

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number **21-318**

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

07/27/01: Endocrinologic & Metabolic Drugs A/C

PAGE 1 TO PAGE 330

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**CONDENSED TRANSCRIPT AND CONCORDANCE
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(1) FOOD AND DRUG ADMINISTRATION
 (2) CENTER FOR DRUG EVALUATION AND RESEARCH
 (3) * * * * *
 (4) ENDOCRINOLOGIC AND METABOLIC
 (5) DRUGS ADVISORY COMMITTEE
 (6) * * * * *
 (7) MEETING
 (8) * * * * *
 (9) FRIDAY
 (10) JULY 27, 2001
 (11) * * * * *
 (12)
 (13) The Advisory Committee met in the
 (14) Versailles Rooms, Holiday Inn Bethesda, B120 Wisconsin
 (15) Avenue Bethesda, Maryland, at 8:00 a.m., Mark E.
 (16) Molitch, M.D., Acting Chairman presiding.
 (17) PRESENT:
 (18) MARK MOLITCH, M.D., Acting Chairman
 (19) THOMAS A. ADKI, M.D., Member
 (20) DEBORAH GRADY, M.D., M.P.H., Member
 (21) WILLIAM V. TAMBORLANE, M.D., Member
 (22) ALLAN R. SAMPSON, Ph.D., Member

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(1) PRESENT (Continued):
 (2) LYNNE L. LEVITSKY, M.D., Member
 (3) MARIE C. GELATO, M.D., Ph.D., Member
 (4) KATHLEEN REEDY, Executive Secretary
 (5) ROBERT A. KREISBERG, M.D., Consultant
 (6) ERIC S. HOLMBOE, M.D., Ph.D., Rick Management
 (7) Consultant
 (8) JODY L. PELOSI, F.N.P., Ph.D., Consumer
 (9) Representative
 (10) HENRY G. BONE, III, M.D., Guest
 (11) BRUCE V. STADEL, M.D., M.P.H., FDA
 (12) BRUCE S. SCHNEIDER, M.D., FDA
 (13) GEMMA KUIJPERS, Ph.D., FDA
 (14) DAVID G. ORLOFF, M.D., FDA
 (15) JOHN JENKINS, FDA
 (16)
 (17)
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 (20)
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(1) P-R-O-C-E-E-D-I-N-G-S
 (2) (8:08 a.m.)
 (3) ACTING CHAIRMAN MOLITCH: Good morning. (4) My
 name is Mark Molitch. I'm the acting chair this (5) morning.
 This is the meeting of the Endocrinologic (6) and Metabolic
 Drugs Advisory Committee.
 (7) Today we're going to be discussing NDA 21- (8) 13 - I'm
 sorry - 318, Forteo, teriparatide injection (9) or recombinant
 DNA origin. The presenters will be Eli (10) Lilly and Company
 and the FDA.
 (11) We'll begin by introducing members of the (12) table up
 front.
 (13) May I remind everybody that the (14) microphones are ac-
 tivated by pressing on the right to (15) speak, and after you've
 spoken, please then turn off (16) the microphone to decrease
 the ambient noise in the (17) room.
 (18) And we'll start on the left with Dr. (19) Holmboe.
 (20) DR. HOLMBOE: Hi. My name is Eric (21) Holmboe. I'm a
 general intern from Yale University (22) serving as a consultant
 today.

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- (1) DR. PELOSI: I'm Jody Pelosi. I'm an (2) oncology nurse practitioner at the Phoenix Indian (3) Medical Center, and I'm here as the consumer rep.
- (4) DR. AOKI: I'm Tom Aoki from the (5) University of California, Davis, in Sacramento, (6) California.
- (7) DR. LEVITSKY: I'm Lynne Levitsky. I'm (8) Chief of the Pediatric Endocrine Unit at Mass. General (9) Hospital in Boston.
- (10) DR. TAMBORLANE: I'm Bill Tamborlane, (11) Chief of pediatric endocrinology in the Pediatric (12) Pharmacology Research Unit, Yale University.
- (13) DR. GELATO: I'm Marie Gelato. I'm a (14) professor of medicine and an endocrinologist at SUNY, (15) Stony Brook.
- (16) DR. KREISBERG: Bob Kreisberg from Mobile, (17) Alabama.
- (18) MS. REEDY: Kathleen Reedy, Executive (19) Secretary of the Endocrinologic and Metabolic Drugs (20) Advisory Committee, CDER.
- (21) DR. GRADY: I'm Deborah Grady. I'm a (22) professor of medicine and epidemiology from the

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- (1) University of California in San Francisco.
- (2) DR. SAMPSON: I'm Allan Sampson. I'm (3) professor of statistics, University of Pittsburgh.
- (4) DR. BONE: I'm Henry Bone, Director of the (5) Michigan Bone and Mineral Clinical in Detroit, (6) Michigan.
- (7) DR. STADEL: Bruce Stadel, Medical Officer (8) in the Division of Metabolism, Endocrine Drug (9) Products.
- (10) DR. SCHNEIDER: Bruce Schneider, Medical (11) Officer, Division of Metabolic and Endocrine Drug (12) Products, CDER, FDA.
- (13) DR. KUIJPERS: Gemma Kuijpers, (14) pharmacology reviewer at the Division of Metabolic and (15) Endocrine Drug Products, FDA.
- (16) DR. ORLOFF: I'm Dr. David Orloff, (17) Director of the Division of Metabolic and Endocrine (18) Drug Products at CDER.
- (19) MR. JENKINS: And I'm John Jenkins. I'm (20) the Director of the Office of Drug Evaluation II in (21) CDER at FDA.
- (22) ACTING CHAIRMAN MOLITCH: Thank you,

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- (1) everybody.
- (2) Kathleen Reedy will now read the meeting (3) statement.
- (4) MS. REEDY: The conflict of interest (5) statement for Endocrinologic and Metabolic Drugs (6) Advisory Committee, July 27th, 2001, considering (7) Lilly's Forteo.
- (8) The following announcement addresses the (9) issue of conflict of interest with regard to this (10) meeting and is made a part of the record to preclude (11) even the appearance of such at this meeting.
- (12) Based on the submitted agenda for the (13) meeting and all financial interests reported by the (14) committee participants, it has been determined that (15) all interests in firms regulated by the Center for (16) Drug Evaluation and Research present no potential for (17) an appearance of a conflict of interest at this (18) meeting with the following exceptions.
- (19) In accordance with 18 United States Code (20) 208(b), a fully waiver has been granted to Drs. Mark (21) Molitch, Barbara Lukert and William Tamborlane. A (22) copy of the waiver statements may be obtained by

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- (1) submitting a written request to the agency's Freedom (2) of Information Office, Room 12A-30 of the Parklawn (3) Building.
- (4) In addition, we would like to disclose for (5) the record that Drs. Deborah Grady, Robert Kreisberg, (6) Barbara Lukert, Lynne Levitsky, and William Tamborlane (7) have interests which do not constitute a financial (8) interest within the meaning of 18 United States Code (9) 208(a), but which could create the appearance of a (10) conflict.
- (11) The agency has determined notwithstanding (12) these interests, that the interest of the government (13) in their participation outweighs the concern that the (14) integrity of the agency's programs and operations may (15) be questioned.
- (16) Therefore, Dr. Grady, Dr. Kreisberg, Dr. (17) Lukert, Dr. Levitsky, and Dr. Tamborlane may (18) participate fully in today's discussions.
- (19) With respect to the FDA's invited guests, (20) there are reported interests which we believe should (21) be made public to allow the participants to (22) objectively evaluate their comments.

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(1) Dr. Henry Bone would like to disclose for (2) the record that he was an investigator on a Phase 3 (3) study of Raloxiphene Evista (phonetic), one of the (4) competing products to Forteo, from 1994 to 1999. Dr. (5) Bone has participated as an investigator in several (6) clinical trials of Alendronate and other competing (7) product to Forteo, some of which are still current. (8) He's also acted as a consultant to Merck.

(9) In addition, Dr. Bone's clinic has (10) received an unrestricted educational grant from (11) Novartis. He has given lectures sponsored by Merck (12) and Novartis.

(13) Lastly, Dr. Bone is an officer of the (14) Michigan Consortium for Osteoporosis, which has (15) received supplementary support from Merck and Procter (16) and Gable.

(17) Dr. Bone receives no salary from the (18) Michigan Consortium for Osteoporosis, but is (19) reimbursed for his expenses.

(20) In the event that the discussions involve (21) any other products or firms not already on the agenda (22) for which an FDA participant has a financial interest,

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(1) important aspect of FDA's review and regulatory (2) decision making for new drugs, affording an (3) opportunity for us to hear from experts in the field, (4) from members of the public, as well as from the (5) sponsor on the subject application.

(6) At the outset, it should be understood by (7) all in attendance that we, the agency, enter into this (8) meeting without an established course of regulatory (9) action. We are here to engage in a discussion between (10) the committee and FDA and the sponsor on the (11) scientific merits of the investigations, clinical and (12) otherwise, of this drug and of the ramifications of (13) the resultant data for a decision regarding marketing (14) of the product for the proposed indications.

(15) I want to remind everybody that the tone (16) and outcomes of the deliberations today and the (17) opinions expressed by the committee, as well as those (18) expressed by the presenters for FDA, do not represent (19) final agency stance on the application. Regulatory (20) action will come only after further review, internal (21) discussion, and clearly discussion with the sponsor.

(22) So, again, as Director of the division

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(1) the participants are aware of the need to exclude (2) themselves from such involvement, and their exclusion (3) will be noted for the record.

(4) With respect to all other participants, we (5) ask in the interest of fairness that they address any (6) current or previous financial involvement with any (7) firm whose products they may wish to comment upon.

(8) I mentioned Dr. Barbara Lukert, who was (9) not able to be with us today.

(10) ACTING CHAIRMAN MOLITCH: Thank you, Ms. (11) Reedy.

(12) We'll now have an opening statement from (13) Dr. Orloff.

(14) DR. ORLOFF: Good morning. I want to (15) extend my own welcome to the committee and thank you (16) in advance for the service to the agency and to the (17) drug regulatory process.

(18) I'm basically going to read a statement (19) that I read yesterday since there's a new audience, a (20) new sponsor, as well as additional members of the (21) Advisory Committee.

(22) The Advisory Committee process is an

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(1) that is responsible for review and regulatory action (2) on this product, I want to thank you for being here, (3) welcome you. I'll have further remarks later when I (4) charge the committee after the sponsor's and FDA (5) presentations.

(6) And I'll turn it back over to Dr. Molitch. (7) Thank you.

(8) ACTING CHAIRMAN MOLITCH: Thank you, Dr. (9) Orloff. (10) The company, Eli Lilly, will now give (11) their presentation. They've requested that we hold (12) questions for various speakers until the end of their (13) presentation, and then at that point they'll be open (14) for discussion amongst the members of the panel.

(15) So we'll start with Dr. Stotka, who is the (16) Executive Director of U.S. Regulatory Affairs of (17) Lilly.

(18) DR. STOTKA: Slides on, please.

(19) Good morning. My name is Jen Stotka. I'm (20) a physician and the Executive Director of U.S. (21) Regulatory Affairs for Eli Lilly & Company.

(22) On behalf of Lilly, I thank you for the

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(1) opportunity to discuss teriparatide, which we will (2) also refer to as recombinant human PTH 1 to 34.

(3) The proposed trade name for teriparatide (4) is Forteo.

(5) The indication for which we are currently (6) seeking approval is the treatment of osteoporosis in (7) post menopausal women and in men.

(8) The advantages and safety profile of this (9) new therapy will be highlighted in subsequent (10) presentation today. The extensive contents of this (11) application meet or exceed all expectations contained (12) in applicable FDA and ICH guidelines, and our clinical (13) trials were conducted with advisement from and (14) agreement with the FDA's Division of Metabolic and (15) Endocrine Drug Products.

(16) Today we will provide data that support (17) the position that teriparatide is the first clinically (18) useful agent in a new class of osteoporosis therapies. (19) These new drugs are bone formation agents in contrast (20) to the anti-resorptives currently on the market, and (21) it will provide an important new choice for the (22) treatment of osteoporosis in post menopausal women and

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(1) in men.

(2) Comprehensive information from clinical (3) trials enrolling over 2,800 women and men in 20 (4) countries was submitted to the FDA as a new drug (5) application in November of 2000. Our clinical (6) evaluation of teriparatide began shortly after our (7) initial IND filing in August 1995. The clinical (8) development plan was formulated following input from (9) a number of external consultants and the FDA.

(10) Key points of the FDA's draft guidelines (11) on the clinical development of osteoporosis drugs (12) published in April of 1994 were taken into (13) consideration when we designed our clinical program.

(14) The pivotal study in post menopausal women (15) with osteoporosis began in December of 1996, while our (16) pivotal study in men with osteoporosis began in July (17) of '97.

(18) In December 1998, Lilly reported to the (19) FDA an unexpected finding of osteosarcoma in a two- (20) year rat carcinogenicity study. We informed the FDA (21) of our decision to voluntarily stop all ongoing trials (22) with teriparatide while this nonclinical finding was

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(1) evaluated further.

(2) In April 1999, Lilly submitted the (3) recommendations of an external oncology advisory board (4) to the FDA. This advisory board was convened to (5) assist in the evaluation of the nonclinical (6) osteosarcoma finding.

(7) Lilly and the FDA discussed the (8) appropriate follow-up for patients.

(9) Shortly thereafter an observational study (10) was implemented to continue to collect safety (11) information in all patients previously enrolled in our (12) Phase 3 program of teriparatide.

(13) In July 1999, Lilly, the FDA, and external (14) experts from our oncology advisory board participated (15) in a meeting held at the FDA's request to discuss this (16) nonclinical osteosarcoma finding. In September 1999, (17) we met with the FDA to discuss preliminary safety and (18) efficacy results of our pivotal Phase 3 study and to (19) propose the content for an NDA.

(20) Agreement was obtained from the FDA that (21) the NDA package was adequate to support submission of (22) teriparatide as a new agent for the treatment of

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(1) osteoporosis in post menopausal women.

