though the incidence of
6 osteosarcoma in the low dose teriparatide group
7 appeared fairly small, was about six percent for males
8 and females, average, this translates to a relative
9 risk in this dose group of 30-fold. Obviously the
10 relative risk was increased in a dose dependent
11 manner.

12 As the sponsor has clearly demonstrated,
13 teriparatide markedly and dose dependently increases
14 bone mass in the rat and in other species at all bone
15 sites examined. However, this positive effect of
16 teriparatide must be balanced against the adverse
17 effect observed in the carcinogenicity study.

18 Those results were that teriparatide
19 causes osteoblast neoplasms. The tumor induction is
20 dependent on the dose and on the treatment duration,
21 and occurred earlier in the higher dose groups. Tumors
22 were detected in all dose groups and a no effect dose

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1 or threshold dose level was not established.

2 The main question we are now confronted
3 with is what's the relevance of these animal findings
4 for humans or what can we conclude from these data
5 regarding the risk of bone tumors in humans treated
6 with teriparatide.

7 First, some remarks about hormonal
8 carcinogenesis. The current thinking is that in the
9 multi-stage process of carcinogenesis, hormones can
10 act as tumor promoters or co-carcinogens through a
11 nongenotoxic or epigenetic mechanism. Specifically,
12 a hormone can stimulate target cell proliferation and
13 in that way confer a selective growth advantage to
14 precancerous or initiated cells.

15 Although the exact mechanism underlying
16 the teriparatide induced formation of bone tumors has
17 not been elucidated, it's a plausible hypothesis that
18 in conjunction with its positive effect on
19 osteogenesis, repeated hormonal stimulation of the
20 osteoblast would cause an increase in cell
21 proliferation which would drive the accumulation of
22 genetic errors and increase the chance of neoplastic

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1 transformation.

2 One other factor that could contribute to
3 an increased chance of survival of precancerous cells
4 is the inhibition of apoptosis, or programmed cell
5 death, which is thought to be one of the effects of
6 intermittent activation of the osteoblast PTH
7 receptor.

8 Having said all this, the clinical
9 relevance of the rat tumor findings depends on whether
10 the mechanism of tumor promotion is operative in
11 humans. Since we don't know whether this is the case
12 or not, the simple conclusion here will be that the
13 relevance of the rat tumors is not clear.

14 A number of considerations have been put
15 forward to suggest that the rat bone tumor findings
16 are unlikely to have any clinical relevance. These
17 are the validity of the rat model, the lack of bone
18 tumors in an 18-month monkey pharmacology study, and
19 the lack of an association between hyperparathyroidism
20 in humans and osteosarcoma.

21 Dr. Schneider will expand on the last
22 points in his presentation, and I will elaborate on

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1 the validity of the rat model.

2 The sponsor has argued that the tumors
3 found at the two-year study are unlikely to be
4 predictive of an increased risk of osteosarcoma in
5 humans. This position is based on the notion that the
6 rat model is different from the human.

7 In fact, there is an exaggerated bone
8 response to teriparatide that may be related to a
9 difference in skeletal biology between rats and
10 humans.

11 Also, the animals were treated from a
12 young age and for a relatively large part of their
13 life span.

14 Although true, all of these arguments
15 relate to quantitative aspects of treatment and
16 quantitative aspects of the two-year study carried out
17 in the rats. I'd like to emphasize at this point that
18 these kind of quantitative differences between animal
19 and human studies, such as regarding dose and
20 treatment durations, are intentional differences that
21 are put into place in any type of toxicity study in
22 order to maximize the ability to pick up any signal

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1 for a possible adverse event.

2 Despite the possible differences,
3 quantitative differences between the rat model and the
4 human, the main point, however, here is that there's
5 no evidence that the human osteoblast is in any
6 qualitative way different from the rat osteoblast in
7 its response to intermittent PTH receptor activation.
8 In fact, there is very strong evidence that the
9 osteoblast mediated bone response to teriparatide is
10 similar in rats and in humans, namely, an increase in
11 trabecular and periosteal bone formation.

12 In our opinion, this qualitative
13 similarity of the skeletal response to teriparatide is
14 a strong reason to believe that the rat is an
15 appropriate test model for evaluating effects of
16 teriparatide on osteoblast behavior, including cell
17 proliferation or neoplastic transformation.

18 Therefore, we believe that the
19 quantitative difference in bone response between rats
20 and humans related to the difference in treatment
21 duration is no convincing reason to dismiss the tumor
22 findings as irrelevant.

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1 It is also our opinion that the tumor
2 findings are likely to be relevant for any species
3 that response to intermittent PTH receptor activation
4 with an increase in bone apposition. To illustrate
5 this, osteosarcomas have been observed in both rats
6 and mice employing intermittent dosing with another
7 PTH receptor like an analogue of PTHRP, which is a
8 compound that acts on bone in a similar manner as
9 teriparatide.

10 This indicates that the current tumor
11 findings are neither specific to the animal's strain
12 or species, nor specific to teriparatide. Rather, it
13 seems to be related to intermittent PTH receptor
14 occubation (phonetic) and the cellular events that are
15 mediated by this particular type of receptor
16 stimulation.

17 From the available data from the rat
18 study, it cannot be concluded at what age the animals
19 are susceptible to the proliferative effects of
20 teriparatide. It's also unclear what duration of
21 exposure to teriparatide is necessary to give an
22 initiated cell a chance for neoplastic transformation.

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1 For that reason, the sponsor is currently
2 carrying out, as was mentioned this morning, a follow-
3 up rat carcinogenicity study in which animals are
4 treated from either a young age or an older age, a
5 young age of two months or an older age of six months,
6 and for different periods of time, either six months
7 or 24 months.

8 In this study the animals are followed up
9 until an age of 26 months before they're sacrificed.

10 The sponsor is also carrying out a monkey
11 carcinogenicity study in which ovariectomized females
12 are treated for 18 months and then followed up for
13 another three years.

14 The results of these studies are not yet
15 available.

16 In conclusion, the clinical relevance of
17 the rat bone neoplasms induced by teriparatide is, in
18 our opinion, unclear, and it would not be justified to
19 dismiss the tumor findings as irrelevant until further
20 information is available.

21 Therefore, we cannot exclude that there is
22 a potential increase in the risk of bone neoplasms in

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1 humans treated with teriparatide.

2 I thank you for your attention, and Dr.
3 Bruce Schneider will now address the clinical safety
4 of teriparatide.

5 DR. SCHNEIDER: It's still morning. So
6 good morning, everyone. I'm Dr. Schneider. I'm the
7 endocrine and metabolic -- Division of Endocrine and
8 Metabolic Drug Products. I'm an endocrinologist.

