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P A R T I C I P A N T S

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S. James Kilpatrick, Ph.D.
Joel Mindel, M.D.
Susan Cohen, B.S.
Milton Orkin, M.D.
Madeleine Duvic, M.D.
William Rosenberg, M.D.

Consultants:

Eva Simmons-O'Brien, M.D. (voting)
Fred Miller, M.D. (voting)
Eduardo Tschen, M.D. (voting)
Henry Lim, M.D. (non-voting)

FOOD AND DRUG ADMINISTRATION STAFF:

Tracy Riley, Executive Secretary
R. Srinivasan, Ph.D.
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Jonathan Wilkin, M.D.
Michael Weintraub, M.D.

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P R O C E E D I N G S

DR. MCGUIRE: My name is Joe McGuire, and I'd like to welcome you all to the Dermatologic and Ophthalmic Drugs Advisory Committee Meeting. This is number 48. I can't imagine anyone is interested that it's 48, but it's 48. The sponsor today is Merck, and they're going to discuss Propecia. This is an open session, and the meeting is now in order, and Tracy Riley, who is the executive secretary, will read the conflict of interest statement.

MS. RILEY: Good morning.

The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

In accordance with 18 U.S.C. 208, general matters-waivers--excuse me; I'm on the wrong day.

DR. MCGUIRE: Wrong page. It sounded fine.

MS. RILEY: It sounded fine until I got to a certain point.

[Laughter.]

MS. RILEY: Okay; based on the submitted agenda for the meeting and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug

Evaluation and Research present no potential for an appearance of a conflict of interest at this meeting with the following exceptions: in accordance with 18 U.S.C. 208(b)(3), full waivers have been granted to Ms. Susan Cohen and Dr. Joel Mindel which permit them to participate in all official matters concerning Propecia.

Copies of the waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A30 of the Parklawn Building. In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record.

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

In addition, the committee has invited the following consultants to participate in this meeting as temporary voting members: Dr. Fred Miller, Dr. Eva Simmons-O'Brien and Dr Eduardo Tschen. In addition, the committee has invited the following non-voting guest to participate in the meeting, and that's Dr. Henry Lim. Thank you.

DR. MCGUIRE: Before we have the introduction from the agency, I'd like to go around the table and have members introduce themselves. Just give your name and affiliation. Start with Dr. Wilkin.

DR. WILKIN: Jonathan Wilkin, Division of Dermatologic and Dental Drug Products, FDA.

DR. KO: Hon-Sum Ko, Division of Dermatologic and Dental Drug Products, FDA.

DR. SRINIVASAN: Srinivasan, Division of Biometrics for FDA.

DR. PARKER: Frank Parker, Department of Dermatology, Oregon Health Sciences University.

DR. SIMMONS-O'BRIEN: Eva Simmons-O'Brien, Departments of Dermatology and Internal Medicine, Johns Hopkins.

DR. MILLER: Fred Miller, Department of Dermatology, Geisinger Medical Center, Danville, Pennsylvania.

DR. KILPATRICK: Jim Kilpatrick, biostatistics, School of Medicine, Medical College of Virginia, Virginia Commonwealth University.

MS. RILEY: Tracy Riley; I'm the executive secretary to the committee.

DR. MCGUIRE: Joe McGuire, Dermatology and

Pediatrics, Stanford.

DR. MINDEL: Joel Mindel, Departments of Ophthalmology and Pharmacology, Mount Sinai Medical School, New York.

DR. LIM: Henry Lim, Henry Ford Hospital, Detroit, Michigan.

DR. TSCHEN: Eduardo Tschen, Department of Dermatology, Albuquerque, New Mexico, University of New Mexico.

MS. COHEN: Susan Cohen, and I am the consumer member.

DR. ORKIN: Milton Orkin, University of Minnesota Department of Dermatology.

DR. DUVIC: Madeleine Duvic, Dermatology and Internal Medicine, M.D. Anderson Cancer Center, Houston, Texas.

DR. ROSENBERG: Bill Rosenberg, Dermatology, University of Tennessee College of Medicine.

DR. MCGUIRE: Dr. Weintraub just entered, and I'll introduce him, and he'll make the introductory remarks for the agency.

DR. WEINTRAUB: Thank you very much.

You know, it seems I make these remarks or some variation of them every time, but it's important to outline

just how we feel about the advisory committee, besides enjoying your visits and appreciating them very much. But you're our advisors. You're approximately like or somewhat like the industry's advisors, except, of course, you do your work in public, and it's all right, because we're part of the Government, and that doesn't bother us, really, and I hope it doesn't change the quality of your advice or the type of your advice, but you do your work in public.

Now, it may appear to you that you're sitting between the sponsor and the FDA, and we've set it up like that because of some special feeling, but we don't ask you to adjudicate between the sponsor and the FDA. That's not what we see as your main role here. We don't expect you to judge the quality of the evidence and come down and say FDA, you were right or sponsor, you were right.

We don't ask you to be a science court. That's a term I don't even think--I'm not sure it's correct, that anything could be a science court. However, not that we want you to adjudicate. What we want is to hear the discussion. I wish we didn't have to have the votes. Sometimes, we have to have the vote, and I know that the press, for example, will write down the vote very carefully and worry about a split vote and how many people voted for and how many people voted against.

I wish that we didn't have to have the votes, just the discussion. So, in a sense, I'm very much in favor of the kinds of questions we're asking you today and the things we're trying to ask you to do for us today. What we're asking you to do is discuss a variety of issues. Not even the efficacy is in question here. The FDA agrees that the sponsor has shown an effect in vertex baldness. Okay; we can all go home.

No, we can't. We want you to look at the safety database and its applicability to the questions before us, and we'd like you to give us your advice on several of the efficacy questions as well: frontal baldness, for example; prevention of further progression of baldness or changing the natural history of baldness, these are large and important questions. They're actually relatively new on the horizon. So, we want you to tell us about what you think about that, what you think about the data.

Now, some people might say that gee, the division should have had everything prepared ready to go and its opinion ready to go; you shouldn't have to ask us these questions; we should just think of the big issues, vote on that. Sometimes, because we ask you to do this kind of-- give us your advice in this kind of manner, it's because we haven't really finished the review. We need your advice to

help us finish up the review, to help us decide on these large questions and on the applicability of the science, the applicability of the safety database.

I think that what we're trying to do is maybe adjust the way we use the advisory committees to a certain extent, but in any case, we have to have your judgment, your thoughts, your discussion, your--and I hope some interplay on these very big and large issues.

Dr. McGuire, I turn the chair over to you, and I'll be happy to answer any questions if anybody has any, and also, do you have any--oh, okay.

DR. MCGUIRE: Thank you very much, Dr. Weintraub.

One of the things that Dr. Weintraub just told the committee, and I hope all of you are aware of it, is that the primary and secondary reviewers' report is not in your briefing book. So, if you spent last week looking for it, you're going to hear it today. It's not there. So, we are at an interesting point in time with regard to reviewing the sponsor's product, and the questions that we will vote on later, we will take apart, we will deconstruct them and construct them however the committee wishes.

It's my understanding that there is no one from the public speaking today; is that correct?

MS. RILEY: I have no applicants.

DR. MCGUIRE: Okay; then, we'll go right ahead to the sponsor, and we will hear from Dr. Robert Silverman, who will introduce the product.

[Pause.]

DR. SILVERMAN: Good morning, Mr. Chairman, members of the advisory committee, FDA and ladies and gentlemen. My name is Bob Silverman. I am senior director of regulatory affairs for Merck Research Laboratories. I shall provide some brief introductory remarks before we present the results from our clinical development program for Propecia.

Before beginning, I would like to thank the advisory committee and FDA for the opportunity to present our results which support the new drug application for Propecia, Merck's trade name for finasteride, 1 milligram, for the treatment of men with male pattern hair loss. Finasteride is, in fact, an established medication. Finasteride is an orally-administered highly specific inhibitor of the enzyme 5-alpha Reductase. This enzyme catalyzes the metabolic conversion of testosterone to dihydrotestosterone. Under the trade name Proscar, finasteride has been widely prescribed for the treatment of men with benign prostatic hyperplasia or BPH at a dose of 5 milligrams per day.

It is estimated that cumulative worldwide use of Proscar now exceeds 3.5 million patient/years. It has been available in the United States since 1992. The very large aggregate experience with Proscar in both marketed and long-term clinical trial use has established the excellent safety profile for finasteride in men at a dose five times that which we are here to discuss today.

In today's presentation, we will discuss efficacy and safety data supporting the use of finasteride at a dose of 1 milligram per day for the following indication: Propecia, Merck's trade name for finasteride 1 milligram, is indicated for the treatment of men with male pattern hair loss, also called androgenetic alopecia, to increase hair growth and prevent further hair loss in those men with this condition.

Merck has carried out a comprehensive clinical development program to explore the efficacy and safety of finasteride in the treatment of young men with male pattern hair loss. This program encompassed clinical studies which involve more than 3,000 men. The core Phase III program included three large, randomized, double-blind, placebo-controlled clinical trials. Two replicative trials were conducted in men with predominantly vertex hair loss. A third trial was conducted in men with predominantly frontal

hair loss in order to confirm therapeutic efficacy throughout the affected scalp.

Efficacy was determined using four separate end points which measured different aspects of the response to therapy. These included hair counts and visual assessments of improvement and satisfaction by the patients and investigators. An excellent safety profile, specifically in young men with male pattern hair loss, has been accumulated from approximately 3,000 patient/years of experience in our clinical studies. The advisory committee members have received a background package from Merck Research Laboratories that summarizes a large body of information which we believe demonstrates that finasteride 1 milligram is efficacious and safe for the treatment of men with male pattern hair loss.

Following upon this introduction, Dr. Keith Kaufman, leader of our clinical program for Propecia, will next provide you with a comprehensive review of our clinical development program, including the methodologies and results of our most informative studies. Finally, Dr. Elizabeth Stoner will provide concluding remarks. In addition to our speakers, Merck Research Laboratories has brought several consultants to the meeting today. These experts are available to facilitate the advisory committee's discussion

and deliberations. They are listed on the next two slides: Dr. Olson from North Carolina; Dr. Price from California; Dr. Rietschel from Louisiana; Dr. Imperato-McGinley from New York; Dr. Cash from Virginia; Dr. McConnell from Texas; Dr. Overstreet from California and Dr. Roland from California.

At this time, I would like to turn the podium over to Dr. Kaufman.

DR. KAUFMAN: Good morning, ladies and gentlemen, chairman and members of the FDA and the advisory committee. I'm Keith Kaufman, senior director of clinical research in endocrinology and metabolism at Merck Research Laboratories. I was primarily responsible for the majority of the clinical studies to be reviewed today in support of the use of finasteride in the treatment of men with male pattern hair loss.

Today, I would like to share with you our work with our patients with androgenetic alopecia, including the rationale for the use of finasteride in men with this condition. I will review the data from our clinical program with emphasis on the efficacy and safety data from the core Phase III studies as well as present analyses of specific safety issues of relevance.

In discussing a therapy for male pattern hair loss, it is appropriate to review some general aspects of

hair biology. All hair undergoes a process known as cycling. In normal scalp, shown in the upper part of the slide, the hair growth cycle is marked by a long production phase known as anagen followed by a brief transition phase before entering a resting phase known as telogen. Following this resting phase, the hair is shed as a new hair appears in the follicle and begins the cycle again. This hair growth cycle results in the slow turnover of thick, visible terminal hairs.

In balding scalp, in men with male pattern hair loss, there is shortening of the length of the production phase of the hair growth cycle. This shortened production phase results in the appearance of thinner, shorter, lighter and less-pigmented hairs. Because the length of the resting phase is unchanged, the overall hair growth cycle is shortened, leading to a higher turnover of smaller, lighter hairs. This shortening of the hair growth cycle characteristic of male pattern hair loss leads to the loss of hair that patients complain of. This is due to replacement of cosmetically-important visible terminal hairs by small, thin, light miniaturized hairs. The progressive loss of visible hair results in what patients perceive as thinning.

The high turnover of hairs due to the short cycle

results in what patients may perceive as increased shedding. Over time, areas of the scalp become covered with miniaturized hairs, resulting in baldness.

A key to the understanding of the pathogenesis of male pattern hair loss came from the observations of James Hamilton, the anatomist, over 50 years ago. Hamilton noted that men who lack testicular hormones did not develop male pattern baldness; administration of testosterone to these men easily produced a classic pattern of scalp hair loss. Thus, based on Hamilton's observations, androgens were established as a causative factor in the development of male pattern hair loss.

Some 30 years later, Dr. Juliana Imperato-McGinley, whom we are pleased to have with us today, and others identified patients with a genetic deficiency of the enzyme steroid 5-alpha-Reductase, which catalyzes the conversion of testosterone to dihydrotestosterone. Males with genetic deficiency of 5-alpha-Reductase were born with ambiguous genitalia which virilizes at puberty. As adults, these men have a grossly underdeveloped prostate but are otherwise healthy with normal male libido and bone and muscle mass and sparse facial and body hair. Most importantly for today's presentation, these men appear to be protected against the development of male pattern hair loss.

The observation in these men with 5-alpha-Reductase deficiency, as well as other investigations, have resulted in the identification of distinct physiological roles for testosterone compared with those for dihydrotestosterone. Testosterone, the principal androgen in man, is necessary for normal spermatogenesis, bone and muscle mass and male libido and potency. Dihydrotestosterone, or DHT, does not appear to have any essential physiological role in the adult male but is involved in the production of beard and body hair, enlargement of the prostate with age and development of male pattern baldness.

Thus, DHT was established as a causative factor in male pattern hair loss as the specific androgen. This suggested that one would be able to treat this condition by reducing DHT by pharmacological means. Recently, two distinct forms or isoenzymes of 5-alpha-Reductase have been identified. Type II 5-alpha-Reductase, shown on the right side of this slide, the enzyme affected in patients with genetic deficiency is, as expected, found in the prostate gland as well as in beard and chest skin. More recently, immunohistochemical localization studies have identified Type II 5-alpha-Reductase within scalp hair follicles.

Type I 5-alpha-Reductase, shown on the left, is

prominent in sebaceous glands and may play a role in the pathogenesis of acne. Both enzymes are present in the liver, contributing to the pool of circulating DHT.

The hair follicle may respond to DHT from both local production and from circulating levels. In the hair follicle, the presence of Type II 5-alpha-Reductase allows for local conversion of testosterone to DHT. Because of the rich capillary beds feeding hair follicles in the scalp, circulating levels of DHT are also likely to play an important role in the pathogenesis of male pattern hair loss.

In summary, the rationale for the current clinical development program is based on the following: the androgen basis of male pattern hair loss is clearly established; genetic Type II 5-alpha-Reductase deficiency implicated the specific androgen DHT in pathogenesis, and the Type II 5-alpha-Reductase enzyme has been localized directly to hair follicles.

This led to the hypothesis that targeted inhibition of Type II 5-alpha-Reductase, which will inhibit the production of DHT, offers the potential to treat an important causative factor in male pattern hair loss. Decreasing DHT offers the potential to improve hair growth and prevent the continued miniaturization of scalp hair,

thus reducing the balding process.

Finasteride was a logical choice as a potential therapy for men with androgenetic alopecia. This was based on its being a highly specific Type II 5-alpha-Reductase inhibitor. Finasteride is not an anti-androgen, and it has no affinity for the androgen receptor. Thus, it does not block the beneficial and necessary physiological roles of testosterone when administered to men. Finasteride has also demonstrated efficacy in another DHT-mediated disorder, benign prostatic hyperplasia, and finasteride has an established excellent safety profile in men based on the extensive clinical trial and marketed use of the 5 milligram dose for the treatment of symptomatic benign prostatic hyperplasia, making it appropriate for use in this new cosmetic indication in men.

Based on the strong rationale for the use of finasteride, the Phase II program was initiated in men with male pattern hair loss. These initial Phase II studies demonstrated improvement in scalp hair associated with suppression of scalp DHT with finasteride treatment and established the optimal dose of 1 milligram per day in dose ranging studies up to 1 year. The Phase III studies which followed were designed to definitively establish the safety and efficacy of finasteride at the 1 milligram daily dose,

and these Phase III trials were additionally supported by specialized safety studies.

The predefined hypotheses for the Phase III program were that treatment with finasteride, 1 milligram per day, will improve hair growth in all areas of the scalp affected as assessed by a quantitative increase in hair density and by clinical improvements by three specific measures; that treatment would prevent further hair loss in men with androgenetic alopecia and that treatment would be safe and well-tolerated.

The Phase III program consisted of three randomized placebo-controlled studies in men 18 to 41 years of age, all with a diagnosis of androgenetic alopecia. This included the U.S. and international pivotal studies, protocols 087 and 089, which were replicate trials in men with predominantly vertex hair loss and the frontal study which enrolled men with predominantly frontal hair loss.

The modified Norwood-Hamilton classification scale of hair loss patterns is displayed on this slide. The entry criteria for the Phase III pivotal and frontal studies were based on this classification system. For the two pivotal studies, men were eligible if they had mild to moderately severe vertex hair loss designated at II vertex, III vertex, IV or V as outlined in this red box. Men were eligible to

enroll in the frontal hair loss study if they had mild to moderate frontal thinning regardless of whether they had vertex hair loss based on the entry criteria in the dashed blue line.

Together, the Phase III pivotal and frontal studies enrolled a population of men with a broad spectrum of hair loss patterns with significant overlap between the studies. The percent of patients in each of the hair loss categories are shown for each of the three Phase III studies. The two pivotal studies enrolled a similar distribution of hair loss patterns with approximately one-third of patients categorized into the most severe pattern or Grade V.

These two pivotal studies, when combined with the frontal study, together incorporated a large number of patients from mild to moderately severe frontal and vertex hair loss with overlap between the different studies consistent with the spectrum of patients seen in clinics seeking treatment.

Baseline demographics for this Phase III patient population are summarized on this slide. Men randomized into the three Phase III studies were primarily caucasian with the proportion of black men in the U.S. pivotal study approaching that of the U.S. population. The average age of

men in these trials was 32, with an average of 5 to 10 years of hair loss prior to study entry.

In the Phase III studies, a comprehensive set of four predefined efficacy endpoints were used to measure response to therapy. These included scalp hair counts and global photographic assessment which were based on photographic methods and investigator clinical assessment and patient self-assessment of changes in scalp hair growth.

I will now present the one-year results from the two Phase III pivotal studies in men with predominantly vertex hair loss for each of the four efficacy endpoints. A typical patient from the pivotal studies is shown in this photograph with the anterior portion of the head in the upward part of the slide. In the pivotal studies, hair counts were obtained in a representative area of active hair loss at the anterior leading edge of the vertex thinning area. The center of this hair count area was tattooed at baseline, as in this patient, to ensure accurate relocalization of this area of scalp at each followup measurement.

After identification and tattooing of the center of the hair count target area, a one-inch diameter circle of hair was clipped short, as shown in the left panel. This clipped area was then photographed, shown in the middle

panel, using the tattoo as center with a preset macro camera system. Enlarged macro photographs, shown on the right, were then reviewed at the central photography center for technical quality.

At the end of the study, all hair count macro photographs were converted into dot maps of each visible hair by trained technicians validated for precision who were blinded to patient treatment group and time sequence. Hair counts were obtained from these dot maps using computer-assisted imaging technology.

These are two sample macro photographs representing the low and high ends of the range of hair counts observed in the Phase III clinical trials demonstrating the wide quantitative sensitivity of this photographic method of counting hairs. The number of hairs in each of these macro photographs is shown underneath.

This pair of macro photographs is from an individual patient taken at baseline on the left and followup on the right. For every patient, analysis of change and hair count was determined at each followup time point compared to baseline, and mean changes were determined for each treatment group. Differences between treatment groups and hair count are demonstrated for the U.S. pivotal study in the left panel and for the international pivotal

study in the right panel. The Y axis shows the mean change from baseline and the number of hairs in the representative one-inch diameter circular area, while the X axis shows the time course.

The data clearly demonstrate the superiority of treatment with finasteride over placebo. In each study, there was a significant increase from baseline for finasteride at month 6 with further improvement at month 12, while there was a significant loss of hair in the placebo group in each study. The net improvement in hair count in the one-inch diameter circular area for finasteride patients at the end of the 12-month study was 106 hairs in the U.S. study and 107 hairs in the international study, compared to placebo.

An alternative way of viewing these hair count data is by displaying the individual hair counts at baseline, shown in the purple dots and at month 12, shown in yellow, for all patients. On the left are the actual baseline and month 12 hair counts for all finasteride patients with the hair count shown on the Y axis. On the right are similar data for placebo patients. In the left panel, the data demonstrate that increases in hair count are observed in the majority of patients on finasteride, and this response is seen regardless of baseline hair count. In

the right panel, the majority of patients on placebo are noted to lose hair, with the month 12 value below the purple baseline, consistent with the natural history of male pattern hair loss. Overall, finasteride treatment resulted in a marked shift in the proportion of patients who lost hair compared to baseline based on the hair count measure.

In summary, finasteride increased hair count in each of the Phase III studies at 6 months with further improvement at one year. Patients treated with placebo had a decrease in hair count, and a significantly greater proportion of patients on placebo than finasteride lost hair based on the hair count.

