

1 And so that one can't really say
2 specifically. One can project the trajectory of these
3 curves, but one cannot do that with absolute precision
4 during the terminal elimination phases.

5 Furthermore, the statement that the total
6 elevation of PTH over 24 hours is less than what is
7 normally seen I don't think could be substantiated on
8 the basis of those data.

9 Now, what this means I don't know. I mean
10 there's certainly -- if one just looks at calcium and
11 so on, we've discussed that, but strictly speaking, my
12 impression is that, that in the terminal elimination
13 phases of the curve, an undetectable level can still
14 exist with twice the upper limit of normal on the
15 basis of bioactivity.

16 ACTING CHAIRPERSON MOLITCH: Other
17 questions from the panel?

18 DR. GRADY: Can somebody clarify for me
19 how good the data is that there's no increase in risk
20 of osteosarcoma in primary hyperparathyroidism? I
21 mean, you know, this has been mentioned a couple of
22 times, but what kind of studies are these, and what

1 are the denominators and so forth?

2 DR. STADEL: About all I can tell you is
3 that I went through PubMed looking for everything that
4 dealt with the issue and could not find any evidence
5 of convergence. They were usually a series of
6 patients with hyperparathyroidism.

7 There was one report of osteosarcoma in a
8 patient with hyperparathyroidism, and the authors of
9 that had done a lot of searches of the literature on
10 hyperparathyroidism and had not been able to find any
11 other cases, and that was about all I can -- I did not
12 find anything like, for example -- I really didn't
13 find any good studies of osteosarcoma in the
14 literature. It's too rare.

15 DR. MITLAK: Dr. Grady, if I could, in my
16 presentation I included some work that we had done
17 using the national cancer registry in Sweden. We had
18 searched the literature in the same way as Dr. Stadel
19 and had found this one single case.

20 We then went in a systematic way through
21 the records in that database covering 40 years and the
22 entire population in Sweden. Dr. Unell (phonetic),

1 who assisted us, both searched the hospital discharge
2 database to look for patients who had been
3 hospitalized with a diagnosis of hyperparathyroidism,
4 and we also looked in the cancer database for patients
5 who had been entered for reason of adenoma, which by
6 law in Sweden needs to be entered.

7 We crossed both of those groups of
8 patients, about 12,000 patients, 114,000 patient-years
9 of exposure, with a set of terms that might include
10 osteosarcoma, and as I had stated before, found in no
11 case was there both diagnoses in the same patient.

12 DR. BONE: I had a couple of questions
13 about the emergence of timing of some of these
14 laboratory abnormalities. We had some episodes of
15 hypercalcemia and hypercalcuria (phonetic), and the
16 issue was, you know, didn't the adjustment of the
17 patient's calcium intake bear on this question about
18 need for monitoring.

19 Is there an identifiable time period in
20 which these increases in serum reviewing calcium
21 typically become apparent or can this be at any time
22 during the exposure?

1 That might be a question for either Dr.
2 Stadel or Dr. Schneider.

3 DR. SCHNEIDER: In the review of the
4 clin.-pharm. data and actually the population based
5 data, the hypercalcemia was the peak in the calcium,
6 was about four to six hours after the dose. I guess
7 anyone on the sponsor's side could --

8 DR. BONE: I meant in terms of weeks of
9 exposure.

10 DR. SCHNEIDER: Oh. Oh, I'm sorry.

11 DR. BONE: For example, with patients who
12 were treated with calcitriol, most of the patients who
13 are going to develop hypercalcuria or hypercalcemia
14 manifest this within about three months, which is when
15 the peak calcitriol levels that we saw were also
16 achieved.

17 My question was: for example, does this
18 speak to monitoring patients at three months, just for
19 an example?

20 DR. MITLAK: If I could, we have looked at
21 this question, and again, while we have shown that the
22 elevations in calcium are transient, there is no

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 increase in calcium prior to the next dose.

2 We did look at the question that you have
3 suggested from the Vitamin D literature. In our
4 analysis of the data, if patients had a calcium
5 measurement within the first three months that was not
6 elevated, there was a very low likelihood that they
7 would have an elevated calcium in any subsequent point
8 during the study.

9 DR. BONE: Well, that's kind of
10 qualitatively what I was getting at, but I'd be very
11 interested in the actual numbers. I'm sure you
12 actually have that, the time point at which the dose
13 adjustments for the calcium are made and at which
14 those elevations that result in intervention occurred.

15 And maybe after lunch you could give us
16 those data.

17 The same question for the creatinine
18 elevation. When did that become apparent?

19 DR. GRADY: This is a question for the
20 sponsor, and I think, of course -- I'm sorry. I can
21 wait.

22 ACTING CHAIRPERSON MOLITCH: We'll let

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 that wait until this afternoon.

2 Any other questions for the FDA speakers?

3 (No response.)

4 ACTING CHAIRPERSON MOLITCH: Then I think
5 we'll move to the final phase of this morning's
6 session, which will be the open public hearing. We
7 have three speakers who will present comments, Ronald
8 White, Deborah Zeldou, and Dr. Peter Lurie.

9 And if they would come up to the front
10 microphone and please speak your name, your sources
11 from where you're coming, and any potential conflicts
12 and financial conflicts that you may have with regard
13 to your statement.

14 Dr. White.

15 DR. WHITE: Good afternoon. I'm Ronald
16 White, Assistant Executive Director for Education,
17 Research, and Community Affairs at the National
18 Osteoporosis Foundation.

19 On behalf of our more than 350,000 members
20 and donors, I want to thank you for the opportunity to
21 testify before you today.

22 The National Osteoporosis Foundation is

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealgross.com

1 the nation's leading nonprofit voluntary health
2 organization dedicated to reducing the widespread
3 prevalence of osteoporosis through programs of
4 research, education, and advocacy.

5 The NOF is proud of its broad base of
6 funding support which comes from large and small
7 individual contributions, memberships and memorials,
8 foundations and corporations including Eli Lilly &
9 Company, federated campaigns, special events, and
10 federal and state agencies.

11 One of our most successful federally
12 funded programs is the NIH osteoporosis and related
13 bone diseases national resource center, which is
14 located on our Washington, D.C. headquarters facility.

15 Osteoporosis is a widespread disease that
16 affects the health of ten million Americans and is
17 responsible for an estimated 1.5 million bone
18 fractures each year. One third of American women over
19 age 50 will eventually have the vertebral fracture,
20 and fractures also occur in younger people, as well,
21 due to secondary causes.

22 Approximately 12 to 24 percent of hip

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 fracture patients will die in the year after fracture,
2 usually from fracture related complications such as
3 pneumonia or blood clots in the lung or from the
4 surgery to repair the fracture.

5 Quality of life is greatly impaired in
6 persons with severe osteoporosis not only because of
7 pain and deformity, but also because of limited
8 ability to move and be active, as well as the fear of
9 future fractures.

10 In addition to the significant impacts on
11 health, osteoporotic fractures result in medical,
12 nursing home, and societal costs of approximately \$14
13 billion each year.

14 The Foundation is very encouraged by the
15 evidence from the research literature of fracture
16 reduction in osteoporotic patients using Forteo. The
17 availability of a treatment option for osteoporosis
18 that builds bone mass and improves bone architecture
19 would be an exciting addition to currently available
20 anti-resorptive medications.

21 Thank you very much for your attention.

22 ACTING CHAIRPERSON MOLITCH: Thank you.

1 Let's hear, please, from Deborah Zeldou.

2 MS. ZELDOU: Good morning. My name is
3 Deborah Zeldou, and I'm the Senior Director at the
4 Alliance for Aging Research.

5 Thank you for the opportunity to come
6 before this committee today to address the promising
7 findings of PTH.

8 The Alliance for Aging Research works to
9 stimulate academic, governmental and private sector
10 research into the chronic diseases of human aging. We
11 receive funding from a wide mix of foundations,
12 private philanthropies, corporations and individuals.

13 For the last 12 months, contributions to
14 the Alliance from Eli Lilly & Company have represented
15 less than 3.5 percent of our total operating budget,
16 income in the form of unrestricted educational grants.

17 As the Strategic Director of a not-for-
18 profit group eager to find cures, preventions, and
19 overall better health and vitality for the elderly, my
20 views on osteoporosis reflect the medical needs of the
21 growing population of older Americans. Our
22 organization takes up the cause of the vast majority

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 of Americans who fervently wish to benefit from
2 scientific discoveries that improve the human
3 experience with aging.

4 Survey research we conducted in June tell
5 us that most Americans believe the federal government
6 has a critical role to play to prepare the way for new
7 medical breakthroughs and to hurry applications of
8 science and health care in order to relieve human
9 suffering and improve the quality of life for their
10 family members and for themselves.

11 Osteoporosis is one of our most
12 significant public health challenges. Experts predict
13 that the number of hip fractures for both men and
14 women will more than double in the next 50 years with
15 the pending senior boom. Because this insidious
16 disease can operate quietly and without recognition
17 for decades, the silent thief steals more than bone
18 mass. It takes an enormous toll on human life, often
19 crippling its victims and causing them pain, grief,
20 permanent disability, loss of independence, diminished
21 quality of life, and sometimes death. It burdens our
22 health system and care giving infrastructure.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 Osteoporosis and the 1.5 million
2 associated fractures it causes cost our nation 14
3 billion annually or 38 million a day in medical
4 expenses alone. The graying of America is expected to
5 quadruple annual medical costs more than 60 billion by
6 the year 2030.

7 Better information and education about the
8 disease and improving technologies are brightening the
9 outlook for people with osteoporosis. Updated
10 labeling by the FDA, for example, on foods and
11 nutritional supplements, on calcium content in
12 consumable products has helped guide consumers to
13 purchase those items that help build and maintain
14 strong bones.

15 Using diagnostic tools, physicians today
16 can identify patients who already have osteoporosis,
17 who are at risk for it before fractures occur.

18 New medications are also available to
19 prevent or treat this disease, and advances in
20 research are being made each day. Despite these
21 advances, there is no cure, and new approaches to
22 preventing, detecting, and treating osteoporosis are

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 urgently needed.

2 Studies suggest that osteoporosis may be
3 a quickly progressing disease once a fracture occurs,
4 making prevention of future fractures critical for
5 those patients who already have suffered from them.

6 Current treatments for osteoporosis only
7 slow down or stop bone destruction. They do not have
8 the ability to stimulate the formation of new bone.
9 The suffering from osteoporosis need a treatment that
10 can do more than slow or stop bone loss. PTH at this
11 juncture shows promise for fulfilling this unmet need.

12 We are hopeful about the promise of PTH in
13 improving the quality of life for millions of
14 Americans as they age. We urge the FDA and its
15 advisors to carefully consider the many benefits to
16 patients and quickly move advanced therapies for the
17 treatment of osteoporosis to the mainstream.

18 Thank you.

19 ACTING CHAIRPERSON MOLITCH: Thank you
20 very much.

21 We'll now hear from Dr. Lurie.

22 DR. LURIE: Good afternoon. I wanted to

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 spend my time just summarizing the comments that have
2 been handed out and should be on your table, and in
3 particular, those things that have been relatively
4 underemphasized so far.