9 I'm going to spend the next 20 minutes
10 giving you a very brief overview of the agency's view
11 and interpretation of the efficacy results, and then
12 I'm going to speak a little bit about my concerns
13 relating to the risk of osteosarcoma.

14 I think we're all in agreement, and as
15 I've indicated in my briefing document, that there is
16 currently need for an anabolic agent for the treatment
17 of many individuals with osteoporosis. I think it's
18 clear that we have taken the strategy of using anti-
19 resorptive therapy, including combinations of anti-
20 resorptive therapy, about as far as we can go.
21 They've been effective. They're helpful to many
22 people, but there clearly is an unmet medical need for

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1 an anabolic agent.

2 Our task now is to consider whether in the
3 case of teriparatide the benefit to risk profile
4 merits approval. This decision made by the agency,
5 which will be made by the agency, depends on our
6 estimates of clinical efficacy, and these estimates
7 must be derived solely from randomized placebo
8 controlled clinical trials.

9 Other data are interesting, but we can't
10 really accept them as efficacy data, and these must be
11 balanced against safety concerns, and the principal
12 one is the concern of osteosarcoma.

13 In a few minutes you'll hear a more
14 complete safety review by Dr. Stadel.

15 Now, let me state at the outset that the
16 results of the pivotal controlled clinical trials GHAC
17 and GHAJ clearly established efficacy in the case of
18 GHAC in post menopausal osteoporosis, osteoporotic
19 women. The trial clearly established efficacy in
20 reducing fracture risk and increasing bone mineral
21 density in this population.

22 And trial GHAJ, the other pivotal trial,

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1 also clearly established efficacy in increasing spinal
2 BMD in men with osteoporosis.

3 Although we don't have head-to-head
4 comparisons, it's clear at least to me or it seems to
5 me that for both men and women the beneficial effects
6 at the lumbar spine, including BMD effects and
7 fracture prevention, appear to exceed those of any
8 currently approved agent.

9 Accordingly, these results would certainly
10 be sufficient to meet efficacy criteria for approval
11 of osteoporotic drugs based on our current criteria in
12 the absence of any safety concerns.

13 These outcomes were the result of an
14 extensive and thorough preclinical and clinical
15 development program. The preclinical program, as
16 you've heard, included mechanistic studies which
17 clearly established anabolic action on bone and
18 positive effects on bone quality.

19 The clinical Phase 1 and 2 studies
20 demonstrated rapid anabolic action of teriparatide in
21 humans with pharmacodynamic effects which were dose
22 dependent in the 15 to 40 microgram range. The no

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1 effect dose was established at six micrograms. At
2 doses greater than 40 micrograms, there was a rapid
3 increase in adverse events in these early studies, and
4 the positive effects were variable.

5 Safety tolerability profile was built up
6 during these early studies, which led to, in my
7 opinion, the proper dose selection for the pivotal
8 clinical trials, GHAC and GHAJ and the other trials.

9 My only comment here is that it would have
10 been interesting to have studied the effects of less
11 frequent dosing, for example, 20 micrograms given
12 every other day in terms of safety and patient
13 acceptability.

14 And then finally, not shown on this slide
15 I should bring up the fact that the assay usually,
16 immunoradiometric assay that was employed, had a lower
17 limit of detectability of 50 picograms per mL of PTH
18 1 to 34, which translates on a molar basis to about
19 123 picograms per mL of PTH 1 to 84, which is clearly
20 above the upper limit of normal for PTH 1 to 84, and
21 therefore, comments about absence of PTH 1 to 34 in
22 the range that is below the hyperparathyroid range

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1 should be taken with caution.

2 The pivotal trial GHAC was described in
3 detail by the sponsor. I'll just review it very
4 briefly. The primary efficacy objective of this trial
5 which studied the effect of teriparatide in the
6 treatment of post menopausal women with osteoporosis,
7 the primary efficacy objective was a reduction in the
8 proportion of patients with new morphometric vertebral
9 fractures. This trial had eight secondary efficacy
10 endpoints and it enrolled about 540 patients in each
11 of three treatment arms, as shown here.

12 The primary endpoint results are shown
13 here. They were clearly achieved. There was a 65 or
14 69 percent reduction in the proportion of patients
15 with new morphometric vertebral fractures which
16 translates to about a nine to ten percent absolute
17 risk reduction. These results were very robust, and
18 the p value was less than .001 for each comparison of
19 PTH versus placebo.

20 There were other fracture results which
21 were not prespecified as outcome results, but which
22 were methodology derived, and these are shown here,

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1 and I'm mentioning them because I thought they were
2 quite impressive. There was an 80 to 90 percent
3 reduction in the proportion of patients with multiple
4 new vertebral fractures and a similar reduction in
5 fracture severity using the Gennant grading system
6 that the sponsor employed.

7 The key secondary endpoint was the
8 proportion of patients with new nonvertebral
9 atraumatic fractures combined. The study lacked the
10 power to detect site specific differences at
11 nonvertebral locations, such as the hip or wrist,
12 which are very important for osteoporotic patients,
13 and as shown here, there was about a 53 or 54 percent
14 relative risk reduction in the incidence of all such
15 fractures, with an absolute risk reduction of about
16 three percent.

17 The p value was less than .02 for each
18 comparison versus placebo without adjustment for
19 multiple comparisons, so that these results were not
20 quite as robust as the results at the lumber spine.
21 Nonetheless, they were statistically significant.

22 This slide summarizes the percent of

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1 patients with fractures at each of seven different
2 extravertebral sites, and there were very few such
3 fractures throughout the study. All in all, the 20
4 microgram dose of PTH, for example, prevented two or
5 three hip fractures in 540-some odd women treated for
6 the duration of the trial, which is about a median of
7 19 months' exposure, and there were a few risk
8 fractures that were also prevented by treatment.

9 None of these comparisons were
10 statistically significant. The changes were in the
11 anticipated direction.

12 The other secondary efficacy endpoint
13 results are shown in this slide. In GHAC there was a
14 significant increase relative to placebo in bone
15 mineral density at the lumbar spine, hip, and total
16 body. There was no effect in bone marrow density at
17 the forearm. There was no effect on height loss in
18 the entire population as a whole.

19 I might add that the effects in other
20 trials of other agents have shown very small and
21 inconsistent treatment related decreases in the
22 populations when taken as a whole, treatment related

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1 differences of about one to two millimeters, which
2 have been statistically significant.

3 Subgroup analyses of patients who do
4 fracture consistently show greater height loss in that
5 subgroup, but they can't be considered as efficacy
6 outcomes because they're trial derived subgroups
7 unless they're prespecified.

8 In any case, there was no effect on height
9 loss in this population despite the substantial BMD
10 and fracture prevention efficacy at the spine.

11 The histomorphometry results have been
12 described. I won't go into them. They were basically
13 positive. There was a positive effect, anticipated
14 effect on biochemical markers which demonstrated an
15 anabolic action of teriparatide.