(2) In July of 2000, Lilly and the FDA held a (3) pre-NDA meeting. Agreement was reached with the FDA (4) that the data with teriparatide also appeared to be (5) adequate to support submission of teriparatide as a (6) new agent for the treatment of osteoporosis in men.

(7) The NDA was submitted in November of 2000. (8) The requisite four-month safety update was submitted (9) in March of 2001, and today we will demonstrate that (10) the data submitted in our NDA meet or exceed the (11) burden of proof for efficacy and safety.

(12) Our presentations today encompass a number (13) of scientific and regulatory matters. In fact, we (14) will address all questions that the FDA has asked you (15) to consider regarding the mechanism of action of (16) teriparatide, efficacy in women and men, bone quality, (17) and overall safety.

(18) We will also review the rationale for the (19) selection of our 20 microgram dose, and we will (20) provide you with an assessment of the overall benefit- (21) risk profile.

(22) We will follow this agenda. First, Dr.

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(1) Robert Lindsay, Professor of Clinical Medicine at (2) Columbia University, College of Physicians and (3) Surgeons, Chief of Internal Medicine at Helen Hayes (4) Hospital, and past president of the National (5) Osteoporosis Foundation, will discuss history, (6) mechanism of action, and the unmet medical need.

(7) Following him will be presentations by (8) Lilly scientist: (9) Dr. John Vahle, veterinary pathologist, (10) will cover non-clinical pharmacology and toxicology.

(11) He will be followed by Dr. Bruce Mitlak, (12) Medical Director for the teriparatide team, who will (13) review the clinical efficacy data.

(14) Next Dr. Gregory Gaich, senior clinical (15) research physician, will present an overview of the (16) safety profile of teriparatide.

(17) And finally, Dr. Mitlak will provide the (18) overall benefit-risk summation in our conclusions.

(19) We look forward to a full discussion of (20) the issues raised. Dr. Mitlak will facilitate Lilly's (21) response during the discussion period.

(22) Additionally, we have a number of our key

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(1) scientific staff and external experts available here (2) today to help respond to your questions.

(3) In fact, we wish to thank the following (4) experts for working with us and for being here today (5) to assist with your deliberation: Dr. Adamson, (6) Bellizikan, Chabner, Lindsay, Neer, Potts, and (7) Stewart.

(8) We ask for your active consideration to (9) approve teriparatide for the treatment of osteoporosis (10) in post menopausal women and in men. We believe the (11) documentation provided will support such action, and (12) we look forward to a mutually productive session.

(13) I now have the pleasure of introducing Dr. (14) Robert Lindsay for the scientific overview.

(15) DR. LINDSAY: Thank you very much, Dr. (16) Stotka.

(17) Mr. Chairman, ladies and gentlemen, (18) members of the advisory panel, it is a considerable (19) pleasure for me today to introduce to you the topic of (20) parathyroid hormone, an agent that my group has had (21) considerable interest in for the past 15 years.

(22) To set the stage, I shall briefly review

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(1) the history, mechanism of action, and clinical need (2) for recombinant 1 to 34 human parathyroid hormone as (3) a treatment of osteoporosis in both women and men. (4) Much of the data I will use comes from our specialized (5) center of research funded by the National Institutes (6) of Health.

(7) The parathyroid glands were originally (8) identified by Sandstrom some 121 years ago, and for (9) the next 25 years, their function was hotly debated.

(10) In 1906, Erdheim produced evidence that (11) the parathyroid glands were intimately linked in (12) calcium homeostasis, and in 1925, Collip, working with (13) Eli Lilly Company, prepared a purified, stable extract (14) that was clinically active, and was subsequently (15) marketed.

(16) That parathyroid hormone can be anabolic. (17) It's not new nor novel. In 1929, Orb (phonetic) (18) working with Fuller Albright, first demonstrated the (19) anabolic effect by injecting the extract prepared by (20) Collip into rodents, a finding confirmed some three (21) years later by Hans Selye.

(22) These experiments were largely forgotten

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(1) until the early 1970s when Nile, Jerry Aerbach, John (2) Potts first sequenced and synthesized the 1 to 34 of (3) minor terminals of parathyroid hormone and (4) subsequently the complete peptide.

(5) This allowed sufficient purified peptide (6) to be synthesized to more fully evaluate its (7) pharmacological profile. Today, of course, 1 to 34 (8) human parathyroid hormone is reduced by recombinant (9) technology rather than by protein synthesis.

(10) Initial experiments confirm the anabolic (11) action in rodents and subsequently in other species, (12) including dogs and nonhuman primates.

(13) The first human experiments were initiated (14) in the 1970s by the late John Parsons in collaboration (15) with John Potts, Bob Neer, Jonathan Reeve and Pierre (16) Munier (phonetic) and others. These studies confirmed (17) that parathyroid hormone could exert an anabolic (18) effect on the human skeleton, first published in 1980.

(19) During the 1990s, several relatively (20) small, controlled clinical trials have been completed. (21) These trials all showed that one to 1 to 34 human (22) parathyroid hormone could produce marked increases in

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(1) bone mass, particularly in the lumbar spine, but also (2) in the total hip.

(3) The doses that were used varied from 400 (4) to 800 units, international units, in the original (5) concept, roughly equivalent to the dosage used in the (6) Phase 3 studies about which you will hear later.

(7) These data are exemplified by data from (8) our own group published by Felecia Cosman (phonetic) (9) and colleagues in 2001 that demonstrate an increase in (10) vertebral bone mass over a three-year period of (11) approximately 13 percent in an experiment in which (12) parathyroid hormone was delivered by daily (13) subcutaneous injection on top of already coexisting (14) hormone replacement therapy. These data show the (15) increase in bone mass in the spine.

(16) In addition to these changes in the spine, (17) there was also a significant increase in bone mass in (18) the hip, again, over a three-year period, somewhat (19) less than in the spine, but amounting to slightly more (20) than four percent.

(21) Similar data have been published using (22) parathyroid hormone by itself.

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(1) Although this study was not powered to (2) detect reductions in fracture, we were able to (3) demonstrate statistically significant reductions in (4) vertebral fracture during the three years of the study (5) primarily because we actually saw no fractures in the (6) PTH treated group.

(7) The effects of PTH on bone mass occur by (8) mechanisms that differ markedly from currently (9) available anti-resorptive agents. About a year or so (10) ago, Tony Hodgeman (phonetic) published data on iliac (11) crest bone biopsies obtained one month after starting (12) parathyroid hormone. After only four weeks of (13) therapy, Hodgeman demonstrated an increase in osteoid (14) surface, an increase in the surface of bone covered by (15) osteoblasts, and a dramatic threefold increase in bone (16) formation rate.

(17) Later this year at the American Society of (18) Bone and Mineral Research, we will present further (19) data from these biopsies that demonstrate that those (20) increases in bone formation occur not only in sites of (21) prior resorption, but also on inactive surfaces, and (22) that they occur in both the trabecular bone and osteo

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(1) bone and periosteal bone.

(2) Our biochemical data confirm these (3) histomorphometric responses. This slide demonstrates (4) the increase in osteocalcin, a marker of bone (5) formation, and an NTL (phonetic) peptide, a marker of (6) bone resorption during the early course of treatment (7) with parathyroid hormone.

(8) You can see that osteocalcin increases (9) dramatically and quickly, such that by one month of (10) treatment there is about a 55 percent increase. There (11) is a slower lag in the increase in NTX (phonetic), but (12) by six months the full pharmacological effects of (13) parathyroid hormone are evident. Parathyroid hormone (14) stimulates both bone formation and also bone (15) remodeling.

(16) The consequence of these phenomena is not (17) only an increase in bone mass, but an improvement in (18) the structure of the skeleton with normal amellar (19) (phonetic) bone being laid down.

(20) Data currently in press from the studies (21) that we have conducted in collaboration with John (22) Bellizikan demonstrate that in both men and in women

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(1) there is improvement in the connections among (2) trabeculari (phonetic) within a bone.

(3) These trabecular connections are best seen (4) in a single patient slide shown in the next slide in (5) which we have compared a biopsy from a 64 year old (6) woman before parathyroid hormone, with an iliac crest (7) biopsy from the opposite side in the same woman (8) approximately two and a half years after parathyroid (9) treatment.

(10) It is clear that not only is there more (11) bone present in the slide on the right, but also there (12) are increases in the numbers of trabeculari that are (13) present.

(14) In addition to the numbers of trabeculari (15) and the proved connectivity shown here, there is also (16) rather surprisingly to us initially an increase in (17) cortical thickness shown here and shown here. These (18) improvements in cortical thickness differentiate the (19) use of parathyroid hormone as an anabolic agent when (20) delivered by subcutaneous injection from the disease (21) primary hyperthyroidism.

(22) Currently available treatments for

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(1) osteoporosis are clearly effective. These agents work (2) by reducing bone remodeling and allay bone loss. (3) However, many patients remain at significant fracture (4) risk.

(5) Osteoporosis – I beg your pardon. Remain (6) at significant fracture risk.

(7) Next slide.

(8) The reductions in fracture risk that one (9) sees with anti-resorptive agents amount to some 35 to (10) 55 percent over a three-year period in patients with (11) vertebral fracture. In addition, these agents are (12) unable to restore bone matrix or architecture in the (13) way in which we have demonstrated with parathyroid (14) hormone.

(15) We believe, therefore, that an unmet (16) medical need continues to persist. Osteoporosis is (17) not a trivial disease. We are well accustomed to the (18) concept that hip fracture is associated not only with (19) increased morbidity, but also with increased (20) mortality.

(21) Data published from the fracture (22) intervention trial by Jane Collie (phonetic) and

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(1) colleagues just last year demonstrated one feature of (2) the disease, and that is that not only is hip fracture (3) associated with an age adjusted increase in the (4) relative risk of mortality, but that spine fractures (5) are also, and that there is almost a linear (6) correlation between the number of spine fractures that (7) present and also the increase in mortality.

(8) Data that we published in the Journal of (9) the American Medical Association earlier this year (10) demonstrates that when a patient presents with a new (11) vertebral fracture, he or she will have a 20 percent (12) increase in the likelihood of yet another fracture (13) within a single year.

(14) Next slide.

(15) Unlike current agents, parathyroid hormone (16) stimulates new bone formation and remodeling, rapidly (17) increases bone mass, and by this unique mechanism of (18) action, restores skeletal architecture.

(19) In conclusion, therefore, ladies and (20) gentlemen, teriparatide or recombinant human (21) parathyroid hormone 1 to 34, as will be shown in the (22) following presentations, reduces fracture risk

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(1) significantly, and as I have demonstrated, works by a (2) unique mechanism of action that I believe changes the (3) paradigm for the treatment of osteoporosis and offers (4) benefits to patients with osteoporosis that cannot be (5) seen with current therapeutic options.

(6) It's now my pleasure to introduce Dr. (7) Vahle from the Eli Lilly Company, who will review the (8) preclinical data.

(9) DR. VAHLE: Thank you, Dr. Lindsay.

(10) My name is John Vahle, and I am a (11) veterinary pathologist with the teriparatide team.

(12) I will briefly review the key findings (13) from the animal studies conducted with teriparatide. (14) Overall our nonclinical pharmacology and safety (15) studies meet or exceed all worldwide regulatory (16) guidances.

(17) First, I'll describe the skeletal effects (18) of teriparatide in our most relevant animal model, the (19) mature ovariectomized Cynomolgus monkey.

(20) Then I'll review the nonclinical safety (21) data by briefly reviewing key findings from the animal (22) toxicity studies.

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(1) And I will conclude by presenting the (2) results from the two-year rat study previously (3) mentioned by Dr. Stotka in which osteosarcomas were (4) observed.

(5) In monkeys, teriparatide increases bone (6) mass and improves skeletal microarchitecture. These (7) high resolution CT scans of the fifth lumbar vertebra (8) were obtained in an 18-month skeletal pharmacology (9) study in which ovariectomized monkeys were given (10) teriparatide for up to 18 months and illustrate (11) increased trabecular bone from a monkey given five (12) micrograms per kilogram per day as compared to that (13) from an ovariectomized control monkey. (14) Histomorphometry of the vertebra show that (15) teriparatide stimulated new bone formation on both (16) cortical as well as trabecular surfaces, resulting in (17) increases in trabecular number, in connectivity, as (18) well as increases in cortical area.