Hair counts describe quantitative changes in hair density in a defined area. In order to quantitatively describe changes in hair growth at a more global level, we developed a method of assessing patients' scalp hair using standardized clinical photographs. These global clinical photographs were reviewed by an expert panel of dermatologists experienced in the evaluation of scalp hair blinded to treatment group using a standardized seven point rating scale shown on this slide from greatly decreased to greatly increased hair growth centered at no change.

Prior to the taking of these global clinical photographs, patients were placed in a stereotactic

positioning device with hair combed in a consistent manner, as shown on the left panel. Standardized photographs were taken with preset camera systems using fixed focus lighting and image size to ensure reproducability of this technique over time.

Each expert panel member independently reviewed paired baseline and followup global photographs for each patient, as shown as an example on this slide, under controlled conditions in random sequence blinded to treatment group. The percent of patients in each treatment group rated by the expert panel in each category on the standardized seven-point scale is shown on this graph for the combined pivotal studies. The results of the individual pivotal studies are similar. At month 12, 48 percent of patients on finasteride, shown in the yellow, were rated as slightly, moderately or greatly improved, compared with only 7 percent of patients on placebo. The overwhelming majority of placebo patients, 93 percent, were rated as unchanged or worsened, consistent with the natural history of male pattern hair loss, while only 1 percent of finasteride patients were rated as worsened. This shift in the distribution was highly statistically significant in favor of finasteride.

I would like to now show you representative

photographs of patients in each treatment group rated by the expert panel in each of these categories. For each of these comparisons, the baseline global photograph will be on the left, and the one-year followup photograph will be on the right. This is a patient treated with placebo for one year who was rated as having a moderate decrease in hair growth at the end of the one-year study.

This is another placebo patient, again, baseline on the left; the one-year followup photograph on the right, rated as having a slight decrease in hair growth by the expert panel. The next group of patients will all be patients treated with finasteride for one year. This is a patient rated as having no improvement by the expert panel at the end of one year based on global photographs. This is a second patient, again rated as no change in hair growth at the end of one year and a third patient with a broader area of hair loss rated by the panel as having no change at the end of one year.

The next series will be patients rated with a slight improvement by the expert panel, again, treated with finasteride for one year. This first patient is rated with a slight increase in hair growth. The second patient, with a somewhat different hair loss pattern, rated with slight improvement at the end of one year and a third patient with

a somewhat broader hair loss pattern at baseline rated as slightly improved at the end of one year. I think in addition to the hair that is apparent has improved in the center of this vertex area, this patient also exhibits some efficacy in the frontal area with some additional density compared to the baseline photograph.

This is a black patient from the U.S. pivotal trial rated as being slightly improved at the end of one year of finasteride therapy.

The next series will be patients rated as moderately improved by the expert panel. This first patient demonstrates significant cosmetic benefit at the end of one year of finasteride therapy; a second patient with blonde hair also demonstrating a moderate improvement at the end of one year of finasteride therapy; and a third patient, again, with a somewhat broader hair loss pattern at baseline, rated as moderately improved by the panel.

The next series will be patients rated as greatly improved by the expert panel. The first patient here, filling in in the vertex area after one year; a second example; and a third patient, again, with a broader area of hair loss at baseline rated as greatly improved at the end of one year by the expert panel. This same patient will be shown on the next slide using an alternate view that focuses

on changes occurring in the frontal scalp. Now, anterior is down; posterior is at the top of the slide. In this slide, the previous patient has been photographed using a superior frontal view with hair recombed in the center part to demonstrate the change observed in the frontal area between baseline and one year of therapy with finasteride.

In summary, global photographic assessment is a precise technique for evaluating cosmetic change in scalp hair. This technique demonstrates a superiority of finasteride over placebo to improve hair growth; provides a visual demonstration of clinical gain or loss and has a minimal placebo effect.

Investigators participating in the pivotal trials evaluated overall changes in patient scalp hair at each clinic visit using the same standardized seven-point rating scale used for the global photographic assessment. The results of the investigator's assessment of patient scalp hair from the combined pivotal studies is shown on this graph. Again, the data are highly statistically significant for the shift in distribution in favor of finasteride. By this assessment, two-thirds of finasteride patients, shown in the yellow, were rated as improved by the investigators compared with approximately one-third of placebo patients.

In summary, the investigator clinical assessment

also demonstrates the superiority of finasteride over placebo to improve hair growth and has a larger placebo effect than seen with global photography.

Because male pattern hair loss is a cosmetic condition, patient self-assessment is critical to interpreting the clinical relevance of the improvement in hair counts from the patient's perspective. Patient assessment was by a self-administered validated hair growth questionnaire that consisted of seven questions assessing change from baseline. These included four questions on treatment efficacy and three questions on patient satisfaction with the appearance of their scalp hair.

The results of analysis of the patient questionnaire at month 12 are shown for each of the Phase III pivotal studies. For each of the seven questions, the response scale is shown in the parentheses next to the question, and the mean score is shown for each treatment group in each of the two pivotal studies, U.S. and international. For each question at month 12, the data significantly favor finasteride over placebo, and the results are remarkably similar between the two studies. For five of these seven questions, clinical worsening is demonstrated for the placebo group as well in each of the two studies.

A more intuitive way of viewing these data is to examine the percent of patients in each treatment group who reported improvement for each of the seven questions. For each of the four questions related to treatment efficacy, size of the bald spot getting smaller, improvement in the appearance of hair, increase in the growth of hair and efficacy in slowing down hair loss, the data significantly favor finasteride over placebo. At month 12, nearly 70 percent of finasteride patients reported that treatment was effective in slowing down their hair loss, and over one-half reported that the growth and appearance of their hair had improved.

For each of the questions related to patient satisfaction with the appearance of their hair, including satisfaction with the appearance of the frontal hair line, satisfaction with the appearance of the hair on top and satisfaction with the appearance of hair overall, the data again significantly favor finasteride over placebo therapy. By month 12, nearly 40 percent of men on finasteride indicated that they were satisfied with the appearance of their hair overall.

In summary, patient self-assessment demonstrates significant improvement for patients on finasteride for each question in each of the Phase III pivotal studies.

The results of the Phase III pivotal studies at the end of the first year demonstrate consistent results in determining efficacy of finasteride compared to placebo in each of the four predefined measures. The increases observed in hair count led to clinical improvement by three separate measures, and treatment with placebo led to significant loss of hair.

Now, these one-year pivotal studies in men with predominantly vertex hair loss were extended for an additional year as double-blind placebo-controlled studies. The objective of these extension studies was to demonstrate the effects of now 2 years treatment with finasteride, compared with 2 years of treatment with placebo and to demonstrate the effects of withdrawal of therapy with finasteride after one year. The extension studies utilized the identical efficacy measures as used in the first year.

The design of these extension studies is shown on this first slide. Most patients originally randomized to finasteride at the beginning of the initial one-year studies were continued on active therapy for an additional year, referred to as the one-milligram/one-milligram group. This was to assess the maintenance of efficacy of continued finasteride therapy out to 2 years. A small percentage of patients originally randomized to finasteride were switched

to therapy with placebo to assess the effect of withdrawal of therapy, referred to as the one-milligram/placebo group.

The majority of patients originally randomized to placebo were switched to therapy with finasteride in the second year, referred to as the placebo/one-milligram group, to assess reversal of ongoing hair loss after switch to active therapy, and a small percent of the placebo patients originally randomized were continued on placebo therapy to observe the natural history of male pattern hair loss, referred to as the placebo/placebo group.

The four treatment groups just described are shown for the change in hair counts from baseline out to month 24 on this graph. Patients continued on finasteride out to 2 years, the one-milligram/one-milligram group, maintained the improvement in hair counts observed at month 12 while patients on continuous placebo therapy continued to lose hair throughout the 2-year period. Patients who were switched from finasteride to placebo lost the beneficial effect of finasteride seen at month 12 within a year's time while patients switched from placebo to active therapy demonstrated reversal of the hair loss mentioned in the first year.

For patient self assessment at the 2 year time point, patients on finasteride continued to improve compared

to the results at month 12, while patients on placebo continued to worsen.

Global photographic assessment at the 2-year time point demonstrated significant further improvement for patients on finasteride and significant further clinical worsening for patients on placebo. At month 24, two-thirds of finasteride patients were rated by the expert panel as improved compared to approximately half at month 12, and one-third of placebo patients were now rated as clinically worsened, compared to 12 percent at month 12.

I would now like to show you examples of the progression of changes in scalp hair in patients as assessed by global photography between the first and second year. In each of these examples, the expert panel reviewed only the paired baseline and followup photographs at either the year one or year two time point and did not actually rate all three at the same time, but I am displaying these in sequence for illustrative purposes. This is a patient on placebo who progressed from having a slight decrease in hair growth at the end of the first year based on the expert panel review to having a moderate decrease in hair growth at the end of year two.

This is a patient on placebo who was rated as having no change in the first year and in the second year

progresses to a slight decrease in hair growth.

The following will be patients treated with finasteride for 2 years continuously. This patient was rated as having no change in hair growth at the end of the first year of finasteride therapy and then progresses and improves to a rating of slightly improved at the end of the second year. Another example of a patient originally in the first year rated with no change in hair growth; with continued finasteride therapy, rated as slightly improved at the end of the second year.

This is a patient rated with slight improvement at the end of the first year of finasteride therapy who progresses to a rating of moderate improvement at the end of the second year.

A second patient rated with slight improvement at the end of the first year who progresses to moderate improvement at the end of the second year. This patient was rated as moderately improved at the end of the first year and progresses to great improvement at the end of the second year. A second patient rated moderately improved at the end of the first year progressing to great improvement at the end of the second year. The next two patients will be patients who are rated as greatly improved at the end of the first year, which is at the end of the positive response

scale and, therefore, great improvement is the highest rating that can be obtained in the second year as well. I'm showing these to demonstrate the maintenance of the improvement seen in the first year out to the second year.

To summarize the efficacy of finasteride at the end of the second year from the extension study data, maintenance of efficacy was clearly demonstrated between the first and the second year in all predefined efficacy measures. Significant further clinical improvement was observed by global photographic assessment in the second year compared to the data at year one. Treatment with placebo led to progressive hair loss for patients continued on that therapy for 2 years based on continuing decline in hair count and continued clinical worsening by global photographic assessment.

A further objective of the Phase III studies was to confirm that treatment with finasteride prevented further hair loss in men with a diagnosis of androgenetic alopecia. The ability of finasteride to prevent further hair loss in these patients was demonstrated by a number of clinical observations from the studies that I've just described to you. Finasteride was superior to placebo in slowing down hair loss based on this question in the patient self-assessment questionnaire. Finasteride prevented the hair

loss seen in hair counts in the parallel placebo groups in each of the two pivotal studies.

Finasteride reversed the hair loss seen in hair counts in the placebo group, which was switched to active therapy in the second year, and additionally, there is histological evidence of the reversal of the balding process from scalp biopsies in patients in the trial.

Scalp biopsies were obtained in a cohort of men in the U.S. Phase III pivotal study. Four-millimeter diameter punch biopsies were taken adjacent to the hair count area at baseline and at study end one year. Biopsies were sectioned horizontally and read blinded for the determination of terminal and miniaturized hairs. These data demonstrate that finasteride effectively reversed the otherwise ongoing miniaturization process characteristic of androgenetic alopecia. This is demonstrated by an increase in the number of terminal hairs between baseline and month 12 in finasteride patients and a decrease in the number of miniaturized hairs in these patients, while placebo patients had no significant change.

So, to summarize in this schematic, the effect of finasteride on scalp hair follicles can be described in the following manner: by blocking the conversion of testosterone to dihydrotestosterone, finasteride is able to

treat male pattern hair loss by recruiting short, fine, hypopigmented miniaturized hairs to become long, thick, pigmented, terminal hairs as evidenced by the increases seen in hair counts, the improvements that patients and investigators observe and by the changes easily observed in the clinical global photographs.

At the same time, inhibition of DHT formation achieves prevention of the ongoing miniaturization process such that long, thick, pigmented, terminal hairs in androgen-sensitive regions no longer are acted upon by DHT to become miniaturized but are preserved in patients on continuous therapy.

I will now review the results of the third Phase III study, the frontal hair loss study. This study was similar in design to the pivotal studies in men with predominantly vertex hair loss except that hair counts were obtained in a one-centimeter squared circular area in the frontal scalp instead of the one-inch diameter circular area of the vertex scalp, as in the pivotal studies. Additionally, global photographic assessment was based on the superior frontal view as opposed to the vertex view.

For patients in the frontal study, hair counts were obtained in a representative area of the frontal thinning scalp. As in the pivotal studies, the center of

this target area was tattooed at baseline to ensure accurate relocalization of the same area at followup visits. The hair count macro photograph shown on the slide used in the frontal study used a smaller, one-centimeter squared, template which is approximately one-fifth the area of the one-inch diameter circle used in the pivotal studies. This smaller hair count area was chosen for the frontal study for patient acceptability.

The mean changes for hair count in the smaller, one-centimeter squared circle in the frontal area are shown on this graph. Treatment with finasteride resulted in a significant increase in hair at both months 6 and 12, while treatment with placebo resulted in loss of hair. The net improvement for finasteride patients at the 12-month time point was 12 hairs in the one-centimeter squared circle, which, for comparison to the vertex studies, can be multiplied by five for an approximate equivalent net increase of 60 hairs compared to placebo.

The results of the patient self assessment from the frontal hair loss study at month 12 are shown on this slide. These data demonstrate significantly greater efficacy for finasteride over placebo for each question, and these results are similar to the results seen in the two pivotal studies at the same time point.

In the frontal hair loss study, global photographic assessment was done using a superior frontal view to image the area of frontal thinning. As in the pivotal studies, patients were placed in a stereotactic device for consistent positioning as shown on the left, and baseline and post-treatment global photographs were reviewed by a separate expert panel. As with the pivotal studies, I would like to show you a few examples of representative patient photographs illustrating the changes seen in global photography for patients in this study. This is a patient on placebo; baseline on the left; one-year photograph on the right who is rated with a slight decrease in hair growth by the expert panel.

This is a patient on finasteride rated as having no change at the end of one year. This is a patient on finasteride who was rated as having a slight improvement based on this superior frontal view at the end of one year by the expert panel; a second patient rated as slightly improved by the expert panel at the end of the year of finasteride therapy; and a patient rated as moderately improved by the expert panel after one year of finasteride therapy.

To summarize the efficacy results from the overall Phase III program, all primary and secondary endpoints were

highly positive in favor of finasteride in each of the three studies. Efficacy was demonstrated in both vertex and frontal scalp. The 2-year data from the placebo controlled extension studies demonstrated maintenance of the improvements in hair counts seen in the first year and further clinical improvement by global photographic assessment. The significant further clinical improvement in global photographic assessment in the second year, while hair count was not changing, supports that continued treatment with finasteride resulted in improvement in the quality of hair.

Treatment with finasteride, a specific Type II 5-alpha-Reductase inhibitor, increased hair growth in both vertex and frontal scalp, prevented further hair loss in balding men and interrupted the progression of the balding process. These results confirm the central role of DHT in the pathophysiology of male pattern hair loss in men.

I will now review the safety data supporting the use of finasteride in men with male pattern hair loss from the same clinical trials. Safety data supporting the current development program derived from evaluation of over 3,200 men with nearly 3,000 patient-years of exposure to finasteride at a dose of one milligram per day or greater. In addition to general clinical and laboratory evaluations,

specific studies were conducted as part of the clinical development program to evaluate potential pharmacological effects of finasteride in this young patient population. The safety profile of finasteride is also supported by the extensive experience from long-term clinical trials and over 5 years' marketed experience with finasteride 5 milligrams in older men with benign prostatic hyperplasia.

The average duration of exposure for the 1,879 men participating in the three one-year Phase III studies was just under one year. The overall clinical adverse experience summary for the three Phase III studies is listed on this table. For each treatment group, approximately equal numbers of patients reported an adverse experience. Drug-related adverse events were reported by 7 percent of patients on placebo and 7.7 percent of patients on finasteride. Serious adverse events were reported in approximately 2 percent of patients in each treatment group. One death was reported in a patient in the finasteride group due to trauma. The discontinuation rate due to an adverse event was low and balanced between the treatment groups.

Only three drug-related clinical adverse experiences were reported by at least 1 percent of men in either treatment group in these Phase III studies. These were decreased libido, erectile dysfunction and ejaculation

disorder. The majority of men reporting ejaculation disorder actually reported decreases in ejaculate volume. Each of these three adverse events occurred in under 2 percent of men, but they were slightly more frequent on finasteride than on placebo.

3.8 percent of finasteride patients versus 2.1 percent of placebo patients reported any sexually-related adverse experience, and this achieved statistical significance. In approximately one-third of these patients, these adverse events resulted in discontinuation from the study.

We attempted to obtain followup on all patients reporting sexually-related adverse experiences. Of the 36 patients on finasteride reporting these adverse experiences, 21 reported resolution of the adverse event while continuing finasteride therapy. Seven reported resolution following discontinuation from the study, and seven had persistence of the adverse event while continuing in the study on finasteride therapy. The pattern for patients on placebo was essentially similar, with most patients resolving either on or off drug, four patients reported persistence of the adverse event while remaining on placebo therapy.

To further explore the impact of this low incidence of sexually-related adverse experiences, all

patients completed a validated sexual function questionnaire. This consisted of four domains: sexual interest, erections, ejaculation and perception of problems and a global question regarding the patient's overall satisfaction with their sex life, as shown on the left side of this graph. The results for all patients at month 12 are shown on the left and for those reporting sexually-related adverse events in the trials, the changes are shown on the right-hand panel.

For the all patients analysis, as shown on the left, the results at month 12 demonstrate that finasteride produced slight but significant movement on the response scale for some of these domains. However, these small changes were not associated with any differences between treatment groups in the patients' overall satisfaction with their sex life. Moreover, these small changes were five to tenfold smaller than the changes seen for patients who reported sexual adverse experiences.

In summary, sexually-related clinical adverse experiences occurred at a low incidence, slightly more often for finasteride than placebo patients. These side effects resolved in men who discontinued therapy and in many who continued treatment with finasteride. Analysis of the validated sexual function questionnaire demonstrated that

overall patient satisfaction with their sex life is not affected by finasteride therapy.

As part of the clinical development program, we conducted an extensive analysis of the hormonal effects of finasteride one milligram in this patient population. As anticipated, finasteride markedly reduced scalp and serum dihydrotestosterone. Circulating testosterone was maintained with a small increase from baseline that remained within the normal range, and these changes in DHT and testosterone had no effect on the pituitary gonadotropins LH and FSH. A small increase in serum estradiol was also observed which was similar to and correlated with the increase seen in serum testosterone.

These parallel small increases in serum testosterone and estradiol resulted in no alteration in the ratio of testosterone to estradiol in treated subjects. Lastly, finasteride 1 milligram did not alter serum prolactin levels from baseline.

Based on the hormonal pattern observed as well as data from the postmarketing experience in older patients with finasteride 5 milligrams, we carefully evaluated any reports of adverse experiences related to the breast. In Phase III, there were four such reports related to the breast in each of the two treatment groups for an equal

incidence of 0.4 percent. For all four patients on finasteride, resolution of these adverse experiences related to the breast occurred while they remained on finasteride.

As outlined in your background package, a specific safety study in 181 normal male volunteers was conducted to evaluate other potential effects of finasteride in men in this age group. The data from this study demonstrated that finasteride, 1 milligram per day for 48 weeks, produced an anticipated but small decrease in prostate volume and serum PSA.

To assess for any subtle effects of finasteride 1 milligram on male fertility, a cohort of 79 men underwent standardized, quality controlled semen analyses at baseline and every 24 weeks. After 48 weeks of treatment or four complete spermatogenic cycles, no effects on semen production or spermatogenesis were observed for any of the standardized semen analysis parameters. In a separate cohort of 82 men, treatment with finasteride resulted in no deleterious effects on bone, based on measurements of both bone mineral density and markers of bone turnover. Lastly, finasteride treatment had no effect on the fasting lipid profile.

To summarize the safety profile of finasteride 1 milligram in men with male pattern hair loss, finasteride

was very well tolerated by men in these trials. Discontinuation rate was under 2 percent for drug-related adverse experiences. A small number of men experienced a drug-related sexual adverse experience, less than 4 percent on finasteride and roughly 2 percent on placebo. These adverse experiences often resolved with continued therapy and resolve in men who discontinue therapy with drug. No evidence of an increase in adverse experiences has been observed in continued surveillance in our longer-term extension studies.

To conclude, the goal of therapy for men with male pattern hair loss is to improve the appearance of scalp hair and prevent the continued loss of hair. Finasteride treatment leads to significant increases in hair count and clinical improvements confirmed by patients, investigators and by an expert panel of dermatologists reviewing patient photographs. The durability of these effects are demonstrated in 2-year double-blind and 3-year open extension studies, and the excellent safety profile demonstrated makes the drug appropriate for its intended use.

Finasteride 1 milligram offers a new, safe therapeutic modality for the treatment of men with male pattern hair loss. Thank you.