16 And a final secondary outcome was health
17 related quality of life indicators. The sponsor used
18 five different instruments to measure health related
19 quality of life changes.

20 I might add that every one of these
21 indicators had back pain as a specific domain, and two
22 were osteoporosis specific, and there was no effect

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1 seen. Back pain, which we've heard about about three
2 or four times during the discussion this morning, was
3 reported or recorded as a safety outcome, as an
4 adverse event outcome with a p value attached to it,
5 which I cannot accept as an efficacy outcome.

6 The other pivotal trial was GHAJ, the
7 effects of teriparatide in the treatment of men with
8 primary of idiopathic osteoporosis, and with
9 osteoporosis associated with primary hypogonadism, the
10 primary efficacy objective here was an increase in
11 spine BMD, and the secondary endpoints were
12 essentially the same as with GHAC.

13 This trial was smaller and enrolled about
14 145 patients in each of three treatment arms. The
15 exposure was fairly small because of the early
16 termination of the trial, of all the clinical trials.
17 Actually there were very few dropouts relative to
18 osteoporosis trials. There were about 88 percent, 82
19 percent, 74 percent of the patients in study at end.
20 About 87 to 90 percent of patients received six months
21 of treatment, and about 25 to 30 some odd percent of
22 patients received 12 months of placebo controlled

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1 treatment.

2 The results, the primary endpoint was
3 clearly achieved in this trial. They were highly
4 significant increases compared to placebo for both
5 doses, and the increase of 40 micrograms was greater
6 than that achieved with 20 micrograms, and the key
7 secondary BMD endpoints at eight other skeletal sites
8 at 20 micrograms. There was statistical significance
9 relative to placebo at the femoral neck only using
10 endpoint last observation data.

11 For 40 micrograms, there were greater
12 effects at almost every skeletal site, with
13 statistical significance achieved at the total hip,
14 the femoral neck, intertrochanter (phonetic), Ward's
15 triangle, and whole body.

16 And it's for this reason that I raise the
17 question in my briefing document as to whether the
18 dose should be adjusted in treatment of men with
19 osteoporosis.

20 The other secondary endpoint results were
21 similar to GHAC.

22 So our clinical efficacy summary is shown

1 in this slide, and let me go back here. In post
2 menopausal osteoporotic women, teriparatide 20
3 micrograms is highly effective in increasing lumbar
4 spine bone marrow density and BMD at other sites and
5 in reducing the risk of morphometric vertebral
6 fractures.

7 The drug is effective in preventing
8 nonvertebral fractures combined, but the data are not
9 as robust as in the spine. The 20 microgram dose --
10 and this is very important -- is as effective as the
11 40 microgram dose in reducing the risk of fractures,
12 and this would establish in my mind that 20 micrograms
13 is the appropriate dose, and the drug did not prevent
14 height loss in this population.

15 In men with idiopathic osteoporosis with
16 or without hypogonadism, primary hypogonadism,
17 teriparatide 20 micrograms is highly effective in
18 increasing lumbar spine BMD, but is either ineffective
19 or only marginally effective in increasing BMD at
20 other skeletal sites.

21 The 40 microgram dose was substantially
22 more effective than the 20 microgram dose at nearly

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1 all skeletal sites. The drug did not prevent height
2 loss.

3 I must emphasize again there were no
4 fracture efficacy data from GHAJ or from any other
5 randomized controlled clinical trials in men.

6 I should also add that, of course, this
7 trial was truncated. It was stopped after a median of
8 11 months of exposure, and we really don't know what
9 would happen with two years of exposure to the drug.

10 Now, these efficacy outcomes which clearly
11 would meet our approval criteria, must be balanced, of
12 course, against the risks, and the major risk that I
13 see is the risk of osteosarcoma, and in the next few
14 minutes I want to let you know why, although I
15 certainly don't have any answers to this question, why
16 I'm still concerned about it.

17 The major reasons for concern, of course,
18 as we've heard this morning, is that this is a robust,
19 dose dependent occurrence in rats, and we also know
20 now in mice. There was no threshold dose
21 demonstrated.

22 Now, unlike other preclinical outcomes

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1 that we often see, this was a biologically plausible
2 outcome, and it involves hormonal stimulation of known
3 target tissue.

4 In this slide I've listed seven reasons
5 why we're told that we shouldn't be so concerned about
6 it and why it is unlikely that osteosarcoma will occur
7 in humans treated with teriparatide. I've listed
8 every reason that I've heard and every reason that I
9 can think of, and they appear here.

10 High exposure in rat studies. The
11 treatment of rats began at six or seven weeks of age
12 and was virtually lifelong. There's a negative monkey
13 study. Rat bone differs from human. There's no
14 increase in other malignancies in treated rats. Our
15 experience with hyperparathyroidism in humans, and the
16 observations in patients post treatment with PTH.

17 Let's look at each one of these. The
18 argument has been made that rats received excessively
19 high doses of teriparatide, and there was an excessive
20 response in rat tissues. Let's follow this line of
21 reasoning a bit and see where it goes.

22 The rats, according to my calculations,

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1 based on AUC, which is a unit of exposure, multiplied
2 by a fraction of a lifetime, the rats received about
3 25 to 1,000 times the proposed human dose, again
4 assuming that humans would be treated for two years,
5 which is about two or three percent of a lifetime.

6 Now, if the background rate is 0.2 percent
7 in rats, and that's a higher number; it may be a
8 realistic number, but it's a higher number compared to
9 the background rate in humans, which is about four or
10 five per million per year. If the background rate is
11 0.2 percent in rats, then the study dose range led to
12 about a 30 to 200-fold increase in tumors, and one can
13 compose ratios of increased tumor occurrence divided
14 by increased dose, and you get a number like a range
15 of about 0.2 to 1.0 across the dose range, and this
16 would yield a risk in humans of about 1.2 to, let's
17 say, twofold.

18 If the risk is less than twofold, given
19 the low background rate humans, we'll probably never
20 see it. If it occurs, we won't know about it. I
21 don't know how comforting that is, but it will be very
22 difficult to measure.

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1 And so these risk projections depend on
2 the basal rates of tumor recurrence because if the
3 background rate in rats, for example, was 0.2 percent,
4 then you'd have a 300 to 2,000-fold increase in
5 tumors, and you might have a four or five-fold
6 increase in humans exposed, and of course, these are
7 totally speculative extrapolations.

8 One make assumptions of linearity, and so
9 forth, but this is about as far as I can take this
10 argument, and so it doesn't really lay the issue to
11 rest.