(19) These improvements in skeletal (20) architecture are not achieved with anti-resorptives. (21) Most importantly, these effects on bone mass and (22) microarchitecture result in increases in bone strength

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(1) at both the vertebra as well as the hip.
(2) There have been concerns that the (3) substantial increases in trabecular bone produced by (4) parathyroid hormone might occur at the expense of (5) cortical bone. However, in this long-term monkey (6) study, there were no adverse effects on cortical bone (7) based on the following data.
(8) Cortical bone mass was maintained at the (9) mid-shaft of long bones, such as the radius, humerus (10) and femur. Histomorphometry at these predominantly (11) cortical locations revealed the anticipated (12) teriparatide mediated enhancement of cortical (13) remodeling.
(14) A natural manifestation of this process (15) was an increase in endocortical porosity which was (16) accompanied by enlargement of cortical area and (17) thickness.
(18) There were no deleterious effects on (19) cortical bone strength, and in fact, the net effect (20) was that there is increased resistance to fracture at (21) the mid-shaft humerus and radius.
(22) I will now briefly summarize some of the

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(1) key findings from the nonclinical safety studies. In (2) the rat and monkey toxicity studies which supported (3) clinical development, the important effects were (4) primarily related to the known pharmacology of (5) parathyroid hormone on either bone or mineral ion (6) metabolism.
(7) The most important effect in the monkey (8) was the histologic observation of interstitial (9) basophilia in the renal medulla. This effect was (10) closely related to the magnitude and duration of (11) hypercalcemia and did not appear to have an impact on (12) renal function.
(13) In contrast, renal histologic changes did (14) not occur in the 18-month pharmacology study I (15) previously described. As will be shown on the (16) following slide, difference in these two monkey models (17) account for the differing effects on renal histology.
(18) In the toxicity studies in which renal (19) changes occurred, the animals were young, immature, (20) intact male and female monkeys who received a dietary (21) calcium intake approximately six times higher than (22) that of a post menopausal woman receiving calcium

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(1) supplementation.
(2) In the pharmacology study, there were no (3) renal alterations even at doses that cause similar (4) changes in the toxicity studies. The monkeys in this (5) model are mature, ovariectomized females with a daily (6) calcium intake approximately two to three times higher (7) than a supplemented post menopausal woman.
(8) Therefore, the lack of renal effects in (9) this more clinical relevant model in which monkeys (10) were treated for up to 18 months at doses which (11) provided exposures up to eight-fold that of a human (12) receiving a 20 microgram dose provide substantial (13) evidence that the histologic alterations in the (14) toxicity studies do not represent a substantial safety (15) concern.
(16) In addition to the effects in the chronic (17) toxicity studies just described, other important (18) findings included a lack of genotoxicity and a full (19) battery of in vitro and in vivo assays that meet (20) global regulatory standards, and the findings in the (21) two-year rat study.
(22) In the next few minutes I'll review the

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(1) primary findings from this study, which include (2) exaggerated increases in bone mass, bone proliferative (3) lesions, including osteosarcoma.
(4) Importantly, there was no increase in the (5) incidence of tumors in any other tissue or organ. As (6) is standard practice in these types of studies, (7) treatment with teriparatide was initiated in (8) skeletally immature rats six to eight weeks of age and (9) was continued for two years, which constitutes near (10) lifetime treatment.
(11) These high resolution CT images of the (12) proximal femur illustrate the dramatic effects on bone (13) mass that occurred in this two-year study.
(14) This image from a control rat shows a (15) normal pattern of cortical bone, trabecular bone, and (16) intervening marrow space. In all teriparatide treated (17) groups, there is a marked increase in both cortical (18) bone as well as trabecular bone. In fact, the effect (19) is so profound that it leads to near obliteration of (20) the marrow space.
(21) In terms of serum concentrations of (22) teriparatide, these doses provided exposures that were

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(1) three, 20, and 58 times that patients given a 20 (2) microgram dose. These images and the supporting (3) quantitative data show that even the lowest dose in (4) rats results in exaggerated effects on bone mass that (5) do not occur in patients, as illustrate in the (6) following slide.

(7) These figures compare the effects on bone (8) mass in the two-year rat study to those observed in (9) osteoporotic women and in monkeys. In the left panel (10) are data from the diaphysis, primarily cortical bone (11) site. On the right, the vertebra, a primarily (12) trabecular bone site. On the Y axis is bone mineral (13) content, a measure of bone mass expressed in these (14) figures as a percent above control values. On the X (15) axis is systemic exposure to teriparatide expressed as (16) area under the curve or AUC.

(17) The data points are from women with (18) osteoporosis given the high dose, 40 micrograms, in (19) the Phase 3 trial; rats given the low dose, five (20) micrograms per kilogram, in the two-year rat study; (21) and monkeys given the high dose of five micrograms per (22) kilogram in the 18-month pharmacology study.

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(1) These data sets were selected because they (2) are the most closely comparable in terms of duration (3) of treatment, ranging from 18 to 24 months, systemic (4) exposures to teriparatide, and the skeletal locations (5) examined, and they show that over a comparable range (6) of exposures, osteoporotic women and monkeys have (7) similar increases in bone mass.

(8) In contrast, rats have marked increases in (9) bone mass at both cortical as well as trabecular (10) sites.

(11) It is also important to note that this (12) increase in the rat in above peak bone mass for a (13) normal rat, while the value shown for women is the (14) percent above a woman with osteoporosis. So that (15) although women who received teriparatide treatment (16) have increases in bone mass, their bone mass does not (17) exceed peak values for normal, healthy women.

(18) In addition to the exaggerated increases (19) in bone mass, the other important finding in this (20) study was the occurrence of bone proliferative (21) lesions. The majority of these lesions were (22) osteosarcomas that occurred with a dose dependent

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(1) incidence in all dose groups in both males and (2) females. (3) There were 60 rats per sex per group in (4) this study, and at the high dose of 75 micrograms per (5) kilogram, the incidence reached approximately 50 (6) percent.

(7) These lesions occurred at multiple sites (8) in both the axial and appendicular skeleton, and (9) metastasis to soft tissue occurred in approximately (10) one third of the rats with osteosarcoma.

(11) In addition, there was a low incidence of (12) benign proliferative lesions of bone.

(13) In addition to the profound increases in (14) bone mass and the bone proliferative lesions, (15) including osteosarcoma I've just described, there was (16) no increase in the incidence of tumors and other (17) tissues, including the mammary gland and the kidney, (18) tissues with high concentrations of PTH receptors.

(19) Based on the initial observation of bone (20) tumors in rats, Lilly made the voluntary decision to (21) stop treatment of patients in the Phase 3 trials while (22) the findings in the rats could be studied. We

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(1) extensively reviewed these findings with a variety of (2) internal and external experts, including the formation (3) of an external oncology advisory board composed of (4) oncologists, epidemiologists, and pathologists.

(5) After considering data from the rat study (6) and the relevant scientific literature, the advisory (7) panel reached the conclusion that in spite of not (8) identifying a no effect level, the findings from the (9) two-year rat study are not likely to be predictive of (10) an increased risk of osteosarcoma in patients with (11) osteoporosis who were treated with teriparatide.

(12) A variety of factors have been considered (13) in assessing the predictive potential of the findings (14) from the rat model. First, there are important (15) differences between the rat model and the intended (16) clinical use which account for the extreme effects (17) seen in the rodent skeleton.

(18) First, rats are exposed for a relatively (19) long proportion of their lifetime, which is in (20) contrast to patients who would receive treatment for (21) a relatively short proportion, approximately two to (22) three percent.

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(1) In addition, there are distinct (2) differences in skeletal biology between rats and (3) humans. For example, rats continue to have (4) longitudinal skeletal growth throughout life, and (5) their growth plates remain open, which is in contrast (6) to humans whose growth plates close at the time of (7) adolescence.

(8) Also, rats lack the mechanism to replace (9) old cortical bone with new cortical bone, a process (10) known as osteonal remodeling.

(11) Importantly, teriparatide is not (12) genotoxic, and it is known that rodent carcinogenicity (13) assays are not always predictive for non-genotoxic (14) agents. The exaggerated effects, skeletal responses (15) observed in the study were mediated by the interaction (16) of teriparatide with the PTH receptor on the (17) osteoblast, and in two-year rat studies with a variety (18) of agents, it has been shown that continual hormonal (19) stimulation such as this can induce tumors in rats (20) which are not relevant to humans.

(21) For example, proton pump inhibitors, such (22) as omeprazole cause gastric carcinoids in rats due to

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(1) chronic increases in gastrin levels. However, similar (2) neoplastic responses have not occurred in humans (3) treated with omeprazole despite the fact that they (4) also have chronic increases in gastrin levels.

(5) Because of the differences in rats and (6) humans, and there are questions about the predictivity (7) of the rat findings, it is important to consider the (8) data from other species. In terms of other animal (9) data, the most relevant is a lack of bone lesions in (10) an 18-month pharmacology study in which 80 skeletally (11) mature ovariectomized animals were given teriparatide (12) for up to 18 months at exposures up to eight-fold (13) greater than women receiving a 20 microgram dose.

(14) We also carefully reviewed the literature (15) on human hyperparathyroidism, and while we recognize (16) important temporal differences between (17) hyperparathyroidism and the daily administration of (18) teriparatide, there is no evidence of an increased (19) risk of bone cancer in patients with (20) hyperparathyroidism, despite the fact that there is (21) chronic stimulation of the osteoblast in new bone (22) formation in both cases.

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(1) In summary, the nonclinical evaluation of (2) teriparatide has been rigorous, and the following (3) conclusions can be made. The pharmacology studies (4) clearly show that teriparatide stimulates new bone (5) formation resulting in increases in bone mass, (6) improvements in skeletal microarchitecture, and (7) increases in bone strength while maintaining cortical (8) bone quality.

(9) In particular, these improvements in (10) skeletal microarchitecture are not achieved with anti- (11) resorptive.

(12) In animal toxicity studies, effects were (13) primarily related to the known activity of PTH or (14) related peptides on bone or mineral ion metabolism, (15) and the findings do not represent important clinical (16) safety concerns.

(17) And, finally, a thorough review of the (18) two-year rat study in the relevant scientific (19) literature, we believe that the osteosarcoma findings (20) are not predictive of an increased risk of bone tumors (21) in osteoporosis patients treated with teriparatide.

(22) This concludes the nonclinical data

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(1) review. It's now my pleasure to introduce Dr. Bruce (2) Mitlak, Medical Director, who will review the clinical (3) efficacy data.

(4) DR. MITLAK: Thank you, Dr. Vahle.

(5) Good morning, Mr. Chairman, committee (6) members. My name is Bruce Mitlak. I'm a physician (7) and Medical Director on the teriparatide team.

(8) I have the pleasure of reviewing the (9) evidence with you that teriparatide treatment (10) increases bone mineral density, improves bone (11) architecture, and prevents fractures in patients with (12) osteoporosis.

(13) The clinical program included 25 trials (14) that enrolled more than 2,800 women and men worldwide. (15) The study codes and titles for the fully enrolled (16) Phase 3 programs and our ongoing observational follow- (17) up study are shown on this slide. I will use these (18) codes to identify the studies in my presentation.

(19) As I will describe this morning, the (20) pivotal placebo controlled study in women was GHAC, (21) and the pivotal study in men was GHAJ. Studies GHAF (22) and GHAH are supportive studies which are included in

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(1) your briefing document, but will not be included in my (2) presentation this morning.

(3) Study GHBJ is the ongoing observational (4) follow-up study in which prior Phase 3 patients are (5) currently being followed.

(6) This diagram includes the two pivotal (7) clinical studies that I will present this morning. (8) Study GHAC enrolled 1,637 women with osteoporosis to (9) evaluate the effect of teriparatide treatment on the (10) risk of fracture.

(11) Study GHAJ enrolled 437 men with (12) osteoporosis to evaluate the effectiveness of teriparatide (13) on bone mineral density.

(14) In December 1998, we voluntarily stopped (15) these studies and asked patients to complete an early (16) discontinuation visit. This action was taken to allow (17) further evaluation of the finding of osteosarcoma in (18) a concurrent long-term toxicology study as just (19) described by Dr. Vahle.

(20) Women participated in Study GHAC for a (21) median of 21 months and men in GHAJ for a median of 12 (22) months at the time of the respectively study

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(1) closeouts.

(2) We created an observational follow-up (3) study called GHBJ. The primary purpose of this study (4) was to collect safety information and to maintain (5) contact between the study sites and our study (6) patients.

(7) All patients who had been enrolled in (8) these studies, as well as our other Phase 3 studies (9) were invited to participate. Now I will first focus (10) on results from Study GHAC.

(11) Study GHAC, the pivotal study in women, (12) enrolled 1,637 women. It is a prospective, randomized (13) double blind trial that was performed in 99 sites at (14) 17 countries. Post menopausal women who were at least (15) five years post menopausal and who had a (16) radiographically confirmed vertebral fracture were (17) eligible to participate.

(18) The primary endpoint in this study was the (19) proportion of women with one or more new vertebral (20) fractures. All women self-administered a once daily (21) subcutaneous injection that included either (22) teriparatide, 20 micrograms, teriparatide, 40

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(1) micrograms, or placebo, and all women were provided a (2) supplement that included 1,000 milligrams of calcium (3) and 400 to 1,200 units of Vitamin D.

(4) The baseline characteristics for women in (5) the study are shown by treatment group, and in this (6) presentation the placebo group will be shown in white, (7) the teriparatide 20 group in yellow, and the (8) teriparatide 40 group in blue.

(9) The groups were balanced for the (10) characteristics shown, as well as for other factors (11) which could affect the risk of fracture. The mean age (12) was 69 to 70. There was a slightly greater proportion (13) of women greater than 70 years of age in the two (14) teriparatide groups compared with the placebo group.

(15) The mean number of years since menopause (16) was 21 to 22 years. Prior treatment for osteoporosis (17) was reported by 13 to 16 percent of the women, but no (18) treatment was permitted for between six and 24 months (19) prior to the beginning of the study, depending on the (20) specific treatment.

(21) Baseline spine bone mineral density (22) expressed in standardized units was approximately 820

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(1) milligrams per centimeter squared, corresponding to a (2) T-score of about minus 2.6, and as shown, (3) approximately 60 percent of these women had two or (4) more prevalent fractures at the beginning of the (5) study.

(6) Because of early closure, women completed (7) different lengths of time in the study. This panel (8) shows the number of women who completed the specified (9) months on the X axis. Because women were asked to (10) suspend study medication and then were scheduled for (11) their final visit, exposure to study medication was on (12) average eight weeks shorter than the duration shown on (13) this slide.

(14) You can see that the duration of (15) observation was similar across treatment groups. (16) Relatively few women in any group left the study (17) before 18 months. The maximum duration between (18) baseline and final radiograph for a patient was 27 (19) months, and the median was 21 months.

(20) Eighty-one percent of the women in this (21) study had an adequate baseline and follow-up (22) radiograph.

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(1) This figure shows the scale used to grade (2) both baseline and incident vertebral fractures in this (3) study. Vertebral bodies that are either normal or a (4) fracture that is crushed in the anterior, mid or (5) posterior part of the vertebral bodies are shown.

(6) Radiologists who were blinded to treatment (7) assignment called vertebrae either normal or reported (8) to us the presence of a mild, moderate or severe (9) fracture using this scale as specified in the (10) protocol. While this is a semi-quantitative scale, (11) these grades correspond to approximately a 20, 25, or (12) 40 percent or greater loss of height of the vertebral (13) body.

(14) In this study, a fracture was reported if (15) a vertebrae had a score of zero at baseline and was (16) found to have a score of one, two, or three at follow- (17) up. Over the 21 months of the study, 105 women were (18) found to have one or more new vertebral fractures.

(19) Results for the primary efficacy endpoint (20) are summarized on this slide. Let me review the (21) format which will be used also on the subsequent two (22) slides.