DR. MCGUIRE: Let's have the lights, please.

Dr. Kaufman, I would like to have questions from the advisory committee now, and if we can postpone the next presentation for just a few minutes.

Does anyone from the committee have questions?

Dr. Parker?

DR. PARKER: I was wondering if--I realize you've looked at a number of different parameters, but in some of those pictures, does it matter what the hair color of the patient might be or recent haircuts or how they do their hair or things of that sort?

DR. KAUFMAN: The question has to do with the review of the photographs particularly and whether the patient's haircutting, hairstyling might have an influence. As part of a requirement for enrollment in the studies, patients were instructed to maintain the same hairstyle throughout the study and to avoid a crew cut or anything else that would adversely impact on photographic assessments. In general, patients were not specifically instructed as to when to have their hair cut, but this would apply to each of the two treatment groups equally. The issue of hair color, it's worth pointing out that in the global photographs that I've shown you today, the cameras are automated such that the hair color in general will look

darker for a patient with lighter hair and will look lighter for a patient with darker hair based on automated exposure.

We do have examples of patients, clearly, who have blonde hair and red hair as well as black hair or brown hair, but the overwhelming majority of patients did have dark hair. There is no evidence that the hair color had an impact on the efficacy, as rated by global photography.

DR. MCGUIRE: Dr. Kilpatrick?

DR. KILPATRICK: I'd still like to stay with the photographs. With regard to the frontal hair loss photographs, I think I'm correct in saying that you showed us one photograph of a placebo-treated patient. Can you tell us again what the conclusion was after--was that after 12 months?

DR. KAUFMAN: Yes, that was after 12 months.

DR. KILPATRICK: What was the conclusion?

DR. KAUFMAN: A slight decrease in hair growth in that patient from the frontal hair loss study.

DR. KILPATRICK: Were there any instances in that study of patients under placebo who showed no change or an increase in hair?

DR. KAUFMAN: Yes; the majority of placebo patients in both the frontal hair loss study as well as in the pivotal vertex studies were rated with no change at the

end of a year, consistent with the slow progression of hair loss in patients with androgenetic alopecia.

DR. KILPATRICK: Can you put a figure on that percentage?

DR. KAUFMAN: For patients in the vertex studies, 85 percent of placebo patients were rated as unchanged at the end of the first year of therapy.

DR. KILPATRICK: For patients in the frontal hair loss?

VOICE: Eighty-five percent of the placebo subjects were unchanged.

DR. KAUFMAN: It's the same number. Eighty-five percent of patients in the frontal hair loss study on placebo were rated as unchanged at the end of one year by the global photographic panel.

DR. KILPATRICK: As I've indicated before, I'm not a clinician, so, I would like to ask perhaps one of your consultants about the natural history of this type of hair loss. It seems to be an implicit assumption that there is a continuous progression of hair loss. Is this true, or is there a cycle? Is it a change, or do people, as I'm manifesting myself at my advanced age, losing hair progressively?

DR. KAUFMAN: If I could respond to that

initially, I think it's fair to say there is a fair amount of biological variability as far as hair loss is concerned, and the rate of progression in individual patients, of course, can be very variable. I think on average, as demonstrated from the clinical trials, that rate of progression is fairly slow, as evidenced both by the amount of hair loss seen in the placebo group at the end of one and two years, roughly 20 to 30 hairs in the vertex area lost per year and by the large percentage of patients rated as unchanged at the end of a year by the global photographic panel.

However, the 2-year data do demonstrate the further progression such that the changes seen at 2 years would be expected in placebo patients to demonstrate further worsening, meaning that patients would be rated as worsened by the global panel more frequently in the second year than in the first.

DR. KILPATRICK: Thank you, sir.

DR. MCGUIRE: Dr. Tschen?

DR. TSCHEN: I'd like to know what was the minimal and then the average time to start seeing response, and this is mainly if I'm going to prescribe this, how long will I need to prescribe it to start seeing some improvement or changes?

DR. KAUFMAN: In your background package, we provided the time course for most of the endpoints such that even as early as 3 months, patients, for instance, and investigators were able to observe significant improvement for finasteride patients compared with placebo patients. So, both the patients themselves can see improvement within 3 and 6 months, and the investigators and the global photographic assessments also were positive as well as the hair counts at 6 months. So, I think in general, 3 months or more, based on the clinical trial data, is a reasonable estimate in terms of the length of time that patients would be expected to continue treatment before anticipating either the prevention of further hair loss or the improvement in hair growth.

DR. MCGUIRE: Dr. Lim?

DR. LIM: Dr. Kaufman, I have two questions. The first one: are there any biochemical markers that would be able to predict the response among patients who are going to respond or among patients who are not going to respond? The second question is in terms of the number of patients who completed the study. You have mentioned about 3,200 patients to start. How many patients actually completed the entire study?

DR. KAUFMAN: The first question--excuse me; could

you repeat the first question?

DR. LIM: Any biochemical markers.

DR. KAUFMAN: Oh, yes, the first question had to do with biochemical markers that might predict which patients would have a better response than others. We've actually looked at this very carefully, mainly looking at any baseline and followup hormonal parameters that might dictate which patients respond better than others, and we have not been able to identify anything in the serum.

We have also looked at baseline demographic data to try to identify which patients may or may not respond better, and based on those subgroup analyses, it's fairly clear that patients, regardless of their baseline hair count, whether it's low or high, regardless of their hair loss pattern, whether it's mild or severe, and regardless of their age or the number of years that they have been losing hair, all of those subgroups clearly respond compared to therapy with placebo.

In response to your second question, which was--

DR. TSCHEN: How many patients did the--

DR. KAUFMAN: Oh, how many patients completed the trials. In the Phase III trials, the 1,879 men, roughly 85 percent of the patients completed the one-year studies.

DR. TSCHEN: Those who did not complete, what was

the reason for them not completing?

DR. KAUFMAN: The major reason why patients didn't complete the study was lost to followup. They did not return to the clinic at the appropriate visit time, and they were never able to be identified in terms of the specific reasons why they discontinued from the trial, and they are listed as lost to followup.

DR. MCGUIRE: Mrs. Cohen?

MS. COHEN: I have really kind of several questions. Why were not Asians and Hispanics included in your study?

DR. KAUFMAN: Excuse me; the question was why weren't Asians and Hispanics included in the study.

MS. COHEN: Yes.

DR. KAUFMAN: They were included in the study.

MS. COHEN: But you only showed two examples.

DR. KAUFMAN: Yes; that is correct. The percentage of patients in each of the other ethnic subcategories was relatively modest, as you can imagine, based on the percentage of patients who were caucasian. We, of course, did not restrict entry based on any ethnic criteria. The percentage of patients in other ethnic groups besides caucasians and blacks, was on the order of 5 percent for any individual group, and those data were provided in

the clinical study reports that were given to the agency in terms of the breakdown for Hispanics and Asians and then a group just referred to as other.

MS. COHEN: Did you do--since some heart medication does lower libidos, were any of these in your trial taking other medications? And what happened?

DR. KAUFMAN: There were concomitant medications in use in some of these patients who reported sexual adverse experiences, but based on the case report form data given to us, the data that I have shown you is for those that were considered related to the therapy in the study, meaning either finasteride or placebo.

MS. COHEN: But of those examples you showed, were they taking other medications in conjunction with this? Or were they not taking any medication? I guess I'm trying to figure out what your criteria were for choosing the specific people for the study.

DR. KAUFMAN: Oh, as far as entry criteria were concerned, there were a number of medications that patients were excluded from using; obviously, topical minoxadil and a number of agents that might affect hair growth or agents that have specific effects on sexual function, since this would interfere with our ability to review the sexually-related adverse experience profile due to confounding

concomitant medications.

MS. COHEN: Well, that, in itself, is an answer for people who are taking certain kinds of medication. That concerns me because I don't know how much you're going to continue to look at this and what kind of information you will give the consumer.

Also, in one slide you showed, and I'll hold it up--

DR. KAUFMAN: Yes.

MS. COHEN: --how did you decide to draw the line here and the line there?

DR. KAUFMAN: Oh, could I have the first tray, slide number 28?

[Pause.]

DR. KAUFMAN: Mrs. Cohen is asking why we decided to draw the line here. All that's plotted here is in this purple line, which is really a collection of, in this case, 679 baseline values for patients on finasteride and 672 datapoints for patients on placebo. This is just the specific baseline hair count for each of those patients, and we've simply listed them in numerical order just for convenience. I mean, there isn't anything special about the shape of this curve other than the fact that what you can see is that there is a broad and fairly equal distribution

between low and high based on hair counts for patients in the trial, and the average is 876 hairs in the two groups.

MS. COHEN: I have problems with the line, to tell you the truth.

What about genetic predisposition, families where hair thins?

DR. KAUFMAN: The question, I believe, is what about family history of male pattern baldness, and how did that impact on the patients. We, again, looked at that specifically in subgroup analyses both for patients who reported that their primary family members, that is, their parents and siblings, had hair loss as well as their secondary family members, that is, the grandparents, and we did not detect any specific trends in the data with respect to whether patients reported that they had positive or negative family histories.

MS. COHEN: Wouldn't that be beneficial for you to find out exactly what it does do with genetic predisposition in the sample?

DR. KAUFMAN: The question was would it be useful if we knew about the genetic predisposition. I think for the men who have androgenetic alopecia, they already have a genetic predisposition to develop male pattern hair loss, since men, in general, have equal amounts of androgens in

the circulation. They may have an increased sensitivity to the effects of androgens on hair follicles.

MS. COHEN: Thank you very much.

DR. MCGUIRE: Dr. Duvic?

DR. DUVIC: Dr. Kaufman, my question relates to this graph of the hair count and the one-inch diameter circle among crossover patients.

DR. KAUFMAN: Yes.

DR. DUVIC: And in the one-milligram/one-milligram group at 12 months to 24 months, there seems to be a plateau that occurs; yet, you show pictures of patients continuing to approve that's not reflected in the curve that you have drawn. I wonder if you have an explanation for this plateau. You're going to give a drug to people who are going to take it for 20 years. Yet, your data shows no benefit beyond 12 months. If you would comment on that, please.

DR. MCGUIRE: Could we speak from the slide?

DR. KAUFMAN: Sure; it's the second tray; it's slide number 4, yes.

The question has to do with the patients continued on finasteride therapy out to 2 years, and there is maintenance of the increase in hair counts seen at the end of the first year at the second year, and the questioner

referred to it as a plateau. Yet, we see further improvement in global photography between year one and year two, and I think the comment was made that patients may take this for more than one or two years, and yet, they don't have any additional benefit.

I think I would question that last comment about no additional benefit. It's true that the hair counts are essentially the same for the treatment group at 1 year and at 2 years, but the other efficacy measures do demonstrate further clinical improvement, which does suggest that the quality of this newly-grown hair and the quality of the hair on the scalp overall may be continuing to improve between the first and the second year, despite the plateau and the hair count, and recall that the hair count is obtained in a circumscribed but representative area, a one-inch diameter circle on the scalp. The global photography, the patient assessment and the investigator assessment are really evaluating the whole scalp.

So, I think it's fair to say that the other endpoints support that there's additional clinical benefit between the first and the second year with continued therapy, even though the hair count has plateaued between the first and second year.

DR. PARKER: Do the hair biopsies show any

difference between 12 months and 24 months?

DR. KAUFMAN: The question was whether the scalp biopsies show any difference between the first and the second year. Unfortunately, as you may imagine, it was rather difficult to get patients to consent to having biopsies done at baseline at the end of the first year, and we do not have biopsy data in the second year.

DR. MCGUIRE: Dr. Orkin?

DR. ORKIN: Dr. Kaufman, in those that did not continue, the percentage that stopped from the program, what percentage of those were on placebo as compared to the therapy?

DR. KAUFMAN: The question was of the patients who discontinued from the studies, what were the relevant percentages of patients on finasteride and placebo? In the Phase III trials, approximately 15 percent of the patients discontinued, and it was essentially the same, whether they were on finasteride or placebo; in other words, about 15 percent of each treatment group discontinued in the first year of the Phase III trials.

DR. ORKIN: One wonders if, on the placebo, the continuation, if some of them discontinued because of continued hair loss, but perhaps you don't have that information.

DR. KAUFMAN: Actually, we have looked at the difference between patients who at least either dropped out of the study or who elected not to enter the extension study for a second year compared to those patients who did, and with respect to placebo patients, there is a numerical but not statistically significant difference due to the small sample size of the 2-year placebo group--it's about 50 patients--showing that patients who elected not to enter the extension studies did a little bit worse in the first year compared to the second year, but the sample size was too small to draw a statistical conclusion.

DR. MCGUIRE: Ms. Cohen?

MS. COHEN: Would you allow a little levity? This is an article that the Office of Consumer Affairs gave me, and it was in USA Today, and it talks about the medication: the results will show the pill stops hair loss, grows new hair in 86 percent of the men versus 42 percent who took a dummy pill. What is the dummy pill?

DR. KAUFMAN: The dummy pill was placebo, I assume.

MS. COHEN: I thought so, but it struck me very funny.

[Laughter.]

DR. MCGUIRE: Okay; Susan, I expect more from you

than that.

[Laughter.]

MS. COHEN: You're one up on me, Joe.

[Laughter.]

DR. MCGUIRE: I was interested in the global reduction in DHT. Was there any relationship between the nonresponders and the reduction in DHT in those individual patients?

DR. KAUFMAN: We have looked at that early on in our Phase II experience, and we have not found a relationship between the percent reduction in DHT, the baseline level of DHT or testosterone, for that matter, and any of the efficacy variables that holds up.

DR. MCGUIRE: Dr. Mindel?

DR. MINDEL: The drug has an effect on the prostate and the prostate fluid. Is there any evidence of what the effect is on male fertility? You've told all the other hormones and sperm and volume, but the end result, male fertility, has that been looked at?

DR. KAUFMAN: The question has to do with evaluation of male fertility. As I indicated, we've done extensive studies looking at semen analysis, which is a useful marker for looking at any subtle changes that might produce any alterations in male fertility. We obviously

have not done a specific fertility study. I think it's appropriate to say, though, that based on the wealth of animal preclinical data, which demonstrates that there is no effect on fertility in animals treated lifelong with chronic high-dose finasteride, based on the semen studies, as I've indicated, showing no effect of the 1-milligram dose over four spermatogenic cycles and based on the limited data that we have on pregnancies that occurred in the clinical trials, which actually were more frequent for patients on finasteride than on placebo, there is no evidence to support that finasteride would have any effect on male fertility.

DR. MINDEL: I would have thought that it would have been relatively easy to have maybe even just done a questionnaire of the males taking the drug, whether they had tried to produce children, placebo versus nonplacebo and have gotten really a more definitive answer to this.

DR. KAUFMAN: I think that in general, at the initiation of some of these trials, there were still issues that may have prohibited patients from fathering children during the clinical trials due to a previous concern about finasteride appearing in the semen. I think that that would have made it more difficult for us to observe pregnancies in these clinical trials.

I think that the issue, though, is that most of

these men were not deliberately trying to father children during the one or two year course of these clinical trials, and we presumably would hear if there were difficulties such as infertility as adverse experiences if they were thought that they were related to the study drug, and we have not received those reports.

DR. MCGUIRE: I don't recall; I think it's probably in the briefing book, but was sperm motility one of the measurements of the semen analysis?

DR. KAUFMAN: Yes, it was.

DR. MCGUIRE: Dr. Simmons-O'Brien?

DR. SIMMONS-O'BRIEN: Dr. Kaufman, I have two questions: did the patients fill out at baseline a sexual function questionnaire?

DR. KAUFMAN: Yes, they did.

DR. SIMMONS-O'BRIEN: And every time the patients were checked and monitored, did they have to go through a whole point checklist in terms of sexual function at that particular visit?

DR. KAUFMAN: They would fill out the sexual function questionnaire at every visit.

DR. SIMMONS-O'BRIEN: At every visit?

DR. KAUFMAN: Yes.

DR. SIMMONS-O'BRIEN: In any of the groups, was

there a noticeable increase or decrease in their sexual activity over the period that they were on the medication? And did you advise--was there any advice on the men to use condoms?

DR. KAUFMAN: The sexual function questionnaire in the slide that I showed previously did show small but statistically significant changes between the two treatment groups but no effect on the patients' overall satisfaction with their sex life, and the changes that were seen were very small compared to patients who clinically had an adverse event related to sexual function.

I think it's fair to say that there are sporadic reports of patients who actually report increased libido as well as decreased libido on finasteride, and the last part of your question was whether we recommended that patients use condoms. In the Phase III trials, patients were just discontinued if they fathered a child, pending additional animal safety data which confirmed that exposure of women to finasteride through semen was not a risk to the human fetus.

DR. SIMMONS-O'BRIEN: Okay; and I just have one more question. In the breast-related experiences in the Phase III controlled trial, you have increased gynecomastia.

DR. KAUFMAN: Yes.

DR. SIMMONS-O'BRIEN: What was your percentage of

gynecomastia in the Phase II?

DR. KAUFMAN: Yes; could I have the slide which shows the gynecomastia in Phase II and Phase III? This shows all of the reports of breast-related clinical adverse experiences by dose in both Phase III and Phase II, so, the combined experience. As you recall, for the placebo group in the Phase III experience, there were four cases. So, those were shown here. Four of the finasteride 1 milligram cases are shown here from the Phase III experience, and the remainder of these are from the Phase II experience at a variety of doses.

DR. MCGUIRE: Dr. Miler?

DR. MILLER: I have a question about the efficacy frontal versus vertex. It appears that the vertex--it was clearly more efficacious on the vertex if you took hair counts. I think it was 107, and the difference in the frontal area was 59. You have fewer patients with the frontal evaluations, and yet, when patients present, the vast majority present with frontal hair loss, the vertex is a problem but not nearly the problem that the frontal loss is. So, I'd ask you why the difference in response between vertex and frontal and then, why your emphasis on vertex when the frontal is really the area that's more important.

DR. KAUFMAN: The question has to do with the

relative efficacy demonstrated in the frontal hair loss study compared with the efficacy in the vertex studies. I think that the hair count data in the frontal study, as you commented, does show less of an increase from baseline or less of a large treatment effect compared with the vertex studies. But it's worth recalling that the area sampled in the frontal hair loss study is within the frontal thinning area. It is not at the anterior leading edge of active hair loss, as in the vertex study. So, there may be a sampling bias related to those two studies that impacts on the change from baseline and hair counts.

In addition, the actual baseline hair count in the frontal hair loss study was greater than it was in the vertex studies, and the data do support that the lower the hair count at baseline, the higher the increase from baseline. Now, an additional point is that we did evaluate the frontal area in all patients in the vertex pivotal study. So, all 1,553 patients participating in the pivotal vertex studies also had photographs of their scalp taken using that superior frontal view that was used, and in that analysis, using the same expert panel that reviewed vertex photographs, the efficacy in the frontal area was essentially the same in the 1,553 vertex patients as it was in the vertex area. So, I think in answer to your question,

when you look at all of the data from all three trials, there is overwhelming evidence that there is efficacy in both the frontal and the vertex patients and that the vertex patients, when reviewed from the front by the global panel, demonstrate efficacy nearly equivalent to that in the vertex. And I showed you one example of that in the last patient in the vertex series at one year, where the second photograph of that patient demonstrated the efficacy seen in the frontal area, and that efficacy in the frontal area in the vertex studies was essentially the same as seen in the vertex area in those patients.

DR. MCGUIRE: Dr. Parker?

DR. PARKER: Dr. Kaufman, you measured DHT in the skin but not 5-alpha-Reductase. That wasn't measured.

DR. KAUFMAN: We have measured 5-alpha-Reductase in scalp in the past. It wasn't done in the same study where we measured scalp DHT.

DR. PARKER: A couple of questions. Do you know if there is a difference, a significant difference, in the amount of DHT, vertex versus frontal?

DR. KAUFMAN: We have looked at DHT in balding versus nonbalding scalp, and often, that area of balding scalp is taken from the frontal area, because it comes very often from hair transplant patients, and the data support

that balding scalp, compared to hairbearing scalp, has increased levels of DHT. The concentration is increased. I don't believe we specifically looked at vertex versus the frontal area, meaning both areas with hair loss, to see if there were differences. I'm not aware of that.

DR. PARKER: Which might explain some of the differences you might see clinically in vertex and frontal.

DR. MCGUIRE: Dr. Lim?

DR. LIM: Dr. Kaufman, the--I forgot my question; come back.

DR. MCGUIRE: Okay; I have a quick fill-in question for you.

[Laughter.]

DR. MCGUIRE: Dr. Kaufman, would you walk me through the scalp biopsy results at one year? I'm confused--

DR. KAUFMAN: Sure.

DR. MCGUIRE: --about what the denominator is. You show 5.4 mean change in the hairs in the finasteride and one in the placebo in terminal hairs, and I'm not--and there's a baseline count of 16.

DR. KAUFMAN: Right.

DR. MCGUIRE: So, there are 16 in both the placebo--

DR. KAUFMAN: I'm sorry; slide 21 in the second tray.