5 ACTING CHAIRPERSON MOLITCH: Please state
6 your financial --

7 DR. LURIE: Oh, I'm sorry. I have no
8 financial conflict of interest whatsoever. Our group
9 takes no money from either government or industry.

10 The first point with regard to the
11 efficacy study GHAC in women that has not been
12 mentioned is that, in fact, many of the vertebral
13 fractures, in particular, that were mentioned were, in
14 fact, silent.

15 I quote from the Medical Officer review.
16 "Because the majority of morphometric vertebral
17 fractures are clinically silent, it is difficult to
18 evaluate the overall direct clinical impact of these
19 data taken alone."

20 Indeed, the Medical Officer continues,
21 "The sponsor did not provide an analysis of clinical
22 with symptomatic vertebral fractures in this

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 application." I think that's something very important
2 to consider.

3 Another thing we haven't hear much about
4 in all of the laudatory comments about the efficacy of
5 this drug is what the number needed to treat to
6 prevent a nonvertebral fracture is, and we've done
7 that little calculation. It turns out to be for the
8 20 microgram dose 28 people over the 19-month course
9 of the disease. So it certainly is an effective drug,
10 but I think we need to remember how many people will
11 need to be treated and exposed to potential risks in
12 order to benefit a single person.

13 And finally, Dr. Kreisberg did ask clearly
14 about the question of quality of life, and the sponsor
15 didn't make it very clear what the results of the
16 quality of life studies in women are.

17 There was a quality of life study done,
18 and there's no benefit whatever for the drug over
19 placebo. This is true for both the studies in men, as
20 well as the studies in women.

21 Turning now to the efficacy study GHAI in
22 men, obviously the most important point here is that

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 the primary outcome measure was the lumbar spine BMD
2 and not fracture.

3 Also, there's some lack of clarity.
4 According to the medical officer review, the subjects
5 in the end were only followed for approximately 300
6 days or ten months, not as long as sometimes
7 advertised.

8 But most importantly, quoting again from
9 the Medical Officer review, they called into question
10 the importance of BMD data in men as opposed to those
11 data in women, and a quote again from the Medical
12 Officer. "The risk estimates for a given BMD T-score
13 in men are not as well determined as in women.
14 Whatever the cause of the uncertainty, the clinical
15 impact changes in BMD will be more difficult to judge
16 in men compared to women in the absence of fracture
17 data. For that reason, we don't think that in the
18 absence of fracture data this drug should be approved
19 for men."

20 Moreover, the Medical Officer goes on to
21 say, "Since we have no fracture efficacy data for
22 either drug in men" -- this mean alendronate or the

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 PTH drug -- "we have no fracture data for either drug
2 in men, it is difficult to conclude that the 20
3 microgram per day offers any advantage over current
4 therapy."

5 So having talked about efficacy, let me
6 turn then to safety and make the following points that
7 I think in my view make it rather clear that these rat
8 data are absolutely relevant and make a compelling
9 case for the carcinogenicity of PTH in rats and
10 conceivably in humans as well.

11 Most of the landmarks of a positive and
12 important rodent carcinogenicity study are present in
13 this one. Firstly, the increases in tumors are
14 substantial, and they are statistically significant.
15 They are dose related. There is no no effect level
16 identified. There could be sarcomas occurring in
17 these rats at even lower doses than those tested.

18 The higher the exposure, the shorter the
19 time to tumor initiation and death. The increases in
20 tumors occur in both genders.

21 The exposure levels are, in fact, small
22 multiples of human exposures. Dr. Grady asked about

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 this. The area under the curve was measured at 24
2 months and was threefold the human exposure.

3 At 18 months, it was only 1.6-fold higher
4 than the human exposure. So I think that's worrisome.

5 As it has been emphasized, osteosarcomas
6 are very rare tumors in animals. So the appearance of
7 this in these studies is very compelling.

8 Moreover, as has been noted, the tumors
9 are mechanism based. Bone is where you would expect
10 to see the tumors. Bone is where we see the tumors.

11 Moreover, because the formation of
12 osteosarcomas is mechanism based, the fact that there
13 are no positive mutagenicity of genotoxicity studies
14 is basically irrelevant.

15 Let me also point out that the FDA has
16 noted, and there was glancing mention, I think, of
17 this in Dr. Kuijpers' presentation, that there are
18 examples of other parathyroid hormone induced
19 osteosarcomas in other related parathyroid hormone
20 drugs, and so, again, it adds to the likelihood that
21 this is no false positive, to be clear.

22 Let me just point one other thing out

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 about the histology that was done of these animals.
2 They did only look in four bones in a consistent
3 fashion for tumor. So it's quite possible that there
4 were other tumors that were hiding and simply not
5 detected, and even more of the animals might, in fact,
6 have had osteogenetic sarcoma than appears to be the
7 case.

8 My presentation also includes in the
9 written form mention of some of the renal,
10 cardiovascular, and hypocalcemic concerns that have
11 been raised by the committee. So I won't reiterate
12 those.

13 To close then, in our view we do not
14 believe that the data presented by the company provide
15 an adequate rationale for approving this drug in men.
16 There's no evidence that the drug reduces fractures.
17 There's no evidence the drug is any benefit in quality
18 of life.

19 The carcinogenicity studies in our view
20 are very strong, and in this case, we think that this
21 more than outweighs any theoretical benefit that might
22 be gained for the drug in men.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 Clearly, it's a more difficult case
2 regarding the situation in women, but again, we should
3 remember that the absolute fracture reductions
4 themselves are not large, and many of the fractures
5 presumably are asymptomatic, and there's no overall
6 evidence of benefit on the patient's quality of life.

7 Moreover, there are already four drugs
8 that are approved by the FDA for the treatment of
9 osteoporosis, and so we believe much more narrowly
10 that the risk-benefit assessment for women tips
11 against approval as well.

12 However, should the committee choose to
13 vote in favor of approval, there are at least four
14 things that we think you need to do to minimize the
15 risk to patients.

16 First, the drug should be restricted to
17 use as a second line drug to minimize the extent of
18 exposure to the overall population.

19 Second, there needs to be a black box
20 warning, particularly on the osteogenic sarcoma
21 findings.

22 Third, there is a need for the patients

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 for a requirement for a med. guide for patients, and
2 by this we don't mean handing out the doctor's patient
3 package insert, which patients do not understand, nor
4 do we mean the drug company funded documents that are
5 handed out as patient information leaflets in
6 pharmacies which are very often misleading. We mean
7 an FDA mandated med. guide.

8 And finally, we agree with the idea of
9 establishing registries and the like to identify those
10 rare patients with osteogenic sarcoma who show up in
11 order to do case control studies.

12 Thank you.

13 ACTING CHAIRPERSON MOLITCH: Thank you for
14 your comments.

15 At this point we'll take a lunch break and
16 we will resume at 1:45.

17 (Whereupon, at 12:37 p.m., the meeting was
18 recessed for lunch, to reconvene at 1:45 p.m., the
19 same day.)
20
21
22

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

2 (1:49 p.m.)

3 ACTING CHAIRPERSON MOLITCH: Before we
4 start our general discussion this afternoon, Dr.
5 Orloff is going to have some comments for us.

6 DR. ORLOFF: Thank you.

7 Good afternoon. The first thing I want to
8 do is to thank the sponsor and representatives from
9 that side and the FDA reviewers and their
10 presentations, and the testimony in the open public
11 hearing. Everything was clear, and I think we're
12 ready to proceed with the discussion.

13 I have a few remarks to make before the
14 discussion. This is nominally the charge to the
15 committee. As I said yesterday, I'm not going to read
16 the questions. I think they're fairly clear as
17 written. If any clarifications or modifications are
18 required as we go along, we'll be happy to add that as
19 needed.

20 What I'd like to do is take a few minutes
21 and summarize the FDA's concerns and conclusions after
22 review of this application, most of which I think, as

1 I said, were quite clear in the presentations that you
2 heard before lunch.

3 With regard to efficacy, I think it's been
4 clearly stated that we concur generally with the
5 sponsor that efficacy has been demonstrated, and that
6 the weight of evidence from the preclinical studies,
7 from the clinical studies in both men and women, and
8 women to show increases in BMD and reduction in the
9 risk for morphometric fractures and in men to show
10 increases in BMD, do support the efficacy of
11 teriparatide.

12 The issue of the clinical import of the
13 largely asymptomatic vertebral or the impact on
14 largely asymptomatic vertebral fractures that was
15 raised at the end of the last session, I think, is
16 something that bears some comment.

17 As I think most people are aware, we do
18 rely on increased BMD and a reduction in risk for
19 morphometric fractures as valid surrogates, if you
20 will, for an expectation of clinical benefit with
21 regard to reduction in perhaps more clinically
22 significant fractures.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 And so as Dr. Schneider made clear in his
2 presentation, the data that have been presented with
3 regard to efficacy for this drug do or would generally
4 support approval on the basis of efficacy.

5 What we have before us and what we're
6 interested in hearing the committee comment on is the
7 situation in which there is a significant safety
8 concern with the drug, at least as far as we're
9 concerned. I'll touch more on that in a second.

10 But in light of that significant concern,
11 I think it is reasonable to at least be aware that an
12 effort at a formal risk-benefit analysis may become
13 more difficult in the absence of any evidence of hard
14 clinical benefit. I hope that was clear.

15 As I think was understood from the FDA
16 presentations, we do have lingering concerns, if you
17 will, or even significant concerns over the findings
18 of osteosarcoma in rats, and though we agree that rat
19 bone differs from human bone, we also realize, and the
20 other arguments for and against the sort of
21 extrapolation from those studies to an expectation of
22 human risk were discussed in the presentations.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 We also realize that the size and duration
2 of the exposures in the Forteo human studies was
3 adequate only to exclude adverse events, and in this
4 case the risk of osteosarcoma occurring at relatively
5 high rates, and Dr. Stadel and others have touched on
6 that problem.

7 So to us I think the conclusion is that
8 the matter is unresolved. So for the committee, while
9 we realize that like the sponsor and the FDA, you do
10 not have a crystal ball to definitively refute or
11 support a hypothesis of osteosarcoma risk, we are
12 interested obviously in your thoughts and discussion
13 on this issue on whether and what further
14 investigations may be needed before or after approval
15 and how this theoretical risk, albeit arguably
16 biologically plausible, should be managed should the
17 drug be approved for marketing.

18 I want to call the committee's attention
19 and the audience's attention to Dr. Holmboe, who is
20 present at the end of the table here across from me,
21 who actually brings to the committee as a consultant
22 an expertise in risk management, and I would encourage

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 comments from him and questions to him from members of
2 the committee.

3 With regard to the question we'll be
4 asking specifically, we'll ask you in the event of an
5 approval should there be restrictions on the use of
6 this drug by risk category, that is, by fracture risk
7 category; by response to other drugs, that is to say,
8 for example, second line therapy in treatment failures
9 on other established effective therapies or presumed
10 effective therapies; and how the risk of osteosarcoma,
11 should you feel it's significant, should be
12 communicated; and, again, how it should be assessed
13 over time across the populations exposed. You heard
14 some discussion of plans in that regard. We would
15 encourage further discussion or comments.