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(1) The number of women with one or more new (2) fractures in each group is shown on the respective (3) treatment bar. The height of the bar corresponds to (4) the proportion of women within each group with a (5) fracture. The relative risk in 95 percent confidence (6) intervals are shown for each comparison to placebo, (7) and all p values refer to comparisons with placebo.

(8) Teriparatide reduces the risk of vertebral (9) fractures. In women assigned to treatment with (10) teriparatide, the relative risk for fractures were .35 (11) and .31, corresponding to a highly statistically (12) significant 65 and 69 percent reduction in the (13) likelihood of a fracture. The absolute risk of (14) fracture was reduced from approximately 14 percent to (15) five percent and four percent.

(16) Additional analyses were performed to (17) evaluate the effective of treatment on more severe (18) fractures in this study. This figure shows the (19) results for women who had one or more vertebral (20) fractures that were at least of moderate severity.

(21) While ten percent of women assigned to (22) placebo had fractures that were moderate or severe in

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(1) degree, only one and two percent of women assigned to (2) treatment with teriparatide had such a fracture. The (3) relative risk of .1 and .22 corresponds to a 90 and 78 (4) percent reduction in the risk of having a moderate and (5) severe fracture.

(6) In this study, we found that regardless of (7) treatment, women with more severe fractures were more (8) likely to report back pain or to suffer height loss.

(9) This panel shows results for women who had (10) two or more new vertebral fractures during the study. (11) The relative risk for multiple vertebral fractures was (12) .23 and .14, corresponding to a 77 and 86 percent (13) reduction in the risk of having two or more new (14) vertebral fractures (15) Teriparatide treatment reduces the risk of (16) overall nonvertebral fragility fractures. This figure (17) shows the proportion of women who reported one or more (18) nonvertebral fragility fractures both overall and by (19) specific skeletal site.

(20) As specified by the protocol, site (21) investigators determined whether a fracture was (22) associated with excess trauma, such an association

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(1) with an automobile accident or fall greater than a (2) standing height. Fifty-eight women had fractures that (3) did not result from excess trauma, and these were (4) considered fragility fractures.

(5) Teriparatide treatment significantly (6) reduced the risk of nonvertebral fragility fractures. (7) The relative risk of .47 and .46 correspond to a 53 (8) and 54 percent reduction in the risk of fracture in (9) each group compared with placebo.

(10) And while there were a small number of (11) women with fractures at any specific skeletal site, (12) the figure shows that there was a similar or lower (13) proportion of teriparatide treated women with a (14) fracture at each site compared with placebo, including (15) the radius, which I will return to in a few minutes.

(16) This analysis of the same data for the (17) placebo group in white, the teriparatide 20 group in (18) yellow and 40 group in blue now shows the data as time (19) to first event, and it demonstrates that the effective (20) treatment on the risk of nonvertebral fracture became (21) progressively apparent after about nine months of (22) treatment.

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(1) It also shows that at no time during the (2) study was there evidence for an increase in risk for (3) these fractures.

(4) Teriparatide treatment increases lumbar (5) spine bone mineral density. Lumbar spine bone density (6) increased significantly with teriparatide treatment at (7) each visit where it was assessed, including the first (8) visit at three months, where nearly a four percent (9) increment in bone density had already occurred.

(10) At endpoint, the difference in bone (11) mineral density between the 20 microgram group and (12) placebo was nine percent and between the 40 microgram (13) group and placebo was 13 percent.

(14) Ninety-six percent of women in the study (15) assigned to teriparatide 20 micrograms had an increase (16) in bone mineral density. These increases in bone (17) density were associated with rapid increases in (18) biochemical markers of bone formation and secondarily (19) bone resorption.

(20) Teriparatide treatment increases hip bone (21) mineral density. Total hip bone mineral density was (22) measured in approximately one half of the women in the

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(1) decreased about one percent in women assigned to (2) placebo. The difference between the treatment group (3) and placebo was one percent in the women assigned to (4) treatment with 20 micrograms and two percent in women (5) treated with 40 micrograms of teriparatide.

(6) The 40 microgram group differed (7) significantly from the placebo group. This early (8) decrease in bone mineral density likely reflects (9) increases in cortical bone remodeling and as (10) demonstrated by PQCT in a subset of approximately 100 (11) women was associated with preserved cortical thickness (12) and evidence for periosteal new bone formation.

(13) Importantly, it was also associated with (14) a humerally lower number of wrist/forearm fractures (15) in the teriparatide group, as I had previously (16) highlighted for you.

(17) Importantly also, teriparatide increases (18) total body bone mineral. Total body bone mineral was (19) measured in about 400 women at a subset of study (20) sites. Compared with the placebo group which lost .7 (21) percent, the increase in the 20 and 40 microgram (22) groups were 2.6 and 3.5 percent, each comparison

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(1) study at a subset of study sites, and femoral neck (2) bone density was measured in all women.

(3) At endpoint, total hip bone mineral (4) density decreased by about one percent, and in (5) contrast, increased in both of the teriparatide (6) groups.

(7) The mean difference between the (8) teriparatide groups and placebo at endpoint was 3.6 (9) percent and 4.6 percent. Each comparison was (10) statistically significant.

(11) At the femoral neck compared with placebo, (12) the increase in bone mineral density at endpoint was (13) four percent and six percent. Other hip sites were (14) also significantly increased by teriparatide (15) treatment.

(16) Ultra distal and distal radius bone (17) mineral density was measured in about 450 women. At (18) the ultra distal radius, bone density declined (19) slightly in the placebo group, but did not change (20) significantly in any group, nor were there differences (21) between groups.

(22) At the radial shaft bone mineral density

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(1) statistically significant.

(2) This confirms that the increases in spine (3) and hip bone density are associated with a net (4) increase in total body bone mass.

(5) Transiliac bone biopsies were obtained (6) from 61 women at baseline and then again at either 12 (7) months or study closeout. This slide shows the (8) baseline and endpoint bone biopsy from one patient in (9) the 20 microgram group and one patient in the 40 (10) microgram group who had spine bone density responses (11) similar to the mean for their respective treatment (12) groups.

(13) The green stain shows calcified elements, (14) including both the inner and outer cortical shells, as (15) well as trabecular bone.

(16) Also apparent is marrow space and a small (17) amount of extraosteal soft tissue. Trabecular bone (18) volume, TBV, is indicated below each biopsy.

(19) Dr. Eric Erickson, the reader for these (20) biopsies, determined in blinded fashion that there was (21) no evidence for woven bone, abnormal mineralization, (22) cellular proliferation, or abnormal architecture in

(1) these biopsies.
 (2) Among the biopsies taken at 12 months, (3) there was an increase in intra cortical remodeling in (4) the 40 microgram group, but not the 20 microgram (5) group. This was no longer observed in the biopsies (6) taken at study closeout.
 (7) This remodeling transient is consistent (8) with the results observed in the primate study and did (9) not adversely affect biomechanical strength in the (10) monkeys.
 (11) In addition to the favorable effects on (12) trabecular bone volume just shown, there was (13) significant increases or trends to increase in mineral (14) apposition rate, wall thickness, trabecular thickness, (15) and a measure of connectivity, connectivity of the (16) trabeculae.
 (17) So to summarize the results from this (18) study, teriparatide treatment was effective at (19) preventing spine and non-spine fractures in women with (20) osteoporosis. Treatment with teriparatide 20 and 40 (21) micrograms reduced the risk of vertebral fractures by (22) 65 and 69 percent; reduced the risk of nonvertebral

(1) fragility fractures by 53 and 54 percent; increased (2) bone mineral density at the spine and hip but not the (3) forearm; increased total body bone mineral and had (4) favorable effects on bone architecture.
 (5) Now I will present the results from our (6) study in men. Study GHAJ was a prospective, (7) randomized double blind study in men with osteoporosis (8) performed at 34 sites in 11 countries. Four hundred (9) thirty-seven men with osteoporosis either associated (10) with hypogonadism or with idiopathic osteoporosis were (11) enrolled with low bone mineral density at either the (12) spine or the hip.
 (13) The primary endpoint of the study was (14) change in bone mineral density at the spine. All men (15) self-administered a once daily subcutaneous injection, (16) again containing either teriparatide 20 micrograms, 40 (17) micrograms, or placebo, and all were provided (18) supplements containing 1,000 milligrams of calcium and (19) 400 to 1,200 units of Vitamin D.
 (20) The baseline characteristics for men in (21) the study are shown again by treatment group. The (22) groups were well balanced for the characteristics

(1) shown. On average men were 58 to 59 years of age. (2) Twelve to 18 percent reported the use of other (3) treatments for osteoporosis prior to the study, but, (4) again, none were permitted for six to 24 months prior (5) to randomization. Mean baseline T-scores for the (6) spine, femoral neck, and total hip are shown by (7) treatment group.
 (8) This figure shows the exposure in GHAJ (9) from the time of randomization to the time of the last (10) bone mineral density measurement. The median duration (11) of follow-up in this study was 12 months.
 (12) For the same reason as the study in women, (13) the actual time receiving study medication was in this (14) case about four weeks on average less than the (15) duration shown here.
 (16) Teriparatide treatment significantly and (17) rapidly increased spine bone density in men. At (18) endpoint spine bone density had increase 5.4 and 8.5 (19) percent in the 20 and 40 microgram groups compared (20) with placebo. The bone mineral density response was (21) rapid, with a significant increase compared with (22) placebo at the first measurement point in the study at

(1) three months.
 (2) Importantly also, response in bone density (3) was similar in men with osteoporosis associated with (4) hypogonadism and those with idiopathic osteoporosis.
 (5) Because most men were, in fact, completing (6) an early discontinuation visit rather than a formal (7) 12-month visit at the 12-month time point, the data (8) will be shown as baseline to endpoint. At endpoint (9) total hip bone mineral density had increased .63 (10) percent in the 20 microgram group compared with (11) placebo, which itself had increase .54 percent. This (12) comparison reached a p value of .074.
 (13) The mean increase between the 40 microgram (14) group and placebo was 1.6 percent. At endpoint (15) femoral neck bone mineral density had increased 1.2 (16) and 2.6 percent in the 20 and 40 microgram groups (17) compared with placebo. Each of these comparisons was (18) statistically significant.
 (19) However, at other hip sites the comparison (20) for the 20 microgram group was not significant.
 (21) Importantly teriparatide treatment (22) increased total body bone mineral in men. Total body

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(1) bone mineral was measured in 254 men at a subset of (2) study sites. At endpoint total body bone mineral had (3) increase 1.1 and 1.3 percent in the two treatment (4) groups compared with placebo. Each comparison was (5) statistically significant.

(6) So to summarize, treatment with (7) teriparatide was effective at increasing bone mineral (8) density in men. Treatment with teriparatide 20 (9) micrograms and 40 micrograms increased bone mineral (10) density at the spine and femoral neck. Total hip bone (11) density was significantly increased only for the 40 (12) microgram dose.

(13) There was a significant increase in total (14) body bone mineral for both doses.

(15) To further evaluate the effect of gender (16) on response to treatment, we compared the mean actual (17) change in bone mineral density from women in Study (18) GHAC, in men in Study GHAJ. We compared the actual (19) change because we found, unlike percent change, the (20) actual change was independent of baseline bone mineral (21) density, and men in Study GHAJ started with a higher (22) bone density than did women in Study GHAC.

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(1) As you can see, the actual change in bone (2) mineral density for women and men for a comparable (3) period of treatment are nearly identical.

(4) Similarly, actual change in bone mineral (5) density at the femoral neck for comparable period of (6) time is identical for men and women. This is shown (7) for men with a measurement up to the 12-month time (8) point in the protocol.

(9) These two panels support that gender was (10) not an important factor in the expected response to (11) treatment.

(12) So to summarize, despite early study (13) completion, both Studies GHAC and GHAJ clearly reached (14) their specified primary endpoints.

(15) Treatment with teriparatide 20 micrograms (16) and 40 micrograms significantly reduced the risk of (17) vertebral and nonvertebral fractures in both (18) menopausal women. The reduction was similar for each (19) dose.

(20) Treatment rapidly and significantly (21) increased bone density in post menopausal women and in (22) men, and treatment improved bone microarchitecture.

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(1) That concludes this presentation. I would (2) now like to introduce Dr. Gaich, who will review the (3) clinical safety.

(4) DR. GAICH: Thank you, Dr. Mitlak.

(5) Good morning, Mr. Chairman, committee (6) members. My name is Gregory Gaich. I'm a physician (7) on the teriparatide team, and I am pleased to show you (8) the data which establishes the safety and tolerability (9) of teriparatide in the treatment of post menopausal (10) women and men with osteoporosis.

(11) Like the efficacy data just presented, the (12) data that I will show you also supports the 20 (13) microgram dose as the proposed marketed dose.

(14) I'll review the overall safety experience, (15) the results of the clinical and laboratory safety (16) evaluations in our study in post menopausal women and (17) in our follow-up study and in our study in men with (18) osteoporosis.

(19) I'll conclude with the results of the drug (20) interaction and special population studies which were (21) performed.

(22) Our clinical investigations included 25

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(1) trials, which enrolled over 2,800 women and men, more (2) than 1,900 of whom received teriparatide. Does of (3) five to 100 micrograms were used in the clinical (4) pharmacology studies, and doses of 20 and 40 (5) micrograms were studied in our long-term Phase 3 (6) studies. Total patient exposure to teriparatide was (7) over 1,900 patient-years.

(8) This slide shows the overall results of (9) the clinical safety evaluations in the two placebo (10) controlled Phase 3 studies combined. In this slide, (11) the total number of patients in each dose group is (12) shown at the top of the column, and each row shows the (13) number and the percent of patients in each treatment (14) group who had the listed event.

(15) As shown in the table, the number of (16) patients experiencing any adverse event was similar in (17) all three treatment groups. There was a significant (18) increase in the number of patients who discontinued (19) due to adverse events in the 40 microgram group, but (20) not the 20 microgram group.

(21) The discontinuations in the 40 microgram (22) group were primarily due to nausea.