12 The next argument that's been made is that
13 the treatment of rats began at a very early age, six
14 to seven weeks, and the question is are young animals
15 particularly or exclusively susceptible. That is, we
16 have already heard further experiments are in progress
17 now to determine whether the effect is age dependent
18 in rats. The dose it's my understanding is going to
19 be given in a staggered fashion to rats in a long-term
20 study carried out by the sponsor, and I think this is
21 really a critical experiment which will tell us a lot
22 about the timing of tumor formation.

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1 Of course, it's always likely -- not
2 likely; it's always possible -- that the older rats
3 will be more susceptible than the younger ones. You
4 have to do the experiment to find out.

5 The negative monkey study is presented as
6 an example, and again, this does not allay my concerns
7 completely because I believe that the number of
8 animals is far too small to detect even a large
9 increase in tumor occurrence if the background rate is
10 low, and I think what's been absent from a lot of the
11 conversation and the discussion is consideration of
12 the background rate.

13 For example, if the background rate in
14 monkeys, let's say, is even ten times that in humans,
15 and if the drug causes or the doses of the drug cause,
16 let's say, a 100-fold increase in tumor formation,
17 you'd still expect only four monkeys to get
18 osteosarcoma in every 1,000 monkeys studied per year.
19 So that studying 80 monkeys for 12 or 18 months might
20 not be enough.

21 The next argument is that rat bone differs
22 from humans, and certainly it does in terms of its

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1 architecture or growth and remodeling patterns. They
2 all differ. The real question is not architectural as
3 far as I'm concerned, but the following. Do the two
4 species, rat and human, differ in the ability of the
5 osteoblast precursor pools to replicate and expand
6 clonally in response to intermittent hormonal
7 stimulation?

8 This is the key question in terms of tumor
9 promotion as far as I'm concerned, and we don't know
10 the answer.

11 The next is that there's no increase in
12 other malignancies in the treated rats. Clearly PTH
13 is not a carcinogen. The concern here is not with
14 that, but with the promotional effects of a hormone in
15 a specific target tissue.

16 Next is our experience with
17 hyperparathyroidism in humans, and frankly, as an
18 endocrinologist, I can tell you this would be the most
19 compelling reason for me not to worry.
20 Hyperparathyroidism, particularly mild, primary
21 hyperparathyroidism, as we all know, is not uncommon,
22 and I'm sure there were tens, if not hundreds of

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1 thousands of people walking around with mild
2 elevations of PTH.

3 In fact, our clinical practice guidelines
4 afford us the opportunity of delaying or not doing
5 parathyroidectomy at all and letting many, many people
6 live out their lives with mild primary
7 hyperparathyroidism, and osteosarcoma is, to my
8 understanding, unknown in this group.

9 And I think this is really the best
10 experiment of nature which tells us the most, but
11 assuming that there aren't different cellular
12 responses to intermittent versus sustained elevations
13 in PTH, as there are with the overall bone
14 pharmacodynamics, I don't know the answer to that
15 question.

16 And finally, there are the observations in
17 humans post treatment with PTH. We have about 1,450
18 patients treated for more than three months.

19 Again, given the low background rate,
20 which is about four or five per million per year, this
21 number and this period of observation, it would be
22 unlikely that we would be able to detect an increase

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1 in tumor occurrence, given these background rates.

2 Also, what we're waiting for is the
3 occurrence of a clinically obvious tumor, something
4 which presents as pain or swelling, and that, I think,
5 will take some time, perhaps 25 or 30 doubling times,
6 let's say. So that I don't know that two or three
7 years is enough time.

8 And my last slide here is, again, to weigh
9 the benefits versus the risks, and they're the
10 benefits of a new, very promising anabolic agent which
11 really I think offers a lot of hope and is very
12 exciting for treatment of osteoporosis. There are
13 known benefits from the clinical trials, which show
14 substantial bone mineral density increases in men and
15 women and fracture efficacy in women, again,
16 especially at the lumbar spine.

17 We don't know the long-term benefits of
18 these architectural improvements from an anabolic
19 agent. I suspect they'll be quite positive. We
20 really don't know.

21 And these must be weighed against the
22 unknown risk of osteosarcoma.

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1 Thank you.

2 DR. STADEL: Good morning. I'd like to
3 begin by expressing appreciation to Dr. Sunita Zalani
4 and her colleagues at Lilly who have been very
5 forthcoming in responding to rather detailed questions
6 from me. I've tried to explore the database very
7 thoroughly, and I can make a generally brief
8 presentation on the clinical trial program, beginning
9 by saying that in general, with a few exceptions, I
10 agree with the presentation that has been made by the
11 sponsor on the safety findings in the clinical trial
12 program.

13 So I will briefly go over some highlight
14 points about the trials, and then as others have done,
15 I will talk about osteosarcoma.

16 This is something that came out of some
17 discussions as this was going forward. Safety
18 analyses differ somewhat from efficacy analyses, and
19 I've put up here simply that the analyses of efficacy
20 hypotheses are ordinarily specified in advance, and
21 the use of p values is focused on testing the
22 prespecified hypotheses. In analyses of safety, there

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1 usually are no prespecified hypotheses, but there is
2 still a need to assess the data to identify potential
3 areas of concern.

4 P values as a descriptive tool are useful
5 for this, with the understanding that a p value
6 associated with a new safety finding does not have the
7 same meaning as a p value associated with either the
8 testing of a prespecified efficacy hypothesis or a
9 prespecified, a previously observed safety finding.
10 new safety findings from one study should generally be
11 tested in others before arising at conclusions.

12 This is important because I show p values
13 on new associations, and I do not want the opportunity
14 of them being misunderstood.

15 Now, in the preclinical studies, there
16 were some key issues that arose that were on my list
17 of things to understand as I did the safety review in
18 the clinical trials, and these were post dose
19 hypotension and tachycardia, decreases in RR and QTC
20 intervals -- I just put QT -- and increase in serum
21 and urine calcium.

22 I will say that in the clinical trial

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1 program, I found no clinical events in excess in the
2 treated groups which would have been the types of
3 events associated with these phenomena. These are
4 dose related phenomena. The doses in the trial
5 produced minimal tachycardia. I will show some
6 information on that later.

7 I also looked for any other kind of
8 cardiovascular even that might be an offshoot of a
9 hypotensive episode, and I did not find excesses in
10 the treated groups.

11 Now, with regard to electrocardiographs,
12 no electrocardiographs were obtained in the Phase 2 or
13 3 clinical trials. So that I was not able to evaluate
14 electrocardiographic findings under conditions of the
15 kind of clinical setting in which the drug would be
16 used. I did not see clinical events suggesting
17 cardiac bad clinical outcomes, but I could not
18 evaluate electrocardiographic information. I found
19 this somewhat troubling.

20 In the preclinical studies, you've heard
21 before about these issues. So I need not dwell on
22 them.

1 Just a reminder of the size of the key
2 studies. These are the two main studies of the
3 enrollment criteria, the numbers of patients in the
4 treatment arms.

