Page 161

(1) all skeletal sites. The drug did not prevent height (2) loss.
(3) I must emphasize again there were no (4) fracture efficacy data from GHAJ or from any other (5) randomized controlled clinical trials in men.
(6) I should also add that, of course, this (7) trial was truncated. It was stopped after a median of (8) 11 months of exposure, and we really don't know what (9) would happen with two years of exposure to the drug.
(10) Now, these efficacy outcomes which clearly (11) would meet our approval criteria, must be balanced, of (12) course, against the risks, and the major risk that I (13) see is the risk of osteosarcoma, and in the next few (14) minutes I want to let you know why, although I (15) certainly don't have any answers to this question, why (16) I'm still concerned about it.
(17) The major reasons for concern, of course, (18) as we've heard this morning, is that this is a robust, (19) dose dependent occurrence in rats, and we also know (20) now in mice. There was no threshold dose (21) demonstrated.
(22) Now, unlike other preclinical outcomes

Page 162

(1) that we often see, this was a biologically plausible (2) outcome, and it involves hormonal stimulation of known (3) target tissue.
(4) In this slide I've listed seven reasons (5) why we're told that we shouldn't be so concerned about (6) it and why it is unlikely that osteosarcoma will occur (7) in humans treated with teriparatide. I've listed (8) every reason that I've heard and every reason that I (9) can think of, and they appear here.
(10) High exposure in rat studies. The (11) treatment of rats began at six or seven weeks of age (12) and was virtually lifelong. There's a negative monkey (13) study. Rat bone differs from human. There's no (14) increase in other malignancies in treated rats. Our (15) experience with hyperparathyroidism in humans, and the (16) observations in patients post treatment with PTH.
(17) Let's look at each one of these. The (18) argument has been made that rats received excessively (19) high doses of teriparatide, and there was an excessive (20) response in rat tissues. Let's follow this line of (21) reasoning a bit and see where it goes.
(22) The rats, according to my calculations,

Page 163

(1) based on AUC, which is a unit of exposure, multiplied (2) by a fraction of a lifetime, the rats received about (3) 25 to 1,000 times the proposed human dose, again (4) assuming that humans would be treated for two years, (5) which is about two or three percent of a lifetime.
(6) Now, if the background rate is 0.2 percent (7) in rats, and that's a higher number; it may be a (8) realistic number, but it's a higher number compared to (9) the background rate in humans, which is about four or (10) five per million per year. If the background rate is (11) 0.2 percent in rats, then the study dose range led to (12) about a 30 to 200-fold increase in tumors, and one can (13) compose ratios of increased tumor occurrence divided (14) by increased dose, and you get a number like a range (15) of about 0.2 to 1.0 across the dose range, and this (16) would yield a risk in humans of about 1.2 to, let's (17) say, twofold.
(18) If the risk is less than twofold, given (19) the low background rate humans, we'll probably never (20) see it. If it occurs, we won't know about it. I (21) don't know how comforting that is, but it will be very (22) difficult to measure.

Page 164

(1) And so these risk projections depend on (2) the basal rates of tumor recurrence because if the (3) background rate in rats, for example, was 0.2 percent, (4) then you'd have a 300 to 2,000-fold increase in (5) tumors, and you might have a four or five-fold (6) increase in humans exposed, and of course, these are (7) totally speculative extrapolations.
(8) One make assumptions of linearity, and so (9) forth, but this is about as far as I can take this (10) argument, and so it doesn't really lay the issue to (11) rest.
(12) The next argument that's been made is that (13) the treatment of rats began at a very early age, six (14) to seven weeks, and the question is are young animals (15) particularly or exclusively susceptible. That is, we (16) have already heard further experiments are in progress (17) now to determine whether the effect is age dependent (18) in rats. The dose it's my understanding is going to (19) be given in a staggered fashion to rats in a long-term (20) study carried out by the sponsor, and I think this is (21) really a critical experiment which will tell us a lot (22) about the timing of tumor formation.

Page 165

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

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

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

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

Page 166

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

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

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

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

Page 167

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

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

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

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

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

Page 168

(1) in tumor occurrence, given these background rates.

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

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

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

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

Page 169

(1) Thank you.
(2) DR. STADEL: Good morning. I'd like to (3) begin by expressing appreciation to Dr. Sunita Zalani (4) and her colleagues at Lilly who have been very (5) forthcoming in responding to rather detailed questions (6) from me. I've tried to explore the database very (7) thoroughly, and I can make a generally brief (8) presentation on the clinical trial program, beginning (9) by saying that in general, with a few exceptions, I (10) agree with the presentation that has been made by the (11) sponsor on the safety findings in the clinical trial (12) program.
(13) So I will briefly go over some highlight (14) points about the trials, and then as others have done, (15) I will talk about osteosarcoma.
(16) This is something that came out of some (17) discussions as this was going forward. Safety (18) analyses differ somewhat from efficacy analyses, and (19) I've put up here simply that the analyses of efficacy (20) hypotheses are ordinarily specified in advance, and (21) the use of p values is focused on testing the (22) prespecified hypotheses. In analyses of safety, there