DR. MCGUIRE: Yes, that's the slide.

DR. KAUFMAN: Yes; the 4-millimeter punch biopsy is roughly one-fortieth the area of the one-inch diameter circle that we use for hair count, and all of these biopsies were obtained and read by Dr. David Whiting at the Baylor Hair Research Center. As Dr. Whiting has found repeatedly, there are approximately 40 hairs between the terminal and the miniaturized hairs in a 4-millimeter punch biopsy. And if you, then, try to normalize that for the area, since it's one-fortieth of the sites, it gives you about 1,600 hairs in a one-inch diameter circle, and that's about normal. So, of those 40 hairs in this cohort of patients participating in the Phase III U.S. study at Dr. Whiting's site, the average baseline number of terminal hairs out of the total of 40 was 16, and the average number of miniaturized hairs is 24. That's the hallmark of male pattern baldness, that there are far more miniaturized hairs compared to the number of terminal hairs, and that, in fact, is the pathophysiology of what is going on, so that, over time, the percentage of terminal hairs will decrease; the percentage of miniaturized hairs will increase. And so, you have an unfavorable ratio of terminal to miniaturized hairs.

And what finasteride treatment has done is reversed that trend towards a decrease in terminal hairs and an increase in miniaturized hairs by increasing the number of terminal hairs and decreasing the miniaturized hairs and altering the ratio of terminal to miniaturized in a favorable way.

DR. MCGUIRE: That answers my question.

Dr. Lim?

DR. LIM: Yes, Dr. Kaufman, the question that I had before was in the briefing package that you sent us, I believe that there is a statement that African-American males as a group did not respond as well; granted, the number is small, and it's only 11 percent of your total patient population. Could you elaborate on that?

DR. KAUFMAN: Yes; in the subgroup analysis, broken down by ethnic group, it was observed that although all subgroups analyzed clearly respond in favor of finasteride compared to placebo that there was a slight trend towards black patients, perhaps, having a slightly less increase in hair count compared to the rest of the population. But again, the efficacy was clearly there. It turns out that black patients have a slightly different hair count profile as well. They were substantially lower in their baseline hair count than the patients in the trial.

If one looks at the patient hair growth questionnaire, the efficacy of treatment was clearly demonstrated for black patients compared with placebo. Interestingly, there appeared to be a little less satisfaction with the appearance of hair at the end of a year in black patients on finasteride compared with those on placebo, compared to the population as a whole. I don't have a clear explanation for that, but I think it's clear that the patients, regardless of whether they came from one ethnic group or another, clearly responded to finasteride in a favorable way.

DR. MCGUIRE: Dr. Rosenberg?

DR. ROSENBERG: I have an observation and then one question. The observation is that I think Merck are to be commended for bringing with them today authorities in urology and reproductive physiology. You know, I wish that we had peers who could ask them the kinds of questions that I think are appropriate in terms of benefit or risk in this area. I will try one question, however.

The men enrolled in this study, I note, were 18 to 41. The proposed package insert information does not limit the use to young men, who these were. From my reading, I have the impression that some of the side effects that one would hope don't occur are perhaps more prevalent in middle-

aged or somewhat older men than the youthful group whom you tested. So, I wonder about how much reassurance we can draw from these data for those men.

DR. KAUFMAN: The question has to do with the use of finasteride in men who, perhaps, would be older than the specific age range of patients studied in the clinical trials and what reassurance we can provide. I think we have substantial reassurance on the safety side, since we have extensive experience with finasteride at five times the dose being considered today in men with benign prostatic hyperplasia, and that safety profile is well described and well established and, again, would be acceptable for this indication.

The issue on efficacy is slightly different. It's true that we did study men between 18 and 41 in the Phase III trials. The product label will specifically indicate that in the clinical study section. However, the subgroup analysis, looking at patients divided by their age, whether they were between 30 and 40, 35 and 41 or younger, and looking at them from the perspective of how long they've had hair loss, which may be related to age, didn't identify any trends in the data; did not suggest that older patients or patients with more established hair loss had less efficacy.

I think it's fair to say that male pattern hair

loss is a continuum; that there isn't an abrupt change between patients, say, who are 40 and 45. We do have some experience with much older patients from the finasteride 5 milligram Proscar experience, where men in the seventh and eighth decades perhaps would not respond as well, because they may have senescent balding as opposed to male pattern hair loss, but I think between these two age groups, that is, the 18 to 41, and the much older group of patients with BPH, where we have some experience with Proscar, I think it's an individual patient selection with the patient's physician as to whether finasteride is appropriate for them, and they can see for themselves whether the therapy is going to be effective.

DR. ROSENBERG: Do they grow a lot of hair, the older men taking the larger pill?

DR. KAUFMAN: The question was did the older men with BPH grow a lot of hair when they were treated with finasteride 5 milligrams, and we have received anecdotal reports, both reports from the clinical trials as well as postmarketing reports. Some of the reports--they are anecdotal, and I think we can take them from what they are--some of those reports, of course, also come from patients on placebo, but there are anecdotal reports.

I often get photographs of patients 75 years old

showing the--you know, before they started on therapy; after they had been on therapy declaring their surprise at the benefit that they've seen in their scalp hair, but these are anecdotal. We didn't specifically look at this question in the BPH trials.

DR. MCGUIRE: Do you have further questions, Bill?

Mrs. Cohen?

MS. COHEN: I wonder: it says at 12 months, only 14 percent of men treated with Propecia demonstrated hair loss. Fourteen percent is rather a large amount. Did they stop at that point? Or did you continue to treat them for another year?

DR. KAUFMAN: The 14 percent of men who had any further hair loss comes from the hair count data, meaning that the patients had a lower hair count at month 12 than they did at baseline. There is obviously some variability--biological variability--in the hair count measure as well as some variability in the measurement techniques in themselves, but nonetheless, the point that was being made in what I think you're reading, the 14 percent of men, that contrasts with the 58 percent of men on placebo who had a reduction in hair count at month 12 compared to baseline, and I think that dramatic shift in the proportion of patients who can be shown to have lost hair by hair count is

the important point.

MS. COHEN: If one takes this medication, what should a consumer expect? I notice it says, in some cases, 3 months, but what would you advise a person who buys this product in terms of efficaciousness?

DR. KAUFMAN: I think--if I can answer that in two parts, there are two potential benefits from this drug. One is the prevention of further hair loss in men who already have hair loss, and we know from information collected at baseline in all of our trials that preventing further hair loss is critically important to patients. It is actually more important--and even more believable to patients--than improvements in hair growth. So, prevention of further hair loss is something that the patient may have more difficulty appreciating because of the normal, slow progression as part of the natural history of the disorder compared with an impressive increase in hair growth as demonstrated in some of the global photographs.

So, I think patients need to be counseled that they may achieve results within 3 months or more but that patients may benefit from prevention alone, regardless of whether they see improvements in hair growth. Again, it's going to be the patient's own assessment, and they can tell, because they report more often on finasteride than placebo

that the treatment is slowing down their hair loss, and that is very important to them.

MS. COHEN: Thank you.

DR. MCGUIRE: Dr. Kilpatrick?

DR. KILPATRICK: Dr. Kaufman, one of our responsibilities is to be concerned with perhaps obscure safety effects, and I'm chasing a will-o'-the-wisp here to some extent, but there were, of the four patients who died on the study, three on treatment and one on placebo, two of the treated points--I'm referring to table 29 in the briefing book--two of the patients who died on finasteride died from motor vehicle accidents.

DR. KAUFMAN: Right.

DR. KILPATRICK: Perhaps from your Proscar studies, you can assure us that there is not an increased risk of motor vehicle accidents among people taking finasteride.

[Laughter.]

DR. KAUFMAN: I think I can assure you of that fact. In fact, those two cases, if I'm not mistaken, one was a man on a motorcycle who collided with a motor vehicle, and the other one, I think, was a pedestrian who was hit by a car. In fact, neither one of those patients was actually driving a car.

[Laughter.]

DR. KAUFMAN: Not to be flippant, to answer your question, there is no evidence that finasteride would impair one's ability to drive a motor vehicle.

DR. KILPATRICK: I think you may have been doing very excellent research, since you may know that I suffered from a motorcycle accident 18 months ago.

[Laughter.]

DR. KAUFMAN: Hence, the word serendipity.

[Laughter.]

DR. MCGUIRE: Doctor, is anyone going to ask you if you were taking Proscar?

[Laughter.]

DR. KILPATRICK: That's proprietary.

MS. COHEN: Leave it alone.

[Laughter.]

DR. MCGUIRE: Dr. Tschen?

DR. TSCHEN: We know that minoxidil is an over-the-counter product, and patients who have hair loss will use combinations and will start using this. I want to know if there is any study that you have done or you have any information on whether the use of minoxidil will enhance or decrease; a synergistic effect, or will it enhance side effects or produce any other problems to your knowledge?

DR. KAUFMAN: Yes; the question has to do with the potential combination use of finasteride with topical minoxidil. It's a very interesting question that we've often thought about, but there are no clinical data to answer that question. That is, there are no studies that have directly compared either treatment alone and then an arm that had combination treatment with finasteride and topical minoxidil. The two agents do act by different mechanisms, but, unfortunately, until the clinical trial data is available, we really don't know the answer to that.

DR. TSCHEN: Furthermore, the only other question I have is which patient would I select for one or the other? And certainly, the patient who comes to me comes already using minoxidil. Is this patient a good candidate to be switched into using the finasteride? Or should I tell them, well, just use this other in addition to the other product they are using? And that concerns me, because probably in the future, we will have even a stronger strength of minoxidil, and will this even work better or worse? Or what will I tell my patients as a clinician?

DR. KAUFMAN: Well, I'm an endocrinologist, not a dermatologist, and I think I would defer to one of our dermatologic consultants, Dr. Price, perhaps, to give you a response to that question.

DR. PRICE: I'm Vera Price from the University of California, and I'm a consultant, as you heard.

I think the decision will be answered largely by the patient. I think if the patient is pleased with his results with minoxidil, there is no reason for him to stop it. He may want to add something. If the patient prefers to take something by mouth and no longer wants to use something topical, that will answer your question in another way. I think it will take just a little discussion with the patient, but frequently, I think, if he's doing well, you may want to add, and if he's not certain, you may want to substitute.

This wasn't mentioned by Dr. Kaufman, but certainly in the animal model, the stump-tailed macaque, there is evidence that minoxidil 2 percent and finasteride orally, minoxidil applied topically and finasteride orally, have an additive effect, so that the animals using just topical minoxidil showed a certain increase in hair weights in a certain measured area, and the animals taking only finasteride by mouth showed a similar increase in weight over that same period of time, and when the animals were given both agents, it was exactly double the effect.

So, in the stump-tailed macaque, we have some evidence of the additive effect.

DR. MCGUIRE: The committee will have an opportunity to have further questions later, and what I would like to do now is introduce Elizabeth Stoner, who will make some concluding remarks from the sponsor.

Thank you, Dr. Kaufman.

DR. STONER: Good morning, Mr. Chairman, members of the advisory committee, FDA, ladies and gentlemen. My name is Elizabeth Stoner, vice president of clinical research. I would just like to take a few moments to make some brief concluding remarks. In today's deliberation, it is important to consider the demonstrated benefit of finasteride on increasing hair growth on all affected parts of the scalp and its effect on reversing the fundamental hair loss process as well as the aggregate of safety data that has been compiled over the last 10 years.

Dr. Kaufman has shown that androgenetic alopecia is due in part to an acceleration of the normal cycling of the hair follicle. This process can be halted by lowering DHT levels, confirming the central role of DHT in the pathogenesis of male pattern hair loss. This translates into an arrest of the balding process in men with established androgenetic alopecia, resulting in increases in hair growth as well as prevention of further hair loss.

The clinical trials have demonstrated increases in

hair growth in both the vertex and frontal areas of the scalp. Each of the predefined endpoints was significantly improved over placebo and consistently demonstrated cosmetic improvements that were appreciated by the patients themselves and with which they were satisfied. The results are statistically robust, replicative and internally consistent.

The safety experience in the male pattern hair loss clinical trials demonstrated an excellent safety profile in the intended population, now based on approximately 3,000 patient treatment years and built on the already established safety of finasteride in the original 5-milligram application. Finasteride's mechanism of action is targeted specifically at inhibiting Type II 5-alpha-Reductase without other adventitious effects. Further reassurance is provided by the patients with a genetic deficiency of this enzyme who serve as a human biologic model for lifelong pharmacologic inhibition of 5-alpha-Reductase.

In fact, even though these patients have congenital anatomical abnormalities, several pregnancies have been reported with the fathers being the men with 5-alpha-Reductase, demonstrating that even lifelong inhibition of DHT does not appear to alter spermatogenesis.

Extensive long-term animal studies at high doses in rodents and dogs previously reviewed by the agency at the time of our initial approval in 1992 revealed no deleterious effects relevant to man nor any evidence for carcinogenic potential. Since approval, we have continued to conduct long-term controlled clinical trials with finasteride at 5 milligrams, now accumulating more than 20,000 patient treatment years of experience in controlled clinical trials. In none of these have any new safety concerns been identified.

Careful surveillance for malignancy, including prostate and breast cancer, in this extensive safety database, has revealed similar incidences in finasteride and placebo treated patients. In fact, the National Cancer Institute chose finasteride as the chemopreventative agent for a 7- to 10-year placebo controlled study in 18,000 healthy men to test the hypothesis that finasteride could prevent prostate cancer. Additional support for the safety profile of finasteride has been obtained through the detailed review of spontaneous postmarketing reports, and from all of these data, there have been no new safety findings.

The safety profile observed in the younger population with male pattern hair loss at one milligram was

consistent with the prior findings at five times this dose in older men. In summary, then, the extensive safety database which now exists, consisting of preclinical data, clinical trials at both 5 and 1 milligram and the postmarketing experience all unequivocally support the safety of long-term administration of finasteride to young, healthy men. In conclusion, finasteride 1 milligram provides an important therapeutic alternative to men for the treatment of male pattern hair loss.

Currently, patient choices are limited to surgery, topical therapy or hair replacement systems. Finasteride has been studied by state-of-the-art, rigorous, scientific methods which clearly establish its utility and safety for the treatment of men with male pattern hair loss. Therefore, considering the efficacy results and the extensive safety database available, we believe that the data submitted support the overall benefit risk for finasteride in the treatment of male pattern hair loss as being favorable and appropriate for its intended use in men.

Thank you.

DR. MCGUIRE: Thank you, Dr. Stoner.

I would like to postpone questions until after the break. If we could have a break now for about 30 minutes and reconvene at 11:00.

[Recess.]

DR. MCGUIRE: Good morning. I would like to reconvene the advisory committee, if you could be seated.

At this point, I would like for members of the advisory committee to direct questions toward any of the consultants as well as representatives of the sponsor.

Dr. Duvic?

DR. DUVIC: I've been elected to ask the sponsor about the fact that this drug causes birth defects in pregnant women. If they could give us an idea of how much, how long, if there's any plan to educate pregnant women or keep them from getting the drug. It causes birth defects in the fetus.

DR. KAUFMAN: The question has to do with the potential for finasteride to cause birth defects in fetuses if the drug is given to pregnant women. The clinical program that I presented to you today is in men only, and we are seeking an indication for use in men only based on the clinical trial data. The product label for this drug will specifically indicate that the drug is not indicated for use in women; that there will be specific warnings, contraindications, of the use of finasteride in women when they are or potentially may be pregnant because of the potential risk of producing hypospadias in a male fetus if a

woman, when pregnant, takes finasteride.

So, in answer to your question, the drug is going to be indicated for use by men only. It will not be indicated for use in women, and it will be contraindicated for use by women when they are or may potentially be pregnant, and that warning will appear both on the product label, the patient package insert, the product bottle and on the carton.

DR. MCGUIRE: That takes care of your question, Dr. Duvic?

DR. DUVIC: No, it doesn't really. Is there a critical time during the pregnancy that the effect--if someone, perhaps, got pregnant, would they have a leeway to--I mean, women might use this drug even though it's not approved for women.

DR. KAUFMAN: We do know that the differentiation of the external genitalia, which is the issue at risk, if you will, does occur in the latter part of the first trimester, but we have no information in terms of the safety of taking finasteride at any time prior to the end of the first trimester as to whether or not there's a free period, if you will, before there may be a risk. So, clearly, it will be contraindicated in women who are or may potentially be pregnant.

DR. MCGUIRE: Dr. Miller?

DR. MILLER: Dr. Kaufman, before, when we were talking about the frontal hair loss, I thought you said that some of those patients in whom there wasn't an increased growth might have had more advanced hair loss in that area or of longer duration. Did you say that or not?

DR. KAUFMAN: I don't believe I indicated that.

DR. MILLER: Okay; in your studies, have you seen at all that folks, younger folks, regrow the hair more quickly or it's more efficacious in them because of the duration of the hair loss?

DR. KAUFMAN: The question is are patients with a briefer duration of hair loss able to respond better than those with more advanced hair loss, and we did do subgroup analyses to look at this question directly, and we divided the patients by their chronological age, by the number of years of hair loss, by their Hamilton pattern which, to some extent, is an expression of their degree of hair loss regardless of how many years it's been, and in each of those cases, there were no trends in the data suggesting that patients didn't benefit or that they benefitted differently. In fact, patients with more advanced hair loss who also had lower baseline hair counts actually had a greater benefit in hair count compared to the population as a whole. So, in

fact, the data supports that patients, whether in the earliest or in the later stages of hair loss, all will benefit from the product compared to treatment with placebo. There is not a diminishing efficacy with more extensive hair loss based on those analyses.

DR. MILLER: And one other question: would you define frontal as you're using it? You know, we have diagrams here, but our discussion during the break indicated that we might have had different concepts of--how frontal is frontal?

DR. KAUFMAN: The frontal hair loss study--maybe I can show the slide in the first tray showing the demographics based on the Hamilton classification, because I think that will help illustrate. That is slide number 18.

[Pause.]

DR. KAUFMAN: Recall that this red box contains the entry criteria for patients in the pivotal vertex studies. This blue dashed line shows the patients' entry criteria for the frontal hair loss study, and I think you can appreciate that in the frontal hair loss study, patients had either relatively mild or more severe recession of the frontal hair line, and the hair count area for those patients was taken from what the clinician thought was an appropriate representative area in the frontal scalp as

opposed to the vertex scalp. I mean, that's the real difference between the way those two studies were designed.

And again, there is overlap between the patient populations, between the vertex and the frontal studies, but hair count, which was a primary endpoint in all of the studies, was obtained in the vertex area, in the leading edge in the vertex studies and in the frontal area in the frontal studies. Does that answer your question?

DR. MCGUIRE: Dr. Orkin?

DR. ORKIN: I'd like to pursue further the question that Dr. Duvic answered, and I'd like to ask if Dr. Wilkin will also comment on this question that I'll direct toward Dr. Kaufman. I would think that clearly, women are going to be taking--some women are going to be taking the medication, because even though they may not read it; they may not pay attention; they'll say it can't happen to me, but they're going to do it, and I think that is of some concern.

DR. KAUFMAN: I think that we will do everything we can in a responsible manner to educate the physician and the public about the use of this medication and that it is indicated for use in men only, and we will work with the agency in terms of material that is appropriate to make sure that that message is effectively communicated, so that women

understand that there isn't a risk for them, but it is a risk for them if they are pregnant to a male fetus, a potential risk if they take the drug.

DR. MCGUIRE: Dr. Simmons-O'Brien.

DR. ORKIN: Would Dr. Wilkin comment about--I asked if he would comment.

DR. MCGUIRE: Yes, please do, John.

DR. ORKIN: Yes.

DR. WILKIN: Well, I think Dr. Orkin's assumption, you know, probably will come true that some women will. We know that any medication that is approved can be used outside of the indication as part of the practice of medicine, so, there will be a learned intermediary; there will be a physician, and the sponsor has indicated a willingness to work on educational information in the labelling, perhaps something in addition to that which can also encourage physicians to think about this if a woman comes in and asks for the product.

DR. MCGUIRE: Dr. Simmons-O'Brien?

DR. SIMMONS-O'BRIEN: Along those lines, and I know we can't control what people do and what--and many of us would argue that we are not supposed to be doing that, but it kind of goes back to, you know, what is in a name, that which we call a rose, and Propecia, I am sure, was

thought about, and it has Proscar; it has alopecia. It's pro, it's for, it's anti, it's against loss. I'm wondering: did you ever consider calling it by the same name, Proscar 1 milligram?

I think that--I can see the adds in the magazine: Propecia, hair loss, and a lot of women are going to be interested, and some, I agree, will find a way to take the medication, and I think a name of a medication can have a lot of persuasive power. So, did you ever consider keeping it the same name?

DR. GOLDMAN: The trade name has actually gone through review through the agency as well as tested, and we did go through almost a 2-year process to make sure there are no medication errors, et cetera, for trade name.

The bottom line is that we are clearly, as Dr. Wilkins commented, you cannot get this over-the-counter. There is a learned intermediary, and we would not just be having that the drug is for male pattern hair loss; it's for men, and that is going to be clearly carried. Proscar has been out on the market for about five-plus years. This information has been disseminated clearly and is actually a well-known aspect of the drug, and we know that from people who are taking it, et cetera, and there has been education in that arena also, even though the indication there is

clearly simply a male indication.