5 Again, just a reminder of what size
6 studies are we dealing with. The main studies I've
7 shown, GHAC and AJ, AC the main study in women, AJ the
8 study in men. Two other studies that were important
9 supportive studies that had active controls I've
10 listed. Just to give the denominators a sense, I will
11 be showing numerators with percents and p values.
12 This is your opportunity to know what the denominators
13 are.

14 Now, this, I think is very important
15 information. In terms of the issue of possible long-
16 term effects of duration of use, and this is a sort of
17 lead to the osteosarcoma discussion later, this is
18 most of what we know in the two main trials about
19 duration of use. That is, 85 percent of the women
20 were in the 13 to 23 months exposure to study drug,
21 and 87 percent of the men in the six to 14 month
22 exposure.

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1 This is a way of looking at it a little
2 differently. In the total program, 1,452 patients
3 were treated for at least three months. Now, that
4 provides 95 percent confidence that you will detect an
5 event if it occurs once in 484 or fewer patients. You
6 may notice I have not put person-time here. One can
7 make this function for any number of person-years.
8 You could say that number of people studied for five
9 years would give you that confidence of seeing it in
10 484 patients followed for five years.

11 The reason I have emphasized the number
12 itself is that for rare outcomes, the question of
13 individual susceptibility to an adverse effect is at
14 least as important as the duration of follow-up. So
15 that I wanted to put some emphasis on this is the n
16 that we're dealing with.

17 I think for a clinical trial program I'm
18 not criticizing the n. In terms of dealing with the
19 potential for a comparatively rare, but extremely
20 important adverse event, one needs to understand the
21 limitations that are inherent to the follow-up of such
22 a data set.

1 I look now at many things, but I'll just
2 mention serious adverse events as defined by the Food
3 and Drug Administration are listed here. In this
4 analysis, co-genital anomalies and drug overdoses
5 don't matter much. So the main things are on the top.

6 I looked at each of these separately. I
7 will show you, as you've seen a little of this before,
8 but here it is for the two main trials and the
9 supported trials, that the aggregate rates of patients
10 who had one or more serious adverse events by
11 treatment arm were very good. There is no increase.

12 I looked at these by individual adverse
13 event terms by study, and there is only one serious
14 adverse event term which is statistically significant,
15 and that was that actually in GHAC the rate of breast
16 cancer was lower in the treated groups than it was in
17 the placebo group.

18 I do not put great weight on that as a
19 finding, but it was statistically significant.

20 No other analysis was statistically
21 significant or even met the criteria of a trend, of a
22 .1 screen. So quite a generous screen.

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1 Looking at adverse events of any severity,
2 you've seen some of this. So I'll just mention again
3 briefly back pain was decreased at both doses. Nausea
4 and headache, not increased at 20, but increased at
5 40. Leg cramps increased. Gout and arthralgia and
6 urolithiasis, both potentially important, gout because
7 of the uric acid elevation and urolithiasis because of
8 the calcium elevations in the urine; both of these as
9 clinical events were not present.

10 Dizziness, syncope and vertigo I analyzed
11 very carefully because of the postural hypotension.
12 There was nothing in dizziness or syncope -- excuse me
13 -- in syncope or vertigo. There were a few cases of
14 patients who had more severe dizziness in the treated
15 groups, and I wanted to mention that. So there was a
16 little bit of a difference, but not enough that I
17 would generalize it as an important overall finding.

18 Now, in routine measurements, there were
19 no differences between treatment groups in sitting
20 blood pressure measurements. However, very little
21 post dose data were obtained. In only one clinical
22 trial involving a relatively small number of post

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1 menopausal women, there was post dose data, and I've
2 showed you there.

3 Now, one hour after dosing with 40
4 micrograms was the maximal effect, and it was quite
5 modest, a mean increase of five beats per minute, and
6 an interesting thing. The range, it seemed to involve
7 the bottom coming up rather than the top rising, which
8 I thought was kind of unusual. I don't know if it
9 would replicate in another data set, you know, but I
10 do nonetheless feel somewhat uncomfortable that we
11 don't know more about post dose heart rates and
12 electrocardiographic findings under the general
13 conditions of usage.

14 So since the electrocardiograms were not
15 done in the studies, we have discussed that if the
16 drug is approved, that there would be a Phase 4
17 commitment to obtain these data and sort of round out
18 the data set in the absence of any clinical events to
19 give greater concern. I'll leave it at that.

20 Now, a couple of things that have been
21 discussed before, but I feel that I should show. One
22 is the frequency of four-hour post dose hypercalcemia,

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1 and I've put this out by showing the number of
2 patients with one episode and the number with two or
3 more and then a group p value, and then the range of
4 the hypercalcemias, 2.65 to 2.89 millimoles per liter.

5 So there are episodes. Most of the
6 patients have one. Some have two or more. A
7 difficulty one faces with what appear to be small
8 numbers in a clinical trial like this is that three
9 percent of a couple of 500 patients isn't that many,
10 but when a drug goes into the marketplace and
11 thousands are treated, the dimensions expand.

12 And I just want to bring that up now and
13 then as a reminder because I lose track of it
14 sometimes, and I think probably everyone does looking
15 at these data.

16 Now, this, I think, is an important slide.
17 This shows actions that were taken in close temporal
18 proximity to the serum calcium measurements. It's not
19 clear that they were taken, definitely caused by the
20 elevations. The nature of the data don't allow one to
21 be, I think, absolutely sure of that, but I think it's
22 probably reasonably sure that these events were

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1 related to the detection of hypercalcemia in the
2 patient.

3 And I think it's important because I think
4 what it says is that the physicians involved in caring
5 for these patients were watching this, and when they
6 saw things go too high, they were making adjustments,
7 and I think that bears on the question of whether
8 there's ever any need to monitor.

9 You know, so these patients were
10 monitored.

11 You see study drug adjustments. I pushed
12 the wrong button somewhere. Study drug adjustments
13 were also made significantly, but study
14 discontinuation not.

15 I have managed to push a wrong button.
16 Thank you, George. Thank you very much.

17 Okay. Now, this is the 24-hour urine
18 calcium. You'll notice here that although the median
19 has increased, there is not a meaningful increase in
20 the frequency of episodes. Actually it was one
21 percent higher for one episode in placebo, and then
22 two percent higher for two episodes, two or more

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1 episodes in 20 microgram.

2 So it looks like that although there was
3 an increase in load of calcium on the kidney, this was
4 not manifesting itself as defined hypercalcurea
5 (phonetic), and I think that's of some comfort, and
6 you can see the range, again, at the bottom that I've
7 put of where the hypercalcurea episodes fell from 7.6
8 to 20.2 millimoles per liter for 24 hours.