Page 170

(1) usually are no prespecified hypotheses, but there is (2) still a need to assess the data to identify potential (3) areas of concern.
(4) P values as a descriptive tool are useful (5) for this, with the understanding that a p value (6) associated with a new safety finding does not have the (7) same meaning as a p value associated with either the (8) testing of a prespecified efficacy hypothesis or a (9) prespecified, a previously observed safety finding. (10) new safety findings from one study should generally be (11) tested in others before arising at conclusions.
(12) This is important because I show p values (13) on new associations, and I do not want the opportunity (14) of them being misunderstood.
(15) Now, in the preclinical studies, there (16) were some key issues that arose that were on my list (17) of things to understand as I did the safety review in (18) the clinical trials, and these were post dose (19) hypotension and tachycardia, decreases in RR and QTC (20) intervals – I just put QT – and increase in serum (21) and urine calcium.
(22) I will say that in the clinical trial

Page 171

(1) program, I found no clinical events in excess in the (2) treated groups which would have been the types of (3) events associated with these phenomena. These are (4) dose related phenomena. The doses in the trial (5) produced minimal tachycardia. I will show some (6) information on that later.
(7) I also looked for any other kind of (8) cardiovascular even that might be an offshoot of a (9) hypotensive episode, and I did not find excesses in (10) the treated groups.
(11) Now, with regard to electrocardiographs, (12) no electrocardiographs were obtained in the Phase 2 or (13) 3 clinical trials. So that I was not able to evaluate (14) electrocardiographic findings under conditions of the (15) kind of clinical setting in which the drug would be (16) used. I did not see clinical events suggesting (17) cardiac bad clinical outcomes, but I could not (18) evaluate electrocardiographic information. I found (19) this somewhat troubling.
(20) In the preclinical studies, you've heard (21) before about these issues. So I need not dwell on (22) them.

Page 172

(1) Just a reminder of the size of the key (2) studies. These are the two main studies of the (3) enrollment criteria, the numbers of patients in the (4) treatment arms.
(5) Again, just a reminder of what size (6) studies are we dealing with. The main studies I've (7) shown, GHAC and AJ, AC the main study in women, AJ the (8) study in men. Two other studies that were important (9) supportive studies that had active controls I've (10) listed. Just to give the denominators a sense, I will (11) be showing numerators with percents and p values. (12) This is your opportunity to know what the denominators (13) are.
(14) Now, this, I think is very important (15) information. In terms of the issue of possible long- (16) term effects of duration of use, and this is a sort of (17) lead to the osteosarcoma discussion later, this is (18) most of what we know in the two main trials about (19) duration of use. That is, 85 percent of the women (20) were in the 13 to 23 months exposure to study drug, (21) and 87 percent of the men in the six to 14 month (22) exposure.

Page 173

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

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

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

Page 174

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

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

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

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

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

Page 175

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

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

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

Page 176

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

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

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

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

Page 177

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

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

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

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

Page 178

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

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

(9) You know, so these patients were (10) monitored.

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

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

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

Page 179

(1) episodes in 20 microgram.

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

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

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

(22) Now, the post treatment follow-up study

Page 180

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

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

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

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

(22) This I wanted to show. This is the

Page 181

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

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

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

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

Page 182

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

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

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

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

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

Page 183

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

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

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

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

Page 184

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

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

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

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

(22) SEER covers about – I just got that from

Page 185

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

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

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

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

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

Page 186

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

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

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

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

Page 187

(1) quite confident.

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

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

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

(22) So to some degree, I think it really cuts

Page 188

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

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

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

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

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

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

Page 189

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

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

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

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

(22) If the incidence is four per million up

Page 190

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

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

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

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

(22) And so whatever your decisions are in

Page 191

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

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

(10) Thank you.

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

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

Page 192

(1) So how do we reconcile these two numbers?

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

(7) DR. STADEL: The majority.

(8) ACTING CHAIRPERSON MOLITCH: – much (9) smaller?

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

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

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

Page 193

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

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

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

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

Page 194

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

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

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

(22) DR. STADEL: One of the things I had

Page 195

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

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

(13) DR. STADEL: Thank you.

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

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

Page 196

(1) that– do you know what I –

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

(4) DR. GRADY: Yeah.

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

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

(22) DR. KUIJPERS: On the database, yes.

Page 197

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

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

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

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

(22) DR. GRADY: And one more question. Also

Page 198

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

(4) DR. STADEL: Made it up.

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

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

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

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

Page 199

(1) ACTING CHAIRPERSON MOLITCH: Dr. Sampson.

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

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

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

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

Page 200

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

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

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

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

Page 201

(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

Page 202

(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),

Page 203

(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?