So, we have already--I mean, it is not an unknown feature of the drug, and we will continue to, in fact, make sure that's even more prominent.

DR. PARKER: Do you know of any instances where you've had the trouble--

DR. MCGUIRE: That's Dr. Parker.

DR. PARKER: Do you know of any instances where you've had problems with Proscar in this regard?

DR. KAUFMAN: The question is do we know of any instances where we've had problems with Proscar. Are you referring to off-label use in women? There are some prescriptions that are being written for women for Proscar in the marketplace that can be made available through information sources. Generally, the precautions about pregnancy, since this, again, is a prescription drug, are communicated to the patient by the physician. Women seem to understand this part of the safety profile of the drug.

DR. MCGUIRE: Dr. Mindel?

DR. MINDEL: I had a question for Dr. McConnell or an area of questions.

I'm interested in a specific subset of patients, the ones that have had prostate CA and radical prostatectomies and now have a zero PSA. The detection

limit at my institution is 0.04 for recurrence. We saw that on the slide that the level is reduced by I guess that's a mean value of 0.2, and then, of course, there is a standard deviation and such. But what I am concerned about is that the patient who has a recurrence after his radical prostatectomy, that young man, relatively young man, will not be detected as the cancer is growing because of the relatively small but definite reduction in PSA.

DR. MCCONNELL: Let me answer that three different ways. First of all, in the reduction in serum PSA levels in men in these studies that point to decreases from a higher baseline, so, it's not that you're going to lower by 0.2 in everyone, and therefore, someone would have to have a PSA rise of greater than 0.2 before you'd pick it up. So, I think you can extrapolate from this database.

There is some experience in using finasteride in several trials, actually, following radical prostatectomy, and although there is some partial suppression of PSA, it is not complete. And so, I think it's exceedingly unlikely that there would be enough suppression that you would have any significant delay in the diagnosis or the identification of recurrence. The most important thing, though, is although we have all pushed for these more sensitive assays that allow us to detect recurrences biochemically when the

level is 0.05 or whatever, there is absolutely no clinical evidence that that allows us to manage our patients in a better way.

There is still intense debate about how to manage patients who have biochemical relapse following radical prostatectomy. Some people feel they should have radiation therapy, but if that is the case, there is no evidence that giving that radiation therapy when the value is 0.04 as opposed to 0.2 really makes any difference in clinical outcome.

So, I think to summarize, finasteride would not completely suppress PSA relapse in a patient who was destined to relapse, and second of all, it probably would not change clinical management in any way.

DR. MINDEL: The relatively sensitive assays are new, I think, so that to some extent, it really isn't known, say, the natural history of treating patients with 0.04 or 0.05 as opposed to 0.1 or 0.2 or 0.4.

DR. MCCONNELL: Well, that's technically true, but we do know several things, and that is that men who relapse early, in the first 2 years following radical prostatectomy, actually do quite poorly in response to radiation therapy or any sort of adjunctive therapy, whereas, men that tend to relapse more than 2 years following their original surgery

tend to respond better to radiation therapy.

And these ultra-sensitive assays have been around for at least 2 or 3 years, and again, I don't think that there would be any evidence to suggest that this would--that lowering DHT levels and lowering PSA levels would delay clinical diagnosis in any significant way. Certainly, I wouldn't personally have any concern about that.

DR. MINDEL: And that's--I'd like to ask a second question of you, which is that the question of the finasteride--of the lowering of the alpha-Reductase activity in fertility, it was mentioned that congenital--patients with a congenital absence, it has been reported that they have had offspring. Is that--I imagine this isn't a very common abnormality.

DR. MCCONNELL: Yes.

DR. MINDEL: But is there any comment that could be made as to whether this is--do they have fertilities essentially normal or essentially abnormal?

DR. MCCONNELL: We should let Dr. Imperato-McGinley answer that question.

DR. IMPERATO-MCGINLEY: Good morning. I'm Julianne Imperato-McGinley, an endocrinologist from Cornell University Medical College who was involved in the initial description of the syndrome of 5-alpha-Reductase deficiency

and has studied this condition--I'm shy about saying this--for over 20 years.

With that information, I can tell you because these patients have a lifelong deficiency of DHT which starts in utero which is causing a genital defect, many of these patients do have undescended testes, or some of the patients have testes that descend at puberty. So, because of the fact of the undescended testes, you have substantial damage to spermatogenesis, so that you cannot answer this question with many patients. But we have a patient who had descended testes who had essentially a normal sperm count, but because of inadequate hypospadias repair, paternity was achieved through intrauterine insemination twice. The first child was a healthy boy; the second children were twins, a boy and a girl.

There have been two other patients that have achieved pregnancy reported from the group in Sweden, two of three siblings. One has one child, and the other just had a second child. So, of course, this is a rare disease. There are a limited number of patients, and the spermatogenesis question is hampered by the basic defect which develops in utero, but yes, despite that lifelong defect, I'll tell you one other interesting, although anecdotal but nonetheless powerful.

Because of my 20-year followup of certain patients, I've found a sperm count done in 1977 and then a repeat sperm count in this patient that I had been in contact with over the years 18 and 20 years later, and essentially, there has been no change in the sperm count in that patient; in fact, the last count was higher than his count in 1977.

DR. MCGUIRE: Ms. Cohen, you had a question.

MS. COHEN: I think Dr. Kaufman mentioned that during the period of the clinical trials, there were people, several people who became pregnant, and I'd like to know if those children born had any birth defects or they were just healthy children.

DR. KAUFMAN: Ms. Cohen remarked that in the clinical trials, a number of pregnancies were reported, obviously, not in the patients in the trial but in the partners of the patients in the trial.

MS. COHEN: I agree.

[Laughter.]

DR. KAUFMAN: And in all of those cases, there are no congenital anomalies in any of the offspring of any of those patients.

MS. COHEN: Were they followed?

DR. KAUFMAN: They were all followed once the

pregnancy was identified all the way--to try to establish the date of conception all the way to birth and the outcome for all patients.

MS. COHEN: Thank you for my education.

[Laughter.]

DR. MCGUIRE: Further questions?

Dr. Kilpatrick?

DR. KILPATRICK: I'd like to ask a question about study 092, the frontal hair loss, as I understand it. I'm concerned about an apparent discrepancy, which may be fictitious, between the hair count picture shown in figure 14 of the briefing book, page 44, and the histograms shown in the appendix for 092. I'm looking at pages 135, et cetera. Now, the figure, based on hair count, persuades me that there is an important improvement of finasteride over placebo, and yet, and I'm coming back to this point, about a quarter to a third of the nontreated or placebo treated patients said that they were satisfied or more than satisfied and happy with the improvement in hair loss, some increase; that the placebo seemed to be effective.

This is demonstrating, of course, the subjective nature of placebo response, but I would like to have seen some histograms on the proportion of hair count numbers, differences from baseline to 12 months, in the placebo group

and get some idea as to what proportion of placebo-treated frontal hair loss subjects had, in fact, by numerical count an increase in the area that was counted. I'm sorry for such a wandering question.

DR. WALDSTRAICHER: I'm Joanne Waldstraicher from Merck Research Lab, and I monitor the frontal hair loss study. May I have JW Number 1? Let me just review the data that you're referring to, since there were several slides that you discussed.

DR. KILPATRICK: Right.

DR. WALDSTRAICHER: This is the frontal hair count data from the frontal baldness study, and you can see here a clear treatment effect. This is the finasteride group; this is the placebo group. This study went into open extension, unlike the vertex studies you've seen. So, all patients at a year were crossed over into the finasteride arm, but you can see in the finasteride treated group, over the first year, there is an increase in hair growth, which was about 12 hairs, in the one-centimeter square circular area, and there was maintenance of this efficacy through the second year of treatment.

And, as Dr. Kaufman told you, this is a smaller circle than the vertex studies that translates into about a 60 hair growth. May I have the next slide, please?

Now, you were referring to the placebo effect in the patient hair growth questionnaire, and here are the results for the patient hair growth questionnaire, and even though there is a placebo effect, which you see with every clinical study, especially in an endpoint as subjective as patient assessment, all of the six questions, and the next slide has the six questions, but leave this one on. The next slide has the other questions. All of these questions were statistically different from placebo. There was more important on finasteride than with placebo. In fact, as early as month 3, the global analysis was significant, and the overall appearance of hair and slowing down hair loss, those individual questions were also significant at month three, and each question was significant at month six.

May I have slide number JW 4? Just for comparison, and I am showing you the data on the percent of patients who had a positive response on finasteride versus placebo in the frontal hair loss study versus the vertex hair loss study, and you can see here that there is a remarkable similarity between the percent of patients with a positive response on the hair growth questionnaire in the vertex and the frontal studies and in the placebo groups from the two studies as well, which is what I think you were discussing. Here is the placebo effect again, which we see

in all of our clinical studies with subjective endpoints, and here is the finasteride treatment effect, very similar between the two, and, as Dr. Kaufman showed you, slowing down hair loss is the most robust question assessed by patients: 68, 65 percent of patients noted improvement in slowing down of the hair loss in those patients.

Does that answer your question?

DR. KILPATRICK: I take your point, except that there is a need for placebo control and that you have shown significant differences in hair count. My question explicitly asked for but I did not hear for a proportion in the frontal study of hair loss placebo-treated individuals who, by hair count, appeared to improve or not--basically, you've treated the hair loss as a quantitative measure. I'm saying could you degrade that into a classification improved or not improved?

DR. WALDSTRAICHER: We don't have the exact number pinned down, but between 50 to 75 percent of placebo-treated patients did have loss of hair by hair count.

DR. KILPATRICK: So that 25 percent were other that appeared to have no loss of hair by hair count.

DR. WALDSTRAICHER: Correct.

DR. KILPATRICK: Is this consistent with my expectation that hair loss is continuous?

DR. KAUFMAN: Maybe if I could respond from a slightly different vantage point: the hair growth questionnaire, the global photography, the investigator assessment and the hair count are actually measuring slightly different things, and although these measures are correlated, the correlations between changes in hair count and what the patient reports in terms of improvement or worsening or what the global photographic pattern reports, they're in the same direction; they're positive, but they are not highly correlated in the way that one might expect hair counts and hair weights, for instance, if one were to do both of those measures.

Remember that the hair count is in a specific, representative, circumscribed area, and that's done for reproducibility. We obviously can't take hair counts from the entire scalp. All of the other measures are assessing changes across the entire scalp, and so, similar to subjective and objective measurements in other disease categories, you get appropriate correlations between changes in hair counts and changes in subjective assessment such as the patient's own report.

So, there are some patients who have increases in hair count who report that they have improved, and there are others who may have increases in hair count who may not

report that they improved, because from their perspective, they have not achieved enough improvement. Does that help?

DR. MCGUIRE: Dr. Silverman, did you want to comment? Oh, yes, identify yourself, please.

DR. RIETSCHEL: I'm Bob Rietschel from New Orleans.

I appreciate your concern about what the placebo patients were doing, and in doing hair studies over the last 15 years, placebo responses have bedeviled almost all clinical investigators. This study was different in that you were able to see that there was progression of hair loss in the placebo-treated patients by a very sensitive measure, hair count, and that has been unique, in my experience as an investigator, to actually see that trend downward when we are trying to track that number.

In addition, when you had global photographs--I participated in the frontal panel that reviewed those--you have virtually no placebo effect when we reviewed global photographs in the frontal or vertex. It's a really tiny effect that gets labelled as placebo when we look at the real picture of the real head. And so, I was very impressed with the data that came out of this study indicating a significant difference from placebo by global assessment and by the very sensitive hair count assessment. It's something

that's somewhat unique to this study as compared to others I've seen.

DR. KILPATRICK: Thank you, sir.

I'd just like to follow up, Joe, if I may.

DR. MCGUIRE: Please.

DR. KILPATRICK: One more point.

I think that what I'm after here is asking if one looks at those people who were treated and did not respond, have they got any characteristics that differ them from other individuals, including the--or again, in the placebo group, there were some who responded, so, was there any subgroup analysis in that sense of the responders and non-responders?

DR. KAUFMAN: When the data were specifically looked at to address that kind of a question, that is, patients on placebo who did not have improvement in hair count, many of those patients may have reported improvement from patient self-assessment due to a placebo effect presumably or due to the fact that changes were occurring outside of the hair count area. This is, again, something that is germane to the fact that we are measuring slightly different things with the various endpoints, and it's the combination of those four endpoints that gives us sort of a comprehensive picture of what are the changes being achieved

with the drug.

So, in answer to your question about placebo patients, we cannot predict from the hair count data what the response in that patient is going to necessarily be in responding to the hair growth questionnaire aspect.

DR. KILPATRICK: I understand; and the other, the treated?

I broadened the question to ask about treated patients who did not respond, and there were a fair number of them, again, roughly a third, I think you said. And did they have any characteristics that would--may indicate a labelling restriction?

DR. KAUFMAN: We were not able to identify any characteristics about patients before they began on study drug or during the study that would help us decide a year later whether they would be in the group that reported a response from their own perspective or that had improvement in global photographs or in hair counts.

DR. KILPATRICK: Thank you.

DR. MCGUIRE: Further questions?

Dr. Wilkin?

DR. WILKIN: This might be a replay, because I got up to close the door; there was a racket outside; they were actually having an interview. And when I got back and put

my chair here, I heard Dr. Kaufman concluding on what the description of frontal was, and I guess if I could just hear that briefly, because I think under one slide, where you were looking at vertex, there was a band of hair just anterior to that which was, on that particular person, that was as far forward as the hair would grow, and I think you were defining that as frontal. And I see here in the graphic that Dr. Kilpatrick is referring to that it's actually talking about frontal hair line. I'm wondering: does frontal really go from the furthest extent of where the hair is back to the most anterior edge of the vertex? Is this all frontal? Or is it, you know, what one might think of as anatomically frontal scalp as opposed to the frontal part of the hair that's there?

DR. WALDSTRAICHER: JW 12, please?

We were fortunate enough to have Dr. Ronald Savin, who has developed the Savin scale, come to our investigators' meeting and train each of our investigators in how to divide up the scalp and how to look for the frontal and mid area of the scalp, and I hope you can see this with the lights up, but basically, here, in this black circular area, is the vertex area, which I think everyone can recognize as the balding spot. Ahead of that, in red here, is what has been defined as the mid area, and you can

see here, the definitions, and ahead of that is the frontal area.

The frontal area actually encompasses both the frontal hair line and frontal region as well as the mid area, and in our protocol and at the investigators' meeting and in our personal training sessions with the investigators, and we actually had patients at the meeting whom they practiced on, we worked on identifying this region of the frontal and mid area which we generally term as the frontal scalp, and hair counts were obtained in this frontal region, which is both the frontal and mid area of the scalp.

DR. MCGUIRE: You're satisfied, Dr. Wilkin?

DR. WILKIN: Yes; I appreciate very much hearing their operant definition for the word frontal.

DR. MCGUIRE: Further questions?

Yes, Dr. Miller?

DR. MILLER: This is, again, clarification on the Type I and the Type II 5-alpha-Reductase. Does finasteride have any effect on Type I at all? And in your study, you know, you really didn't measure Type II, but yet, you're saying, you know, reasonably dogmatically that it's working just on the Type II, and yet, we know that the Type I is in the skin and in the sebaceous glands, and is there a way to measure just hair itself for this enzyme?

DR. HARRIS: We know that there is--

DR. MCGUIRE: Could you identify yourself?

DR. HARRIS: Georgianna Harris.

We know that there is a hundredfold difference in the affinity of finasteride for the Type I and Type II enzyme, and we do know about the localization of Type I and Type II in scalp, if you would like to see. We can't measure separately, you know, inhibition in hair follicles versus the remainder of the scalp. Did I answer the question?

DR. MILLER: I just wondered, because we're saying, you know, that it's Type II that--and there's also some affinity for Type I, though, too.

DR. HARRIS: Well, we know from circulating DHT that there is residual DHT that we now know is due to the Type I 5-alpha-Reductase from the clinical studies.

DR. WALDSTRAICHER: Let me just share some experience that we've had with finasteride, which is the Type II inhibitor, obviously, that we're discussing today. Over the years, we have gone up to very high doses of finasteride for the development of Proscar, our 5-milligram dose. Even up to 80 milligrams of finasteride, you don't actually get more than about the same 70 percent suppression in DHT that you get with even lower doses of finasteride.

If it would have an effect on the Type I enzyme, it would suppress DHT even further, probably down to detectable levels. In fact, we have done an experiment with a Type I 5-alpha-Reductase inhibitor which we have, and if you take patients on finasteride who have this 70 percent suppression of DHT and add just a touch of the Type I 5-alpha-Reductase inhibitor, very easily, within a day or two, you can suppress DHT down to the lower limits of sensitivity. So, does that answer your question?

DR. MILLER: Yes.

DR. KILPATRICK: Joe?

DR. MCGUIRE: Dr. Kilpatrick? Oh, I'm sorry; Dr. Tschen?

DR. TSCHEN: Was there any effect in these patients, any other methodological effect, as far as decrease in the oiliness of the skin, decrease in seborrhea or seborrheic dermatitis or acne? I know there are differences, but were these questions asked to these patients, if their acne was better or if their skin got drier?

DR. WALDSTRAICHER: Right; the question is whether we've asked about sebum production, oiliness of skin or acne in our clinical studies. We did a 6-week study looking at scalp-skin DHT levels, and in those same patients, on 6

weeks of finasteride at multiple doses, we also measured sebum output using sebatape, which is an established method, and we did not see a significant suppression of sebum output with finasteride.

We also have not observed any reports of acne worsening or improving in either group different from placebo.

DR. MCGUIRE: Further questions?

DR. KILPATRICK: Joe?

DR. MCGUIRE: Yes?

DR. KILPATRICK: I should indicate before asking this question that I have been very impressed by the presentation both orally and written today, so, my comments are more concern to elucidate what's going on than to appear to be critical.

I'm concerned now with adverse effects, specifically in other than caucasian subjects, and in the briefing book on page 93, table 44, there are approximately twice as many adverse effects, total 16 over 9 in the testosterone treated individuals than in the placebo-treated individuals. The text states, on page 94, that this difference is not significant. I want to ask first of all, were the black and other groups combined to increase the power of the test? Or was this done for each group: black,

eight, versus four, and other, eight, versus five?

MR. BINKOWITZ: I'm Bruce Binkowitz from Merck Biostatistics.

DR. KILPATRICK: Hi. Finally, I got somebody up there who can talk my language.

[Laughter.]

MR. BINKOWITZ: We did the test a couple of ways. One way was we did an overall test of interaction for all three of the groups--

DR. KILPATRICK: Right.

MR. BINKOWITZ: --that you see on that page versus that. That was not significant. We then looked at each one of those individually, in other words, two by two tables--

DR. KILPATRICK: Yes.

MR. BINKOWITZ: --and showed that none of those were significant. We did not do all sets of two out of three.

DR. KILPATRICK: I understand. Can you give me some idea of the power of that test, the global test?

MR. BINKOWITZ: The global test of interaction?

DR. KILPATRICK: The global test of interaction.

MR. BINKOWITZ: The power that we did to test the interaction.

DR. KILPATRICK: Yes.

MR. BINKOWITZ: We used the Breslow-Day test, which is not one of the more powerful tests. I don't have the exact number. The P value overall turns out to be 0.16.

DR. KILPATRICK: The next question is do you have any plans to follow up this in a Phase IV? I mean, there is some concern here that not only do blacks and others have less effective, less effect from finasteride, but they may be at a higher risk from adverse effects. Any plans to follow up?

DR. STONER: We'll move back from biostatistics back to the clinic, but in the 5-milligram experience with Proscar in this really huge experience that we have in controlled clinical trials, they have been done around the world, and we did do a special study that included a large number of both blacks and Hispanics, and in all of these data, and we've looked at the Asian population as well as the black population separately, there were no differences in safety or efficacy observed in the other populations, and this now represents about 10,000 patients treated around the world.

DR. KILPATRICK: Thank you very much; that convinces me.

[Laughter.]

DR. MCGUIRE: Ms. Cohen?

MS. COHEN: I'm looking at women should not handle crushed or broken Propecia tablets. That's very scary when I read that, and I am concerned that, as always, the wrong people take the medication they shouldn't be doing. What kind of education do you anticipate in terms of speaking with pharmacists or giving them information? I can really see some physician writing a prescription for a woman. So, what kind of outreach, what kind of education are you going to do to make sure that the pharmacists understand that--

DR. ROSENBERG: Pharmacists are women. Pharmacists are women.

DR. KILPATRICK: Women pharmacists.

MS. COHEN: I am sorry; you lost me.

DR. ROSENBERG: I said the pharmacists are women.

MS. COHEN: Yes, now, I get it; I get it. Thank you; I have to admit that I didn't think of that. I give you credit. But in terms of that, I'm very concerned when I read this and knowing what consumers are like, and I just am worried that the wrong people are going to get the medication, and can a pharmacist, in fact, refuse to fill a prescription if it's made out to a woman for this medication?