16 And I think with that I'll let the
17 discussion proceed. So I'm going to turn it back over
18 to Dr. Molitch.

19 Thank you very much.

20 ACTING CHAIRPERSON MOLITCH: Thank you,
21 Dr. Orloff.

22 And the floor is now open for discussion

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 amongst members of the panel, who can address
2 questions to each other, to the sponsor, to the FDA,
3 and make comments in general.

4 Dr. Gelato.

5 DR. GELATO: I just wonder if we could get
6 some comments from our consultant on the risk-benefit
7 ratio and what his thoughts are in this regard. It
8 might be helpful.

9 ACTING CHAIRPERSON MOLITCH: Thank you.

10 DR. HOLMBOE: I think when you consider
11 the risk management, it's helpful to break that down
12 into its component parts first. I think of three main
13 elements.

14 The first is identification of the risk
15 both from a population point of view, but also from a
16 patient point of view. So starting at the population
17 point of view, we know at this point that there appear
18 to be three main categories.

19 The first is what I call pathologic, which
20 has the greatest concern around the osteosarcoma risk,
21 which at this point has been found only in an animal
22 model, but at fairly high rates, as pointed out by the

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 FDA. And so that certainly raises a lot of concern
2 and will clearly raise a sense of dread and concern in
3 patients any time you talk about a risk for cancer in
4 taking a drug. So that's the first issue.

5 Second is in the metabolic things we heard
6 about, and then finally the symptomatic, which are
7 less certainly serious than the first that everybody
8 is concerned about.

9 The second is assessment. You know, how
10 are we going to assess these risks if this drug is
11 approved? As we heard earlier, there's a problem with
12 the signal. By that I mean that we're talking about
13 a condition, osteosarcoma, that occurs at a fairly low
14 rate, somewhat rare.

15 So, therefore, how are we going to monitor
16 that down the road?

17 We also have to be concerned as we think
18 about assessing risk, if approved, about what's going
19 to happen as it's used in expanded populations. Most
20 of these trials are really designed to look at
21 efficacy, as we've heard.

22 The issue will then become is this

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 effective from an epidemiologic point of view when we
2 put it out in the general population, and that
3 patients who would not have been enrolled in the
4 original trials will be exposed to this drug with
5 other co-morbidities, that may enhance their risk in
6 unknown ways.

7 Finally, this drug is likely to be used in
8 combination therapy, even if not approved for such.
9 How are we going to monitor that risk? How are we
10 going to assess that?

11 And then finally, as we heard, there are
12 some issues in methodology regarding assessment, case
13 control, population databases, things like the SEER
14 database.

15 The one thing we haven't talked a lot
16 about yet today is communication, and that
17 communication has to go across several levels.

18 The two most important, I believe, are
19 going to be communication to the physicians who would
20 use this drug, and the second is going to be how that
21 communication then occurs with the patient, and there
22 are a number of challenges, I think, that confront.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 When you consider informed decision
2 making, there are a number of elements that need to go
3 into that, and I think it's very important to place
4 that context with regard to Forteo and how that might
5 look between a patient and physician contact.

6 Clarence Braddock and Wendy Levinson have
7 developed a very nice model, University of Chicago,
8 with the elements that need to go into that. Three of
9 those elements are, one, to discuss the risk and
10 benefits of the therapy with the patient.

11 Another element is to discuss the
12 uncertainty surrounding the therapy, and I think,
13 again, that's one of the big issues for this drug.

14 And then finally, discuss the
15 alternatives.

16 Part of the difficulty here is that we
17 don't have a lot of head to head comparisons with this
18 drug, and so that's going to be a real challenge for
19 the physician.

20 The other thing is what should the
21 physician tell the patient in how should that baseline
22 assessment look like. I'd be curious to hear from the

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 sponsor about what they think should be part of the
2 baseline assessment for all patients: calcium, X-
3 rays, et cetera, and how they feel that should be
4 communicated to the patient.

5 From a personal point of view, I think
6 that it is important to disclose the potential risk of
7 osteosarcoma, again, if this drug should be approved,
8 recognizing that it may be very rare.

9 I think that we do have some history to
10 look back that may help us. It was mentioned earlier
11 by the sponsor this morning regarding omeprazole and
12 carcinoids. There's a tremendous amount of concerns
13 about gastronomas that was not realized. However, the
14 fact that it was not realized did not reduce the
15 burden or need to inform patients of this risk.

16 And as a general internist using this drug
17 almost 15 years ago, I can tell you that was part of
18 the discussion and I think an important part of the
19 discussion. So I think that's something else we need
20 to consider.

21 So as you think about risk management,
22 it's really those elements, identification, assessment

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 and communication, that really need to be considered,
2 and I think we do need to spend a little bit of time
3 thinking this afternoon if this drug is approved that
4 that patient-physician communication needs to be part
5 of the dynamic because that's most likely where
6 adverse reactions and problems are going to occur.

7 We have seen that with other drugs, for
8 example, Cisapride. Despite multiple attempts by that
9 sponsor to inform physicians of the risk of that drug,
10 the drug continued to be used inappropriately, and so
11 I think, again, those are other things that we have to
12 think about as we look at the risk issues surrounding
13 Forteo.

14 ACTING CHAIRPERSON MOLITCH: Thank you.

15 Other comments?

16 (No response.)

17 ACTING CHAIRPERSON MOLITCH: I'll start
18 then if nobody has any yet at this point. I'd like to
19 ask the sponsor about one of the concerns that you
20 raised with the osteosarcoma was that this was unique
21 to the rat model because of the differences in the
22 remodeling or lack of remodeling, if you will, in the

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 rat model.

2 So what has been done in other species
3 that do have remodeling to start drug very early in
4 the weanling stage and then continue it lifelong?

5 I presume that there are other long-term
6 studies going on in different species that can shed
7 light on this. Can the sponsor answer that, please?

8 DR. VAHLE: Certainly. Let me do that in
9 two ways. First, let me discuss the differences in
10 remodeling and some of the differences between
11 primates and rats. Would that be useful as a part of
12 the response?

13 If I could have slide 4233, please.

14 It is true that rats differ in skeletal
15 biology from humans, including primate, and then I'll
16 discuss what our follow-up studies in primates are.

17 With respect to the remodeling that you
18 mentioned, two things to consider. One is rats lack
19 the ability to break down cortical bone prior to
20 forming new cortical bone. So they have really little
21 or no cortical osteonal remodeling while that
22 particular process is present in humans, as we

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 mentioned during our presentation.

2 They also continue to grow throughout
3 life, as opposed to humans or primates where growth
4 ceases at adolescence.

5 Another, as I understood it, portion of
6 your question was around bone turnover, and this
7 really combined a physiologic difference with some
8 differences in duration kinds of comparisons that may
9 be useful in your deliberations.

10 If you evaluate rats for a given period of
11 time, say, two years, they will have undergone
12 approximately 25 to 30 bone turnover cycles in that
13 particular time. This is in contrast to humans who
14 during that time would have one to two bone turnover
15 cycles or the Cynomolgus monkey, two to four bone
16 turnover cycles.

17 So the second part of the question: what
18 have we done to address that? Briefly mentioned in
19 the response this morning, and I could just bring back
20 up slide 4222, additional studies in primates are
21 limited to the 18 month treatment duration followed by
22 a three-year observation period.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 So in respect to a species that has
2 similar bone physiology remodeling types of phenomena,
3 this study which we mentioned earlier is the extent of
4 our evaluations.

5 ACTING CHAIRPERSON MOLITCH: And what is
6 the background osteosarcoma rate in the monkey?

7 DR. VAHLE: Unfortunately the spontaneous
8 background rate for osteosarcomas has not been
9 defined. We are not able to find in the literature
10 any background incidence rate. There are sporadic
11 occurrences of osteosarcoma reported in the literature
12 for monkeys. These are individual case reports, but
13 not population databases.

14 Part of the difficulty with that is
15 monkeys come from many different sources. The
16 demographics, if you will, are very different. So we
17 do not have a firm estimate.

18 If we were pushed to speculate, we would
19 say it's somewhere between the four in a million that
20 was quoted for humans in that particular population.
21 Again, these are mature ovariectomized monkeys, and
22 the rate in rats, which is higher, about .2 percent.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 ACTING CHAIRPERSON MOLITCH: And you
2 haven't studied other species?

3 I mean if you're trying to say that this
4 is unique to the rat, I don't know that that's true
5 yet. I'd like to see some other data in other species
6 to show that it's unique to the rat.

7 It would be nice to look at another
8 species that has a certain background rate and do
9 enough of a population of long-term studies to show
10 that it doesn't exist in those animals.

11 DR. VAHLE: The reason we chose the
12 Cynomolgus monkey as the appropriate species, and this
13 was in agreement and consultation with the agency, is
14 because it has the most similar skeletal biology.
15 Many of the other species do not have significant
16 osteonal remodeling, and likewise, it is difficult to
17 find other animal species where the known rate of
18 osteosarcoma is precisely defined.

19 We're able to define it in the rat simply
20 because we have large, two-year studies from which to
21 determine a database.

22 ACTING CHAIRPERSON MOLITCH: Dr. Levitsky.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 DR. LEVITSKY: If this --

2 DR. GRADY: Just before we leave that, can
3 you tell us the sample size in those two studies?

4 DR. VAHLE: The sample size in the follow-
5 up monkey study, which is 18-month duration, is 30
6 monkeys per group.

7 DR. LEVITSKY: If this were to be approved
8 and used as a second line drug, which one would assume
9 would be its use because of the injection nature of
10 the treatment, it would be important to have some idea
11 of or at least an informed physiologic guess about
12 what would happen to people who had been receiving
13 long acting bisphosphonates for five years and then
14 were given this drug.

15 Is there anyone in this room who feels
16 that they could comment on what they think would
17 happen since I gather there aren't any hard data?

18 ACTING CHAIRPERSON MOLITCH: I presume the
19 sponsor has some data in animals showing the combined
20 use.

21 DR. LINDSAY: I can comment from the point
22 of view of clinical -- short-term clinical trial data

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 which we published in the Journal of Clinical
2 Endocrinology about two years ago, in which we looked
3 at people who were already on alendronate ten
4 milligrams a day.

5 And we looked for biochemical responses
6 similar to the ones that I showed this morning and
7 demonstrated an almost identical response in terms of
8 osteocalcin increases and later increases in
9 antilo peptide (phonetic) in the presence of
10 alendronate as we had seen in the presence of HRT.

11 DR. LEVITSKY: Are there any data related
12 to bone mineralization? They're all short term?

13 DR. LINDSAY: The human data are short
14 term. There are animal data in rodents that are
15 mixed. There are animal data in aged ewes that are
16 also mixed. There are some positive studies and some
17 neutral studies.

18 Part of the problem is that in the animal
19 data relatively large doses of bisphosphonates were
20 used, in excess of what you'd normally use in a human
21 situation.

22 So the meaning of those studies in terms

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 of human responses is far from clear.

2 Dr. Potts is reminding me that similar
3 studies in rodents with HRT and in humans with HRT
4 have shown essentially no difference in response, and
5 there is a cyclical study in which parathyroid hormone
6 was used with a calcitonin, and again, there was no
7 essentially negative outcome.

8 DR. LEVITSKY: The problem though with the
9 bisphosphonates is they're not like HRT. They're
10 there and they're there and they're there, and that's
11 what I'm wondering about.