Page 204

(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

Page 205

(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

Page 206

(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

Page 207

(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

Page 208

(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.

Page 209

(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

Page 210

(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.

Page 211

(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

Page 212

(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

Page 213

(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

Page 214

(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 GHAJ in (22) men, obviously the most important point here is that

Page 215

(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

Page 216

(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

Page 217

(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

Page 218

(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.

Page 219

(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

Page 220

(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.)

Page 221

(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

Page 222

(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.

Page 223

(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.

Page 224

(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

Page 225

(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

Page 226

(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

Page 227

(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

Page 228

(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.

Page 229

(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

Page 230

(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

Page 231

(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

Page 232

(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

Page 233

(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.

Page 234

(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.

Page 235

(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.

Page 236

(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

Page 237

(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) antilopeptide (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

Page 238

(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

Page 239

(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?

Page 240

(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

Page 241

(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?

Page 242

(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,

Page 243

(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

Page 244

(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

Page 245

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

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

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

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

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

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

Page 246

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

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

DR. POTTS: I'm John Potts.

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

Page 247

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

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

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

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

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

Page 248

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

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

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

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

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

DR. VAHLE: Just to clarify, I think there

Page 249

(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 an din 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

Page 250

(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

Page 251

(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

Page 252

(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.

Page 253

(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

Page 254

(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

Page 255

(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

Page 256

(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.

Page 257

(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

Page 258

(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

Page 259

(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

Page 260

(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

Page 261

(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

Page 262

(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

Page 263

(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

Page 264

(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

Page 265

(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

Page 266

(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.

Page 267

(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

Page 268

(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

Page 269

(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

Page 270

(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?

Page 271

(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.

Page 272

(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.

Page 273

(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.

Page 274

(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

Page 275

(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

Page 276

(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

Page 277

(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

Page 278

(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

Page 279

(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

Page 280

(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

Page 281

(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

Page 282

(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,

Page 283

(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.

Page 284

(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

Page 285

(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

Page 286

(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

Page 287

(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

Page 288

(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

Page 289

(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.

Page 290

(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

Page 291

(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

Page 292

(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

Page 293

(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

Page 294

(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

Page 295

(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

Page 296

(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

Page 297

(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

Page 298

(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

Page 299

(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

Page 300

(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

Page 301

(1) elicit your response with regard to whether you think (2) the database as it stands adequately defines the full (3) safety profile of the drug. In other words, are you (4) left confident of what the risks of the drug are or do (5) you feel that more information is needed?

(6) DR. GRADY: In that case –

(7) DR. ORLOFF: Let me just say that this is (8) separate from the question of approvability.

(9) DR. GRADY: In that case I vote no for (10) both.

(11) ACTING CHAIRPERSON MOLITCH: Dr. (12) Kreisberg.

(13) DR. KREISBERG: No for both.

(14) DR. GELATO: No for both.

(15) DR. TAMBORLANE: No for both.

(16) DR. LEVITSKY: No for both.

(17) DR. AOKI: Same.

(18) DR. PELOSI: No for both.

(19) DR. HOLMBOE: No for both.

(20) ACTING CHAIRPERSON MOLITCH: And I agree (21) no for both, and I guess all of our concern is with (22) respect to the still unknown risk of osteosarcoma.

Page 302

(1) DR. LEVITSKY: Actually the further (2) concern as to how this is going to work in patients (3) who have been treated with other drugs. So the (4) osteosarcoma is the major risk. I still am not (5) entirely sure that.

(6) ACTING CHAIRPERSON MOLITCH: Thank you.

(7) Did other people who voted no have other (8) concern other than the two that were mentioned?

(9) DR. HOLMBOE: I just want to mention the (10) issue of the combination therapy. I think we know (11) very little with regard to safety.

(12) ACTING CHAIRPERSON MOLITCH: Thank you.

(13) DR. GELATO: I also think that patients (14) need to be monitored. I'm not sure I feel comfortable (15) with putting them on this and calcium supplements and (16) just say, "You don't need to check calciums," and some (17) of the metabolic issues, although I don't think (18) they're major, but I think they at least need to be (19) considered.

(20) ACTING CHAIRPERSON MOLITCH: I think that (21) this may well come up as we pursue along with our (22) discussions about what might be appropriate to say

Page 303

(1) what patients might be safe to take the drug to begin (2) with and then appropriate monitoring of that patient (3) once they're on drug.

(4) We'll move on to number three, and I guess (5) we'll come back. I don't know. Dr. Orloff, do you (6) want us to discuss that aspect now or later?

(7) DR. ORLOFF: You can move on to Question (8) 3.

(9) ACTING CHAIRPERSON MOLITCH: Okay. We'll (10) then move on to approvability, and based on the data (11) presented by the sponsor and the NDA, do you recommend (12) approval of teriparatide (a) for the treatment of post (13) menopausal osteoporosis and (b) to increase bone (14) mineral density in men with osteoporosis?