9 Now, I put this up. It's not significant,
10 but I put it up because it's not significant. These
11 patients do have an increase in alkaline phosphatase
12 when they go on the drug, which is expected, but the
13 fact that at the 20 microgram dose you have no
14 increase in people above the upper limit of norma I
15 think has some value with regard to if you are
16 following the patient and they have a very high
17 alkaline phosphatase. You don't write it off as due
18 to the drug. You work it up.

19 And so I think that's a valuable finding
20 actually with regard to the 20 microgram dose. It
21 means that alk-phos can still be used in work-up.

22 Now, the post treatment follow-up study

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1 briefly. These are the number of patients, about 77
2 percent aggregate and quite uniform from the different
3 trials actually enrolled in the study.

4 Now, this study, there was still blinded
5 treatment at first, but then it became open label, and
6 of course, with this number of enrollees, there's the
7 potential for selection bias. So this gets into
8 really an observational data set analysis and is much
9 less reliable, I think, than the blinded randomized
10 data.

11 I did want to show the number of serious
12 adverse events simply to show that in this follow-up
13 data, although it goes from 12 percent to 17 percent,
14 then it goes down to 13 percent in the main trial in
15 women, it does go up in men. It's not significant,
16 but then in the two other trials in women it's
17 actually fairly strongly in the other direction.

18 So I conclude that this is not meaningful,
19 and I'm somewhat reassured by that. I don't see a lag
20 phenomenon, you know, in follow-up of something
21 emerging.

22 This I wanted to show. This is the

1 survival curve. Where those bars are is when people
2 finish the studies. So this is from the beginning of
3 randomization to the end of the observational follow-
4 up study to give you the death rates by treatment
5 group. As you can see, they're very, very close.

6 Now, interestingly enough, they're even
7 closer when you correct for a small problem. In the
8 large study in women, purely by chance, the women in
9 the two treatment arms were each on average one year
10 older than the women in the placebo group, the
11 randomization p value of .1, and in fact, when you
12 correct for age, it brings the death rate slightly
13 closer together.

14 And I was a little concerned when I first
15 saw them because although there was no significance,
16 there were more deaths in the treated arms. And so
17 when I was able to get some balance out of that, I
18 felt better about it.

19 I have two findings which I regard as
20 tentative that we've been working on from the follow-
21 up study. There is an entity in adverse event coding
22 called cardiovascular disorder, which is a place where

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1 people put things they don't know where else to put,
2 things that don't go under coronary heart disease,
3 that don't go under congestive heart failure, that
4 don't go under the specific entities; go under
5 cardiovascular disorder, things in the cardiovascular
6 system.

7 So this was quite a collection of things.
8 It turned out that it was about 55 percent heart
9 murmurs. The reason I show it, the reason I'm a
10 little concerned about it is that the pattern was
11 present in this subset during the trial, and when I
12 looked at all patients randomized during the trial,
13 the pattern is there. It's not statistically
14 significant, but the pattern is there.

15 And then in follow-up it gets a little
16 stronger, and when you take it into the aggregate, it
17 gets a little stronger.

18 Incidentally, your handout has a slight
19 numeric error on this one, just in case it's of
20 concern to anyone. It says 39 percent where it should
21 be 55 percent, and a couple other things.

22 So we've been still working that up. I

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1 bring back the caveat at the beginning about new
2 safety findings and p values and so forth. In
3 stratifying this by age and looking at the effective
4 age, there's more of an association over 70 than
5 under, and the possibility that tighter control of age
6 may dissipate is still there. I haven't done that
7 yet. I've looked at a lot of things about it.

8 The last thing I'd mention I do think needs
9 to be mentioned, and again, it's another tentative
10 finding. This was found at the first. This
11 represents events found at the first visit in the
12 follow-up study where there was an increase in the 20
13 microgram group that I've shown here, but there was
14 also a similar increase in the 40 microgram group.

15 My slides are 20 microgram group because
16 that's what's proposed for marketing, but for
17 consistency scientifically, there was also a similar
18 increase in the 40 microgram group, and there was a
19 bit of an increase in this direction in the Mayo
20 study.

21 So I've wanted to follow this up. I don't
22 have any strong interpretation to place on it. The

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1 creatinine clearance distributions were not different
2 between treatment groups, and follow-up has been done
3 on 18 of these patients thus far, 18 including the 40
4 microgram set, and that's a little reassuring. It
5 looks like it may regress towards the mean.

6 So I will simply mention those are the
7 things in progress. I don't see anything alarming in
8 the data, and I will now turn to the topic of
9 osteosarcoma.

10 I think from my standpoint as an
11 epidemiologist, I think we have to know about when
12 approaching this, one of the most important things to
13 realize is in women and men 50 years of age or older,
14 the approximate treatment population to this drug,
15 that the annual incidence, the average annual
16 incidence is four cases per million per year. That's
17 from the SEER system data for recent years.

18 Of course, it's a little lower at the 50
19 year age and a little higher at the upper ages, and
20 that means a total in the country of about 300 cases
21 per year.

22 SEER covers about -- I just got that from

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1 using population figures, and the occurrence is
2 generally similar by gender and race. So that's the
3 dimension of what one's dealing with as a base rate.

4 And the question is: how do you detect an
5 effect on something like this? It's not easy.

6 I should stop to mention the one really
7 important risk factor involved. For anyone who's not
8 familiar with it, Paget's disease is a resorptive
9 disease of bone in which osteosarcoma -- in patients
10 who have serious Paget's disease, clinically manifest
11 and followed for long periods of time, osteosarcoma
12 occurs with about a one to five percent frequency in
13 the reported series. These are cumulated frequencies
14 over varying durations of follow-up.

15 And most of the cases are in Paget's
16 patients who were over 50. Most of the osteosarcomas
17 that arise in Paget's patients. They have to have
18 Paget's disease for a long time.

19 And so I wanted to mention that and to
20 mention a little bit about Paget's disease in the U.S.
21 population. Now, we were speaking previously about
22 overt clinical Paget's disease. Now I'm speaking

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1 about subclinical, little foci that are found on X-
2 rays. This was using the national health and
3 nutrition examination survey data from the early
4 1970s.

5 There was a read done of the X-rays, and
6 one comes out that the prevalence of Paget's disease
7 in the over 50 age group is about one percent on
8 average and increases with age, similar by gender and
9 age. In other countries, it's a little higher in
10 Britain, and a little lower in some other countries.

11 It may have gone down somewhat. There's
12 some reason to believe that the prevalence of Paget's
13 disease may be going down, but this is to give just
14 some idea of a ballpark idea of what the underlying
15 prevalence of a disorder that one is a little nervous
16 about because would PTH potentially stimulate any of
17 this.