12 DR. LINDSAY: Yes, and in a human we only
13 have short-term biochemical data.

14 ACTING CHAIRPERSON MOLITCH: If we can
15 continue just with this, I understood that perhaps
16 some of the protective effect in the human against the
17 osteosarcoma is, in fact, the remodeling that occurs
18 against a constant stimulation.

19 If we do combine therapy with an anti-
20 resorptive drug that's quite potent like alendronate
21 or residrinate and then add the PTH, does that affect
22 this protective effect at all for the development of

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 osteosarcoma at least in theory?

2 I realize there are probably no data, but
3 would that alter our assessment of the risk or should
4 that alter it?

5 Maybe one of the bone biologists can help
6 us with this.

7 DR. VAHLE: First, let me clarify a
8 statement that may have been taken in error. We do
9 not suggest the fact that humans or monkeys have
10 cortical remodeling as being protective. We're simply
11 highlighting that as one of the differences. So I can
12 clarify on that.

13 Then I'd ask if there are any of the
14 consultants who'd like to address the concept of the
15 combination therapy any further than Dr. Lindsay
16 already did.

17 So we are simply pointing out that it is
18 one of the differences between the two species. We're
19 not suggesting that it's causal or protective.

20 ACTING CHAIRPERSON MOLITCH: Dr. Bone,
21 we've got about 20 bone biologists over there. Would
22 any of you like to comment on this?

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 My question is: would the risk of
2 osteosarcoma in relationship to PTH be affected in any
3 way by the concomitant administration of a
4 bisphosphonate in theory at least?

5 DR. BONE: Well, I think if we had a
6 theory, a specific theory about how -- if parathyroid
7 hormone does increase the risk of osteosarcoma, how it
8 might do that, then we would be able to better answer
9 the question. We know that like C-fas (phonetic) is
10 induced and all kinds of things are.

11 There's a very complex cascade across two
12 signaling pathways downstream of PTH, and we don't
13 know if there is an effect, and if so where in all of
14 that it could be.

15 Bisphosphonate therapy appears to
16 dramatically reduce the risk in Paget's disease, but
17 of course, the presumed mechanism is completely
18 different. I think the only thing we can say is that
19 there's nothing whatsoever to suggest that this
20 phosphonate therapy would increase the risk in any
21 independent way or probably modify the risk very much.

22 ACTING CHAIRPERSON MOLITCH: It sounds

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 like if anything, it might have a protective effect
2 and probably not an additive effect.

3 DR. BONE: I wouldn't want to go that far
4 to say that there would be a protective effect, but I
5 don't think there's any reason to think it would --
6 that bisphosphonate therapy would increase the risk
7 here.

8 To the extent that osteoblast activity
9 might be indirectly stimulated by osteoclast (phonetic
10 activity, which does appear to be the case in
11 spontaneous remodeling without parathyroid hormone
12 stimulation, modulation of that bone resorption and
13 decreased release of growth factors from the matrix
14 might conceivably have a moderating effect here.

15 But I think the main point is I think it's
16 hard to imagine a mechanism by which the
17 bisphosphonate would add to the risk.

18 DR. LEVITSKY: Henry, do you think that,
19 say, five years of bisphosphonate treatment would
20 alter the response to PTH in terms of its ability to
21 enhance bone remodeling and increase bone mineral and
22 reduce fracture?

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 DR. BONE: Well, I don't even know who's
2 going to win to the World Series. So --

3 (Laughter.)

4 DR. BONE: -- I think you could reasonably
5 expect that patients who had prior or continuing
6 bisphosphonate therapy would be responsive to
7 parathyroid hormone. Whether their response would be
8 similar to or a little bit less or a little bit
9 greater than that that we see with parathyroid hormone
10 alone, I think that's an empirical question and we
11 could make up stories either way.

12 I think it would be unlikely that the
13 patients would fail altogether to respond. Some
14 people think that you might see a better net effect in
15 cortical bone with a combination, but that's, again,
16 a speculation.

17 The idea behind that would be that
18 controlling bone resorption at the same time that you
19 enhance bone formation might give you a positive focal
20 remodeling balance and perform wonders, but I think
21 that probably most people here in the bone field would
22 expect patients who have had extended treatment with,

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 for example, alendronate, which is where there's the
2 greatest relevance because of its availability for the
3 longest period of time, would probably respond, you
4 know, but to predict whether there would be a
5 modulation of the response would be, I think,
6 guessing.

7 ACTING CHAIRPERSON MOLITCH: Dr. Neer, did
8 you have a comment?

9 DR. NEER: I just wanted to make a point
10 of information that the committee might want to be
11 aware of with respect to Dr. Levitsky's question, and
12 that is that the National Institutes of Health is
13 currently funding several studies, including one at
14 our institution to try to answer exactly that question
15 because nobody knows what the answer is.

16 ACTING CHAIRPERSON MOLITCH: Marie.

17 DR. GELATO: Dr. Bone, I'll ask you a
18 question, too. Is there any information that you
19 could think of if the tissues and things were
20 available from the animals who developed the
21 osteosarcoma, anything that could be gotten
22 retrospectively that would help in understanding

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 mechanism or shed light on the issue?

2 I mean, I know sometimes retrospective
3 studies, you know, are almost impossible, but if
4 tissues could be looked at, I mean, is there
5 something?

6 DR. BONE: Well, I'm certainly not an
7 expert on the molecular pathogenesis of osteogenic
8 sarcoma. I would be very interested in whether the
9 consulting committee that advised the sponsor was
10 asked to address that question, and if so, what their
11 specific recommendations were.

12 I asked a couple of rather naive
13 endocrinologist type questions about, well, were they
14 receptor positive and that kind of thing. I wouldn't
15 regard those as very sophisticated questions, and the
16 sponsor apparently felt that they were not worth
17 pursuing. I don't know exactly how they were advised.
18 One could imagine.

19 DR. CHABNER: I'm Bruce Chabner. I'm an
20 oncologist, and I chaired the committee that
21 considered the question. I think this is, from an
22 oncologist point of view, it's a very interesting

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 animal model of osteosarcoma, and we did suggest that
2 the company support studies that would look at the
3 biology because I think there's something to learn
4 about the disease, if not about the risk.

5 And they will do that. They're planning
6 to do that in terms of looking at gene arrays and the
7 molecular defects in these tumors.

8 We don't know a lot about osteosarcoma in
9 people. So it's, I think, a stretch to think that we
10 can solve this problem very quickly by studying these
11 animal tumors.

12 You know, one of the interesting questions
13 is how does this tumor relate to what we see in
14 people. So parallel studies would have to be done in
15 human tumors as well.

16 We do know something about the molecular
17 basis of osteosarcoma in people. It occurs in people
18 that have a defect in the RB pathway, in retinal
19 blastoma deficient patients and retinal blastoma gene
20 deficient patients.

21 It also occurs in certain families
22 associated with P53 abnormalities. But those are very

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 isolated cases, and the other risk factors that we
2 know about are exposure to radiation therapy,
3 thoratrast, osteomyelitis, a history of osteomyelitis,
4 all of them not very well understood in terms of how
5 that leads to osteosarcoma.

6 I think the company is going to undertake
7 studies to look at that. The plan isn't entirely
8 clear, and one of the reasons is that we just have so
9 little information about what causes human
10 osteosarcoma.

11 DR. POTTS: I'm John Potts.

12 I did want to add something particularly
13 to Dr. Bone's comment, following up on what Dr.
14 Chabner said. We do know a fair bit about the state
15 of receptor in osteosarcoma cells, as some of you may
16 know. One of the classic cells that's used is called
17 an ROS cell. It's a rat osteosarcoma cell line, and
18 the important point for the committee to appreciate is
19 that these are receptor positive, and they respond to
20 PTH. The receptor doesn't have anything to do with
21 the transformed nature of the cell. In fact, it's
22 used as a model of a normal osteoblast.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 So the pathorward (phonetic) hormone is
2 not really playing at the time you look at the cell
3 anything particularly about it. In fact, if anything,
4 it has an anti-proliferative effect.

5 So it's because something else has
6 happened in the genetic make-up of the cell at the
7 beginning which has caused it to develop its oncogenic
8 potential, and then the pathorward hormone receptor is
9 there, and it responds the same way a normal
10 osteoblast cell line does.

11 It doesn't help very much, but I think Dr.
12 Chabner has really touched on the reasons why it's
13 hard for anybody to say exactly how these studies will
14 go forward, but they are planning to do them.

15 There's something about the genetic make-
16 up of these inbred rat strains that clearly makes them
17 susceptible to tumors of various types, which is why
18 they're used, and the PTH, when you take the cell out,
19 responds as it does in a normal cell.

20 DR. BONE: John, thank you for your
21 comment. Are you speaking specifically of the tumor
22 cells that were isolated from these tumors?

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 DR. POTTS: No. What I'm saying is very
2 analogous cells of the same type have been derived,
3 and as they brought out, I believe, for you this
4 morning, that the company has not done studies of that
5 type specifically with these.

6 We're all struggling with this, and so in
7 terms of making a prediction, this is a pretty
8 reliable one, what you might expect, but there is no
9 such data.

10 DR. BONE: Well, I thought that might be
11 one of the early steps in attempting to characterize
12 these cells.

13 DR. POTTS: And perhaps the company can
14 respond to that.

15 DR. BONE: Simply looking for uniformity.
16 For example, if these cells are -- the common features
17 from these tumors from one animal to another would be,
18 for example, one thing to look at if they're very
19 heterogeneous or homogeneous in some of these kind of
20 biological characteristics, that would be a starting
21 point.

22 DR. VAHLE: Just to clarify, I think there

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 was a request that sponsor clarify. We've not done
2 that with any tumor cells from the original study. It
3 is one of many things that have been considered not
4 only in consultation with the consultants we have
5 here. It has included consultations with Kevin
6 Raymond, who is a molecular pathologist with expertise
7 in osteosarcoma.

8 DR. GRADY: Just to get oriented here,
9 could somebody review for me what is the exact
10 indication we're considering? And is the use of this
11 drug proposed to be restricted to any risk group, to
12 duration of treatment?

13 I think you say two years, or to prior use
14 of other drugs, and are you proposing any kind of
15 work-up or follow-up?

16 DR. MITLAK: The indication that we have
17 requested is for the treatment of osteoporosis in post
18 menopausal women and in men. As I included in my
19 presentation this morning, the indication would also
20 reflect that the duration of treatment should be for
21 up to two years and that patients who are otherwise at
22 increased risk for osteosarcoma should not receive

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 treatment.

2 The type of evaluation that we think would
3 be appropriate is consistent with the standard
4 evaluation of a patient who is being considered for
5 treatment or prevention of osteoporosis, and there are
6 standard practice guidelines that are in place for
7 this.

8 We think that these would be appropriate
9 to exclude secondary causes of osteoporosis, such as
10 hyperparathyroidism, and also to exclude Paget's
11 disease.

12 DR. GRADY: So you have no proposal that
13 it would be restricted to any -- for example, these
14 studies were conducted in women with prior fractures.

15 DR. MITLAK: We think that women and men
16 at increased risk for fracture would be candidates for
17 this, and those would include, for example, women who
18 have had fractures or women with low bone density who
19 are at high risk for fracture.