(15) And now we'll start back on the other (16) side.

(17) DR. HOLMBOE: I'd say yes to A with (18) limitations, no to B.

(19) DR. PELOSI: I would say yes to A but no (20) to B.

(21) DR. AOKI: I'd say yes to both.

(22) DR. LEVITSKY: Yes to both.

Page 304

(1) DR. TAMBORLANE: Yes to both.

(2) DR. GELATO: Yes to A, no to B.

(3) DR. KREISBERG: Yes to A, no to B.

(4) DR. GRADY: Yes to both.

(5) DR. SAMPSON: Yes to A and no to B.

(6) DR. MITLAK: And I will say yes to both

(7) MS. REEDY: And that tally for Number 3, (8) approvability for the treatment of post menopausal (9) osteoporosis, yes ten, no zero.

(10) For the increase of bone mineral density (11) in males, yes five, no five.

(12) ACTING CHAIRPERSON MOLITCH: I think we're (13) going to make a C question here as well, which comes (14) up on the next page about whether this will be (15) appropriate to use as first line versus second line (16) therapy, and perhaps with this approvability that (17) we've just talked about, perhaps we can go back – or (18) maybe even a C and a D – as a proof for first line (19) drug versus second line drug, and maybe we can just do (20) this by comments around the table, and again, I think (21) we will just go around the table and talk about (22) whether people think this would be appropriate for

Page 305

(1) first versus second line therapy.
(2) Dr. Holmboe.
(3) DR. HOLMBOE: I think given the safety (4) concerns that have been raised, I think it should be (5) second line therapy at this time. I think with regard (6) to men, I don't think we have enough clinical outcomes (7) yet to conclude that it should be approved for that (8) indication at this time.
(9) DR. PELOSI: I would concur with that.
(10) DR. AOKI: I agree.
(11) DR. LEVITSKY: I concur that it should be (12) approved for second line therapy, but I'm still a (13) little uneasy as to what it should be second line (14) therapy as second to because I don't think we have (15) enough information yet to be sure.
(16) DR. TAMBORLANE: I would approve it for (17) first line therapy also.
(18) ACTING CHAIRPERSON MOLITCH: Everybody (19) else said second line. So you are first line or (20) second line?
(21) DR. TAMBORLANE: I said first line.
(22) ACTING CHAIRPERSON MOLITCH: Thank you.

Page 306

(1) DR. TAMBORLANE: Sorry. The "also" was (2) confusing.
(3) ACTING CHAIRPERSON MOLITCH: Yes.
(4) DR. GELATO: I would approve it for first (5) line for women with some, I guess, specifications of (6) the group that gets it first line. For men if it were (7) going to be approved, I would approve it as second (8) line.
(9) DR. KREISBERG: I would approve it for (10) first line therapy in women, but I think the (11) indications ought to be clearly defined.
(12) DR. GRADY: I'd be in favor of restricting (13) it to as a second line drug because I think the (14) efficacy and safety of the other first line drugs is (15) much better.
(16) DR. SAMPSON: I'm going to pass on that as (17) a non-clinician.
(18) ACTING CHAIRPERSON MOLITCH: I like Dr. (19) Lindsay's description of the patients who might be (20) considered as first line therapy, the patients with (21) very severe disease or the patient who has a fracture (22) who's at high risk for a second fracture in the near

Page 307

(1) future. So I'm not sure that I would want to actually (2) restrict it to being a second line therapy, although (3) I think that's probably how I would use it for most (4) patients.
(5) So I'm not sure how to answer my own (6) question.
(7) (Laughter.)
(8) ACTING CHAIRPERSON MOLITCH: I guess I (9) would not restrict it.
(10) MS. REEDY: The tally on that is as first (11) line therapy, four; as second line, five.
(12) ACTING CHAIRPERSON MOLITCH: We'll then go (13) on to Question 4. If the answer to either question in (14) Number 3 is yes, which I think it was, given the (15) theoretical risk for the development of osteosarcoma (16) in humans treated with teriparatide, (a) should the (17) treatment be limited, and if yes, how much or how (18) long; (19) (b) Should the use of teriparatide be (20) recommended only for certain subgroups of patients? (21) If yes, please comment on the recommended target (22) populations.