DR. MCGUIRE: Would you like to respond?

DR. BLOIS: Yes, David Blois from Merck. I think

that we have had experience, as has been alluded to earlier, with the statements that you just read in the Proscar experience, and in our past 5 years, we've found that that has been effective in providing information to women, be they pharmacists, be they caregivers, in terms of people who might be helping to administer the tablet to an elderly gentleman that that has been an effective way in communicating that.

It is on the bottle; it's in the package circular; it's in the patient package insert that accompanies Proscar as a product. So, there have been numerous ways of communicating that information.

DR. MCGUIRE: I think you have further questions, Susan.

MS. COHEN: No, I was just thinking how physicians get their information on drugs, and it's usually the detail man who comes into his office. Is there an outreach program, say, with Merck with pharmacists? Do they go and visit them and discuss these things with them? Or is it just that you hope that they know that women should not take the medication?

DR. BLOIS: Well, again, it is our intention to ensure and do all that we can to ensure that the drug is used as we are recommending it; that is, that it be used in

men, and we would join with the FDA in doing whatever is necessary to make sure that that message gets across clearly and to the population that needs to hear it.

DR. MCGUIRE: Are there further questions about safety and--yes, Dr. Orkin?

DR. ORKIN: We're going over this again, but, of course, the Proscar is used for BPH, which is not a situation which occurs in women, and we know that the androgenetic alopecia is exceedingly common in women, and I wonder whether something that, in relation to more specific, perhaps, limitation to pharmacists as in a recent drug that we discussed would be appropriate to--I know several of us are just not comfortable with what we've heard so far.

DR. SCOLNICK: My name is Dr. Scolnick. I'm president of the Merck Research Labs, and let me just reassure you that if the committee or the FDA is uncomfortable, we do not want this drug used in women, just as you do not want to use this drug in women. The label will say that; the PPI will say that; the box will say that. And if it is felt to be prudent to tell all pharmacists in the country, as part of the information about Propecia, that the drug is not for use in women, we will be happy to do that, and if there are other prudent, rational ways of reassuring that fact, we will do them, and we will take your

suggestions, because we don't want it used in women either--at all.

DR. MCGUIRE: Questions?

Yes, Dr. Duvic?

DR. DUVIC: I just wanted to change the subject a little bit. Suppose a man who's 30 uses Proscar or finasteride for 30 years. Is there an anticipated effect on his prostate gland? In other words, will you reduce the frequency of BPH or prostate cancer? Or have you anticipated such an effect long-term?

DR. MCCONNELL: This is John McConnell. Nobody has a 30-year experience with the drug, but several lines of observation here: one is the experiment of nature with the 5-alpha-Reductase deficiency state, where we know that there is certainly no further growth of the prostate in that model but also specifically not the development of prostate cancer in any of these men, and Juliane, correct me if I'm wrong, there has not been a reported case of prostate cancer; is that correct?

DR. IMPERATO-MCGINLEY: Absolutely, or BPH.

DR. MCCONNELL: Or BPH. So, at least in the experiment of nature, there is no evidence of the development of prostatic disease in those men. We also know, from a recent trial that was completed, the so-called

PLESS trial, that at least over a 4-year time frame, the 5-milligram dose of finasteride, which reduces prostate volume by roughly 20 percent, appears to prevent any further growth of the prostate from that point from men who are on drug, again, at the 5-milligram dose, and significantly reduces their risk of long-term complications like the development of acute urinary retention, for example.

It's unclear whether the 1-milligram dose would have a similar beneficial effect long-term, but it would be hard to speculate that there would be any long-term detrimental effect. So, there may be a beneficial effect, but that would have to be proven in a long-term trial with the 1-milligram dose. Does that answer your question?

DR. DUVIC: There's no data on this?

DR. MCCONNELL: There's no data.

DR. MCGUIRE: Dr. Tschen?

DR. TSCHEN: I'd like to know if the patients who responded, also, did they grow hair in other, unwanted sites? I guess, ears, nose or dorsum of the hands? Or would I use it to grow hair in my chest or some other areas?

DR. KAUFMAN: Dr. Tschen has asked whether there are effects of finasteride on hair other than on the scalp in patients who had a response in the scalp, and we have two sources of information to answer that question. One is

reports of adverse experiences where patients may tell us that they've noticed increased growth of hair on their extremities or on their chest or whatever, and we have essentially equal proportions of patients reporting both increases and decreases in body hair by adverse experience reporting in either finasteride or placebo. So, there is no information provided from the adverse experience review that tells us that finasteride has any effect on non-scalp body hair.

We separately conducted a questionnaire in the U.S. Phase III pivotal study where we directly asked the patient whether they noticed any change in hair growth at the beard, at the chest or in the extremities, and the result of that, which is listed in your background package, shows that placebo patients more often than finasteride patients actually reported a slight increase in hair growth in the beard--excuse me, on the chest and on the extremities compared to finasteride. Both treatment groups reported small increases. Placebo was greater than finasteride.

Essentially, there doesn't appear to be any clinically significant effect on non-scalp body hair with finasteride therapy compared with treatment with placebo.

DR. MCGUIRE: Okay; it looks to me like we're winding down. Are there further questions before we have

our lunch break?

[No response.]

DR. MCGUIRE: Okay; then, I think we break, and we will resume at 1:00, and I have not heard from anyone who wants to speak at the open public hearing, and so, we will begin with the agency presentation at 1:00.

[Whereupon, at 11:55 a.m., the meeting recessed for lunch, to reconvene at 1:06 p.m.]

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

DR. MCGUIRE: The afternoon session of Advisory Committee meeting number 48 will now begin, and as of earlier today, we had no one speaking from the public sector this afternoon. Is that still the case?

And so, we'll go right ahead with the agency presentation, and the first speaker is Jonathan Wilkin.

DR. WILKIN: Thank you, Dr. McGuire.

I have no slides, so, I'll just speak from here and say basically some general comments, and then, Dr. Hon-Sum Ko will get into some of the reviewed details along with Dr. Srinivasan.

The first comment I would make is that what the committee is considering is somewhat unique in that generally, the committee is looking at something that has already received a regulatory action letter, and we're coming back and trying to sort things out after the fact. This time around, we're actually in the review process. A regulatory letter has not gone out, and we're trying to get committee input during the year we have to do the review of the data, and that's what the FDA does. The FDA reviews information that the sponsor has provided. And one of the understandings with the prescription drug user fee act is that the new drug application, when it comes in, and it came

in last year, would be complete.

So, we're looking at the material that was submitted at that time. It is possible that the sponsor has additional information that we do not have. That happens all the time. It's their choice whether, you know, they would want that information to come in, but they may truly have information that will help us answer some of the questions that we're going to be looking into later in the afternoon, and the key thing I wanted to let you know about is you'll need the identify if something is being presented that the agency has not had an opportunity to conduct its own review. That generally does not happen.

Having given that introductory statement, it also conveys to you the notion that we're still putting reviews together within the division, and we did receive the sponsor's briefing package early enough that we had a good look at it, and we thought we could add a few slides of our own, and it's not that we agree word-for-word with everything that the sponsor has in there; we would maybe portray something a little bit different, but in general, we do think it's a nice package; it's well-organized. And so, we are comfortable with our slides at the same time that one looks at the sponsor's materials.

Okay; so, we don't have a separate--you're not

getting our reviews at this time.

Next, I'd like to move on to a recurrent theme. At least three of the presenters for the sponsor mentioned 5-alpha-Reductase deficiency, the patients who have this, that this is an experiment of nature, and they took us into, I think, a thought experiment on, you know, how we can use that kind of information to think about safety, potential benefits and also causality. And the first item is safety, and we have with us today--the sponsor has with them today--Dr. Imperato-McGinley. We know her through the literature. We do literature searches as well, and what we haven't been able to find, and perhaps later, she could respond to this, is what kind of information do we really know about the health of the patients who have the 5-alpha-Reductase deficiency?

That is, we know that they don't live forever, but how do they die? Do we know how they die? Is it really the same way that, you know, everybody else dies, same order, heart disease, these sorts of things? Or does cancer jump up high on the list?

The second utility of the 5-alpha-Reductase deficiency as an experiment of nature came with Dr. McConnell, where he talked about potential benefits and made no promises; I thought it was very well-stated, but it was

possible that there might be a decrease in BPH in the future in this population because, in the 5-alpha-Reductase, that is, those who take finasteride because those with the 5-alpha-Reductase deficiency experience that.

Again, one of the thoughts with both the safety and the benefits is that 5-alpha-Reductase deficiency is not really the same thing as finasteride. There may be other aspects of finasteride, things that are known or even unknown, that could be occurring. There may be a pharmacology that is beyond 5-alpha-Reductase deficiency. Likewise, finasteride doesn't seem to completely suppress; in some of the patients who have the deficiency, it is quite a profound deficiency. They have virtually no detectable activity.

The third utility I thought I heard from the 5-alpha-Reductase as an experiment of nature is the notion of causality, and here, I will, as I'm stepping out onto some very thin ice, because I do remember--I have a bachelor of arts, not science--that one of the things we learned at the beginning of class was that I think it was Aristotle said that, you know, wisdom is a--a test of wisdom is to be able to determine and appreciate causality, causal events. So, this puts me on notice.

Ever since Aristotle, causality has been a major

theme with logicians and philosophers and trying to decide what the rules are, and I think over the last 150 years, the philosophers have mostly spent their time talking about the defects in analysis of causality by other philosophers. So, I'm not sure we've made major advances. But at least for the last 500 years, I think there are fundamentally two mechanisms that have been appreciated, and one is the associational method; the other is the connectional method, and I thought the sponsor picked up very nicely on one of the connectional or the associational methods. John Stuart Mill came up with five canons of causality, and I thought you met one of them, and that's if you don't have the cause, you don't have the effect, and if you don't have dihydrotestosterone, as in the 5-alpha-Reductase deficient patients, you don't have male pattern baldness. So, that was met.

And I would love to be able to remember all five of Mill's canons of causation. I can only remember three today. But the idea is that if you can't meet any of them, then, it doesn't work with the associational method. One of the canons was if the cause is present, then, the effect should be present, and we know that there are a lot of people, a lot of men, who have normal dihydrotestosterone levels; who have normal functioning 5-alpha-Reductase, and

they have what clinically or, at least, walking down the street, if you see them, they look like they have a full head of hair.

So, it actually, that particular canon of causation is not met. And then, there is another one that's either called correlation or the degree canon, and that goes something like if there is a large amount of the cause, you see a large amount of the effect. If you see a small amount of the cause, you see a small amount of the effect, and that's where we would expect to see either 5-alpha-Reductase activity or levels of DHT corresponding directly to the amount of baldness that someone might have, and I don't really think that we have that from the literature or the sponsor, at least, has not shared those data with us.

So, that's the associational method. The other method is the connectional method or the scientific method or the mechanistic method, and if you look through what dihydrotestosterone is doing, where it's playing this out, you could even go upstream. You could go to, rather than 5-alpha-Reductase deficiency, you could go to eunuchs. Eunuchs, if castration occurs sufficiently early, there won't be male pattern baldness, and if one goes further down the chain, gets androgens, gets the testosterone, the enzyme is present, gets dihydrotestosterone, then, that permissive

factor is there.

But what we think is happening, and it comes out in the name: androgenetic alopecia. Genetic refers to genes. It's thought to be autosomal dominant. We have experts here on hair disease that could probably give us a lot more detailed information. It's, I think, thought to be polygenetic, but it is inherited. And what seems to be inherited, because it's not really 5-alpha-Reductase or DHT levels that correlate with baldness, it seems to be a post-receptor phenomenon, that whatever the gene products are that turn on male pattern baldness, they are products that occur after binding of DHT to the receptors. So, it's a post-receptor sort of thing.

Having said that, I think the idea of causality was playing into the notion of finasteride treating the--and if you'll pardon the pun--root cause of male pattern baldness and that if did, you know, one could then argue at least because of this protracted thought experiment that you were treating something that might, then, prevent further hair loss, and so, I wanted to address this from that point of view.

We have data that we can look at. Dr. Ko will bring this topic up once again, and with that, Dr. Ko.

[Pause.]

DR. KO: Mr. Chairman, committee members, members from Merck, Federal colleagues of the agency and ladies and gentlemen, from the agenda, you can see that I am supposed to present the medical review. However, at this stage, we are still in the review process, and we haven't had a complete review, and that is why you don't have that in your package. And rather, today, I am going to bring up some of the issues encountered in the medical review which will lead to the questions that you're having to address this afternoon.

These are the basic questions for the committee members. The first one is on the generalizability of the presented data. As you have heard this morning from Dr. Weintraub, we do believe that Merck has done a very good job and has had successful study in showing the efficacy of finasteride in the treatment of male pattern baldness. However, there are still some very important issues that need to be addressed, and generalizability of the data from the clinical studies to the target population who will use this drug after marketing has to be properly considered.

The second question concerns the claims for hair growth and prevention of further hair loss, and Dr. Wilkin has mentioned that briefly, and I will go into that in a little more detail. Last but not least is a very important

issue about the long-term safety in the use of this drug in the younger population, even though we have a different preparation of this drug approved for an older population in the treatment of benign prostatic hyperplasia.

As a principle of drug development, one usually tries to explore the treatment effect during Phase II by targeting populations that are most likely to yield a treatment response and then use these data to plan the Phase III trials in which the enrollment should be as inclusive as possible with due considerations being given to the effects on safety and efficacy in different gender, race, age, disease severity, concomitant conditions and medications as well as activities. Therefore, in the Phase III trials, we expect to have studies that are embracing the target population as much as possible rather than restricting to certain patients who may show better response.

In the Phase III trials for Propecia, I have listed here some of the criteria for inclusion. The first one is the willingness to use a certain brand of shampoo supplied by the sponsor throughout the study. Second, the inclusion restricts to men between 18 to 40 years of age, ambulatory and in good physical and mental health. The third criterion listed here, being certain degrees and patterns of baldness, as described under the

Norwood/Hamilton classification: grades II vertex, III vertex, IV or V in male pattern baldness for the pivotal trials, with moderate vertex balding. And the patients must have had progressive hair loss and/or recent onset of balding within the last 3 years.

Now, concerning the first criterion that I have just shown about the specific shampoo required to be used by the patients, we have the following issues: the shampoo is a medicated, tar-based shampoo, which the sponsor was trying to use it for the prophylaxis of seborrheic dermatitis in the patients which might interfere with the assessment. There are no clear directions for use in the clinical studies, and, therefore, we have the following questions that need to be thought over: since it is used for the prophylaxis of seborrheic dermatitis, does it have any effect of the pilosebaceous unit? And does it have an effect on the assessment of the treatment response through staining of cosmetically unimportant hair, since this is a tar-based shampoo? And how would the labelling really address this concomitant usage?

Concerning the other two issues about generalizability, I just mentioned that during an earlier stage of the development of the drug, interaction between the agency and the sponsor resulted in the sponsor agreeing

to consider expanding eligibility to broader age and Hamilton classifications in the Phase III program. However, we still, in the Phase III trials, had men with certain age limitations and degree and pattern of baldness restrictions.

This slide just shows you the actual mean age of the enrolled patients and the range in the two pivotal trials and the third one for the--the third trial for frontal baldness. We see that the age really ranges between 18 to 41, and the mean is in the low thirties. So, one of the things that you committee members may need to address is how are we going to handle this kind of restriction in the label? Again, concerning the Norwood/Hamilton classification, there are certain classes or grades that were required for enrollment, and you have seen this picture earlier or a similar one by Dr. Kaufman.

Here, the blue dots indicate the Norwood/Hamilton grades required for the pivotal studies, while the boxed patterns are for the frontal baldness trial. As you can see, the enrollment has limited the patients to classifications that are not the severest for the vertex pattern baldness, while for frontal pattern baldness, you have basically those that are having a very mild degree of balding. Again, how to handle this in the label is one of the issues that will face both the agency and your committee

members.

This just shows you, in the two pivotal trials, again, the enrollment involves Hamilton grades II vertex, III vertex, IV and V without VI and VII, and most of those are within the III vertex, IV and V. The next issue concerns the frontal balding. A symptoms have seen in the earlier slide about enrollment, the boxed area shows the degree of severity which the patient is enrolled into this particular study: 092. And the enrollment result is shown in this slide. You can see that over 50 percent of the patients also had vertex pattern baldness. Now, II vertex and III vertex constitute over 60 percent in the finasteride group of 166 patients. It's 50 percent in the 160 patients of the placebo group, so that the total is about 55 percent of the 326 patients.

Also, you have seen this slide earlier this morning from the sponsor in which they have shown you their definition of frontal baldness, and by frontal, using the scale developed by Dr. Savin, it actually overlaps with the mid area. So, this is frontal, and that is mid area. So, in fact, most of the area anterior to the vertex will be considered frontal in this study, and that gives us a problem as to how exactly to analyze the data to show that it's really supporting frontal rather than both frontal and

mid-region scalp.

This slide shows the hair count data in study 092, and there is a definite positive treatment effect by finasteride, and you can see that it's up to 6 percent in the first 12 months, but most of the effect is seen in the first 6 months, and in the next 6 months, the increase is less compared with the first 6 months. Interestingly, the placebo group also had some increase between month six and month 12.

Apart from the hair count data, which is one of the primary parameters for these clinical studies, there is a co-primary endpoint which is the patient self-assessment. Unfortunately, in this study, 092, the patient assessment questionnaire is almost the same as the patient assessment questionnaire for the vertex pattern baldness apart from subtracting one question that involves the balding spots at the top of the head, and it is very difficult to interpret the answers to the questions, as they are not necessarily pertaining to frontal baldness, except for one question, the question 4-A, which deals with the appearance of the frontal hair line.

It is a five-point scale which has been rescaled by the sponsor sot the neutral is in the middle with positive response and negative response being satisfied or

not satisfied. As you can see, there is a definite treatment effect, although it's mostly around zero. You have seen the histograms which show the responder analysis. Now, that gives you the idea of all positives or all positives in the finasteride group and all positives in the placebo group regardless of the degree of positivity. So, it may be more appropriate to look at another endpoint in this study which was collected by the sponsors while using the Savin scale, because that can address more appropriately the different areas rather than investigators' assessment, because the investigator assessment asks a question which, in my opinion, is very difficult to interpret.

The investigator is supposed to answer the question: as the investigator, how would you subjectively rate the patient's hair compared to baseline, and this is not specifically addressing the frontal condition.

The Savin scale is a balding scale which gives increasing numbers with increasing baldness, so that a decline indicates decreasing baldness. And this scale measures six things. It measures three regions: the frontal, mid-area and vertex. And in each of these, there is a measurement of density and the pattern. This slide shows you the treatment effect on frontal density. Again, you can see that the treatment effect is definite but small,

and it's mostly around scale IV, which is somewhere in the middle.

For the frontal pattern, this is also showing a very small treatment effect, although again, this is a definite improvement from time zero to third month. After that, the line looks somewhat flat. Since the response's frontal definition involves mid-area, we also looked at the results on the mid-area density. This shows a similar curve with very small treatment effect but definite and the mid-area pattern, which by month 12 looked almost indistinguishable.

The sponsor has also collected data on the global photographic assessment for this study. In the global photographic assessment, the protocol states that three types of photographs are taken from the frontal, anterior and temporal regions, and so, I would have more confidence in the interpretation of the global photographic assessment as compared with the investigator assessment, which was addressing a rather non-specific question.

The global photographic assessment was handled by a panel of three dermatologists who read those photographs in comparison with a baseline picture, and these are the scores given by the three dermatologists for this study. Again, you can see a definite treatment effect. However,

one of the dermatologists did not exactly agree very well with the others for the month six to month 12 change, and so, we do know that there is a positive treatment effect, but there is some disagreement among the panel.

So, to sum all this up about the frontal baldness study, these are the issues that we would like to be addressed. The study enrolled very mild degrees of frontal baldness patients, with over 50 percent of them having concomitant vertex baldness, which may complicate the patient self-assessment and investigator assessment to the question that they had to answer. There is a small treatment effect shown in the frontal baldness studies, but we are very perplexed with this last item, which is not the least being the frontal includes both actual frontal and mid-area scalp, so that it is not certain which patient exactly had the frontal area addressed in this study.

The next item that I would bring up for the committee members is about the claim from the sponsor in the treatment for increase for hair loss and prevention of increase in hair growth and prevention of further hair loss. There was an end of Phase II meeting in November 1994 in which the agency agreed that the proposed clinical development plan does not necessarily support an indication for the prevention of further hair loss as proposed by the

sponsor, but demonstrating an overall increase in the number of hairs on the scalp does not necessarily indicate that further loss of hair had been prevented.

Now, this morning, Dr. Kaufman has shown you a diagram about the hair cycle. I'm just reshowing the hair cycle diagram in order just to make the point that to grow the hair, you also need to have the old hair shed, and in the treatment of male pattern baldness, the undesirable hair, of course, is the vellus hair, which has a shorter hair cycle, so that it will be shed and lost when you grow your new, stronger, terminal hair.