18 I will mention that there was one case of
19 Paget's disease diagnosed in the clinical trial
20 population, and that was a man who was diagnosed a
21 couple of months after he had finished a year of 40
22 microgram treatment, and the diagnosis seems to be

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1 quite confident.

2 The initial read at the time of diagnosis
3 did not describe the presence of any pathologic uptake
4 on the bone scan then. Subsequent reads apparently
5 have been that maybe some disease was present. So I
6 think it's -- I'd have to say it's a bit unclear to
7 me.

8 I guess with regard to conclusions, I'd
9 have to agree with both the investigator and Lilly.
10 I think it's possibly drug related and possibly
11 coincidental. I really wouldn't want to tie.

12 I would want to say one thing that's
13 important here. From the previous slide I showed you
14 with the one percent prevalence of occult Paget's
15 disease in a clinical trial program involving a couple
16 of thousand women, there must have -- patients, women
17 and men -- there must have been a reasonable number of
18 people, you would think, playing the odds, who had
19 suboccult Paget's disease who were enrolled in the
20 trial and who were treated with the drug. The only
21 case we've seen is this one case.

22 So to some degree, I think it really cuts

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1 both ways. I think it provides a measure actually on
2 the positive side, although I think most people would
3 agree, and your proposed labeling would agree that if
4 Paget's disease is known, you would try to avoid the
5 drug.

6 Well, to get to the end of it, what can be
7 done? Well, continuing to follow up the patients in
8 the observational study is a good idea. I've tried to
9 convey earlier what the limitations of numbers are,
10 the realities.

11 One learns something, but it doesn't
12 answer a lot of questions.

13 Mapping drug use data I think is extremely
14 important to know if the drug goes into the
15 marketplaces, to know where does it get used, where
16 could it be studied, where are the potentials.

17 And of course, we have to deal with
18 adverse event reports, and I'll talk a bit on the last
19 slide about that again.

20 We talked about two kinds of surveillance,
21 getting referral centers and doing case ascertainment,
22 first off, to find out how many cases one can get hold

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1 of, and then there's the potential of using those
2 cases for case control studies. I think you'd have to
3 use controls from the residential areas of the cases
4 or something along those kind of lines to get a
5 reasonably unbiased assessment.

6 The sponsor has talked about the potential
7 of getting quite a large percentage I think, up to
8 about 40 percent of the cases diagnosed in the
9 country, which if that were done, it would help.

10 And the other is what's called the SEER
11 system. It's an excellent resource for doing cancer
12 research. It's an NCI sponsored, National Cancer
13 Institute sponsored program. The only limitation is
14 for very rare tumors, it covers 14 percent of the
15 country.

16 So I will close with this slide. This has
17 a couple of interpretations. This is purely
18 hypothetical. I want everyone here to understand that
19 I am not talking about risks that are real. I'm
20 talking about a scenario for the purpose of trying to
21 convey an idea.

22 If the incidence is four per million up

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1 here, okay, that one is, I think, a fact. Let us
2 suppose that the drug was marketed and we reach a
3 state and there was a relative risk of three, large
4 enough for most people to think it has some
5 importance.

6 If you look at the numbers, then a
7 tripling of risk would take four per million to 12 per
8 million, and you subtract out the base rate, the
9 attributable risk is eight per million per year.

10 Well, if early in marketing a quarter of
11 a million people used the drug at that threefold risk
12 level, that would give two attributable cases per
13 year. No study would work that out. We would not be
14 able to.

15 So I think one of the most important
16 things to convey is that if any epidemiologic effort
17 is made to assess, it's going to take years. The drug
18 would have to be in the marketplace for quite a long
19 time before it would be possible to get hold of an
20 association. I think everyone who's looked at it
21 agrees about that.

22 And so whatever your decisions are in

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1 weighing benefits and risks, one's talking about a
2 substantial period of uncertainty, four, five years,
3 something of that kind.

4 The last comment is that this kind of data
5 can help us in one way, is that it gives us some idea
6 of how many exposed cases to expect if there were no
7 effect, knowing the four per million per year,
8 knowing how much drug is used, and that provides a
9 basis against which to judge spontaneous reports.

10 Thank you.

11 ACTING CHAIRPERSON MOLITCH: The FDA's
12 presentation is now open for questions. I'll just
13 start with the first question for you, Dr. Stadel.

14 If the risk of Paget's in this population
15 is one in 100 and the risk of osteosarcoma in the
16 Paget's population is probably one in 100, as you've
17 said, or maybe even one in 1,000 if you wanted to go
18 down to patients that don't have symptomatic disease
19 that's known, then we're still talking about a one in
20 10,000 or even one in 100,000 risk of osteosarcoma in
21 the general population, which is far less than what is
22 actually clinically detected.

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1 So how do we reconcile these two numbers?

2 And then the final thing is that if the
3 sponsor who wishes to exclude everybody with Paget's,
4 how many patients develop osteosarcoma who don't have
5 preexisting Paget's disease? And are we talking about
6 a --

7 DR. STADEL: The majority.

8 ACTING CHAIRPERSON MOLITCH: -- much
9 smaller?

10 DR. STADEL: to the best of my knowledge,
11 in older patient groups where the Paget's association
12 is strongest, it still only accounts for less than
13 half of the osteosarcomas, association in the reports
14 I've read.

15 If anyone knows otherwise, please speak
16 up, but I've really looked for that and I've only
17 found a couple of reports.

18 I think I can address your question in two
19 ways. One is that we don't know. This is Paget's
20 disease. The people who did this know what they're
21 doing, I believe, but we don't know if these very
22 small foci of Paget's disease have the same meaning

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1 with regard to the osteosarcoma risk as the lesions
2 that are large enough that represent the cases that
3 were followed in the clinical series, and I can only
4 assume that it doesn't because otherwise, as you're
5 pointing out, the numbers would work out differently.

6 ACTING CHAIRPERSON MOLITCH: I don't know
7 whether you know or anybody else can help us with
8 this. In patients who develop osteosarcomas in the
9 absence of Paget's disease, do they develop elevated
10 alkaline phosphatase levels? They do?

11 DR. BONE: I can probably add a couple of
12 points here. In a couple of studies where population
13 based or at least reasonable efforts have been made to
14 get a population based estimate of the risk of Paget's
15 associated osteosarcoma, the risk for all patients who
16 could be identified as having Paget's disease, in
17 other words, for this kind of risk population, it's
18 probably in the one to 1,000 to one in 10,000 case
19 range rather than the one to 100, but this is
20 confounded by the variable observation periods.

21 So it's probably something like one per
22 10,000 per year is my assessment from having reviewed

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1 this not too long ago. So I think if you have a ten-
2 year observation period, you might see one out of
3 1,000 patients, and this is roughly what you see in
4 treated Paget's disease with effective therapy. You
5 get a big reduction in the risk. There are only two
6 or three cases that I'm aware of in the world of
7 effectively treated Paget's disease in which sarcoma
8 emerged after that.