Page 308

(1) (c) Should teriparatide be limited to use (2) as a second line therapy? If yes, please comment on (3) what criteria should be used to define second line (4) therapy.
(5) And (d) comment on how it should be (6) labeled in the labeling for the bolded warning or (7) black box, and I think we can – this is more of a (8) general discussion at this point, and why don't se (9) start with Dr. Holmboe again?
(10) DR. HOLMBOE: I'll go through each of (11) these. With regard to A, I actually agree with the (12) sponsor that given the amount of data we have at this (13) time, I would agree with the two-year limitation on (14) the therapy with close monitoring.
(15) With regard to B, it really relates to my (16) previous answer. I, again, would restrict to women at (17) this time, given the clinical efficacy data, and again (18) I would recommend it as a second line agent, although (19) I was somewhat persuaded by your argument with regard (20) to those who are at higher risk as first line therapy, (21) i think which gets to C.
(22) D, please comment on how the findings. I

Page 309

(1) think there are several things that I would recommend. (2) I actually would recommend a bold warning with regard (3) to the osteosarcoma risk. I think that would be very (4) important.
(5) Number two, I do think some patient (6) education materials and provider education materials (7) should be developed.
(8) Although I appreciate the sponsor's (9) response with regard to being transparent about the (10) risk and certainly reporting in conference proceeding, (11) I can tell you as a general internist a lot of the (12) things I don't see, and it often takes time to (13) disseminate that sort of information through that (14) particular mechanism.
(15) So I think that there's going to be a need (16) for other mechanisms to get this warning out, and I (17) also think that it would be helpful for them to (18) provide some guidelines with regard to monitoring even (19) though metabolically overall things look fairly safe. (20) There is still some concerns with regard to some of (21) the metabolic changes.
(22) DR. PELOSI: I agree that it should be two

Page 310

(1) years as well until we get more data.
(2) In terms of B, I think I agree with the (3) sponsor in terms of those people who should not (4) receive it, in terms of those with Paget's disease, (5) the adolescents.
(6) For certain subgroups, I would see women (7) who have already experienced fractures.
(8) Number C, should it be limited as a second (9) line use, I think we've had that discussion, and I did (10) vote yes on that, but I think we do need to have some (11) more criteria. I'm not sure at this point what that (12) would be.
(13) My concern would be, again, making sure (14) that we have a registry of all patients, whether it's (15) first or second line, to follow. I also would caution (16) us in terms of looking at the SEER database. Again, (17) it doesn't cover the entire United States. I think (18) working with M.D. Anderson and some of the other (19) places that have sarcoma centers is wise, but tumor (20) registries really don't have that information and that (21) detail. The question is: do we register physicians (22) like they're currently doing with thalidomide so that

Page 311

(1) we can actually go to that particular physician to get (2) that information?
(3) I think it would be hard to pull out of (4) the SEER database, and I agree in terms of education, (5) but I would also add education to the nurses because (6) nurses are usually the ones that play a significant (7) role in following, as well as educating the patient.
(8) DR. AOKI: To A it would be yes, 24 (9) months. (10) (b) With the proviso of the Paget's (11) disease, I would recommend that those obviously not (12) receive the drug. (13) (c) I would limit it to second line (14) therapy at the present time. (15) (d) I'd have bolded warning.
(16) DR. LEVITSKY: I think a two year limit is (17) as good as any right now. So I would agree with that.
(18) I would agree with the sponsor's (19) recommendations about eliminating certain subgroups of (20) patients as being reasonable ones to be treated.
(21) I had said that I think it should be (22) limited as a second line therapy, which I think should

Page 312

(1) be the FDA recommendation, although I recognize that (2) there might be certain very sophisticated people with (3) special patients who might choose to use it as first (4) line therapy.
(5) And I think that there needs to be some (6) sort of guideline drawn up so that a few calciums are (7) checked rather than just ignoring that issue.
(8) And I think a bolded warning would be (9) sufficient in regard to the osteosarcoma.
(10) DR. TAMBORLANE: Well, consistent with my (11) neighbors, I would say that two years is fine for A. (12) (b) the stipulations as indicated by the (13) sponsor as far as people should not use the drug is (14) okay.
(15) I voted for first line therapy for the (16) same reasons that Mark had articulated.
(17) And bolded warning. I'm not actually sure (18) I know the difference between a bolded and black box (19) warning, but whatever says "beware of this finding in (20) rats" is important.
(21) DR. ORLOFF: Maybe we should clarify that (22) because the question mentioned black box warning, and

Page 313

(1) a couple of people have talked about bolded warnings, (2) and those are maybe strangely, but they are different (3) in regulatory terminology.

(4) A black box warning is just that. The (5) information is usually set off at the very beginning (6) of the labeling. It's enclosed in a black box, and (7) it's designed to bring your attention to that, the (8) first thing you see. It also has implications for (9) promotion of the drug. When a product has a black box (10) warning in the labeling, it limits the ability of (11) sponsors to hand out promotional materials without (12) handing out the full prescribing information.

(13) So handing out, you know, the trinkets, et (14) cetera, is restricted because you have to hand out the (15) full prescribing information.

(16) That's opposed to a bolded warning, which (17) simply means that somewhere in the labeling – it (18) could be at the beginning; it could be in the warning (19) section; it could be anywhere – you put it in bolded (20) type, but doesn't have all of the same promotional (21) implications.

(22) DR. TAMBORLANE: Well, I'm glad I asked.