20 ACTING CHAIRPERSON MOLITCH: Dr. Pelosi.

21 DR. PELOSI: I have three questions that
22 basically hopefully tie together when we really look

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 at if this drug is approved, things that we as
2 clinicians need to look at.

3 And if the sponsors could tell me in terms
4 of compliance, since we're looking at daily injections
5 and oral supplements for two years, what was your
6 compliance rate in terms of this actually occurring,
7 and did you see any dose intensity? In other words,
8 how much did they truly have to take in that period of
9 time so that we knew that the results you get really
10 can be seen in the patient population?

11 DR. MITLAK: In the clinical trials,
12 compliance was assessed by measuring return study
13 medication. Compliance was very good in the clinical
14 trials. I believe that roughly 80 percent of the
15 doses that had been distributed to patients were
16 taken.

17 DR. PELOSI: The reason that I ask that,
18 I'm in oncology, but in oncology many times we see if
19 we don't get a certain percentage of the dose, we
20 obviously see a difference in the outcome. And so is
21 there any plans for long-term follow-up in those who
22 may be under your 80 percent to see if there was a

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 difference in those?

2 DR. MITLAK: No, we don't have plans now.

3 DR. PELOSI: The second question that I
4 have is in terms of your claim to reduction of pain.
5 Could you just give us a brief overview in terms of
6 how that was assessed and at what points, and if the
7 pain -- a decrease was seen after people went off
8 medication?

9 And I ask that because I guess my thought
10 is, again, with certain medications that we have seen
11 a reduction in pain. Patients are very reluctant to
12 go off of those medicines, and if we're having a risk
13 or a concern that there may be a risk, we need to plan
14 for that.

15 DR. MITLAK: The information that were
16 reported on back pain included results from patients
17 reports, spontaneous reports at visits of new and
18 worsening back pain. There were instructions in the
19 protocol to the physicians to alert them for how they
20 should consider reports of back pain with respect to
21 this likely being or potentially being part of the
22 syndrome of vertebral fractures.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 So these questions -- the reports of back
2 pain essentially were elicited by the sites when they
3 discussed how the patient had been doing since their
4 last visit at the clinic.

5 The data we showed you showed a lower
6 proportion of patients reporting back pain, and we saw
7 that pattern continue beyond the time the treatment
8 had stopped.

9 DR. PELOSI: And the very last thing, in
10 terms of quality of life data that you said really you
11 didn't see an effect, was there or is there any way to
12 look at those patients who actually went off study?
13 Because I didn't see the quality of life data on those
14 patients who self-selected to go off study actually
15 was gathered because that may be valuable information,
16 again, to say why is it that they truly went off.

17 And if we look at it post treatment, as
18 well, a year later, has that quality of life changed
19 and how did they view that experience while they were
20 on?

21 DR. MITLAK: We do not have data for you
22 in follow-up to the patients who had discontinued from

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 the study in a general way. We have offered patients
2 the opportunity even after discontinuing from the
3 Phase 3 studies to come back from the follow-up study
4 so that we do track them, but I do not have a precise
5 answer for you.

6 DR. PELOSI: Okay. My only comment was I
7 was a little disappointed not to see more minorities
8 represented in the studies.

9 Thank you.

10 DR. GRADY: Could I ask you one more
11 question about quality of life? I guess I found it
12 odd that you didn't find any improvement. Those are
13 fairly commonly used measures, and with continuous
14 outcomes usually.

15 You did suggest there's an improvement in
16 back pain. Did you look at the various elements of
17 the quality of life? Was there improvement, for
18 example, in pain and a decrement in some other of the
19 factors?

20 DR. MITLAK: We saw little significant
21 change in the quality of life instruments, but I think
22 there are several things that need to be considered

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 with that.

2 One is that we needed to use several
3 different types of instruments because this study was
4 performed in different countries, and we needed to use
5 instruments that were validated in the patient's
6 native language. This may have affected the power of
7 particular instruments to detect a signal.

8 Two, the studies were stopped early, and
9 I think, frankly, the difference from placebo or
10 actually the patients who had not received active
11 treatment had perhaps not been followed long enough to
12 see as much of a signal as might have been present
13 toward a longer period of observation.

14 And finally, we are looking forward for
15 instruments that may be a little more specific for
16 specifically the back pain that we detected as an
17 adverse event signal to follow this up prospectively
18 with patients.

19 DR. GRADY: Isn't it true that in your own
20 studies of Raloxiphene that within, you know, up to
21 two years of treatment with less of a reduction in
22 risk of vertebral -- and these were also morphometric

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 vertebral fractures -- there was an improvement in
2 quality of life, I think, using these very same
3 instruments?

4 DR. MITLAK: What we showed in
5 Raloxiphene, and I think what we also show here, is
6 that regardless of treatment, patients who suffer
7 fractures have an impairment in quality of life. I
8 think our data support that also, but what we did not
9 show was a specific treatment effect.

10 ACTING CHAIRPERSON MOLITCH: Dr. Aoki, did
11 you have a comment?

12 DR. AOKI: I have two questions primarily
13 for the sponsor, but for anybody who can answer this
14 question. It seems that we're not going to be able to
15 resolve at least at this meeting and probably not in
16 the near future that the mechanism for the
17 osteosarcoma issue. So it seems to me that the post
18 market surveillance is going to be key, and that's
19 basically, I think, how we're going to get the
20 adequate power for this and any analysis, and so I'd
21 like to address this primarily to the sponsor because
22 I'm sure they have thought of the same problem.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 How are you going to design a post market
2 surveillance program that is designed to pick up cases
3 of osteosarcoma to see if, one, this is a problem or,
4 two, it is not a problem?

5 The second question I had was: if the
6 therapy is only going to be offered for two years, 24
7 months, does this mean that the patient then goes off
8 the drug, never to go on it the rest of his or her
9 lifetime, or is there a rest period and then they
10 restart the medication?

11 DR. MITLAK: With respect to the design of
12 the follow-up study, I highlighted in my presentation
13 some of the elements that we think are important and
14 appreciate the tremendous assistance and collaboration
15 we've had in discussing this with our reviewing
16 officers at the agency.

17 The elements of the program, obviously,
18 first are to be able to identify cases regardless of
19 what sort of treatment the patients may have had
20 before, and I think we have identified two approaches
21 for this.

22 One is to use stable population based

1 databases, and the second is to proactively go to
2 sites where patients are cared for. It turns out that
3 this, because it is a rare disorder and because there
4 are specialized treatments, that most patients in the
5 country are cared for at a fairly small number of
6 sites.

7 We have already begun a discussion with
8 one of the molecular pathologists at the M.D. Anderson
9 and have begun discussions on how we might actually be
10 able to link between sites so that we would know in a
11 way with a sense of immediacy when cases are brought
12 to the attention of the site, whether it is because
13 the patient has come to the site or because the site
14 is reviewing pathology slides in the consultation.

15 And in that way we begin to establish an
16 ongoing case series, a database. We would then have
17 to use epidemiologic techniques, such as those
18 suggested by Dr. Stadel, to create case control
19 studies to follow up on any signals that might occur.

20 And, again, just from the standpoint of
21 where we are on this, we do not expect to see a
22 patient develop an osteosarcoma as a result of Forteo

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 treatment, but we are going to do this diligently to
2 confirm that this is the case.

3 With respect to the overall duration of
4 treatment, I think that for now two years is two
5 years, until we have further information on the drug.

6 ACTING CHAIRPERSON MOLITCH: Dr. Holmboe.

7 DR. HOLMBOE: I have a couple of questions
8 regarding your communication program, if this drug
9 would be approved. The first would be since it is a
10 time limited drug, how are you going to educate
11 physicians in that regard, particularly given the
12 patients often change physicians? I think you hear
13 earlier that patients may be reluctant to come off of
14 it if they're getting actually some benefit, and there
15 may be some confusion about when they started it.

16 So have you thought about how you would
17 manage that, to make sure that they truly only get the
18 drug for two years?

19 The second thing is how are you going to
20 educate physicians. I gather that you plan for this
21 drug to be used or not be restricted to certain
22 groups' physicians such as endocrinologists, but be

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 open for primary care practitioners. So it really
2 raises an important question of educating the primary
3 care practitioners and those who use this drug with
4 regard to some of the risk communication issues with
5 patients.

6 So I just wondered if you could address
7 what sort of plans you have for those issues.

8 DR. MITLAK: In considering your
9 questions, we look to the physician as really the
10 person who is going to have to work with their
11 patients to communicate information about this. It is
12 a theoretic risk, and there are many things that need
13 to be considered.

14 We have already highlighted that from the
15 outset we have tried to be transparent with respect to
16 the findings. We have included information about the
17 animal findings at the scientific presentations that
18 have taken place. We have included a discussion of
19 the findings in the manuscript that has recently been
20 published on the results.

21 We would propose to be sure that our sales
22 force and the individuals in the company who interact

1 with the physicians are well prepared to be able to
2 communicate this information and would expect that the
3 physicians will have to help communicate this to their
4 patients.

5 DR. HOLMBOE: Have you designed any
6 educational materials to help physicians in this
7 regard?

8 DR. MITLAK: We have not as yet.

9 ACTING CHAIRPERSON MOLITCH: Dr.
10 Kreisberg.

11 DR. KREISBERG: I've been trying to think
12 how I would use this drug as a physician, and it's my
13 understanding that anything that changes the balance
14 between bone formation and bone resorption in a
15 positive way is likely to be effective, and that in
16 some of the studies with anti-resorptive agents, the
17 relative risk reduction has been of the same order of
18 magnitude even though the change in the bone density
19 has been strikingly different among different drugs.

20 So the question that I have is do you see
21 this as a drug to be used right from the very
22 beginning in the management of a patient with

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 osteoporosis, or do you view it as a drug to be used
2 when other therapies for osteoporosis fail?

3 And if it is to be sued in the beginning,
4 how do you decide which patient to use a drug that
5 increases bone formation over a drug that interferes
6 with resorption?

7 DR. MITLAK: What I'd like to do is ask
8 some of our consultants to provide their comments for
9 you. If I could ask Dr. Lindsay if he'd be willing to
10 come up.

11 DR. LINDSAY: I wrestled with the same
12 questions over the last several years that we've been
13 interested in parathyroid hormone, and I draw a number
14 of conclusions.

15 The first is that patients who present to
16 me with fracture, especially if the fracture is
17 relatively recent, are at a dramatically increased
18 risk of future fracture and deserve something that
19 will reduce that risk fairly rapidly.

20 An agent like teriparatide can increase
21 bone density far more rapidly and far more greatly
22 than other agents and, therefore, might be considered

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 to be the treatment of choice for those individuals.

2 There are also individuals who present
3 whose bone density is sufficiently reduced that the
4 change in bone density that would occur with an anti-
5 resorptive agent would not bring them back into the
6 normal range, sometimes even for the age, and
7 certainly not into the normal range for young adults.

8 Again, here this agent would have the
9 clear advantage and be more likely to be able to
10 achieve that.

11 The more difficult issue, I think, that
12 you raise is what do you do with people who are
13 already on treatments because we've already been into
14 the discussion about what the response is, and I think
15 that the theoretical conclusion is that these people
16 will response, based on our biochemistry and very
17 little other data in humans, but that the response may
18 be greater or lesser.