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(1) The number of patients experienced in the (2) teriparatide treated groups experiencing any serious (3) adverse event, cancer, or death was similar or lower (4) in the teriparatide treated groups compared with (5) placebo. No osteosarcoma or other primary bone tumor (6) occurred in any patient.

(7) There were very few deaths in the studies, (8) and the difference in the treatment groups was not (9) statistically significant. None of the deaths were (10) judged to be related to study drug by the (11) investigator, and there were no patterns in the cause (12) of death.

(13) In addition, there was no difference in (14) the mortality among treatment groups in patients in (15) older or younger age groups.

(16) The evaluation of treatment related (17) clinical and laboratory effects is based on the data (18) from all of our studies. I'll focus on the data from (19) the pivotal Phase 3 study in post menopausal women, (20) GHAC, in which 1,637 patients were treated for up to (21) two years.

(22) I'll also show the data from the clinical

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(1) Similar significant reductions or trends (2) in back pain were also observed in the other three (3) phase three studies.

(4) Next I'd like to review the results of the (5) pharmacokinetic and safety laboratory evaluations in (6) Study GHAC. All of the laboratory effects observed in (7) our studies were expected based on the known (8) pharmacology and physiology of parathyroid hormone.

(9) This is a best fit analysis of the serum (10) teriparatide concentrations obtained from 360 (11) patients in Study GHAC. The solid line shows the mean (12) teriparatide concentration following a 20 microgram (13) dose. The hatched area shows the 25th to 75th (14) percentile range.

(15) The upper limit of endogenous parathyroid (16) hormone 1 to 84 is shown in the horizontal line. The (17) serum concentrations of teriparatide peaked at (18) approximately 30 minutes post dose and declined (19) rapidly thereafter, with an apparently elimination (20) half-life of approximately 60 minutes. By three to (21) four hours post dose, very few patients had measurable (22) teriparatide in the serum, and there was no

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(1) pharmacology studies and/or other Phase 3 studies (2) where it provides additional information.

(3) In Study GHAC, the adverse events in the (4) 20 microgram group were general mild and did not lead (5) to discontinuation from the study. Leg cramps were (6) reported by two percent more patients in the 20 (7) microgram group than in the placebo group, and this (8) was statistically significant.

(9) In the 40 microgram group, headache and (10) nausea were significantly increased compared with (11) placebo, but this was not observed in the 20 microgram (12) group.

(13) There was a numerical, although not (14) statistically significant, increase in the incidence (15) of nausea in the 20 microgram group, and nausea may (16) also be treatment related at the 20 microgram dose as (17) well as 40 microgram dose.

(18) There was also a treatment related (19) reduction in the incidence of new or worsened back (20) pain in both treatment groups, and this is consistent (21) with the reductions in vertebral fractures which Dr. (22) Mitlak presented.

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(1) accumulation of teriparatide with repeat dosing.

(2) The average 24-hour exposure of (3) teriparatide and endogenous PTH combined did not (4) exceed the upper limit of normal for endogenous PTH.

(5) Serum calcium was also measured at every (6) visit, and we performed a similar best fit analysis on (7) the serum calcium measurements.

(8) This graph shows the serum calcium (9) analysis overlaid on the pharmacokinetic analysis. (10) The vertical axis on the left shows the teriparatide (11) concentrations, and the vertical axis on the right (12) shows the serum calcium concentrations. The upper (13) limit of normal for serum calcium of 2.64 millimoles (14) per liter or 10.5 milligrams per deciliter as shown by (15) the horizontal line.

(16) As expected, based on the known effects of (17) parathyroid hormone and on the transient exposure to (18) teriparatide following each dose, there was a brief, (19) transient increase in the mean serum calcium (20) concentrations following a 20 microgram dose. The (21) mean baseline serum calcium concentration was 2.3 (22) millimoles per liter or 9.2 milligrams per deciliter,

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(1) and the mean peak serum calcium concentration occurred (2) at 4.25 hours after the dose and was 2.4 millimoles (3) per liter, or 9.6 milligrams per deciliter.

(4) Very few patients even transiently (5) exceeded the upper limit of normal.

(6) Serum calcium returned to baseline by 16 (7) to 24 hours after the dose, and the serum calcium at (8) this endpoint was not increased in either the 20 (9) microgram or the 40 microgram dose.

(10) In the 20 microgram group, these transient (11) changes in serum calcium were small. Median increase (12) was 0.3 to 0.5 milligrams per deciliter at each study (13) visit, and 97 percent of the patients never exceeded (14) 11 milligrams per deciliter. The highest observed (15) value was 11.6 milligrams per deciliter.

(16) Eight percent of the patients had a single (17) high serum calcium and exceeded the upper limit of (18) normal, and three percent exceeded the upper limit of (19) normal on two consecutive four to six-hour post dose (20) measurements.

(21) The transient changes in serum calcium (22) were greater in the 40 microgram group, with a median

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(1) increase ranging from 0.5 to 0.7 milligrams per (2) deciliter and with more patients exceeding the upper (3) limit of normal.

(4) Transient increases in serum calcium which (5) exceeded the upper limit of normal were not associated (6) with clinical adverse events in either treatment (7) group, however.

(8) The pre-dose serum calcium was measured 16 (9) to 24 hours after the preceding dose in a subgroup of (10) approximately 450 patients. This graph shows the (11) medians and the 25th to 75th percentile range for the (12) pre-dose serum calcium at each visit during the study. (13) The upper and lower limits for serum calcium are shown (14) by the horizontal lines. (15) There was a small decrease in the serum (16) calcium in the placebo group at three and six months, (17) but the pre-dose serum calcium in the teriparatide (18) treated groups remain similar to baseline throughout (19) the entire course of the study.

(20) We also observed expected effects on (21) urinary calcium excretion, which were consistent with (22) the known physiology and pharmacology of parathyroid

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(1) hormone. The median urinary calcium excretion in the (2) placebo group was 3.9 millimoles per day or 156 (3) milligrams per day. There was a small increase in the (4) 24-hour urinary calcium excretion for the first six (5) months, and the median increase was 30 milligrams per (6) day at the six month time point.

(7) There was no difference among treatment (8) groups in the number of patients with elevated urinary (9) calcium excretion, and the highest observed 24-hour (10) urinary calcium excretion was similar to placebo and (11) the two teriparatide treated groups. The result (12) showed no increase in the incidence of urolithiasis or (13) related events.

(14) We've shown a lot of data on the serum and (15) urine calcium. Let me summarize those results before (16) moving on to the remainder of the presentation.

(17) The magnitude of the serum calcium effects (18) were small, 0.3 to 0.5 milligrams per deciliter in the (19) 20 microgram group, and the effects on serum calcium (20) were brief, with the serum calcium returning to (21) baseline after every dose.

(22) There were small increases in the 24 hour

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(1) urinary calcium excretion. The median was 30 (2) milligrams a day, and there were no clinical adverse (3) events associated with the increases in the serum or (4) urine calcium.

(5) These data indicate that monitoring of (6) serum in urine calcium is not necessary in patients (7) treated with 20 micrograms a day of teriparatide.

(8) Parathyroid hormone has known effects of (9) uric acid clearance and effects on uric acid were also (10) observed in our studies with teriparatide. This slide (11) shows a dose dependent increase in the serum uric acid (12) which was observed at one month and remained at a (13) similar level throughout 12 months.

(14) The serum uric acid concentration in the (15) placebo group was 270 micromoles per liter or 4.5 (16) milligrams per deciliter. The median increase was 0.9 (17) milligrams per deciliter in the 20 microgram group and (18) 1.2 milligrams per deciliter in the 40 microgram (19) group.

(20) The increases in serum uric acid resulted (21) in 2.8 percent of patients in the 20 microgram group (22) and five percent of patients in the 40 microgram

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(1) group, exceeding the upper limit of normal at least (2) once during the study.

(3) These increases in serum uric acid did not (4) result in an increased incidence of gout or (5) arthralgia, however.

(6) There are a number of conditions that have (7) been historically associated with hyper (8) parathyroidism. We examined our clinical trial data (9) to determine if these conditions were associated with (10) teriparatide administration.

(11) The incidence of cardiovascular disease, (12) hypertension, peptic ulcer disease, renal (13) insufficiency, and urolithiasis were not increased in (14) the teriparatide treated patients.

(15) The next few slides summarize the renal (16) and hemodynamic evaluations in more detail. Clinical (17) and laboratory data were examined in order to evaluate (18) potential effects on the kidney. There was no (19) significant effect on the incidence of urolithiasis or (20) related terms, on serum creatinine concentrations, on (21) measured creatinine clearance, or on routine (22) urinalysis during the study.

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(1) Routine vital signs were obtained in the (2) Phase 3 studies, and more extensive hemodynamic (3) evaluations, including serial orthostatic blood (4) pressure measurements were performed in the clinical (5) pharmacology studies.

(6) In the clinical pharmacology studies which (7) enrolled health volunteers generally over age 50, we (8) were able to detect small changes in the post dose (9) heart rate, which were also detected as a shortening (10) of the RR interval on the electrocardiogram. There (11) was no QTC prolongation or other clinically (12) significant effect on the electrocardiogram following (13) a 20 microgram dose or any other dose study.

(14) There were no significant effects on (15) standing or supine blood pressure in the 20 microgram (16) dose, although there have been occasional subjects who (17) experience transient symptomatic postural hypotension (18) following teriparatide administration. This was (19) observed once following a 20 microgram dose and more (20) frequently at higher doses. Symptoms were relieved by (21) lying down, and they did not preclude further dosing.

(22) A number of subject receive subsequent and

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(1) sometimes higher doses of teriparatide without (2) experiencing orthostatic hypotension.

(3) In the Phase 3 studies in which there were (4) no restrictions in activity. There was not an effect (5) on sitting blood pressure or pulse or on the incidence (6) of postural hypotension. Nevertheless, it is possible (7) that a patient may experience transient, symptomatic, (8) postural hypotension following a 20 microgram dose of (9) teriparatide.

(10) I'd now like to describe the clinical and (11) laboratory effects after discontinuation of treatment. (12) These are the interim results from the ongoing follow- (13) up study, GHBJ. Patients who had participated in any (14) of the previous Phase 3 studies were invited to (15) participate in the follow-up study. Approximately 80 (16) percent of the women and men who enrolled in the prior (17) treatment studies enrolled into Study GHBJ.

(18) The patients have completed the first two (19) visits, which were approximately six and 18 months (20) after the end of the prior treatment studies. This (21) represents a total of 39 months of cumulative (22) observation for the women previously enrolled in the

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(1) previous Study GHAC and 30 months in the men (2) previously enrolled in the pivotal study GHAJ.

(3) When we first discussed the results of the (4) patients previously enrolled in Study GHAC, at the (5) first study visit approximately six months after the (6) end of the treatment study, there is no longer a (7) difference from placebo in nausea, headache, leg (8) cramps or clinical laboratory endpoints, except for (9) the serum uric acid.

(10) The increase in serum uric acid (11) concentration had declined to less than two percent, (12) but it was still statistically significant.

(13) The number of patients in the teriparatide (14) treated groups with abnormal serum uric acid (15) concentrations was no longer different from placebo. (16) There was a small, a less than two percent, but (17) statistically significant increase in the serum (18) creatinine. There was no decrease in the measured (19) serum or I'm sorry. There was no decrease in the (20) measured creatinine clearance, and only one patient in (21) the placebo group and one patient in the 40 microgram (22) group had a clinically significant increase of greater

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(1) than 0.4 milligrams per deciliter.
 (2) These effects were not observed in the (3) other Phase 3 studies.
 (4) Through visit two of the follow-up study, (5) approximately 18 months after the end of the treatment (6) study, there were no new clinically significant safety (7) issues identified. There continued to be no increase (8) in the incidence of cancer, urolithiasis, gout or (9) arthralgia, and there continued to be a reduction in (10) the incidence of new or worsened back pain, which is (11) consistent with the observed continued reduction in (12) radiographic vertebral fractures.
 (13) We also recorded non-vertebral fractures (14) in the follow-up study, and this analysis shows the (15) time to first non-vertebral fragility fracture for the (16) women in Study GHAC, who were then followed in Study (17) GHBJ. This horizontal line represents the period of (18) time during which treatment was discontinued.
 (19) The initial part of this curve is (20) identical to the one previously shown by Dr. Mitlak. (21) The risk of non-vertebral fracture following (22) discontinuation of treatment did not increase in the

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(1) teriparatide treated groups. The absolute risk (2) reduction in teriparatide treated patients at the end (3) of study GHAC was three percent, and the absolute risk (4) reduction was approximately five percent at GHBJ visit (5) two.
 (6) That concludes the presentation of the (7) safety data in the pivotal study and the follow-up (8) study in post menopausal women.
 (9) I'd now like to briefly review the safety (10) evaluations in the men with osteoporosis. Study GHBJ (11) was the pivotal study in 437 men with osteoporosis, (12) and the results are similar to the study in post (13) menopausal women.
 (14) This slide shows the results of the (15) clinical and laboratory effects in the study in men. (16) As was observed in the post menopausal women, there (17) was a dose dependent increase in the number of (18) patients with at least one serum calcium exceeding the (19) upper limit of normal at four to six hours after the (20) dose, but the number confirmed on repeat testing was (21) only 1.3 percent in the 20 microgram group.
 (22) The magnitude and the time course of the

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(1) serum calcium was also comparable to what was shown in (2) the post menopausal women.
 (3) There was a significant increase in nausea (4) and headache at the 40 microgram group, but not the 20 (5) microgram group.
 (6) There was no trend towards increase in leg (7) cramps in the men. However, there were too few events (8) in this study to evaluate that effect adequately.
 (9) There was also a significant increase in (10) the number of men, again, in the 40 microgram group, (11) but not the 20 microgram group who discontinued due to (12) adverse event, and just as was the case in the post (13) menopausal women, the discontinuation in the 40 (14) microgram group were largely attributable to nausea.
 (15) The other clinical and laboratory effects, (16) such as effects on serum urine calcium and urinary (17) calcium excretion were also comparable to the effects (18) in post menopausal women.
 (19) We also performed pharmacokinetic (20) measurements in the men. The time to peak (21) concentration and the apparent elimination half-life (22) were similar in men and women, but the serum

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(1) concentrations of teriparatide were 20 to 30 percent (2) lower in men than in women.
 (3) As Dr. Mitlak and I have described, the (4) effects on spine and hip bone mineral density, (5) clinical adverse effects, and laboratory tests were (6) similar in men and women.
 (7) Well, not an endpoint in Study GHAC, spine (8) radiographs were obtained as a screening test and (9) follow-up spine radiographs were obtained at visit two (10) of the follow-up study of GHBJ in order to provide a (11) more complete set of data with which to compare to the (12) women.
 (13) This slide shows the vertebral fracture (14) incidence in men and the time between the baseline and (15) follow-up radiographs includes both the treatment and (16) follow-up phase, a total of 30 months.
 (17) There were fewer fractures in this study (18) than in the pivotal study in post menopausal women, (19) and there were too few fractures to have adequate (20) statistical power.
 (21) Nevertheless, the observed patterns in (22) vertebral fractures in the men and in moderate and

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(1) severe vertebral fractures in the men was similar to (2) the patterns observed in the post menopausal women.