Page 314

(1) So the black box sounds the most appropriate for me.

(2) DR. GELATO: I think two years is (3) reasonable based on what the sponsor said and also the (4) information that Dr. Neer gave us.

(5) I think that, again, I agree with the (6) sponsor that it should be very clearly laid out the (7) patients who should not be given this drug in terms of (8) a variety of things, any of the risk for osteosarcoma, (9) renal insufficiency, and so on.

(10) And I did say that I thought it could be (11) used as first line therapy in women, but again, I felt (12) that it should be limited to those women as suggested (13) by Dr. Lindsay who had fractures and were at increased (14) risk to fracture again because there I think you might (15) want to go with something that's going to benefit them (16) relatively quickly.

(17) And I would keep it as second line for men (18) who have maybe failed other therapies, and I agree (19) with the black box warning.

(20) DR. KREISBERG: I think that two years is (21) reasonable. I think there should be specific (22) indications and contraindications for the use of the

Page 315

(1) drug as first line or second line therapy.

(2) I agree that it should not be used in (3) patients with Paget's and children and a variety of (4) other things. I'd like to add the contraindication (5) right now that it should not be used in combination (6) whether they are anti-osteoporosis drugs because we (7) don't have any information on that that obviously (8) could be removed in the future.

(9) The indications, I think, ought to be not (10) only for recent fractures, but for failure of previous (11) therapy, and it can be used in patients with very (12) severe osteoporosis even in the absence of fractures, (13) and I think it needs a black box warning.

(14) DR. GRADY: I more or less agree with all (15) of that. I think two years is reasonable. I think (16) the contraindications suggested by the sponsor were (17) reasonable. I think it should be a second line (18) therapy both for women and for men, and perhaps used (19) as first line therapy in women at very high risk if (20) they have had prior fractures or very low bone (21) density.

(22) It's actually the final issue that worries

Page 316

(1) me the most. I think that our two options for how to (2) kind of get more data on this are to – and perhaps we (3) ought to discuss a little bit the idea of recommending (4) that the sponsor wait to market this drug until the (5) findings in the new animal studies are completed.

(6) Actually I personally don't think that's (7) going to help us a whole lot. I think the sample (8) sizes are too small and we'll be still stuck with this (9) prior rat study where 50 or 60 percent of them got (10) osteosarcoma, and I believe that that leaves us only (11) with some sort of registry, and I'd like to hear a (12) little more discussion about that.

(13) You know, we keep saying registry, but in (14) my mind registry means that the people who take the (15) drug sign up at the time they begin to take it and (16) that you get identifiers for those people, that (17) typically that would be, you know, full name, full (18) birth date and Social Security number so that you can (19) subsequently link with the tumor registry and perhaps (20) also link with the national death index because I (21) think anybody who gets osteosarcoma dies in relatively (22) short order, and that's usually the cause of death,

Page 317

(1) and that would clearly be, I think, the strictest way (2) to go, is to sort of require prospective follow-up on (3) persons who take this drug.

(4) I'm not quite sure how registries usually (5) work.

(6) DR. KREISBERG: Why don't we just come (7) back to this whole issue? That's actually Question 5 (8) about the post marketing surveillance also. I think (9) this whole issue of how to do this should merit full (10) discussion. So why don't we come back to that before (11) Dr. Stadel speaks?

(12) DR. GRADY: Yes, and I like the black box.

(13) DR. SAMPSON: I think I agree with the (14) sponsor's recommendation of two years in duration.

(15) Abstaining on B and C, and bolded warning (16) on D.

(17) ACTING CHAIRPERSON MOLITCH: I agree about (18) the 24 months. I think the certain subgroups of (19) patients I would like to have very clearly defined (20) clearly the Paget's and the adolescents, but then (21) other secondary causes of osteoporosis, which it (22) should not be used in. It should be outlined in the

Page 318

(1) package insert and certainly in educational, (2) promotional materials, and maybe even specific tests (3) recommended such as alkaline phosphatase and PTH (4) before we start any therapy in patients that are (5) essentially mandatory, and I would think also serum (6) calcium level is mandatory prior to starting, and (7) perhaps at designated intervals after starting therapy (8) at three months and then perhaps calcium and alkaline (9) phosphatase every six months for the duration of (10) therapy would seem to me to be a reasonable thing to (11) do in these patients.

(12) As far as the warning, I think it should (13) be a black box warning pending any additional (14) information, and then I think we do need to come back (15) to this whole issue of how are we going to track (16) patients. What kind of either post marketing or (17) perhaps as Dr. Bone suggested even pre-marketing (18) studies or continuation studies to follow patients (19) like this, and additional ideas, I think, are welcome.

(20) Then we can start perhaps with Dr. Stadel (21) and then come back through Dr. Sampson.