19 And I would see that there certainly is a
20 cohort of patients who fracture on current therapies,
21 who may then be amenable to this sort of agent as in
22 that case a second line therapy rather than a first

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 line therapy in the first two cases.

2 We all realize when we give anti-
3 resorptive agents that we're reducing risk, but of
4 course, when a patient fractures, the patient
5 considers that to be a treatment failure, and I think
6 that that would drive that particular prescription.

7 ACTING CHAIRPERSON MOLITCH: Dr. Jenkins.

8 DR. JENKINS: I'd like to ask the question
9 of the sponsor, and you may have answered this this
10 morning. I had to step out for part of the
11 presentation. It's a follow-up of Dr. Grady's
12 question and Dr. Aoki's question that goes to the
13 proposed indication.

14 Can you articulate for me what's the
15 rationale behind your decision to recommend limiting
16 duration of therapy to two years? And could you
17 address that from an efficacy and a safety
18 perspective?

19 DR. MITLAK: I think that the most
20 straightforward answer is this is the data. We
21 believe that this is the duration of treatment that
22 the data that we have accumulated support. We have a

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 high degree of confidence in the effect of treatment
2 over this period of time and, therefore, are
3 comfortable going forward.

4 We think that it is an important piece
5 when considering the overall risk-benefit for this
6 drug, which we feel is an important potential new
7 treatment to be sure that as its use is begun that,
8 again, we do this within the context of the data that
9 we have in hand.

10 DR. JENKINS: Is there any particular
11 efficacy reason that you would go for two years versus
12 one year versus 18 months versus three years? I'm
13 just asking.

14 And also it sounds like you're suggesting
15 limiting duration based on some safety concern.
16 Because we often for drugs like this, we have two or
17 three-year data for drugs for treatment of
18 osteoporosis, and those drugs don't have duration
19 limitations in their labeling.

20 DR. MITLAK: What we have is the data that
21 established that 18 to 24 months of treatment is a
22 very effective regimen for reducing the risk of spine

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 and non-spine fractures and are very comfortable with
2 that.

3 We do not see any specific safety
4 concerns. We think that given the uncertainty that
5 this panel is dealing with with respect to the animal
6 findings, that it is important from balancing risk-
7 benefit to have a set duration of treatment, and we
8 think that the studies support two years.

9 ACTING CHAIRPERSON MOLITCH: Dr. Bone.

10 DR. ORLOFF: Can I just follow up with one
11 more question related to efficacy?

12 Could you make a comment on whether
13 there's bene consideration and whether you believe
14 there would be any rationale for perhaps even limiting
15 the duration not as part of the overall directions for
16 use, but let's say limiting duration based upon BMD
17 response. So that you can imagine individuals who
18 might have a robust response in a fairly short time
19 frame such that let's just say for the sake of the
20 discussion that they reach an incremental BMD that is
21 in line with the mean seen in the clinical trials that
22 demonstrated efficacy and safety.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 DR. MITLAK: Let me answer this in part
2 and perhaps ask one of our consultants also to
3 comment. I think that we are in the position with
4 this drug where there is not a very close correlation
5 between change in bone density and reduction in
6 fracture risk. So I think to gauge change in bone
7 density as an adequate surrogate for duration of
8 treatment is not supported by the data that we have.

9 I think what we do have is the study
10 results which showed that 18 to 24 months is an
11 effective regimen for reducing the risk of fractures.

12 PARTICIPANT: I'd like to make a comment.
13 I've struggled with this thought also about how long
14 to administer therapy, and my initial impression
15 before Eli Lilly discovered this osteosarcoma finding
16 was that this therapy should be administered until
17 bone mineral density reached a normal level or until
18 bone mineral density stopped increasing, whichever
19 occurred first.

20 I think that it's important to recognize,
21 again, that there's never been an osteosarcoma
22 occurring in a patient treated with this agent, and so

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 one approach might be to just adopt the position I
2 just articulated.

3 A more cautious and conservative approach
4 would be to limit the therapy to some duration until
5 more information was available from studies of a
6 larger number of humans, admitting that the risk is
7 unclear in humans. It would obviously be desirable to
8 have more information before one used it without
9 limit.

10 Two years is a compromise position, and I
11 think that it can be defended on a couple of grounds.
12 One, as you heard today, the beneficial effects on
13 bone mineral density are time dependent, and bone
14 mineral density increases most rapidly in the first
15 year, somewhat more slowly in the second year, and
16 then as Dr. Lindsay pointed out, there's still some
17 increased bone density in the third year, but during
18 that third year indices of bone formation and
19 resorption in his studies have returned to or toward
20 normal.

21 In fact, they start returning to or toward
22 normal after 18 months in some studies. So while it

1 seems to me unreasonable to give it without limit, it
2 also seems to me unreasonable to stop therapy after
3 only 12 months because what we're trying to do is help
4 patients, and it's clear to me that they're helped
5 more by 24 months of therapy than by 12.

6 I don't see any absolute way to answer the
7 question because there's no empirical basis on which
8 to answer.

9 DR. BONE: I have a couple of questions
10 that came up in the morning's discussion in which the
11 sponsor was asked to come up with some data, and since
12 they've done all of this work now, I think we're
13 anxious to see it.

14 Three specific questions had to do with
15 the time course of developing hypercalcemia and
16 hypercalcuria; time course of seeing the increase in
17 the serum creatinine level; and the spectrum of 25
18 hydroxy Vitamin D levels at baseline and how they
19 predicted the response to treatment.

20 DR. MITLAK: I'm going to answer your
21 third question first. At baseline the mean 25 hydroxy
22 Vitamin D level was 79 across the board. It was even

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 in all three treatment groups. The reference range is
2 25 to 153.

3 Pardon?

4 So that is in nanomoles per liter, and the
5 reference range is, again, 25 to 153.

6 DR. BONE: And the mean was how much?

7 DR. MITLAK: Was 79.

8 DR. BONE: And what was the distribution?

9 DR. MITLAK: The standard deviation was
10 24. So if you assume a normal distribution and go
11 down to minus two standard deviations, that takes us
12 down to 34. So you have about two and a half percent
13 of the patients between 25 and 34, at the low end of
14 the spectrum.

15 ACTING CHAIRPERSON MOLITCH: Thank you.

16 Any other questions?

17 DR. BONE: Oh, excuse me. I meant to ask
18 one more.

19 And what relationship was there, if any,
20 between -- or did you look at the relationship between
21 the baseline 25 hydroxy Vitamin D level and either
22 fracture risk or BMD response?

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 DR. MITLAK: We've not specifically done
2 that analysis, but it is certainly one of interest to
3 us and that we hope to get to perhaps starting next
4 week.

5 Serum calcium -- sorry.

6 I'm sorry. I stand corrected. We don't
7 have a statistical analysis, but we did do the
8 pharmacokinetic analysis, and there was no
9 relationship between baseline 25 hydroxy D and either
10 fractures or bone mineral density response.

11 Let's go on to the serum calcium question.
12 The question was what was the time to onset of the
13 transient increases in serum calcium.

14 If we could start with slide 4415, please.

15 I'll show you two slides in this respect.
16 The first is the time course, the by visit analysis of
17 the four to six-hour post dose serum calcium in the
18 pivotal study in post menopausal women, and this,
19 again, shows the median and 25th to 75th percentile
20 range for the serum calcium, again, measured at its
21 peak four to six hours after each dose at each visit
22 during the study.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 And as the graph shows, there was a
2 significant increase as early as one month, and after
3 three months, the medians were very similar throughout
4 the remainder of the study.

5 So this data would suggest that all of the
6 transient calcemic effects should be apparent by
7 approximately three months.

8 If we could see slide 452, please.

9 And this next is actually a time to first
10 even curve of the time to the first post dose increase
11 in serum calcium. While it's getting up, let me just
12 remind you that these changes are transient, and even
13 in the patients who have increased post dose serum
14 calcium, it's back down to baseline by 16 to 24 hours
15 after the dose.

16 DR. BONE: Yeah, but as Dr. Grady pointed
17 out, you adjusted therapy in seven percent of the
18 patients. So that's where we were particularly
19 interested in at what time point those therapeutic
20 adjustments were going to be.

21 DR. MITLAK: Okay. I'll show you this,
22 and then I will provide that data.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 Could you zoom into this part of the
2 graph, please, just the box?

3 This is the time to first event in the
4 placebo, 20 microgram, and 40 microgram groups, and
5 this is the time the first patient had a four to six-
6 hour post dose serum calcium which exceeded the upper
7 limit of normal.

8 And as you can see, there was a very small
9 number of patients throughout the study in the placebo
10 group who occasionally exceeded the upper limit of
11 normal, and that's what's expected based on our lab
12 reference ranges.

13 You can also see that especially in the 24
14 microgram group, but even also in the 40 microgram
15 group, the patients who exceeded the upper limit of
16 normal even transiently were by and large identified
17 within the first three to six months of the study.

18 Now, there were some dose adjustments
19 allowed, in fact, required by the study, and let me
20 back up just a little bit.

21 You can turn that slide off now. Thank
22 you.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 Let me just back up a little bit and
2 describe the reasons why we monitored serum calcium
3 and did dose adjustments in the study.

4 We did that so that we could describe the
5 effects on the serum calcium in this patient
6 population, and we put in the requirements for dose
7 adjustments for two reasons.

8 One is because we were not certain how big
9 the effects would be and wanted to make sure that
10 there was protection for the patient.

11 And, two, we much preferred from an
12 intention to treat analysis and provide as much data
13 as possible on the patients to keep a patient in the
14 study on a lower dose rather than forcing them to
15 discontinue due to a laboratory abnormality if, in
16 fact, that could be handled by a dose adjustment.

17 In the 20 microgram dose, there were --
18 there are a small number of dose adjustments and a
19 very few in the first six months. In fact, only 2.4
20 percent of the patients in the first six months of the
21 study had a reduction or discontinuation of study
22 drug, and so basically what you see, the data through

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 six months is data for 97.6 percent of the patients.

2 DR. BONE: Are you speaking only of the
3 PTH or are you also speaking of calcium?

4 DR. MITLAK: That was the injectable study
5 drug reductions.

6 We haven't done oral calcium supplement
7 analysis the same way that we've just done the
8 injectable study drug analysis, but in general, oral
9 calcium supplements were adjusted prior to injectable
10 study drug. Even though that was not the case, the
11 physicians were free to adjust either downwards as
12 they felt fit.

13 I'd also remind you that, you know, again,
14 even the number of patients having adjustments in oral
15 calcium supplementation was fairly small. It was less
16 than ten percent.

17 DR. GRADY: Could I ask you a quick
18 question? Was this fancy 28-day injectable injection
19 device used in the trial, the same one that you're
20 going to market?

21 DR. MITLAK: We did use I wouldn't call it
22 a fancy injection device. It actually does represent

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 our expertise in delivering injectable drugs to
2 diabetes patients in a convenient way, and it was used
3 in the trials, and the patients accepted it very, very
4 nicely. There were very few patients who withdrew
5 from the study due to problems taking the injection.