(3) In addition, the number of men sustaining (4) new vertebral fractures or new moderate to severe (5) vertebral fractures was identical in the 20 and 40 (6) microgram groups.

(7) While this analysis is not a pre-specified (8) analysis of the study, it does illustrate the (9) similarity of the similarity of the response to (10) treatment in men and in women, and it supports the 20 (11) micrograms as the appropriate dose in men as well as (12) in women.

(13) In addition to examining potential gender (14) differences, we also examined special populations (15) based on age, renal function, cardiac function and (16) blood pressure. There were no clinically significant (17) pharmacokinetic or safety findings in these special (18) populations, and restrictions or special monitoring of (19) patients with these conditions are not necessary.

(20) We also performed clinical pharmacology (21) studies which evaluated potential pharmacodynamic and (22) safety interactions with hydrochlorothiazide,

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(1) furosemide, calcium channel blockers, Atenolol, (2) Digoxin, hormone replacement therapy, and Raloxifene. (3) There were no clinically significant interactions with (4) teriparatide in these drug interaction studies, and (5) restrictions or special monitoring of patients taking (6) these medications was also not necessary.

(7) Now, let me conclude by summarizing the (8) results of the clinical and safety evaluations of (9) teriparatide. In the Phase 3 studies, leg cramps and (10) possibly nausea were treatment related at the 20 (11) microgram dose.

(12) Forty micrograms per day was more likely (13) to cause nausea, headache and discontinuation due to (14) adverse events.

(15) The increased incidence of symptomatic (16) postural hypotension observed in the clinical (17) pharmacology studies was not observed in the Phase 3 (18) studies.

(19) Finally, there was a lower incidence of (20) back pain in both the 20 and 40 microgram groups, (21) which was consistent with the reduction in vertebral (22) fractures.

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(1) The laboratory evaluations showed the (2) expected transient effects on serum calcium, and the (3) expected pharmacologic effects on serum uric acid and (4) on urinary calcium excretion. These effects were (5) small and were not associated with clinical adverse (6) effects, and 40 micrograms a day was more likely to (7) cause increased serum calcium and serum uric acid.

(8) After discontinuation of treatment, (9) nausea, headache, leg cramps, and the laboratory (10) effects quickly resolved, except for the small (11) increase in serum uric acid. Through 18 months of (12) post treatment follow-up no new clinically significant (13) adverse effects were identified, and there continued (14) to be no increase in the incidence of cancer, (15) urolithiasis, gout or arthralgia, and there was no (16) increase in the rate of nonvertebral fractures.

(17) There continued to be a continued (18) significant reduction in the incidence of new or (19) worsened back pain.

(20) In conclusion, teriparatide 20 micrograms (21) and 40 micrograms a day were safe and well tolerated (22) in our studies of treatment of post menopausal women

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(1) and men with osteoporosis. The effects on the (2) clinical laboratory tests were small and consistent (3) with the known physiology and pharmacology of (4) parathyroid hormone, and routine laboratory monitoring (5) in patients taking 20 micrograms a day is not (6) necessary.

(7) Likewise, restrictions or monitoring in (8) the special population study are not necessary. There (9) were no significant drug interactions identified, and (10) finally, although both doses were safe, teriparatide (11) 20 micrograms a day was associated with fewer adverse (12) effects.

(13) I thank you very much for your attention, (14) and Dr. Mitlak will conclude this morning's (15) presentations with the summary and conclusions.

(16) DR. MITLAK: Mr. Chairman, members of the (17) committee, I have the pleasure of concluding the (18) formal presentation from Lilly this morning.

(19) We've provided evidence for you that (20) teriparatide is a bone forming agent that increases (21) bone mineral density, improves bone microarchitecture, (22) and prevents fractures in patients with osteoporosis.

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(1) Teriparatide was safe and well tolerated by patients (2) in the clinical trials.

(3) To summarize the presentations, Dr. (4) Lindsay outlined the pressing clinical need for such (5) an agent and reviewed the breadth of prior experience (6) with teriparatide.

(7) Dr. Vahle presented nonclinical data (8) demonstrating that teriparatide is a bone forming (9) agent that increases bone mass and strength in several (10) species. He also described the finding of (11) osteosarcoma in a long-term study in rats and outlined (12) factors that are important in understanding the (13) relevance of the findings to the proposed use in women (14) and men with osteoporosis.

(15) Dr. Gaich and I presented the favorable (16) overall clinical profile for teriparatide.

(17) Let me begin now by reviewing our (18) considerations on the nonclinical findings. In 1999, (19) the following experts were convened to review the (20) findings in the nonclinical study and to provide (21) advice on the follow-up of study participants. These (22) include Drs. Chabner, Adamson, Antman, Henderson,

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(1) nonclinical and clinical information and have had (2) ongoing discussions with our consultants and with the (3) agency. In specific, as described by Dr. Vahle, no (4) skeletal lesions were observed in an 18-month study in (5) monkeys given four to eight times the exposure of (6) subjects in the Phase 3 trial.

(7) While we recognize that there are temporal (8) differences in the profile of PTH exposure in patients (9) with hyperparathyroidism and those who had received (10) teriparatide as treatment for osteoporosis, osteoblast (11) stimulation occurs in both, often to a greater extent (12) in patients with hyperparathyroidism, and patients (13) with hyperparathyroidism can have elevated levels of (14) parathyroid hormone for years.

(15) New bone formation also occurs in patients (16) with hyperparathyroidism, but resorption usually (17) occurs to a greater degree.

(18) We identified a single case report of the (19) co-occurrence of hyperparathyroidism and osteosarcoma (20) in the literature. Dr. Olaf Unell (phonetic) then (21) assisted us by performing a systematic search of the (22) national cancer registry in Sweden which covers the

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(1) Fletcher, Raymond, Kronenberg, and Doppelt. Drs. (2) Chabner and Adamson are in attendance with us today.

(3) This PTH oncology board reviewed the (4) available non-clinical and clinical data and provided (5) the following conclusions for us.

(6) Based on current information, the findings (7) in the rat study were unlikely to predict for the (8) development of bone tumors in patients who had (9) received teriparatide in the clinical trials. This (10) conclusion was reached with considerations of the (11) following:

(12) The lifetime duration of treatment in the (13) rats compared with a relatively brief exposure (14) intended in humans;

(15) The fact that treatment was initiated (16) during the rapid growth phase of the animals;

(17) The difference in rat and human bone (18) biology and response to PTH;

(19) And the lack of clinical association (20) between hyperparathyroidism and osteosarcoma in (21) humans.

(22) Since then we have evaluated additional

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(1) entire population and 40 years of exposure. We were (2) able to identify 12,644 patients who had been (3) identified as either having a parathyroid adenoma or (4) parathyroid hyperplasia and linked this to the cancer (5) registry.

(6) There was no case where the diagnosis of (7) hyperparathyroidism and osteosarcoma occurred in the (8) same patient.

(9) As previously described also, Study GHBJ, (10) the observational study, was designed with input from (11) the oncology board and to date has provided (12) approximately 2,000 additional patient-years of (13) follow-up. No primary bone tumors have been reported (14) in any patient.

(15) We've concluded that it is unlikely that (16) the findings in the long-term study in rats predict a (17) risk for bone tumors in patients who had received (18) teriparatide for treatment of osteoporosis.

(19) We have promptly shared information about (20) the animal findings with the scientific community and (21) with the regulatory agencies. We reported the rodent (22) findings in clinical presentations, the initial

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(1) presentations given at the Endocrine Society by Dr. (2) Neer, at the American Society of Bone and Mineral (3) Research by Dr. Marcus, and the American College of (4) Rheumatology by Dr. Gennant, and it included (5) information about the animal findings in many (6) subsequent presentations.

(7) We have also included a description of the (8) animal findings in the primary publication of the (9) study data.

(10) The GHBJ study was also designed to (11) collect some additional safety information, but also (12) to facilitate information sharing and, therefore, we (13) had set the study up to maintain contact between the (14) physicians and our prior study patients.

(15) Now, looking forward, we would propose to (16) exclude groups that increased risk for osteosarcoma, (17) such as those with Paget's disease, unexplained (18) elevations of alkaline phosphatase, adolescents or (19) those with open epiphyses (phonetic), and those with (20) a history of radiation to increase the certainty with (21) which we can begin to exclude or further exclude a (22) relationship with teriparatide treatment over time.

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(1) To insure the most favorable benefit-risk (2) for this important potential therapy for patients with (3) osteoporosis, we also proposed to limit the duration (4) of treatment for up to two years in post menopausal (5) women and men based on currently available data.

(6) We continue to put patient safety first (7) and provide a commitment to the following elements of (8) a post approval safety surveillance program. Lilly (9) has a worldwide system for assessing spontaneous (10) adverse reports that is already in place to collect (11) information on men and women who did not elect to (12) participate in Study GHBJ. This system will be used (13) to track safety in a post approval setting.

(14) We will continue long-term follow-up of (15) women and men in Study GHBJ, and by 2005, we'll have (16) accrued approximately 7,000 patient-years of follow-up (17) on these subjects.

(18) We are working with the agency to create (19) an active program with a goal of collecting and (20) assessing information on a substantial proportion of (21) cases of osteosarcoma that occur in the United States (22) each year regardless of any treatment they may have

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(1) received.

(2) Because of the very low incidence of this (3) disorder, we propose to utilize large, stable, (4) population based databases, such as the NCI's SEER (5) database, and also to work with sentinel sites, that (6) is, specialty referral centers where such patients (7) with the disorder receive care.

(8) We will provide a periodic update on (9) prescriptions by geographic region to the agency. We (10) will work and review new information on a periodic (11) basis with an external safety review board. This (12) program will be ready to be implemented at launch.

(13) Now, to summarize the clinical data. (14) Teriparatide treatment improves skeletal architecture. (15) These CT scans of baseline and follow-up iliac crest (16) bone biopsy from a patient treated with teriparatide (17) provides evidence for enhanced architecture, that is, (18) improvement in the trabecular network of bone from the (19) baseline state to the follow-up state after treatment. (20) It is data similar to that which was shown earlier (21) this morning by Dr. Lindsay.

(22) This effect of teriparatide was associated

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(1) with significant favorable effects on clinical (2) outcomes on study patients, that is, treatment (3) prevented fractures.

(4) We have considered the following in dose (5) selection. In the Phase 3 trial, vertebral and (6) nonvertebral fracture risk was reduced to a similar (7) extent in the 20 and 40 microgram groups in women. (8) While there was a rapid and dose related increase in (9) the surrogate outcome of bone density at the spine and (10) hip in women and men, the actual increase in spine and (11) femoral neck and total hip bone density was similar (12) for women and men.

(13) The 40 microgram dose was more likely to (14) cause adverse events, transient elevations in serum (15) calcium, and resulted in a higher rate of (16) discontinuations from the trials in women and in men.

(17) Teriparatide 20 micrograms is an (18) appropriate dose for treatment of osteoporosis in post (19) menopausal women and in men.

(20) Pharmacokinetic and pharmacodynamic (21) analyses supported that dose adjustment is not (22) required for gender, weight or age.

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(1) To summarize the effect of teriparatide 20 (2) micrograms, in women in Study GHAC, teriparatide 20 (3) micrograms reduced the risk of vertebral fracture by (4) 65 percent; reduced the risk of nonvertebral fractures (5) by 53 percent; increased bone mineral density at the (6) spine and hip without a significant effect at the (7) forearm; and increased total body bone mineral. There (8) was no increase in fracture risk for at least 18 (9) months after cessation of treatment.

(10) In the study in men, teriparatide (11) significantly increased bone mineral density at the (12) spine and femoral neck without significant effect at (13) the total hip, and there was a significant increase in (14) total body bone mineral.

(15) The adverse effects associated with (16) teriparatide treatment in the Phase 3 clinical trials (17) in women were nausea and leg cramps. The overall (18) pattern was similar in men, except for that leg cramps (19) were not reported at an increased frequency.

(20) In the clinical pharmacology studies, (21) postural hypotension was observed, but almost always (22) after doses of 40 micrograms or greater.

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(1) While the incidence of clinical apparent (2) postural hypotension was not different among groups in (3) the Phase 3 trials, we believe that this is a (4) potential treatment related effect.

(5) We observed increases in serum calcium (6) between four to six hours post dose that had returned (7) to baseline by 16 hours post dose. The levels (8) transiently exceeded the normal range of repeat in (9) only about three percent of women, and there was no (10) difference from baseline in pre-dose serum calcium at (11) any visit.

(12) There was a median increase in serum uric (13) acid of about 20 percent without effect on the (14) incidence of gout or arthralgia.

(15) There was no increase in the risk of (16) cancer, no primary bone tumors were reported, and (17) there was no effect on mortality.

(18) Teriparatide treatment restores bone (19) architecture and bone mass. No other osteoporosis (20) treatment can do this. The now demonstrated ability (21) to prevent fractures confirms that teriparatide can (22) fulfill an important unmet medical need in women and

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(1) in men with osteoporosis.