This diagram has been shown in your briefing package and also again shown in the slide by Dr. Kaufman this morning. It gives putative mechanism of finasteride action. By blocking dihydrotestosterone, the finasteride will putatively prevent the progressive miniaturization of the hair follicle and perhaps can reverse the process so that the vellus hair follicle will eventually be replaced by a terminal hair follicle.

Now, a couple of points I would like to make on this side: first, although this is one possible mechanism that the action of finasteride may be local at the hair follicle, we really do not have definite evidence that it is working right there. As you remember, one of the answers

this morning was that the actual hair has not been assayed in terms of 5-alpha-Reductase, and that the change in the hair follicle is progressive. It is through a number of hair cycles, not that the terminal hair becomes a vellus hair or a vellus hair becomes a terminal hair, but rather, there are cycles in which you have to shed the cosmetically less important hair to yield the more important hair.

Again, another point about the effect of finasteride. As I just said, we do not have clear evidence that it is working at the level of the hair follicle. At the same time, we know that, as you have seen earlier this morning in the data, that the finasteride use will drop serum DHT level by two-thirds. We do not know what contribution of the serum drop of DHT and the contribution of local effect of finasteride is in the hair follicle.

The methodologies used in the Phase III clinical trials involve an objective assessment of hair count and several subjective assessment: patient self-assessment questionnaire, investigator assessment, and the photographic globals. Now, the hair count data is very useful, and it provides us with the information on the net change in the number of hairs in the target area being counted, which is equal to the newly-detected hair minus the hair shed, while the subjective assessments are all involving comparison with

baseline conditions. So, in all these cases, we are dealing with both growth and loss at the same time, and it's very difficult to sort out whether we have decreased the hair loss, because you may have both an increase of hair growth and loss in terms of a general increased turnover which may be necessary for the cosmetically more important hair to be shorn and counted.

Now, I'm just going to show you some of the data involving hair loss presented by the sponsor. You have this picture in your briefing package. It's on page 33, figure nine. This shows a responder kind of analysis for the percentage of patients who had any positive response, no matter how small the treatment effect may be. We do see the treatment effect of finasteride and placebo, and, as explained by Dr. Kaufman, there is substantial placebo effect in this kind of assessment.

It appears that the inclusion of a zero time point here is a little misleading, because these are comparisons with baseline, and the data really starts to be collected from month three, so that inclusion of a baseline shows really somewhat dramatic increase at month three. If you look at the data slightly differently, using the actual scoring system in this slide, you will notice that, again, finasteride has a definite treatment effect compared with

placebo. I would mention here that the scale from -3 to +3 here has been rescaled by the sponsor. The patient actually responded to the questionnaire with a seven-point scale from 1 to 7, and this is rescaled just to show that negative is worsening, and positive is better.

If you look at the respondent analysis by the sponsor, these were the two curves that you have seen in an earlier slide and also in your briefing package that I just mentioned. These include all the responders, no matter how small the treatment effect is. But we are also interested in seeing those who have better than just a very small improvement, and so, I'm showing you here curves for finasteride and placebo for those patients who show both somewhat better and a lot better responses and those that show the best response, a lot better responses.

This slide shows that if you include any positivity, you will see a very dramatic improvement, but if you look at those with a lot better at the end of 12 months, then, although there is a definite treatment effect, the difference is substantially smaller.

This slide shows the reverse of the last slide, in the sense that I'm showing those with no change and worsening. You can see that most of the patients in both groups were in the no change area, and people who got more--

who get higher degrees of worsening or any worsening are not that many. So, that was one of the questions on--about hair growth. It was on hair appearance to the patient.

The next question is about the actual hair growth as perceived by the patient. This is also in your briefing package as an all-responder analysis, anyone who had a positive effect. Again, finasteride has shown a definite treatment effect compared with placebo, starting about -3.

But if you look at the actual scores, also, you will see that these mean scores are showing mostly within the zero to one region, with a definite but very small difference between treatment and placebo. This slide is similar to the one on question two, and I am not going to belabor the whole process again, just to indicate to you that the top two curves are similar to what you have seen in the package and given by the sponsor, but we would also like to see higher degrees of response with both finasteride and placebo and the reverse of the condition, those with no change or a worsening.

So, it seems that there is a definite treatment effect for finasteride in increasing the hair growth. Now, we come to question number four, which handles slowing down of hair loss. This is, again, an all-responder analysis, as shown in your package, finasteride and placebo, showing that

there is a substantial treatment effect when all patients who had positive answers are shown. This slide shows the actual mean scores for the hair loss question. There is--I have some issue with this particular question because the question in the questionnaire was using a four-point scale in which the patient had to respond with answers one to four, and in the analysis, this has been rescaled so that there is an addition in between the two middle responses, and so, you have a five-level answer in this particular question.

And so, basically, what you are seeing here, between minus one and one, was seen by the patient as a one-level difference, and here, we have a two-level difference. And since most of the treatment effect is around the zero area, this has been presumably magnified.

I think I am not going to show this confusing slide, because this is similar to what you have seen in the slides for hair growth, and it just indicates to you that most of the responses that you saw with the all-responder analysis at the higher level will be seen lower when you look for those who have the best responses.

So, concerning the prevention of hair loss, this is one of the issues that we would like your advice. As the evaluations and the clinical trials provide data on a net

change in scalp hair condition, can these methods of assessment adequately assess the turnover of hair so as to support the claim of prevention of further hair loss? We understand from some of the slides presented this morning that in the extension trials after the first year, by the end of 24 months, there is a maintenance of the treatment effect in the finasteride group but no additional increase, and again, we have to bear in mind that this is a dynamic process in which, to get the cosmetically important hair to appear and be counted, then, you need to have the shedding of the cosmetically less-important hair, and so, I would just leave that part for your subsequent discussion.

Now, I'm coming to the issue of safety, this last question on your list. The clinical trials for Propecia include men with a mean age in the low thirties. This is, in fact, one of the slides you have seen earlier, because the enrollment is basically between the age of 18 to 41. The sponsor has accumulated a lot of safety information on the 5-milligram preparation of finasteride, Proscar, and, as you can see here, the long-term placebo-controlled studies for Proscar involve patients whose mean age is actually doubled that for the Propecia group.

And so, this is somewhat worrying, whether the data from this older age group can easily be extrapolated to

the younger age group, because there may be different concerns. The drug-related sexual adverse experiences for finasteride in the Propecia trials are between 1 to 2 percent, including decreased libido, ejaculation disorder, which usually is a decrease in ejaculation volume, and erectile dysfunction. This is about half of that for the Proscar group, but we have to bear in mind also that this is a group of patients who are younger, and any impairment of fertility may not be as acceptable as in the older age group.

And there are a number of factors that can affect the male fertility: change in libido and erectile dysfunction; these, we cannot address in detail at this point, because there are no further studies by the sponsor except from the sexual function questionnaire in the clinical trials. The sponsor did perform an additional safety study, 094, in which they also evaluated the change in ejaculatory volume. Changes in the spermatogenesis have not exactly been evaluated, apart from the analysis of the semen parameters in study 094.

Now, this slide shows you some of the data in that particular safety study, which is 48-week treatment with 1-milligram finasteride in normal individuals and followed up to see reversibility of any changes if detected. The

sponsor used a larger sample size for the prostate volume assessment but used a smaller sample for looking at ejaculatory volume and the semen parameters, and the conclusion from the sponsor was that really, there are not significant differences between the treatment groups. However, we have some issues in the powering of this part of the 094 study, and at this point, I will call on Dr. Srinivasan, our statistician, to address the issue of powering in this study.

DR. SRINIVASAN: Thank you, Dr. Hon-Sum.

I'm going to discuss the statistical approach which we thought correct to study the effect of finasteride on the semen production, giving the results of the safety study 094. The advisory committee briefing document and the label provided by the sponsor and today's presentation by Dr. Kaufman all have a pervasive problem. The results of the safety study 094 are presented as supporting the claim that there is no difference between finasteride 1 milligram and placebo relative to semen production. The sponsor's conclusion is based on the P values that are shown in table 51 on page 103 of the advisory committee document.

However, the P value alone is inappropriate for demonstrating no difference, that is, equivalence. If an inadequate sample size is used, then, the hypothesis of no

difference will be erroneously accepted on the basis that P is larger than 0.05, even if the true difference is considerable. This is what we call type II error. In all of the safety analyses, we are more concerned about type II error, that is the probability of roundly accepting the hypothesis of no difference when, in fact, there exists a difference.

The P value approach is also not in tune with both the sponsor's protocol and the ICH guidelines. We will illustrate this on the example of ejaculate volume. The protocol of study 094 is consistent with the ICH guidelines, and it requires that the decision rule on the effect of finasteride on ejaculate volume should be based on the 90 percent confidence interval. According to the protocol, the minimal clinically important difference relative to ejaculate volume is 10 percent. Slide one, please.

Let us denote the difference as the true difference between finasteride 1 milligram and placebo relative to median percentage change in ejaculate volume from week 48 to baseline; that is the null hypothesis, H_0, is the difference is less than -10 percent, or the difference is greater than +10 percent; that is, there is no difference, against the alternative H_1, that the absolutely value of the difference is less than 10 percent; that means

no difference. So, we are trying to test there is difference against no difference. Second slide, please.

In this case, the decision rule is as follows: if the 90 percent confidence interval for the difference in the median percentage change falls within plus or minus 10 percent, then, reject H_0 and accept H_1, that is, conclude that there is no difference between finasteride and placebo relative to ejaculate volume. However, if the 90 percent confidence interval falls outside these plus or minus 10 percent limits, then, the data support H_0, and we cannot reject H_0; in other words, the data fail to support the claim of no difference between the treatment groups.

Let just look into the results of study 094. Slide, please. The following is a quotation from the NDA 2788 results on ejaculate volume in study 094, especially paragraph four on page 6,726. The slide reads as follows: the 90 percent confidence interval for the median difference was lower-limit -10.4 percent, upper limit, 13.1 percent. This confidence interval includes plus or minus 10 percent, which was the minimal clinically important difference stated in the protocol. Therefore, it cannot be concluded that the difference between the two treatment groups was less than the 10 percent clinically important difference.

All other analyses also fail to support the claim

of no difference between finasteride and placebo relative to ejaculate volume. The table on this slide shows that at both weeks 24 and 48, in both protocol and ITT populations, for both median and mean, all the lower bounds in the 90 percent confidence intervals for the difference between finasteride and placebo fall beyond 10 percent, which was the clinically important difference. Can you just show the lower limits? The lower limits are all -12.2, -10.4, -13.5, -12.5, -15.5. The first one is for week 24; the rest of them are all for 48 weeks.

Therefore, the data in study 04 do not support the claim that the true difference between the treatment groups relative to ejaculate volume is less than 10 percent. Unfortunately, this correct conclusion was not later mentioned by the sponsor. The advisory committee document, pages 102-103, does not present the 90 percent confidence intervals as required by the protocol. Instead of the 90 percent confidence interval, the sponsor showed a P value equal to 0.9, which, alone, is not appropriate for demonstrating no difference that is equivalence. The sponsor's conclusion throughout the document and on page 6 of the label is the effect of Propecia on ejaculate volume was not different from that seen with placebo. This conclusion is not supported by the data.

A correct conclusion should be as follows. Next slide. The results of the safety study 094 fail to support the claim that there was no difference between finasteride and placebo relative to ejaculate volume. This may be due to an inadequately small sample size, 37 patients on finasteride and 30 patients on placebo. The reviewer for this submission is Dr. Valeria Friedlena, and she did the power calculations based on mean percentage change and found that for this sample size, 37 and 34, of course, she took the placebo mean change as -6.3; the standard deviation is 35.5, and just for the fun of it, we did the one-sided alpha; for the two-sided, it is going to be even less. So, just for the fun of it, she did that. The power to detect a 10 percent difference was only 30 percent. This means that the probability of type II error, that is, to say that there is no difference when actually there is a difference, is 70 percent. Normally, FDA requires the type II error to be less than 20 percent.

Of course, power analysis for medians can yield a slightly higher power. That's what the sponsor has done. But this power will be definitely less than the required 80 percent power. This is our thought. Thank you. I will pass on the podium back to Dr. Hon-Sum to continue.

[Pause.]

DR. KO: Thank you very much.

We are very interested in this particular issue of the ejaculate volume, because it relates to male fertility. As you have heard earlier this morning about patients with 5-alpha-Reductase deficiency, they may be fertile, and only some of the patients who had undescended testes are infertile. It is also clear that these patients have very small prostate and very little secretions from the prostate and seminal vesicles, and that may be one of the factors contributing to infertility.

Okay; I mentioned also the issue on spermatogenesis. Again, you heard this morning about 5-alpha-Reductase deficiency in which there are patients who are able to father children, and I understand from Dr. Imperato-McGinley's publication that there are a number of patients who have had normal spermatogenesis. On the other hand, there are also reports indicating that there is impairment of spermatogenesis in some of those patients. The problem is that 5-alpha-Reductase deficiency is a very heterogeneous syndrome. We know that the 5-alpha-Reductase Type II gene has a large number of possible mutations, which may result in different types of enzyme produced with varying degrees of activity. So, you may have different degrees of virilization and fertility, and so, it's really

hard, very hard, to conclude just from one set of data to say that this enzyme is not important in spermatogenesis, and a recent publication did show in animals that inhibition of 5-alpha-Reductase activity can impair testosterone-dependent restoration of spermatogenesis in the animals.

While this slide just shows one of the publications in which people found evidence of abnormal spermatogenesis, including maturation, arrest, low sperm count and decreased sperm motility in 5-alpha-Reductase deficiency, which should really give us some cautious note.

In the study 094, the sponsor also looked at the effects on bone with finasteride treatment. Again, the sample size is rather small, but the study has shown evidence of increase in bone mineral density, although this is not statistically significant, and the end telopeptide of collagen in urine is significantly decreased compared with the placebo group, and also, the bone specific alkaline phosphatase level has a significant difference between finasteride and placebo group, although this is very hard to conclude because there is a big elevation in placebo.

The issue that we have here is this: if it is real that there is a positive effect on bone mineral density, what exactly will be the effect in the long-term? Is it beneficial or harmful? And I think this is something

that needs consideration, as we understand that these patients may be using the drug for many, many years. It is not like in the clinical trial 094, where they will use for only 48 weeks and then stop to see reversibility of the parameters.

This morning, you have heard and also had questions on breast pathology, and our question is whether the effect of finasteride on the hormonal system in the body that affects testosterone and estradiol may cause some sort of imbalance to give rise to such symptomatology.

It is known, and I think this is one of the studies done by the sponsor, that finasteride in very high doses may induce Leydig cell tumor in mice. Recently, there are reports that human prostate cancer cell lines which have become repressed by androgens can be suppressed by dihydrotestosterone and yet stimulated by finasteride when they are put into the nude mouse system, which has been used now for a number of years to assess prostate cancer cell lines. So, in this respect, we have to bear in mind that even in the younger population, if you look at the prostate glands in the earlier decades of life, there may still be evidence of intraepithelial neoplasia, and there may be even invasive cancer in the younger age group, and the long-term treatment of the patients with finasteride, by suppressing

the androgen effect for dihydrotestosterone is, at this stage, unknown, and so, one has to bear this in mind.

Also, in this year, there is a report showing that in a patient treated for benign prostatic hyperplasia, there is an occurrence of severe reversible myopathy associated with finasteride use, and this was clinically and histologically resembling glucocorticoid-induced myopathy.

At this point, I would just like to remind you that finasteride, the molecule, is a steroid-like molecule, and it may have steroid-like properties. And again, as Dr. Wilkin had addressed earlier this point, the presence of finasteride is not the same as the absence of 5-alpha-Reductase II enzyme, because you have an extra pharmacologic agent present; and that 5-alpha-Reductase II is not an enzyme that is specific just for conversion of testosterone. It has other steroid hormonal substrates which are possible, and included in that would be progesterone; you can have 5-alpha-Dihydroprogesterone, and in one of the recent publications, it is known that dihydroprogesterone, the effect on the nervous system is probably the factor mediated for progesterone, because finasteride can abolish the effect of progesterone and not dihydroprogesterone, and also, you can see that dihydrotestosterone also has an effect on the expression of this particular gene in the nervous system.

So, to again reiterate the point that 5-alpha-Reductase II may have other substrates besides testosterone, and I have not the time to go into others like cortisol and aldosterone, which also have 5-alpha metabolites which may have activities.

Now, I am going to give my summary slide that leads back to the questions that we would like you to address about the effect of Neutrogena T-Gel shampoo and how to handle this in the proposed labelling. Also, the restriction in the clinical trials for the different age groups and degrees of male pattern baldness and also how to address this in the labelling; the effect on frontal baldness; the claim on the prevention of further hair loss and long-term safety.

Thank you for your attention.

DR. MCGUIRE: Do the members of the committee have any questions they wish to direct toward the agency, any of the previous three speakers?

Ms. Cohen?

MS. COHEN: Did you say it had a steroid-like effect, finasteride? Did you say that?

DR. KO: It is a steroid-like molecule, and in one application, it was associated with a myopathy similar to a glucocorticoid-induced type of myopathy. That's to the

extent that we know.

MS. COHEN: Would it affect a diabetic?

DR. KO: I am not aware that that one was diabetic.

DR. MCGUIRE: Yes, please, go ahead.

DR. STONER: We certainly agree that the backbone of finasteride is a steroid molecule, but when we began both the animal studies and the clinical studies going back to the early 1980s, we looked very carefully in every organ system possible to see if, in fact, there were any steroid-like effects, and I can assure you that there are none. We did a special study in diabetics in which there was no effect at all on glucose tolerance or hemoglobin A1C. We did ophthalmologic exams in the patients in the BPH studies to look for potential effects in the eye, and there is this one case report that did appear in the literature in the last year, but there have been no other reports at all except for the one case report, and this is now based on almost 4 million patient treatment years of experience in the market.

DR. KILPATRICK: Joe?

DR. MCGUIRE: Yes, go ahead. This is Dr. Kilpatrick.

DR. KILPATRICK: I'd like to ask Dr. Ko or perhaps

one of the Merck consultants what the clinical significance of a reduction in ejaculate volume is. Is this a risk factor for some other thing? I'm trying to get a handle on this.

DR. OVERSTREET: My name is James Overstreet from the University of California. I will not speak to the statistical issues that were raised about these data. I think other members of the Merck team will do that if it's appropriate. With regard to ejaculate volume, I think that the main thing to understand is that all of these values are well within the normal range for fertile men; in fact, these studies were designed to enroll men with normal semen parameters because we wanted to see whether, in the course of four spermatogenic cycles, this drug would affect testicular function, epididymal function, accessory gland function.

And, in fact, there was very little change, and in no case did these parameters move out of the normal range that we would expect to see in fertile men. With regard to the importance of the ejaculate volume in fertility, I think that most fertility experts would suggest that this is probably one of the least important parameters in the semen evaluation, as long as there is sufficient ejaculate volume, and by that, I mean an amount one-half to one-quarter of

that seen in the patients in this trial, we may raise some concern.

What is the function of the ejaculate volume? The function is to deliver the sperm cells to the reproductive tract. Certainly, one ml of ejaculate is more than sufficient to do this. I want to also address this issue while I'm at the podium regarding effects on spermatogenesis. Again, the design of this trial was normal men, four cycles of treatment; do we see any effect? Clearly, we saw no effect. Is this measure, and the most important measure is total sperm number per ejaculate, is this a realistic, valuable measure of spermatogenesis? It's the best we can do in a clinical trial of this type. It is a good, given the frequency of analysis of ejaculates in this trial, this is a very good measure of daily sperm production, and there was no change in that and, in fact, we saw a greater change in the placebo group, and this was a reflection of normal variation. It's well-known that there is normal variation in sperm production of fertile men.

Our methods were sufficiently sensitive that we were able to detect these normal variations and to demonstrate the lack of change in the treated men, and I'll remind you again also that there are extensive preclinical studies in several animal models that showed absolutely no

effect on spermatogenesis. So, as a clinician, I would have no concern that the changes we saw in the treated men would lead to any decrease in their fertility.

DR. ROSENBERG: May I ask a question?

DR. MCGUIRE: Yes, Bill.

DR. ROSENBERG: Were the number of conceptions in the 2-year trial of your subjects smaller than the expected number out of that many subjects of that age over that period of time?

DR. OVERSTREET: My understanding is that the individuals in the trial were actually discouraged from attempting fertility. So, given that prescription against that, I'm not sure that we can--

DR. ROSENBERG: So, they were told not to achieve conception--

DR. OVERSTREET: I believe that's true.

DR. ROSENBERG: --during the trial. So, we don't really know, then, what the effect of this would be in--we have no human data.

DR. OVERSTREET: All we can say is the number of pregnancies which did occur spontaneously, given those instructions in the placebo group and in the treated group were not different, although the numbers were small.

DR. MINDEL: Excuse me; I asked that question

before and was told that there was no information or data. I asked whether there was any information about the fertility rate, and the answer was, I believe, that it wasn't asked, and it wasn't existing.

DR. MCGUIRE: Before you leave the podium, would the previous speaker identify yourself? I think some of us didn't catch your name.

DR. OVERSTREET: James Overstreet, University of California.