(22) DR. STADEL: I don't think I have a hard

Page 319

(1) and fast view about registries, although with such a (2) rare disease, the orientation and discussion has been (3) towards an active mode of case finding with the idea (4) that exposure would be determined through the case if (5) they're still alive or through the case's physician if (6) they're not.

(7) Then if you use that series for a case (8) control study, you would have to mount a parallel (9) measure of ascertainment.

(10) You know, a registry could be used, and if (11) one wanted to sweep the registry, register people (12) through the national death index, that would make (13) sense doing it that way. I think the reason that I (14) haven't thought in that direction is simply that 99.9 (15) percent of the information isn't useful. The outcome (16) is so rare that going in the other direction is much (17) more efficient.

(18) DR. GRADY: Well, I guess I wonder have (19) you done that because it seems to me it takes a long (20) time to do a case control study. You have to (21) accumulate a lot of cases, and then you have to go (22) back and get their exposure data, and I just worry a

Page 320

(1) bit that by the time you're able to accomplish a case (2) control study, there might be a lot of osteosarcomas.

(3) DR. STADEL: What we've been talking about (4) doing would be a system of ascertaining cases in (5) referral centers fairly rapidly, getting basic data on (6) them. Whether they're used to mount a case control (7) study, we haven't worked out all of the details, but (8) the first step would be to ascertain the cases while (9) they're still alive, ascertain them fairly rapidly.

(10) I think we should think more about the (11) issue. As I say, the biggest reservation I have about (12) a registry is simply that it's a lot of work for the (13) patients, a lot of work for the doctor, and most of (14) the registry information would not get used for (15) anything.

(16) ACTING CHAIRPERSON MOLITCH: Dr. Bone.

(17) DR. BONE: Since we're not really voting (18) and just commenting, a couple of thoughts based on our (19) experience with something a little bit analogous, (20) which was the triglitozone (phonetic) issue, and we (21) have major issues there about ascertainment of cases, (22) and there were estimates that the number of cases

Page 321

(1) could be as high as ten times those counted or not, (2) and there was a lot of discussion.
(3) And the other thing is what's the (4) denominator. So I think that whatever needs to be (5) done from that public health sort of approach to (6) ascertainment, as rigorous as possible identification (7) of both the denominator and the numerator would be (8) extremely important.
(9) And I'm inclined to think that Dr. Grady's (10) suggestion would be very useful if it could be (11) implemented.
(12) I'll just mention that complementary to (13) that would be something along the lines I mentioned (14) during the earlier discussion. It won't get you all (15) the way to discovering whether there's a modest (16) increase in the risk, but it will help with being (17) assured there's not a big increase and also address a (18) number of the issues that we've been wrestling with in (19) a way that would be definitive, I would think.
(20) ACTING CHAIRPERSON MOLITCH: Dr. Sampson.
(21) DR. SAMPSON: I think I concur with Dr. (22) Stadel. You're looking for such a rare occurrence,

Page 322

(1) and if this is something that would be noted, it seems (2) to me that just the identification of cases and then (3) proper plan study after that would be a pretty good (4) way to go.
(5) ACTING CHAIRPERSON MOLITCH: Do you have (6) any further comments, Dr. Grady?
(7) DR. GRADY: The term "registry" has been (8) used. I was just wondering how you would usually go (9) about that. What do you mean when you say there's a (10) "registry"?
(11) DR. STADEL: Sorry. I don't understand (12) your question.
(13) DR. GRADY: Well, I think one of the (14) people have been saying, "Oh, well, we should have a (15) registry to get additional post marketing data on."
(16) DR. STADEL: The term "registry" usually (17) means that you register exposure and do follow-up. (18) With the rarity of this outcome, I'd be much more (19) inclined to go after the outcome, and it's a (20) relatively easy exposure also. It's really – at the (21) first cut it's a binary exposure. Have you taken this (22) drug or not?

Page 323

(1) And so I think actually it would be better (2) to put the effort into as wide a case finding as (3) possible, the ability to ascertain exposure in cases, (4) and to use the case series, depending if it reaches a (5) point where it looks like one would learn anything by (6) doing a case control study.
(7) You know, if the intercept is nothing, if (8) you ascertain a large series of cases and none of them (9) are exposed, then you're relatively sure of what the (10) odds ratio will be. So I think this is a case where (11) a lead edge on case ascertainment with the ability to (12) mount a case control study when one has some idea of (13) how the case series is panning out would make sense.
(14) ACTING CHAIRPERSON MOLITCH: Dr. (15) Kreisberg.
(16) DR. KREISBERG: Well, my answer is brief. (17) I think we ought to get some people who know how to do (18) this and have them tell us what to do.
(19) (Laughter.)
(20) ACTING CHAIRPERSON MOLITCH: Dr. Gelato.
(21) DR. GELATO: I would vote with Dr. (22) Kreisberg. I think that's a good idea.