(2) Clinical trials support that 20 micrograms (3) per day is an effective and safe treatment for (4) osteoporosis in post menopausal women and in men.

(5) This now concludes the presentation from (6) Lilly. Thank you very much for your attention.

(7) ACTING CHAIRMAN MOLITCH: I'd like to (8) thank the sponsor for a crisp presentation that came (9) in on time.

(10) We now have the opportunity for the panel (11) to ask questions of the sponsor. At this point we'd (12) like to try to ask questions that are specifically (13) related to the presentation, the data presented, as (14) far as factual questions regarding this.

(15) I think additional philosophical questions (16) and other types of things we'll have the opportunity (17) to discuss later.

(18) So if any members of the panel would like (19) to start with questioning, please do.

(20) Dr. Bone.

(21) DR. BONE: Thank you.

(22) I appreciate your very nice presentation.

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(1) I have one or two – actually I have several (2) questions, but I'll try to ask them one or two at a (3) time.

(4) With regard to the osteosarcomas, when you (5) investigated the animal tumors, what did you find out (6) about their responsiveness to parathyroid hormone? Do (7) they have receptors? Do they respond in vitro to (8) parathyroid hormone? Are these tumors ones that may (9) have been a result of an effect on early (10) differentiation but no ongoing effect of the tumor by (11) the hormone or is it something that's stimulated as we (12) go along?

(13) DR. MITLAK: Let me invite our (14) toxicologist, Dr. Vahle, to response.

(15) DR. VAHLE: We've not isolated the (16) osteosarcoma cells in vitro to study PTH receptor (17) density or responsiveness to teriparatide. So we (18) don't have any direct evidence to address your (19) question one way or the other.

(20) DR. BONE: Was the receptor expressed in (21) the tissue, in the slides?

(22) DR. VAHLE: We've not done any receptor

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- (1) identification in those specific slides or have grown (2) them in culture either.
- (3) DR. BONE: Why?
- (4) DR. VAHLE: Because there are technical (5) difficulties in getting to that PTH receptor in those (6) specific slides. Also, in investigating that, it was (7) not clear whether that was going to give us clear (8) information about their relevance to humans.
- (9) DR. BONE: I'm a little disappointed that (10) you didn't look.
- (11) Okay. I have a couple more questions if (12) nobody else has one right now. Okay.
- (13) Could you show us the nonvertebral (14) fracture data in men, the actual data?
- (15) DR. MITLAK: Well, the actual data are (16) that there were six nonvertebral fractures in the male (17) study, three in placebo, two in the 20 microgram dose (18) group, and one in the 40 microgram dose group. Is (19) that sufficient?
- (20) DR. BONE: Okay. Where were the (21) fractures? What sites? Were they hip fractures?
- (22) DR. MITLAK: No, they were not hip

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- (1) fractures.
- (2) DR. BONE: None of them?
- (3) DR. MITLAK: None of them.
- (4) ACTING CHAIRPERSON MOLITCH: Dr. Levitsky.
- (5) DR. LEVITSKY: Do you have any data or can (6) you summarize data on the serial or concomitant use of (7) bisphosphonates with this agent?
- (8) DR. MITLAK: I'm sorry?
- (9) DR. LEVITSKY: Do you have any data on the (10) serial or concomitant use of bisphosphonates with this (11) agent?
- (12) DR. MITLAK: We have just limited data to (13) share with you on this. Let me ask for slide 4261.
- (14) What this slide shows is information from (15) the 58 patients who had reported prior use of (16) bisphosphonate prior to enrollment in the study. (17) Because the study began enrolling in 1995 and '96, the (18) bisphosphonates that were more commonly used and were (19) available included primarily alendronate. There were (20) also a few patients who received alendronate or (21) toludronate, and in one patient who received (22) abandronate.

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- (1) These data show that compared with (2) placebo, the overall change in bone density was (3) similar to the larger population. I do not have a lot (4) of information on precisely how long the patients used (5) these, but they had stopped treatment for between six (6) and 24 months prior to enrollment in the study.
- (7) DR. KREISBERG: I also have several (8) questions. I'd like to ask whether you conducted any (9) studies in orchietomized (phonetic) male primates. (10) I didn't understand from the presentation in your (11) experimental models whether the male primates were (12) androgen deficient or not
- (13) DR. MITLAK: Dr. Vahle, please.
- (14) DR. VAHLE: Consistent with the guidances, (15) the 18-month pharmacology study I described was (16) limited to ovariectomized females. So we have not (17) studied the similar model in males.
- (18) DR. KREISBERG: The other question that is (19) partially related to that is whether in the human (20) studies, where you were treating hypergonadal men and (21) men with idiopathic osteoporosis, whether the (22) hypergonadal men also received androgen replacement.

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- (1) DR. MITLAK: The study in men included (2) approximately half of the men that had idiopathic (3) osteoporosis and half were hypergonadal. Testosterone (4) treatment, if it was being used by men, could be (5) continued during the study, but was not permitted to (6) be started de novo during the study.
- (7) A small proportion of men, in the range of (8) ten percent or less, had been taking testosterone or (9) an androgen replacement into the study, and as we (10) said, overall the response in men with idiopathic and (11) hypogonadal osteoporosis to teriparatide treatment was (12) similar.
- (13) ACTING CHAIRPERSON MOLITCH: Dr. Aoki.
- (14) DR. AOKI: Do you have any data or are you (15) planning any studies on monkeys older, for periods (16) longer than 18 months, or on rats that are older than (17) six to eight weeks to determine if the osteosarcoma (18) is, in fact, somehow age related in the rats and to (19) see the more relevant model, whether or not the (20) osteosarcoma question can be laid to rest using longer (21) term studies?
- (22) DR. MITLAK: Let me ask Dr. Vahle again to

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(1) comment on the work that's ongoing.
 (2) DR. VAHLE: Since the initial observation, (3) we've worked closely with our experts as well as the (4) FDA in developing some ongoing research that I'd be (5) happy to share with you.
 (6) If I could please have slide 4222, let me (7) briefly highlight the two main components of this.
 (8) First, in response to the second portion (9) of your question, yes, we are conducting a follow-up (10) rat study which looks at two things: one, the effect (11) of treatment duration and, two, the effect of age at (12) treatment initiation.
 (13) In this respect it addresses the question. (14) We have treatment arms which avoid the phase of rapid (15) skeletal growth, and this is a study that was (16) conducted or designed in collaboration with the agency (17) as a Phase 4 commitment.
 (18) In terms of additional monkey work, what (19) we are doing is an additional study which has an 18- (20) month treatment period. This represents approximately (21) eight percent of the monkey's lifetime at exposures up (22) to eightfold human exposures, but it contrasts with

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(1) our prior work in that it's followed by a minimum (2) three year observation period to allow us to have some (3) extended follow-up data in the primate model, and (4) again, this is a study that we are in the early stages (5) of and designed with the agency.
 (6) DR. BONE: Going back to the series of (7) questions, could you discuss what studies you are (8) conducting concerning the – or have conducted – (9) concerning the mechanism by which these osteosarcomas (10) were induced, biological mechanism?
 (11) DR. VAHLE: As part of that ongoing (12) research program, another component of that was to (13) convene a group to try to discern what type of (14) mechanistic studies would be useful in trying to (15) assess the relevance to humans, and again, this is (16) something that we have discussed with the division.
 (17) It has not been clear that there are a (18) direct set of experiments that will help us understand (19) the mechanism in the rat and then clearly (20) differentiate it from the humans at a cellular or (21) molecular level. Rather, we have focused on these (22) effects of treatment duration and age of initiation

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(1) because it's clear these differences between the rat (2) model and the human that we want to more clearly (3) establish.
 (4) In those follow-up studies, we are (5) continuing to evaluate new technologies, such as gene (6) array or genetic characterization to see if they would (7) provide any assistance or any additional insight.
 (8) DR. BONE: Have you completed any studies (9) addressing this mechanism at all?
 (10) DR. VAHLE: No, there have been no studies (11) completed to date. The studies and the concepts I've (12) outlined are all in progress. What I can share though (13) is interim results from the long-term rat study, and (14) that following six months' treatment duration, both (15) during the rapid phase of skeletal growth as well as (16) after the rapid phase of skeletal growth, there are no (17) bone proliferative lesions, and there are the (18) anticipated exaggerated effects on the skeleton, but (19) again, that study is still in progress.
 (20) DR. GRADY: I'd like to ask a little bit (21) about nephrotoxicity. It seemed that in one of your (22) monkey studies at least there was a fair percentage of

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(1) the animals who had nephropathy, and one out of eight (2) in that study with renal failure, and I don't think (3) you talked about that at all.
 (4) DR. MITLAK: Please.
 (5) DR. VAHLE: I'd certainly be happy to (6) address the renal findings.
 (7) If I could go back to the main slide 28, (8) please, we've studied renal tissue and renal function (9) in two different models. In the toxicity studies, and (10) there are a group of three different toxicology (11) studies represented here, we observed these subtle (12) histologic observations in the kidneys of monkeys over (13) a range of doses and over a range of duration of (14) exposure, both three-month studies and up to one year.
 (15) We conducted – because in those routine (16) studies there was no clear evidence that these renal (17) changes had an impact on renal function, we conducted (18) a special study to determine if these changes had (19) effects on renal function.
 (20) That study was conducted at a high dose of (21) 40 micrograms per kilogram. That provides exposures (22) that are in excess of 100-fold what a woman would

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

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

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

(18) Does that address the question?

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

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

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

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

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

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

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

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(1) assessments that we made, we felt we had assessed (2) renal function. We did not measure concentrating (3) capacity. (4) ACTING CHAIRPERSON MOLITCH: And, again, (5) continuing with this line, the patients who were (6) treated with hydrochlorothiazide and furosemide at low (7) dose, plus the PTH, there was no particular change in (8) serum calcium that occurred in those patients; is that (9) correct?

(10) You said there was no drug interaction.

(11) DR. MITLAK: Dr. Gaich.

(12) DR. GAICH: Yes, that is correct. Among (13) the patients treated with thiazide diuretics in our (14) Phase 3 study, we looked at the serum calcium (15) response, and it was similar. (16) In addition, we did a specific clinical (17) pharmacology study to specifically look at the (18) interaction on serum in urine calcium between (19) teriparatide and thiazide diuretics, and likewise (20) there is no interaction there.

(21) ACTING CHAIRPERSON MOLITCH: Dr. Gelato.

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

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(1) through with this.

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

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

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

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

(17) DR. GAICH: Thank you.

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

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

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- (1) not find one.
- (2) Second, all of the calcemic effects that (3) were observed were transient. So even the patients (4) that had the highest serum calciums, the baseline (5) serum or the pre-dose serum calcium is back down to (6) normal.
- (7) And finally – what was your third (8) question?
- (9) DR. GELATO: Was there a relationship to (10) those patients because –
- (11) DR. GAICH: Between serum calcium and (12) urine calcium?
- (13) DR. GELATO: And the elevation of serum (14) creatinine.
- (15) DR. GAICH: Okay. There was not a (16) relationship between – a strong relationship – (17) between the patients who had high serum calcium and (18) high urine calcium, nor was there any relationship (19) between the patients who had high serum calcium (20) transiently and an increase in serum creatinine.
- (21) DR. TAMBORLANE: Again, on the same, just (22) even from that individual animal experiment, the case,

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- (1) it seemed to me I was hearing the suggestion that (2) serum calcium did not have to be monitored during (3) therapy, and maybe under the normal circumstances, but (4) it's likely that patients with hyperparathyroidism (5) might be exposed to the drug, and there's very limited (6) data.
- (7) Is that your continued suggestion that (8) calcium not be monitored?
- (9) DR. MITLAK: Let me invite Dr. Gaich again (10) to help address this question.
- (11) What we are suggesting and what we have (12) observed in the clinical studies is that the (13) incremental change in serum calcium in patients seemed (14) to be independent of the baseline serum calcium, that (15) is, whether somebody is in the low, mid, or upper part (16) of the range, the increment in calcium was fairly (17) consistent with the dosing.
- (18) Therefore, we recommend that high calcium, (19) hypercalcemia be excluded before patients are (20) considered for treatment, and once that has happened, (21) we found based on the clinical trial results that that (22) is a reasonable course of action.

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- (1) Let me see if Dr. Gaich has –
- (2) DR. GAICH: Thank you.
- (3) Could we look at slide 4455?
- (4) We actually did look at a number of (5) factors to determine if there were any particular (6) characteristics of patients who would have higher (7) responses of serum calcium, and I will show you what (8) we evaluated.
- (9) I'm sorry. I need 4455. We need to go (10) one back. There we go.
- (11) We looked at the relationship between the (12) highest post dose serum calcium and baseline serum (13) calcium, baseline serum, 25 hydroxy Vitamin D, the (14) body mass index, the baseline intact parathyroid (15) hormone 1 to 84, and age.
- (16) Now if we can go to 4456, please.
- (17) The only significant relationship or (18) strongly significant relationship was the relationship (19) between baseline serum calcium and the highest post (20) baseline. The correlation coefficient was .45, which (21) was highly statistically significant, and as you can (22) see, based on the graph, the higher the baseline serum

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- (1) calcium, the higher your post baseline serum calcium.
- (2) And this was the only strong predictor of (3) baseline – of post baseline serum calcium.
- (4) As Dr. Mitlak also mentioned, we also (5) looked at the relationship between baseline serum (6) calcium and the change in serum calcium, and there was (7) not a positive relationship.
- (8) So patients who started with high baseline (9) serum calciums did not have an exaggerated response.
- (10) May I have the next slide, please, 4457?
- (11) Among the other things, there were some (12) weak negative and weak positive correlations. There (13) was a weak positive correlation with 25 hydroxy (14) Vitamin D, the correlation coefficient of .13.
- (15) Weak negative correlations of particular (16) interest to your question is there was a negative (17) correlation between baseline intact parathyroid (18) hormone and the highest post baseline serum calcium. (19) So patients who started with higher intact PTH at (20) baseline tended to have lower post baseline serum (21) calciums.
- (22) Nevertheless, we do believe that patients

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(1) with hypercalcemia should not be treated with (2) teriparatide.