DR. KO: Can I just answer Dr. Kilpatrick's question--

DR. MCGUIRE: Dr. Ko?

DR. KO: --before going into this?

DR. MCGUIRE: Go ahead.

DR. KO: You asked what the clinical significance is.

DR. KILPATRICK: And the question was not answered as explicitly as I would like. Implicitly, there is no--I take it from Dr. Overstreet that there was no--that decrease in ejaculate volume was not an indication of something else. That's what I was getting at.

DR. KO: Okay; to address your question, I do realize that taken as a whole, the data may not look significant, but we are going to deal with individual

patients, and there may be patients who are borderline subfertile. And so, any additional push in the wrong direction may make them infertile. Also, the question about infertility in the clinical studies, I don't think this would necessarily be reported, because in the first instance, they are not allowed to father children, and secondly, it would be difficult to perceive that to be reported as an adverse event. So, that would be my answer.

DR. OVERSTREET: Can I be more responsive to the question--

DR. MCGUIRE: Yes, go ahead.

DR. OVERSTREET: --on ejaculate volume?

To my knowledge, this finding implies no other ill effects in the male, either reproductive or otherwise.

DR. KILPATRICK: Thank you.

DR. MCGUIRE: Dr. Kaufman, you were--

DR. MILLER: Joe, can I ask one question?

DR. MCGUIRE: Yes; Dr. Miller.

DR. MILLER: Excuse me; Dr. Overstreet, was there a progressive downward trend in the ejaculate volume over the 2-year period, or don't we have that data, those data?

DR. OVERSTREET: Yes; I think Dr. Kaufman can show you those data, and I will respond to further questions.

DR. KAUFMAN: If I can first just clarify the

comments about the data on fertility in the clinical trials, in response to a previous question, I indicated that we obviously have the anecdotal reports that we collected from the clinical trials, meaning that patients who had a pregnancy in a partner--I think Ms. Cohen actually asked that question earlier--we collected information, and there were more cases of pregnancies in patients on finasteride than on placebo, but that may have just been a chance occurrence in the clinical trials.

The reasons why patients were advised not to father a child is due to the lack of sufficient information about the safety of finasteride in semen. So, at the time of the original initiation of the Phase III trials, patients were discontinued if they impregnated their partner, because we lacked adequate animal data at that time in terms of the safety of finasteride levels in semen, which were very low, but further safety data now has identified that that is not a risk, and that's no longer a requirement for the study.

In answer to the question about the ejaculate volume in protocol 094, can we show the slide from protocol 094 for ejaculate volume at week 48?

[Pause.]

DR. KAUFMAN: What we have here is both the ejaculate volume on the left and the total sperm per

ejaculate in the same patients on the right, measured as a median percent change from baseline. So, here is the percent change from baseline with the 95 percent confidence interval for both of these parameters, and the baseline ejaculate volume and sperm counts are listed.

As you can see, there is no trend at all with increasing time of any further decreases in ejaculate volume, and, in fact, the placebo and finasteride groups are essentially identical at week 48, and for total sperm count at week 48, actually, placebo is numerically lower than finasteride, but the confidence intervals overlap, indicating the lack of effect.

Can we see the same data at week 108? This trial was continued for an additional 60 weeks during a reversibility phase, and again, if you look at this, these data, you see that the placebo group, which clearly represents the normal biological variability, their ejaculate volume varies as much as the finasteride group does during the conduct of the trial, again supporting that there was no effect of ejaculate volume for treatment with finasteride, and there are similar data for each of the parameters that were measured for ejaculate, which is listed in the table in the background package; I think it's table 51.

In response to a question about patients who have a normal ejaculate versus patients, perhaps, who may be marginal, can we see the tertile analysis on the actual median ejaculate volume from 056?

[Pause.]

DR. KAUFMAN: We specifically looked at this issue in a study looking at finasteride 5 milligrams. Finasteride at the 5 milligram dose, in a similar patient population as the patients studied in protocol 094, that is, young men, did result in a small reversible decrease in ejaculate volume. This appears to be a dose-dependent effect. It's seen at the 5-milligram dose in two separate studies. It was not seen at the 1-milligram experiment. This is the change in the median ejaculate volume for the finasteride 5-milligram group in this experiment. This is the on-drug period. There is a decline of about half a cc, about a 20 to 25 percent decrease, and this is the change in the placebo group. But this is statistically significant, and then, this easily reverses upon discontinuation, as you can see.

Now, we look specifically at the patients who had the highest and the lowest and the middle tertile of ejaculate volume to see whether the effect of the drug was, if you will, more impressive on patients with lower or

higher or middle tertiles or whether this was some regression to the mean on ejaculate volume, given the variability that Dr. Overstreet referred to. Can we see the lower, middle and upper tertiles for this?

Okay; this is the middle tertile, and again, these patients started above the mean, slightly above the mean--this is 2.9 ml--and decreased about 0.4 ml on finasteride 5 milligrams. There is reversibility again; here is the placebo group.

Can we see the next slide? This is the upper tertile, and, as expected, as expected, this effect was larger in patients who had a larger ejaculate volume, but part of this is being driven by the normal biological variability. Once the baseline assessment is made, it is more likely that patients with a higher ejaculate volume will have a lower ejaculate volume at followup time points; and then, the lowest tertile. Oh, I'm sorry; that was this slide, right, which has the smallest effect.

So, I think--we have conducted three separate studies evaluating this. There is a small reversible effect on ejaculate volume; this is in the Proscar label at the 5 milligram dose. For the 1 milligram dose, no effect was seen in ejaculate volume or any other parameter measured in the same standardized way as protocol 056, which we just

showed you, suggesting that there is a dose-dependent effect with respect to ejaculate volume with finasteride in young male volunteers which represent the same population potentially indicated for treatment.

DR. GOLDMAN: Bonnie Goldman, regulatory affairs.

A lot of the questions that have been asked are actually things that were in our original application. In fact, we didn't dwell on them in either the background material or anything else. Prahalada will speak to some of the animal data we have which is quite extensive on fertility, and we can also fill in on some of the other issues that have come in.

DR. P. SRINIVASAN: My name is Srinivasan Prahalada. I'm from MRL. I'm going to briefly describe to you how we evaluated the fertility studies in animals, because that is an important point, and we knew from the beginning with the earlier components that we were studying that one of the target issues we need to carefully examine is the testes and its related effect. So, three different species: rabbit, dog, mice and rat, were treated at least for 3 months in the first study. The highest dose that was tested in the 3-month study in rat is approximately 40,000 times the human dose equivalent of the 1-milligram dose in man. At that dose, there was absolutely no effect on the

spermatogenesis based on the testicular weight, testicular histology and followed up that one with a long-term fertility study. This is one of the longest fertility studies that has been done in the rat. I will describe it to you briefly.

In that study, a dose that was 4,000 times the human dose equivalent was studied for approximately 6 months. That's one of the longest fertility studies in the rat. In that process, again, there was no effect on the spermatogenesis nor the fertilizing capacity of the sperm in rat given this drug continuously, daily, hourly at this dose. I want to also point out that we do achieve extremely, at these doses, not only systemic exposure to the drug was high, but the testicular level of this drug was also high, indicating that despite total inhibition of DHT in this species that there was no effect on the spermatogenesis.

In addition, we also studied the dog for 6 months and 1 year as well as the rat for 6 months to 1 year. Again, in those two studies, testicular histology and testicular weight did not show the spermatoid production rate in dog, even after one year of dosing at extremely high doses, had no effect on the spermatogenesis. So there is no evidence, based on all of the studies to date, that

finasteride has any effect on the spermatogenic process in the species that has been studied, and I also want to emphasize, at these doses, as I said, we do achieve almost total inhibition of DHT.

DR. MCGUIRE: Dr. Lim?

DR. LIM: Is it known in the animal models that you studied that the 5-alpha-Reductase is the same type enzyme as it is in humans?

DR. P. SRINIVASAN: The enzyme has been studied in rat. What I want to emphasize is that when you give finasteride, finasteride in rat is not as selective as it is in species such as in man. So, one way we evaluate it is, given such high doses, we can inhibit both Type I and Type II in rat. Therefore, we could achieve almost total inhibition of DHT at the high doses we have studied.

DR. LIM: But in human, I thought earlier on, we were told that the Type I would not be inhibited completely by finasteride; is that not correct?

DR. P. SRINIVASAN: Yes, that is correct.

DR. LIM: So, there would be some differences in the enzymes? Or is it because of the dose effect, do you think?

DR. SCOLNICK: There is a Type I and a Type II enzyme in the rat. It is evolutionarily and biochemically

different. The inhibitor finasteride inhibits somewhat selectively the Type II in rat, but also, with the doses, inhibits both enzymes. In man, it only inhibits the Type II enzyme, and it would, even if you went up to 80 or 100 milligrams of the drug in man.

DR. LIM: Thank you.

DR. MCGUIRE: We have--yes, Frank, go ahead with your question, but as Dr. Parker is framing his question, it's about time to take a break. I'm concerned that some of the consultants need to be leaving fairly soon, and so, I would ask those of you from the sponsor, those of you who are going to be leaving, if you have something to say, go ahead and weigh in before we take the break, but we should take a break fairly soon.

Dr. Parker?

DR. PARKER: I just wanted to ask about the rats on the large doses. Did they produce the same number of offspring? Did you have any evidence that they were infertile?

DR. P. SRINIVASAN: That is correct. In rabbit, for example, in the 3-month studies, we evaluated not only the spermatogenic effect as for lasting fertility, and the fertility is not affected, and the number of fertilizable eggs in finasteride-treated rat also is identical between

finasteride-treated and the placebo. There is no difference.

DR. MCGUIRE: I have a question that was left over from this morning, and in the analysis in which hairs were counted, in which an area was shaved, and then, the scalp was photographed, were those hairs analyzed and scored for being medullated, nonmedulated, pigmented, nonpigmented?

DR. KAUFMAN: The question is in the hair counts, whether the hairs were, in any way, graded for whether they were medullated, nonmedulated. The way that our hair count methodology has been developed, it was designed specifically to look at the cosmetically important hairs, meaning that if it was visible in the macrophotograph, it was, in essence, a cosmetically important hair, and if it was a miniaturized hair, we wouldn't actually be able to see it in our macrophotographs, and we have done a number of experiments to confirm that, to show that we do not count hairs that are the miniaturized type with no medullary cavity and so forth. But we didn't specifically grade them.

DR. GOLDMAN: Bonnie Goldman; thank you, Mr. Chairman.

Because our consultants are leaving, I took down some of the issues that were raised by the advisory. I would like to first ask Dr. McConnell to deal with the

prostate cancer and the cell lines.

DR. MCCONNELL: John McConnell, University of Texas; just in some generic comments about prostate cancer experience in the Proscar database. In the most recently-completed 4-year randomized trial, the PLESS trial, there was very good tracking of prostate cancer cases, and, in fact, these patients were biopsied, a subset of them were biopsied in a longitudinal manner. And in this study, the prostate cancer detection rate was absolutely identical in the finasteride-treated patients as opposed to the placebo-treated patients, and the utility of PSA measurements, defined by receiver-operator characteristic curves and other techniques, was identical in the finasteride group, perhaps even enhanced to some degree.

So, as a practicing urologist, I really no longer have any concern about finasteride suppressing the PSA-driven diagnosis of prostate cancer, so, I think we can put that to rest.

Also, in that experience, it's quite clear that in the cases diagnosed, there were no differences in the phenotype of the tumors, if you will. Gleason-grade estimated tumor volumes, et cetera, were identical in the finasteride-treated patients as opposed to placebo-treated patients. So, I think it's fair to say that to date, there

is no clinical evidence to suggest that if a tumor develops in a patient on finasteride that that tumor would somehow be more malignant or have a more malignant phenotype than a tumor that developed in a patient not exposed to drug, and I think that's supported by the data.

Now, the cell culture study that was reported--I believe this is the study out of Liao's laboratory at the University of Chicago--is problematic, to put it bluntly. This is a very contrived cell culture system which is sub-sub-sub line of the lincap cell line, which is grown under very artificial circumstances. This cell line has a tenfold increase in the level of androgen receptor expression compared to a normal prostate epithelial cell, and it's grown out of its normal environmental regulatory mechanisms with the stromal cell, and without going into details, there are no good cell culture models of prostate cancer, but this particular one is extremely problematic to make any references to because of its very artificial increase in androgen receptor expression, and cell culture models of prostate cancer seldom parallel what we see in vivo. So, I would caution you not to make too many extrapolations from a very artificial cell culture system.

DR. SCOLNICK: John, could I just--

DR. MCCONNELL: Yes, policy .

DR. SCOLNICK: In the paper, I just saw--this is really--what these people did in this paper was select a cell line by depleting it of androgen. They cultured it 100 passages in androgen-depleted medium in order to select for a tumor cell that grew in the absence of androgen. And then, what they did is showed that if you give either testosterone or dihydrotestosterone back, you suppress, then, the growth of the cell. So, they selected for a cell that grows in the absence of androgen. So, then, adding back, without added androgen, finasteride to show it's stimulated, all you're doing is elevating the DHT a little in the cell line, in a cell line you've already selected to grow in the absence of androgen. You're further depleting it of an androgen with finasteride. It's a completely artificial system. It has no relevance whatsoever to the clinical situation.

Neither in the clinic nor in animal studies done, again, with megadoses of finasteride is there any indication that finasteride causes prostate cancer.

DR. MCGUIRE: Dr. Simmons-O'Brien?

DR. SIMMONS-O'BRIEN: I have a question I actually had--I thought of this during the lunch break prior to even hearing about the Leydig cell tumor for a young man who has a very strong family history of prostate cancer, like, there

are cohort families, if he also happens to be balding and wants to go to his dermatologist to see if he can be put on finasteride, and given that, it would seem like he would need to be on it for a lengthy period of time most likely, if it worked for him. What would be Dr. McConnell's advice to this young man about whether or not he should take one milligram of finasteride for several years not knowing that it may or may not be beneficial to his potential prognosis for prostate cancer.

DR. MCCONNELL: Well, there are two parts to that question. One is would it increase his risk in any way? And I think the evidence is that it absolutely not increase his risk, based upon at least a 4-year set of data, and we still have the tool. The tool is PSA to make the diagnosis, and the evidence is that finasteride, even at a 5-milligram dose, does not eradicate the utility of that test as a detection modality. So, I would have no concern about starting drug on that patient and following him long-term.

Now, whether there's a benefit, a prophylactic effect, a preventative effect of the drug on the development of prostate cancer we won't know until the National Cancer Institute trial is completed, which is a few more years down the line. So, I would certainly never recommend that that patient take finasteride as a possible preventative, but I

would have no concerns about giving him the drug as long as he is being monitored closely with PSA and digital rectal examination.

DR. SIMMONS-O'BRIEN: Just in continuing that, for the practicing dermatologist, would you advise that it would be important in their history taking of that particular individual who is coming to them for the medication to question them about family history of prostate cancer and suggest that that person also concomitantly be followed by a urologist?

DR. MCCONNELL: Well, I can answer that personally. As you know, though, the issue of prostate cancer detection is a somewhat contentious one in a public health arena, and I won't get into that, but certainly, personally, I think it would be wise for a dermatologist to be cognizant of two factors. One is family history and the risk that that gives to the patient. The ethnic risk that African-Americans have; increased risk of prostate cancer, and lastly, the effects that finasteride may have on PSA in that there are certain corrections that have to be made. So, in answer to your question, I think dermatologists would need to be educated about it but that I don't think that that precludes use of the drug in any way.

DR. MCGUIRE: Dr. Mindel?

DR. MINDEL: It's my understanding that the reason that PSA is still valuable when someone is taking 5 milligrams a day is that you know it's halved, so, you multiply by two; is that a correct assumption?

DR. MCCONNELL: That is correct.

DR. MINDEL: So, what would be the factor that you would multiply at 1 milligram, and does that complicate the situation and the interpretation? I mean, the urologist knows that his patient is on 5 milligrams a day. Now, we have the dermatologist giving a milligram or two, and maybe the urologist doesn't know about it or, you know, do you feel uneasy with--

DR. MCCONNELL: Hopefully, even urologists can take a history and find out what other medications the patient is on.

[Laughter.]

DR. MCCONNELL: If not, we're in big trouble.

I think it's an excellent question. I mean, in these studies that you've heard today, it's my understanding that PSA reduction was more in the 30 percent range, but that's because these men, by and large, were younger men starting with smaller prostates. They had not yet had the initiation of the hyperplastic process. So, I don't know how to answer your question directly. Maybe someone else

from the Merck team can about what percent corrections would be appropriate to apply.

DR. STONER: In our own studies with one milligram in men with benign prostatic hyperplasia in which we also tested the 1 milligram dose, the reduction in PSA was identical almost with 1 milligram as it was with 5 milligrams, so that for that population of men, we believe that the correction of multiplying by two would hold as well.

DR. MINDEL: Well, I'm confused a little bit. You're saying that it should be doubled on one milligram as well, the value of the PSA should be doubled by the urologist?

DR. STONER: Well, in the age group of men who will be taking this drug for male pattern baldness, PSA is not routinely measured, and PSA would not normally be measured in these men who really are the kinds of men that we studied here. Once you get into the 50 and 60-year-old population of men in which PSA is routinely measured, we have data from our own clinical trials in those men at 5 and 1 milligrams, and in that population of men, when finasteride is given both at 1 and 5, the reduction in PSA is almost identical.

DR. MINDEL: Which you mean--so, it's about half.

DR. STONER: Yes, it's reduced by approximately 50 percent.

DR. MINDEL: But what confused me is the data that we were shown showed a main 0.2 microgram reduction. I know these are not--we're talking about a different age group, but prostatic hypertrophy is not--is it associated with a markedly elevated PSA in itself?

DR. STONER: I think a review of the baseline PSAs would help in this context.

DR. MINDEL: Okay.

DR. STONER: In the male pattern hair loss clinical trials, the baseline PSA is about 0.7, and you have a 0.2 mean reduction. In the clinical trials with BPH, the mean PSA is approximately 2, and obviously, there is some variability among those patients. So, you're talking about a different mean baseline PSA. So, the reduction in the population of men in their fifties, sixties and seventies in which PSA is monitored closely at 1 milligram is approximately the same as it is at 5 milligrams with a baseline of about 2.

DR. MCCONNELL: Just to remember that, you know, the current recommendations, at least American Cancer Society and American Neurological Association, are that annual screening and detection programs should begin at age

50 for the average patient, age 40 for the populations at risk: African-Americans, people with family histories. So, in our average patient, we're talking about a 50-year-old man. The average 50-year-old man is going to have some degree of BPH on average, and the data set from the original Phase III finasteride trials, Proscar trials, give us the answer, that the correct correction is a 50 percent correction. I think the only remaining issue would be an occasional patient who might be 40, family history and has been on the drug for awhile and what corrections should be applied there, and there, I think, just clinical judgment would have to be applied.

And I'd also remind the panel that we don't stop at PSA today. There's the newer version of the PSA test that allows us to measure the percentage of PSA that's free and unbound in the circulation has been really an excellent way to separate out whether a PSA elevation in a given man is due to BPH versus prostate cancer, and we didn't see it today, but it's quite clear that finasteride does not affect the utility of free PSA measurements either, so, we have yet another tool that we can apply to this population.

DR. MCGUIRE: Did you have further remarks?

DR. GOLDMAN: On some of the other issues that came up with consultants who are leaving; not on this

particular issue.

On the fertility issue and also on Dr. Wilkins' general question about the experiment of nature, he asked about the general health of patients with the deficiency as well as cancer specifically, and there were some issues about the fertility that I wanted Dr. Imperato-McGinley to just address again.

DR. IMPERATO-MCGINLEY: Overall, we're quite impressed by the general health of the individuals affected with inherited defect in 5-alpha-Reductase II. Since I have been involved with these patients, which is over 20 years, I am aware of three deaths. One death was from malignant hypertension and renal failure. Can you er do produce normal skin. So, I am not so sure that anything you would do would be to produce normal skin. Your endpoint would be coverage, pain reduction and infection reduction and, hopefully, a little longer a graft that held for periods of time so that there wouldn't be an immediate recurrence, and with any damage to these skins, these skins break down. They break down anyway in the EB. The toxic epidermal necrolysis is different but is still a major problem.

DR. MCGUIRE: I don't want to turn this into an EB symposium, and I won't. I would like to make one point, that is, areas of skin that have been injured and have

blistered are much more likely to blister and be injured again, and you can graft uninvolved skin in EB to areas of involvement and have an outcome that is not bad, especially in terms of covering tumor site.

I would like to hear from the Agency. I would like to know if there are any areas that I have slid by inadvertently.

DR. WITTEN: I would like to thank everyone here for participating. I think from our point of view this has been a very helpful discussion, and we will be moving forward, hopefully, to include this information in a draft of a guidance document.

DR. MCGUIRE: I can tell by the sound of the books and paper rustling that we are about to leave. I would particularly like to thank the outside experts who came and set an example for a cooperative discussion between surgeons and dermatologists. It is probably the first time in fifty years that has happened. We ought to do it again sometime. Thank you very much.

[Whereupon, at 2:40 p.m. the proceedings were recessed.]

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