Page 324

(1) DR. TAMBORLANE: I would, too, except I (2) would try to make sure it was proactive, you know, (3) that there was a plan. Going after the cancer (4) registry sounds like the way to go to me.
(5) DR. LEVITSKY: I have a particular (6) concern, which is that unlike the triglitozone issue, (7) it's not going to be that you take the drug and you (8) turn yellow. It's going to be that you take the drug; (9) you forgot you took the drug; it's 15 years later, and (10) something good happened to you, and I think really you (11) need to have people who know exactly how to do that (12) and to retrieve that information.
(13) DR. TAMBORLANE: Especially since they're (14) 100 years old by then and can't remember.
(15) DR. LEVITSKY: Yeah.
(16) (Laughter.)
(17) DR. AOKI: I agree with Dr. Kreisberg.
(18) DR. STADEL: Something I tried to (19) emphasize, and I'll take the opportunity to say again, (20) this could take a very long time, and we need to be (21) clear that we're talking about a large element of (22) uncertainty that will go on for a protracted period of

Page 325

(1) time even if we do the very best we can.
(2) DR. PELOSI: I would just say with the (3) registry if you register the patients at the (4) beginning, run it through tumor registry, but all of (5) the tumor registries, but not just SEER because SEER (6) isn't comprehensive, but I really like the idea of the (7) death index. It would be actually a quicker way to go (8) to do case findings.
(9) And it's my understanding we're answering (10) number five right now. Is that - well, I would just (11) want to make sure that we did see future studies (12) looking at more mature rats than the immature rats. (13) I think that might be of help, but with a number in (14) the sample that might be meaningful to us.
(15) And I would also hope that we could look (16) at quality of life data post treatment to see if, (17) indeed, what the impact was on their life through this (18) treatment as well.
(19) DR. HOLMBOE: I think from a risk (20) management standpoint I agree with Dr. Stadel that the (21) registry has a lot of logistical difficulties, (22) particularly at the point of care, and these filled

Page 326

(1) out whether it be in the office or in the pharmacy, (2) and I think you'd have to collect a huge amount of (3) data to recognize a signal quickly.
(4) So I think if you're going to do that, you (5) still need to do the kind of surveillance you're (6) suggesting with regard to looking for cases at (7) referral centers using SEER data, you know, from a (8) case control standpoint as well. I don't think you (9) can get around not doing that when you have such a (10) rare outcome.
(11) I think that's where actually case control (12) studies help. It's true, as Dr. Grady points out, you (13) have to wait until the cases occur, and that's the (14) down side to that. So it's always going to be (15) retrospective, and so prospectively other (16) possibilities would be to take advantages of some of (17) the large pharmacy databases that now do exist around (18) the country, including through the DOD and VA and some (19) of the others. I don't know if you have access to (20) those, but sometimes those can be helpful.
(21) DR. STADEL: Only to say that with an (22) expected rate of 400 million per year, I respectfully

Page 327

(1) submit that most of those databases are too small.
(2) DR. HOLMBOE: Agreed, but again, if we're (3) looking for any signal, I wouldn't rule them out (4) because we don't know what the rate is. I mean, (5) granted, if it turns out to be that low, you'll never (6) see it, but we don't know that, and we really don't. (7) So I think taking advantage of what you do have, (8) particularly with regards to some logistical digital (9) registry, I'd still consider taking a look at those.
(10) ACTING CHAIRPERSON MOLITCH: Well, I would (11) agree. I think some post marketing registry does need (12) to be done. I think if we rely upon physicians (13) filling out forms in their office, it's not going to (14) happen, speaking from personal experience.
(15) However, one possible way might be to get (16) patients to send in a $10 rebate slip to the company (17) to register their name and their Social Security (18) number, et cetera, when they get their first dose of (19) drug and perhaps every six months thereafter for the (20) duration of therapy to send in that slip to get their (21) rebate, ten or $15 or $1,000, whatever Dr. Kreisberg (22) thinks is appropriate.

Page 328

(1) (Laughter.)
(2) ACTING CHAIRPERSON MOLITCH: But that may (3) be one way to get some compliance in that regard.
(4) I think right now we'll take any (5) additional comments that any members of the panel (6) might have that might be useful. Dr. Kreisberg.
(7) DR. KREISBERG: Well, I'd only reiterate (8) I'm sure the company - I'm not telling the company (9) anything that they haven't already considered - is (10) head to head as well as combination studies in a (11) prospective randomized fashion would be very helpful (12) to those of us who practice and take care of patients.
(13) I may be naive, but I've always thought of (14) osteoporosis being either increased bone resorption or (15) decreased bone formation or a combination of that, (16) which means there must be some pathophysiologic (17) approach to identification of patients that might (18) benefit from one form of therapy or another, and while (19) that may be pretty unsophisticated, I would hope that (20) the company would look at possible ways of identifying (21) patients right from the very outset without having to (22) resort to fractures or resort to extensive