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

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

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

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

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

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(1) is: is that true?

(2) And then a follow-up question is: how (3) long would you intend to use teriparatide for the (4) treatment of osteoporosis? Do you see that as an (5) indefinite exposure to the hormone? (6) Because I think that gets to the issue (7) that is troubling everybody, and that is longer term (8) exposure might, in fact, bring out some side effects (9) that haven't been brought out by short term exposure.

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

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

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

(22) We subsequently followed those patients

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

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

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

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

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

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(1) about that.

(2) ACTING CHAIRPERSON MOLITCH: Thank you.

(3) Dr. Schneider, do you have one?

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

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

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

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

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

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

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- (1) significant. So it is kind of a gatekeeper strategy.
- (2) DR. SCHNEIDER: I'm sorry. Could you say (3) again something about the primary efficacy variable? (4) How did you handle multiple comparisons on that?
- (5) DR. WANG: The primary efficacy actually (6) is the combined - well, when you look at the (7) particle, it is the combined teriparatide doses, 20 (8) and 40 microgram groups compared with placebo. So (9) that's the primary, and to separate the doses we will (10) also look at the separate doses versus placebo.
- (11) DR. SCHNEIDER: Thank you.
- (12) The second question I had is in GHAJ the (13) primary efficacy variable was noted as a change in (14) lumbar bone mass density, and you presented the (15) percent change and later indicated that the change was (16) independent of baseline.
- (17) Do you have data or analysis on just the (18) change from baseline in lumbar BMD?
- (19) DR. MITLAK: Let me ask our group if we (20) have the slide.
- (21) I can tell you that the analysis of change (22) rather than percent change was identical. The

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- (1) statistical inferences were identical, except for that (2) the change at the total hip, which was not significant (3) by percent change was significant for actual change.
- (4) DR. SCHNEIDER: And the final question I (5) had was in the AC study, did you look at BMI or (6) weight, the effect of that as a covariant in either (7) the adverse experiences or the efficacy variables? (8) And what level of effect did it have?
- (9) DR. MITLAK: Let me invite our (10) pharmacokineticist, Dr. Satterwhite, to come to the (11) microphone to address your questions.
- (12) DR. SATTERWHITE: My name is Julie (13) Satterwhite. I am a senior research scientist at (14) Lilly, and I was responsible for the pharmacokinetic (15) and pharmacodynamic analyses.
- (16) For the pharmacodynamics we looked at - (17) in terms of efficacy, we looked at the biochemical (18) markers and BMD response. We did evaluate body mass (19) index and weight and found that neither one of them (20) was a significant covariant governing response.
- (21) DR. KREISBERG: This was GHAC.
- (22) DR. SATTERWHITE: Yes. We saw that in

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- (1) both AC and AJ, and it was not a significant (2) covariant.
- (3) DR. KREISBERG: Do you remember what the (4) slope was? Was it positive, negative? In fact, the (5) correlation, even though it wasn't significant?
- (6) DR. SATTERWHITE: I can get that answer (7) for you.
- (8) DR. KREISBERG: Thank you.
- (9) DR. GRADY: I'd like to ask about calcium (10) intake. In this study it was recommended that women (11) take, I think, a gram of calcium per day, and I think (12) one of the things we've perhaps been fairly successful (13) at is getting most post menopausal women to take (14) calcium supplementation.
- (15) I wonder if you adjusted calcium (16) supplementation during the study and also if you (17) planned to recommend calcium supplementation in (18) addition to the drug during treatment.
- (19) DR. MITLAK: Let me invite Dr. Gaich up (20) also while I tell you that the mean intake at baseline (21) in the women was in the range of seven to 800 (22) milligrams per day so that a 1,000 milligram

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- (1) supplement resulted in a total of approximately 1,700 (2) to 1,800 milligrams of calcium.
- (3) We expect that going forward, that (4) patients who receive treatment would take calcium (5) supplements. We would recommend that their calcium (6) total intake be adjusted to that recommended for (7) patients with post menopausal osteoporosis or (8) osteoporosis in men.
- (9) I might ask Dr. Gaich to help comment on (10) any dose adjustments that have occurred in the study.
- (11) DR. GAICH: Okay. Thank you.
- (12) First of all, a flat dose of 1,000 (13) milligrams a day was prescribed for all of the (14) patients, was recommended for all of the patients. So (15) we did not adjust based on dietary intake to bring up (16) to some level, and again, we think that's fairly more (17) typical of the clinical practice than doing an (18) extensive dietary survey and doing an adjustment.
- (19) The physicians were allowed to change (20) calcium supplements to or to adjust calcium (21) supplements based on side effects, especially GI side (22) effects with some supplements, and also if the

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

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

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

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

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

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

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

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

(6) Thank you.

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

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

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

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

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

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

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

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

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

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

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

(20) DR. BONE: Thank you.

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

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(1) questions about the uric acid.

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

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

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

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- (1) looking for the interaction.
- (2) DR. BONE: We may come back to that (3) question later. Let me ask you some questions about (4) the Vitamin D status of the patients. Obviously the (5) Vitamin D status of patients who would potentially (6) take this medication is of considerable concern (7) because if we accelerate bone turnover at the same (8) time as having insufficient Vitamin D, we may induce (9) a mineralization defect that might not have been (10) apparent in the clinical trials.
- (11) Can you tell us what the baseline 25 (12) hydroxy Vitamin D status was for your patients and (13) also what was the effect on 125 dihydroxy Vitamin D (14) levels in the patients in the treatment groups?
- (15) DR. MITLAK: Let me ask Dr. Gaich to come (16) to the microphone again.
- (17) Let me also first show you the slide to (18) answer your second question, which is the 125 (19) dihydroxy Vitamin D charge during treatment for the (20) three groups.
- (21) It's slide 4260.
- (22) What this panel shows is measurement of

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- (1) 125 Vitamin D over the first year of the study, and it (2) shows that with treatment, 125 Vitamin D levels (3) increase.
- (4) In combination with this, we actually see (5) a slight decrease in 25 Vitamin D levels, which we (6) presume is part of the conversion process.
- (7) And now if I could ask Dr. Gaich to answer (8) the first part of your question.
- (9) DR. GAICH: Thank you.
- (10) All the patients in our clinical trials (11) required to have a 25 hydroxy Vitamin D above the (12) upper limit of normal. Some of them at screening were (13) below the upper limit of normal, but then came into (14) the normal range with supplementation.
- (15) DR. BONE: I think you misspoke.
- (16) DR. GAICH: I'm sorry.
- (17) DR. BONE: You said that all of the (18) patients had to be above the upper limit of normal?
- (19) DR. GAICH: I'm sorry.
- (20) DR. BONE: I'm sure you didn't mean that.
- (21) DR. GAICH: Had to be above the lower (22) limit of normal. Thank you.

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- (1) DR. BONE: Meaning what?
- (2) DR. GAICH: We used the standard (3) laboratory reference range, and I'd have to look that (4) up for you.
- (5) DR. BONE: Well, as you know, most of the (6) standard laboratory reference ranges are considered to (7) be - in most of the standard laboratory reference (8) ranges what is presented as the lower limit of the (9) reference range is widely regarded by clinicians in (10) this field as consistent with Vitamin D insufficiency.
- (11) So I think it's a specific question we'd (12) like a specific answer to as to what the distribution (13) of 25 hydroxy Vitamin D levels actually was in the (14) trial, and we may want to give some further thought to (15) whether we can really account - I think in the (16) briefing document you said there was about a 25 (17) percent decrease in mean 25 hydroxy Vitamin D levels, (18) and this was explained or supposedly explained by the (19) conversion to 125 dihydroxy Vitamin D, but since the (20) ratio of the actual mass of 25 hydroxy to 125 (21) dihydroxy Vitamin D is a ration of nanograms to (22) picograms, I think that we will have to invoke some

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- (1) additional explanation for that phenomenon, and (2) perhaps you will be able to comment on that after (3) lunch.
- (4) One or two additional questions. One of (5) the striking findings in your results was the failure (6) to protect height. The usual result in trials where (7) there's a substantial reduction in the rate of (8) vertebral fracture, such as you have very nicely (9) described, is that there is also a measurable (10) difference between the height loss in the treatment (11) groups and the height loss in the placebo groups.
- (12) And I'm wondering what you've done to try (13) to identify a basis for that phenomenon. For example, (14) since you have the radiographs, was an attempt made to (15) assess the effect on actual vertebral heights to (16) determine whether the height loss in the patients in (17) the different groups could be explained in that way? (18) Did people look at disk spaces? What was done to try (19) to figure out why there was a discrepancy between your (20) very impressive reduction in fracture rate and the (21) lack of any apparent effect on height?
- (22) DR. MITLAK: We actually don't think that

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

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

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

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

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

(4) DR. MITLAK: Yes, stadiometers were used.

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

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

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

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

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

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

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

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

(22) I think to your question about looking at

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

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

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

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

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

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

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

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

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

(22) So it depends upon trying - if you want

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

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

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

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

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

(18) DR. MITLAK: Yes.

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

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(1) the group that got two years of treatment.

(2) Maybe I'm missing something here.

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

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

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

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

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

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

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

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(1) median duration of treatment was 19 months.

(2) DR. BONE: Right.

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

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

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

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

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

(22) DR. BONE: You haven't analyzed the

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- (1) follow-up data for that purpose?
- (2) DR. MITLAK: That's correct. We have –
- (3) DR. BONE: Thank you.
- (4) DR. GAICH: We just have the data that Dr. (5) Bone asked, and very few patients had a year or less (6) of treatment prior to the study closeout. It was only (7) between ten and 15 percent in each treatment group. (8) so not really enough to do an adequate vertebral (9) fracture analysis.
- (10) DR. BONE: How many had between 12⁺ and 18 (11) months, in other words, below the median?
- (12) DR. GAICH: I'm sorry. You found it?
- (13) DR. BONE: I guess it would be about half.
- (14) (Laughter.)
- (15) ACTING CHAIRPERSON MOLITCH: We'll take a (16) last question before the break from Dr. Tamborlane.
- (17) DR. TAMBORLANE: I think you showed the (18) post – sort of the follow-up data after the study was (19) stopped as far as fracture rate, but in regard to sort (20) of follow-up of Dr. Kreisberg's question, do you have (21) the – because it relates to duration of treatment – (22) do you have the bone marrow density data post

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- (1) discontinuation of the trial?
- (2) DR. MITLAK: yes.
- (3) DR. TAMBORLANE: Over time?
- (4) DR. MITLAK: yes.
- (5) DR. TAMBORLANE: Because that would say (6) whether the density then goes back. I think those (7) data – I don't believe we saw those data.
- (8) DR. MITLAK: Let me ask you to put slide (9) 4304 up, please.
- (10) Let me also explain as a preface, as Dr. (11) Gaich had highlighted, approximately 80 percent of the (12) patients who had previously been enrolled in the prior (13) study elected to continue into the follow-up study, (14) the follow-up study was an observational study. After (15) the primary study database was locked, patients were (16) unblinded to treatment assignment, and in the follow- (17) up phase, patients could take other treatments for (18) osteoporosis.
- (19) About half of the patients by 18 months (20) out had begun to take some other treatment for (21) osteoporosis, but the use of these treatments, whether (22) it was any specific treatment or the use of any

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- (1) treatment was statistically similar across groups. So (2) we have these data shown with that piece of background (3) information.
- (4) What this slide shows for the spine is (5) that in the first – the data shown are for the (6) endpoint of the prior study, the first visit for the (7) follow-up study, and the second visit for the follow- (8) up study. This is six months and then an additional (9) 12 months.
- (10) It shows that the bone density decreases (11) from the endpoint visit, but remains statistically (12) significant for the next 18 months and is different (13) from placebo even 18 months after treatment.
- (14) Let me ask also for you to show the next (15) slide 4305, which is the same type of analysis at the (16) hip.
- (17) All right. Thank you.
- (18) ACTING CHAIRPERSON MOLITCH: I think at (19) this juncture we will take a break. We will be able (20) to ask the sponsor additional questions after the FDA (21) presentation.
- (22) It is now 10:32. We'll resume at 10:47.

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- (1) (Whereupon, the foregoing matter went off (2) the record at 10:34 a.m. and went back on (3) the record at 10:55 a.m.)
- (4) ACTING CHAIRPERSON MOLITCH: We will now (5) continue with the FDA presentation. The first person (6) to present will be Dr. Kuijpers, who will be (7) discussing the preclinical studies.
- (8) DR. KUIJPERS: Thank you, Mr. Chairman, (9) ladies and gentlemen.
- (10) My name is Gemma Kuijpers. I'm a (11) pharmacology reviewer in the Division of Metabolic and (12) Endocrine Drug Products.
- (13) I thank you for giving me the opportunity (14) to talk today about the preclinical safety of (15) teriparatide. After my presentation, Dr. Bruce (16) Schneider will address clinical efficacy, and Dr. (17) Bruce Stadel will talk clinical safety of teriparatide (18) injection.
- (19) In this presentation, I will focus on the (20) main preclinical safety issue that emerged during the (21) development program of teriparatide, namely, that (22) teriparatide injection causes bone neoplasms in the

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(1) rat.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

(22) For most, but not all of the animals that

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

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

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

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

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

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

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

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

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

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

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

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

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

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(1) or threshold dose level was not established.

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

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

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

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(1) transformation.

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

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

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

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

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(1) the validity of the rat model.

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

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

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

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

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(1) for a possible adverse event.

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

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

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

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

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

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

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

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

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

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

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

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

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(1) humans treated with teriparatide.

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

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

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

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

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(1) an anabolic agent.

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

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

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

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

(22) And trial GHAJ, the other pivotal trial,

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

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

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

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

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

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

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

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

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

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(1) should be taken with caution.

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

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

(20) There were other fracture results which (21) were not pre-specified as outcome results, but which (22) were methodology derived, and these are shown here,

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

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

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

(22) This slide summarizes the percent of

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

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

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

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

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

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

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

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

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

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

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

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

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

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(1) treatment.

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

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

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

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

(22) So our clinical efficacy summary is shown

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

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

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

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