6 And so, yes, we would hope to bring those
7 same benefits to the patient with a marketed product
8 if it's approved.

9 ACTING CHAIRPERSON MOLITCH: I have a
10 question about one of the covariants that you talked
11 about this morning and that you said there was no
12 effect of renal insufficiency. I'd like to know how
13 many patients had renal insufficiency and what degree
14 of renal insufficiency it was, and would you really,
15 in fact, want to treat patients who had renal
16 insufficiency with PTH considering the fact that they
17 already have some secondary hyperparathyroidism?

18 So it may be just a question of degree.

19 DR. MITLAK: Okay. Again, I'll start from
20 the bottom and work my way up. First, regarding
21 hyperparathyroidism, the patients in this study were
22 not permitted to be in this study if they had a

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 calcium or a parathyroid hormone level above the upper
2 limit of normal. So patients did not have secondary
3 hyperparathyroidism in the study.

4 With regard to renal insufficiency, this
5 being an older population, based on the measured
6 creatinine clearance, we actually had quite a few
7 patients with mild renal insufficiency, creatinine
8 clearances between 50 and 80. And, in fact, about 40
9 percent of our patient population had a creatinine
10 clearance below 80, most of those being between 50 and
11 80.

12 We had approximately 25 to 30 in the
13 moderate category, between 30 and 50 milliliters per
14 minute. So our study population does represent
15 patients with certainly mild and to a lesser extent
16 moderate renal insufficiency.

17 We also looked at patients with renal
18 insufficiency compared with patients with normal renal
19 function and did not find that there was any
20 significant difference in effects on renal function or
21 on serum calcium or on efficacy. So we were very
22 comfortable that within this age population that range

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 of renal function is well represented.

2 DR. BONE: Speaking of which, you were
3 going to give us the figures on the emergence of the
4 rise in creatinine.

5 DR. MITLAK: Okay. If I could have slide
6 4422.

7 I'm going to try to show you a lot of data
8 from both the treatment studies and the follow-up
9 study because the difference in the serum creatinines,
10 which was described, only occurred at visit one of the
11 follow-up study, which is about six months after the
12 end of the treatment study.

13 This is the serum creatinine during the
14 pivotal treatment study, GHAC, again by visit. These
15 are the means and the standard deviations, with the
16 upper limits and lower limits of normal by the
17 horizontal lines.

18 As you can see, there was no difference
19 among the treatment groups in the mean serum
20 creatinine during the study or at endpoint.

21 In addition, there was no difference in
22 the number of patients with an elevated serum

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 creatinine or with renal insufficiency based on
2 creatinine clearance during the study or at endpoint.

3 Could we have 4417, please?

4 This is just the same data with the
5 measured serum creatinine clearance in the same study
6 population, showing, again, no difference among
7 treatment groups.

8 Could I have 4430?

9 Now, let me move on and describe the
10 findings in the first visit of the follow-up study.
11 First of all, there was no significant change in the
12 measured creatinine clearance, and there was no
13 significant difference in the median serum creatinine
14 concentration at endpoint.

15 There was a difference in the median
16 change from baseline to endpoint, and that difference
17 was about one micromole per liter or 0.01 milligrams
18 per deciliter, which was statistically significant.

19 There was also a significant or a trend at
20 least towards a difference in the number of patients
21 with a serum creatinine above the upper limit of
22 normal six months after stopping study drug, and that

1 was two percent in the placebo group, four percent in
2 the 20 microgram group, and four percent in the 40
3 microgram group.

4 We also looked at patients with individual
5 increases, and our predefined lab limits of a
6 significant increase are 0.4 milligrams per deciliter.
7 So we looked at that, and there was one patient in
8 placebo and one in the 40 microgram group with an
9 increase of at least 0.4 milligrams per deciliter.

10 There was no one with an extremely high
11 serum creatinine. The highest observed serum
12 creatinine at this visit of the study was 1.5
13 milligrams per deciliter.

14 I think the important point is that we
15 also looked across the studies, and we did not see
16 similar trends, and let me just show you the data
17 across the studies, and that is slide 4502, please.

18 And here you can see the change in serum
19 creatinine from baseline to endpoint in the treatment
20 study and post menopausal women, in men, in the study
21 which compared HRT alone to teriparatide 40 micrograms
22 a day plus HRT and the study which compared

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 alendronate ten milligrams a day to 40 micrograms a
2 day of teriparatide.

3 And as you can see, the changes from
4 baseline, you know, all are very small, and studies to
5 study, they go in different directions and have
6 different inferences.

7 So we think that overall, taken as a
8 whole, the data shows that there isn't any adverse
9 effect on renal function.

10 Thank you.

11 Let me just also add a comment on what Dr.
12 Stadel had mentioned. The patients in the follow-up
13 study are in the midst of another study visit, and we
14 do have follow-up on approximately a third of the
15 patients that had serum creatinines above the upper
16 limit of normal, and half of those are now back within
17 the normal range.

18 And so, again, this finding in visit one
19 may just represent some normal variability from visit
20 to visit.

21 We certainly did not see evidence of
22 progressive decline in renal function in any of these

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 patients.

2 DR. BONE: Yes.

3 DR. MITLAK: Any other questions pending
4 from this morning that you'd like me to answer?

5 Thank you.

6 DR. HOLMBOE: I guess this raises the
7 question that we've been talking about: who should
8 receive the drug? But from a risk communication
9 standpoint, who should not receive the drug in your
10 opinion?

11 Most of these people, again, had
12 creatinines that were so relatively normal, which is
13 the usual way of primary incurrence of measure. They
14 wouldn't do a creatinine clearance. They may, you
15 know, calculate and estimate one using the equation,
16 but I guess I'd like to hear who should not get this
17 drug and how, again, will you help primary care
18 practitioners identify these individuals?

19 DR. MITLAK: We think that individuals
20 that have other secondary causes for osteoporosis
21 should probably not receive treatment, and this would
22 include patients with abnormal renal function,

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 disorders of Vitamin D metabolism, and other
2 identified causes.

3 DR. TAMBORLANE: One of the issues that
4 came up was a suggestion with the juvenile rats and
5 stuff. I certainly think once this was approved, if
6 it were approved, that there would be interest in
7 using this in children with osteoporosis.

8 What are your proposals for labeling
9 instructions about use in children?

10 DR. MITLAK: As we had highlighted before,
11 we intend to include a statement that says that
12 individuals at increased risk for osteosarcoma should
13 not be treated, and these will include patients with
14 Paget's disease, adolescents, or those with open
15 growth plates, for example, or patients who had
16 received radiation therapy.

17 DR. TAMBORLANE: The agency, I know, has
18 a concern about the orthostatic hypotension that you
19 saw in the early studies. Was this a first dose
20 effect or was it persistent with multiple doses?

21 DR. MITLAK: When it was observed, it was
22 most commonly with a first or first few doses. As Dr.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 Gaich had highlighted before, in several patients who
2 did have symptoms, when they were given a subsequent
3 dose and sometimes a greater dose, the symptoms did
4 not recur.

5 DR. TAMBORLANE: Is this something that
6 you might think about in the labeling, especially in
7 our older patients, that the first dose they be
8 monitored for several hours?

9 DR. MITLAK: We have included instructions
10 to that effect. We have included an alert to this and
11 instructions that if symptoms occur, that the patient
12 should be allowed to sit or lie down until their
13 symptoms resolve.

14 ACTING CHAIRPERSON MOLITCH: I have a
15 question, again, about the proposed limit of duration
16 of treatment, and I was wondering why you chose not to
17 use a differential duration for men and women, given
18 that the males, I think the median time was nine or
19 ten months, and at 20 micrograms, you have, as Dr.
20 Schneider noted in his write-up, less impressive
21 efficacy.

22 DR. MITLAK: As I included in my

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE, N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 presentation this morning and as we have found quite
2 clearly, gender was not an important baseline factor
3 in either response to treatment, that is, actual
4 change in bone density, nor in the safety profile as
5 assessed by a comparison of the adverse event profile
6 in men or women.

7 Therefore, we think that the database
8 reflects or would support the use of this for two
9 years in menopausal women or in men.

10 DR. SCHNEIDER: If I might make a comment
11 on the gender comparison that you made, those BMD
12 curves, basically the number of men in that study, you
13 were comparing 11 or 12 months' treatment in men to
14 whatever, 12 months of treatment in women, and the
15 number of men who had been exposed to 12 months of
16 treatment was what, 25 percent of the men? And it's
17 an extremely small number, and I felt that the
18 comparison really was unreliable.

19 Furthermore, the critical issue to me --
20 and this came out in my review -- is not so much
21 comparing across genders and two different trials and
22 so on and so forth, but really what happened in the

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 placebo controlled trial in men.

2 I mean, clearly efficacy was reached at
3 the lumbar spine. I won't quibble if it was 5.2
4 percent or 5.3. The really issue whether you want to
5 achieve efficacy within 11 months or a year or
6 whatever at other anatomic sites, and although there
7 were numeric changes in the right direction, it didn't
8 make it anywhere else.

9 DR. MITLAK: Let me make one comment, and
10 then I'd ask Dr. Bellizikan to comment also.

11 With respect to the figures that I showed
12 in my presentation, the data comparing spine was, I
13 believe, an observed case analysis. So all of the
14 data for the spine was included. For the hip where
15 there's a single point at 12 months, what that
16 represents is essentially the 12-month visit, visit
17 six in the protocol.

18 So for patients who had had a measurement
19 before that time point even if it was an early
20 discontinuation visit, it was carried to that visit
21 and included in that analysis.

22 Let me now ask Dr. Bellizikan to make a

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 comment, please.

2 DR. BELLIZIKAN: My name is John
3 Bellizikan. I'm from Columbia.

4 And I'd just like to comment on study
5 that we concluded and was published in the JC&M in
6 September. This work was done in collaboration with
7 Bob Lindsay and his group.

8 This was a study of men with idiopathic
9 osteoporosis, a small group, placebo controlled,
10 blinded with a dosage of PTH, not this particular form
11 of PTH, but analogous with a similar dosage. This
12 study was carried out for 18 months.

13 With regard to the lumbar spine bone
14 density, it was exactly the same in terms of the slope
15 of increase as was shown for this study, but with the
16 18 month data, we saw a clear divergence after 12
17 months such that the PTH treated men showed a clear
18 departure from the placebo, and by 18 months, there
19 was an approximately three and a half percent
20 difference in both density, which was significant from
21 placebo.

22 So carrying out the study as we did to 18

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 months, we were able to show significantly different
2 total hip density and femoral neck density as compared
3 to placebo.

4 DR. SCHNEIDER: That's encouraging.

5 I have a question actually which may be
6 helpful. In dealing with an earlier question about
7 prior use of alendronate, as I recall in GHAC,
8 obviously concomitant use of bisphosphonates was not
9 allowed, but there was a subset of patients there who
10 had been on bisphosphonates, and then of course, they
11 had to be interrupted.

12 Have you done a separate analysis? I
13 mean, perhaps some of the answers are in your own
14 database.

15 You showed that. Okay. All right.

16 ACTING CHAIRPERSON MOLITCH: Any other?
17 Dr. Bone.

18 DR. BONE: Yeah, it seems to me clear that
19 there are two diverging approaches that we can take to
20 obtaining some of the incremental information that
21 everybody is sort of asking about in various ways, and
22 these have to do with cancer risk and the long-term

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 effects of the drug and concomitant use and a lot of
2 other things.