9 I think the two main time points at which
10 osteogenesis sarcoma occurs is in kids and in older
11 adults, and the inference is drawn that an important
12 reason for the bump in the older adults is the Paget's
13 disease, but I think Dr. Stadel is right. It
14 certainly doesn't account for all of the cases. You
15 can't get a very solid figure about exactly what
16 proportion, but half is fair.

17 The elevation of the alkaline phosphatase
18 is not uniform, but it's typical of both Pagetic and
19 non-Pagetic osteosarcomas, but it's not something you
20 can absolutely count on, but the majority of patients
21 will do that.

22 DR. STADEL: One of the things I had

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1 hoped, and I talked to the fellow who did this, Roy
2 Altman, who did this analysis of the NHANES data, as
3 to whether anything was known about the alkaline
4 phosphatase levels in these as to whether these small
5 lesions were associated, but unfortunately it does not
6 appear the information is available.

7 DR. BONE: Typically clinically though the
8 smaller the amount of volume of bone involved, the
9 lower the alkaline phosphatase levels. It's a
10 function of both intensity of the Paget's disease and
11 sort of activity at the site, and the extent of the
12 involvement just as you would imagine.

13 DR. STADEL: Thank you.

14 ACTING CHAIRPERSON MOLITCH: Other
15 questions for Dr. Stadel or the FDA? Yes.

16 DR. GRADY: Well, I'm really confused. So
17 the first speaker suggested that the rat low dose was
18 about threefold the human dose. Then Dr. Schneider
19 suggested it was quite a lot lower than that. So do
20 we have -- I mean, I really think this is important
21 because if the rat low dose was the equivalent of
22 about a three-fold higher human dose, you know,

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1 that -- do you know what I --

2 DR. BONE: Maybe I can ask a question
3 here.

4 DR. GRADY: Yeah.

5 DR. BONE: Do I understand correctly that
6 the first presentation, the animal safety data looked
7 at the ratio of the administered doses in micrograms
8 per kilogram? And Dr. Schneider's presentation
9 further adjusted this according to the percentage of
10 the live span of the exposure, not just years of
11 exposure, but fraction of the life span, which would
12 give about a, you know, 40-fold increase in the
13 apparent dosage because it was estimating that the
14 percent of life span for a human would be about two
15 percent of the life span.

16 DR. GRADY: Right. I think that's what
17 the difference is. But let me just understand this.
18 So that in terms just straightforwardly of dose, the
19 equivalent human dose, I mean, the dose that was given
20 to the rats is about threefold the equivalent human
21 dose. Is that your assessment?

22 DR. KUIJPERS: On the database, yes.

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1 ACTING CHAIRPERSON MOLITCH: But that's
2 based on AUC, not the actual --

3 DR. GRADY: Right, and I think it's
4 somewhat of a leap to then divide that by the sort of
5 percent of life span of use. There's no evidence that
6 that's a reasonable thing to do, is there?

7 DR. SCHNEIDER: I don't know what's
8 reasonable. The sponsor has claimed in this analysis
9 that animals were given a lot of drug times a longer
10 time. So all I did in this really hypothetical
11 presentation was to multiply the amount of drug in
12 terms of AUC times the amount of time in these sort of
13 ARB units, that is, percent of life span.

14 Accordingly, what I got was a number like
15 about at the lowest dose three times the AUC, and then
16 I multiplied that by some number, let's say, like ten
17 times the life span units, and that would go up to the
18 highest dose where you have like a 1,000-fold thing
19 where the AUC differences were about 60 and the life
20 span differences may have been -- I don't know -- 25,
21 30, 40 times, something like that.

22 DR. GRADY: And one more question. Also

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1 in the original presentations, the estimated relative
2 risk in the rats at the low dose was 30, around about
3 30. Where did you get three?

4 DR. STADEL: Made it up.

5 DR. GRADY: You made it up. Okay. Just
6 for illustrative purposes.

7 DR. SCHNEIDER: The relative risk that I
8 derived in those calculations were based on a
9 background rate of 0.2 percent in the rat, which Dr.
10 Kuijpers did a meta analysis of all the data, and so
11 that gave me the risks, and then I could formulate a
12 risk range of 1.2 to 1.0 based on that background
13 rate.

14 But as I cautioned, if the background rate
15 is lower, it can go up tenfold or more.

16 DR. STADEL: The Figure 3 was purely to
17 illustrate the relationship of relatively and
18 attributable risk in a low tumor setting. I picked
19 three because I thought it was reasonable to work
20 with. You could even pick a larger relative risk, and
21 it still comes out as something you can't really well
22 deal with.

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1 ACTING CHAIRPERSON MOLITCH: Dr. Sampson.

2 DR. SAMPSON: Dr. Schneider, Dr. Stadel,
3 there's this current, ongoing carcinogenicity study
4 that the sponsor is doing that's got two different
5 start dates and two different durations of treatment,
6 as I understand it. Is there anything, is there any
7 reasonable outcome that one could expect out of that
8 that would increase either of your levels of comfort
9 if you saw the results of that?

10 DR. SCHNEIDER: Perhaps you'll get two
11 answers. Gemma first.

12 DR. KUIJPERS: I guess one possible
13 outcome would be when one starts treating animals at
14 a later age, starting at six months of age, it might
15 be possible that long-term treatment of those animals
16 would not lead to the development of osteosarcomas,
17 which means that the treatment spent in the early age
18 would be critically important, and it would reduce our
19 level of concern because we're treating -- we're
20 planning to treat humans at a later stage in life.

21 DR. SAMPSON: Do you know when that study
22 is scheduled to be completed?

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1 DR. KUIJPERS: I think the results will be
2 available by the end of 2002.

3 ACTING CHAIRPERSON MOLITCH: Are there
4 other questions from the panel?

5 DR. KREISBERG: I'd like to ask Dr.
6 Schneider if you would go back over the statement that
7 you made about the immunometric assay for the 134
8 molecule vis-a-vis native parathyroid hormone. Was
9 the implication there that the level was sustained
10 higher than would be expected, higher than what would
11 be the normal range for a period of time that was
12 longer than the apparent half-life?

13 DR. SCHNEIDER: All I'm suggesting is that
14 in the terminal portions of that projected curve that
15 the sponsor showed that there would be times in which
16 the -- since the lower limit of detection was 50
17 picograms per mL, that there would be times in which
18 an undetectable level would, in fact, be accompanied
19 by a level of biologically active hormone that was
20 twice the upper limit of normal on a molar basis, that
21 is, that that would translate into about a 120 some
22 odd picograms per mL of PTH 1 to 84.