3 And these are basically observational
4 approaches, trying to do the best job we can with
5 essentially passively acquiring data that's being
6 generated by the use of the drug, and the other is
7 conducting systematic trials, which tend to be more
8 circumscribed in number, but have much better defined
9 denominators and ascertainment.

10 And in our recent experience with drug in
11 the diabetes area, for example, some of these issues
12 were really highlighted about how well you can make
13 these calculations.

14 I just have a couple of thoughts about
15 this. One is that when we're talking about the risk
16 of osteogenic sarcoma, the question has been posed in
17 a sense that could there be an increase of some amount
18 in the risk of osteogenic sarcoma, and it's going to
19 be very difficult, as we've all heard, to tell the
20 answer to that unless the increase is very large over
21 the background rate, particularly if we subtract the
22 Paget's patients from the population.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 Another way to look at that is to say what
2 level of risk can we live with with this horrible
3 disease. I mean it's a really bad thing to have an
4 osteogenic sarcoma. So we could make some calculation
5 about, you know, what level of risk can we live with.
6 Can we live with one in 1,000? Probably not. Can we
7 live with one in 10,000? Maybe. Could we live with
8 one in 100,000? We'll never know the difference
9 between that and the background rate even if it's two
10 and a half times the background rate.

11 So one of the things people could think
12 about is what level of risk can be accepted. Now,
13 generally speaking, people don't like to take any risk
14 of having something really bad happen, and when a new
15 drug is on the market, you have the problem always of
16 having had a sample size which is, you know, in some
17 way achievable, and we always have the problem that an
18 event that's going to occur at a rate of one in 5,000
19 or one in 10,000 individuals probably won't be
20 detected except by sort of a fluke.

21 One of the things we may want to think
22 about is in addition to registry type reporting, which

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 might catch an increase in the background, could
2 several questions be answered by doing a larger scale
3 clinical trial over an extended period?

4 In other words, a couple thousand patients
5 per arm for three to five years, that's the kind of
6 range where you would not eliminate the risk of
7 osteogenic sarcoma, but you could say it's very likely
8 to be below one in several thousand, and I would
9 certainly want the advice of Dr. Stadel and Dr. Grady
10 on this point and others because this is not my area
11 of expertise, but my sort of back-of-the-envelope
12 calculation is that we could probably improve our
13 confidence by about an order of magnitude if you had
14 a study with three arms in it of about that size in
15 duration. I might be wrong.

16 Another thing that could be obtained from
17 that kind of study is you certainly wouldn't do a
18 placebo controlled trial in patients of this risk
19 level over that period of time, but you might consider
20 an active control trial against the best available
21 therapy as an alternative, and an interesting
22 opportunity would then arise of having a combination

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 arm, which should answer for good and ever the
2 question about whether there's a combination effect.

3 We only really answered this question by
4 doing that kind of study when we were talking about
5 bisphosphonates or at least alendronate and estrogen.
6 In that study a bone density endpoint was used rather
7 than a fracture endpoint, which may be more
8 appropriate here.

9 But that seems to me to be complementary.
10 There may be resource issues and a lot of other
11 things, and I wouldn't want to necessarily be
12 considered the author of the Osteoporosis
13 Investigators Full Employment Act of 2001, but that
14 might be complementary information to what would be
15 obtained in the trial that -- in the sort of passive
16 observations that's been proposed for looking strictly
17 at the osteogenic sarcoma. It leaves a lot of the
18 other questions unanswered that people have been
19 coming back to, and it's quite apparent that absent
20 some large scale experience and extended time period
21 experience, we're simply going -- we're going to be
22 asking ourselves the same questions in a year or two

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 or three or five.

2 One of the advantages that we've had in
3 estrogen therapy and in use of particularly
4 alendronate is that there were very long-term studies
5 with estrogen, including particularly Dr. Lindsay's
6 landmark study from Glasgow, and we've had a very long
7 running extension of the pivotal trials for
8 alendronate which have now been just about concluded
9 after ten years.

10 So that there were always a cohort of
11 patients who were being observed systematically who
12 had been treated for a longer period of time than
13 anyone on clinical therapy.

14 Just a couple of thoughts of the committee
15 to kind of chew on.

16 DR. GRADY: Well, you know, it's fun to
17 ask questions, and I think we've learned some things,
18 and maybe even it was helpful. I think we really need
19 to kind of, in the interest of catching my plane,
20 start cutting about some major issues here because I
21 think there are actually quite a few of them.

22 And the key one I think that Dr. Bone has

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 brought up is, you know, we're talking here about a
2 preventive therapy. So we're talking about treating
3 women and men who are at risk for disease, but don't
4 have a symptomatic disease, and so we'd really like
5 for that treatment to be safe and, if possible,
6 completely safe.

7 So I think we're all worried about the
8 incidence of sarcoma. I think if you look at the data
9 the company has provided us and you say a simple
10 thing, that is, there were zero sarcomas out of 2,000
11 people followed for an average of about 18 months, one
12 thing you can say is that the rate of sarcoma is, you
13 know, with about 95 percent confidence unlikely to be
14 higher than 1.5 in 1,000.

15 Now, that's still probably too high for
16 this terrible disease, and perhaps larger trials would
17 answer that.

18 I think perhaps the other way to go at it
19 would be to say, all right, let's take maybe a kind of
20 worst case scenario, which in my mind is that perhaps
21 the underlying rate of osteosarcoma in patients who
22 might get treated with this drug is maybe one in

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 100,000.

2 And even if the relative risk is something
3 like 30, we're now talking about 30 in 100,000 or
4 three in 10,000, which would be the excess risk of
5 this disease, although quite devastating.

6 And I think if you compare that to the
7 number needed to treat to prevent any clinical
8 fracture, which is around about 30, and even the sort
9 of estimated number needed to treat to prevent one hip
10 fracture, which is around about one in maybe 200, it's
11 a low risk.

12 The problem, again, in my mind is that
13 it's a devastating illness, number one.

14 Number two, I'm still a little worried
15 about some of the metabolic findings, although they
16 didn't seem to translate into clinical problems, you
17 know, the hypercalcemia, hyperuricemia, and increased
18 creatinine clearance, serum creatinine.

19 And then finally, there are options. So
20 I think what we really need to spend some time talking
21 about, the labeling for this drug and whether or not
22 it ought to in some way be restricted to women and

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 perhaps to men at much higher risk than the average
2 person who gets treated for osteoporosis.

3 ACTING CHAIRPERSON MOLITCH: Any other
4 comments? Because otherwise I think we ought to start
5 to go down our questions that have been addressed to
6 us.

7 (No response.)

8 ACTING CHAIRPERSON MOLITCH: Hearing none,
9 I think we will start with the first question, which
10 is a question based on efficacy, and the question,
11 there will be an A and B part to this, and I think
12 we'll go around the table. Each person will need to
13 answer yes or no to these questions as we go around.

14 So question one on efficacy is: based on
15 the information presented by the sponsor in the NDA,
16 are the data adequate to establish that teriparatide,
17 20 micrograms per day, is an effective dose?

18 And then (a) for the treatment of post
19 menopausal osteoporosis to prevent fracture risk, and
20 (b) to increase bone mineral density in men with
21 osteoporosis.

22 And so I think what we'll do is go around

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 the table to answer both A and B at this go-round, and
2 then we'll go around to the next question after that.
3 Perhaps we could start with Dr. Holmboe.

4 DR. SAMPSON: Can I ask for just one
5 clarification, please?

6 ACTING CHAIRPERSON MOLITCH: Yes.

7 DR. SAMPSON: On BMD, is that bone marrow
8 density in lumbar spine or to be construed in general.

9 ACTING CHAIRPERSON MOLITCH: My guess is
10 lumbar spine.

11 DR. SAMPSON: Thank you.

12 DR. SCHNEIDER: The lumbar spine was the
13 primary endpoint. We had meant generally BMD in
14 general, that is, given the aggregate BMD responses to
15 20 micrograms.

16 ACTING CHAIRPERSON MOLITCH: Dr. Holmboe?

17 DR. HOLMBOE: I'm not sure I'm a voting
18 member.

19 ACTING CHAIRPERSON MOLITCH: You look
20 confused.

21 DR. HOLMBOE: I am.

22 DR. SAMPSON: I wasn't quite paying full

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 attention. Would you repeat that one more time,
2 please?

3 DR. SCHNEIDER: The primary endpoint was
4 BMD at the lumbar spine. What I meant in the question
5 was given the aggregate BMD increases across the body
6 to 20 micrograms.

7 DR. HOLMBOE: As the questions are
8 written, I would say yes to both.

9 DR. PELOSI: I would answer yes to both

10 DR. AOKI: Same.

11 DR. LEVITSKY: Same. Yes to both.

12 DR. TAMBORLANE: Yes to both.

13 DR. GELATO: Yes to both.

14 DR. KREISBERG: Yes to A, no to B.

15 DR. GRADY: Yes to both.

16 DR. SAMPSON: Yes to A, no to B.

17 ACTING CHAIRPERSON MOLITCH: And I will
18 say yes to both as well.

19 We'll then go on to Question 2. Actually
20 the -- we're supposed to have some -- yeah, can you
21 give us a tally?

22 MS. REEDY: Question 1, fracture risk in

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 treatment of post menopausal osteoporosis, yes ten, no
2 zero.

3 In fracture -- increasing bone mineral
4 density in males, yes eight, no two.

5 ACTING CHAIRPERSON MOLITCH: And I think
6 perhaps, Dr. Kreisberg, maybe you can also give us a
7 reason why you voted no.

8 DR. KREISBERG: Yes, I'll be glad to do
9 that.

10 I believe that the number of men treated
11 is small, that the results are confounded by the fact
12 that a percentage of them had androgen deficiency that
13 was not corrected. It's a heterogeneous group.

14 ACTING CHAIRPERSON MOLITCH: And Dr.
15 Sampson?

16 DR. SAMPSON: I just refer to the
17 company's data, and they certainly show significance
18 in lumber spine, but in a number of the other
19 secondary measures the results don't reach statistical
20 significance.

21 ACTING CHAIRPERSON MOLITCH: Okay. We'll
22 then move on to Question 2 with regard to safety, and

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 the question posed is: based on the information
2 presented by the sponsor in the NDA, are the data
3 adequate to define the safety profile of teriparatide
4 (a) for the treatment of post menopausal osteoporosis
5 and (b) for the use to increase bone mineral density
6 in men with osteoporosis?

7 And we'll start with the opposite side,
8 and we'll start with Dr. Sampson.

9 DR. SAMPSON: I don't think that's quite
10 so fair to switch and ask a statistician to do the
11 lead on that.

12 (Laughter.)

13 DR. SAMPSON: I would say no and no.

14 ACTING CHAIRPERSON MOLITCH: Dr. Grady?

15 DR. GRADY: Could I just as for
16 clarification here? So if what we're interested in is
17 making sure that there's some sort of strict registry
18 follow-up, assuming that I would feel comfortable
19 given that, then am I supposed to vote yes?

20 ACTING CHAIRPERSON MOLITCH: Dr. Orloff,
21 do you want to comment? Dr. Orloff?

22 DR. ORLOFF: The question is intended to

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701