CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-788

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION.

DEC 11 1997

NDA#/Drug class: 20-788/6S

Applicant: Merck

Name of Drug: Propecia, 1mg tablets (Finasteride)

Documents Reviewed: Volumes 1.1, 1.48-1.60, dated December 24, 1996 and data in CANDAR provided by the sponsor

Type of Report: Statistical/Clinical.

Indications: Androgenetic alopecia in males

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I. INTRODUCTION

The applicant has submitted three studies (two US studies, Protocols No. 087 and 092, and an international study, Protocol No. 089) as pivotal evidence to support the claim that propecia, 1 mg tablets (finasteride) once daily, is safe and effective in increasing hair growth and preventing further hair loss in men with androgenetic alopecia.

Throughout the review, the terms 'Study 087', 'Study 089', and 'Study 092' refer to Protocols No. 087, No. 089, and No. 092, respectively. The treatment name finasteride refers to propecia 1 mg tablets. Studies 087 and 089 examined vertex baldness and were identical in design. A frontal/mid area baldness Study 092 had a similar design, with two major differences being that Study 092: a) included men with frontal/mid area hair loss and b) did not use Sexual Function Questionnaire.

II. DESIGN AND METHODS

Primary Efficacy Objectives

a. To determine whether treatment with oral finasteride 1 mg/day increases hair count in men with male pattern baldness (MPB) compared to placebo.

b. To determine whether treatment with oral finasteride 1 mg/day improves male pattern baldness compared to placebo as determined by analysis of a self-administered Hair Growth Questionnaire

Secondary Efficacy Objectives

a. To determine whether treatment with oral finasteride 1 mg/day, compared to placebo, results in statistically significant improvement as determined by analysis of:

- Investigator clinical assessment of patient hair growth/loss change from baseline;
- Independent global photographic assessment by a blinded panel of dermatologists.

b. To determine whether treatment with placebo results in a statistically significant decrease in hair in men with MPB compared to baseline and to determine whether treatment with finasteride prevents further hair loss.

5. Study Design

Each study was a 12-month, double-blind, randomized, placebo-controlled, multicenter study to determine the effect of finasteride on hair loss in men with MPB. After a 2-week, single-blind, placebo run-in period, each patient was randomized to receive either finasteride 1 mg or placebo tablets once daily for 12 months.

During the study there were seven clinic visits, including a screening evaluation and Week -2 (placebo run-in) visit. A medical history was recorded at screening.

A single dot tattoo was placed on the scalp at Week -2. Global photographs were taken at screening (repeated at Week -2 if necessary) and at Months 6 and 12. Macrophotographs were taken at Week -2 (repeated at Month 0 if necessary) and at Months 6 and 12.

A self-administered Hair Growth Questionnaire was given to patients at the Week -2 visit to obtain baseline demographics and at Months 0, 3, 6, 9, and 12 to subjectively measure their perception of hair growth. A Sexual Function Questionnaire was given at the same visits to evaluate any changes in sexual function and activity. An investigator assessment of change in patient hair growth was done at Months 3, 6, 9, and 12.

Macrophotography

Before taking the macrophotographs, hairs in a circular area slightly larger than the final target area (1 inch diameter circle, approximately 5.1 cm square) in size centered at the leading edge of the patient's bald spot were clipped to approximately 1 mm in length. At the beginning of the study, a small (approximately 1 mm in diameter) dot tattoo was placed in the center of the clipped area.

Global Photography

Global photographs were taken prior to preparing the patient for macrophotography. The patient's head was kept in a fixed position by placing it in a stereotactic device. A color card was used to ensure quality control of color processing. Before taking the global photographs, the patient's hair was combed away from the vertex bald spot so that the entire balding area could be viewed.

Efficacy Evaluation

1. PRIMARY EFFICACY VARIABLES

Two primary efficacy variables were used: change from baseline in hair count and patient's assessment of hair growth. Hair count was performed via macrophotographs and patient's assessment was obtained from a Hair Growth Questionnaire.

Macrophotography

Each macrophotograph was blinded to study center, patient, and time. A trained technician placed a transparency over the photograph and, using a fine-point black permanent pen, placed a black dot over each visible hair. The dot map transparency was then counted using computer assisted image analysis. All photographs were dot mapped and counted after patients completed Month 12.

Patient Self-Assessment

A self-administered Hair Growth Questionnaire was given to patients at the Week -2 visit and at Months 0, 3, 6, 9, and 12 to subjectively measure patients' perception of hair growth. The Hair Growth Questionnaire was made up of two parts (HGB, or the baseline questionnaire containing 14 questions, and HGF, or the follow-up questionnaire, containing 7 questions). The seven questions from the HGF questionnaire were:

Question 1--Since the start of the study, I can see my bald spot getting smaller.
Question 2--Because of the treatment I have received since the start of the study, the appearance of my hair is:
Question 3--Since the start of the study, how would you describe the growth of your hair?
Question 4--Since the start of the study, how effective do you think this treatment has been in slowing down your hair loss?
Question 5a--Compared to the beginning of the study, which statement best describes your satisfaction with the appearance of the hairline at the front of your head?
Question 5b--Compared to the beginning of the study, which statement best describes your satisfaction with the appearance of the hair on top of your head?
Question 5c--Compared to the beginning of the study, which statement best describes your satisfaction with the appearance of your hair overall?

2. SECONDARY EFFICACY VARIABLES

I) Change in mean hair count from baseline was used to determine whether there was a significant hair loss in placebo group and Question 4 of the Hair Growth Questionnaire was used to determine whether treatment with finasteride prevented further hair loss.

ii) Investigator Assessment

Investigator assessment of patient hair growth/loss, measured as a change from baseline, was done at Months 3, 6, 9, and 12. The "investigator assessment" is the investigator's opinion regarding the patient's hair status using a 7-point scale as a response to the following question:

As the investigator, how would you subjectively rate the patient's hair at this time point compared to baseline?"

0 = Don't know
1 = Greatly decreased
2 = Moderately decreased
3 = Slightly decreased
4 = No change
5 = Slightly increased
6 = Moderately increased
7 = Greatly increased

iii) Global Photography

Slides were prepared for a blinded assessment by three independent reviewers. These slides were blinded to study center, patient, and treatment. The dermatologists evaluated paired photographs as comparison between baseline and Month 6 and baseline and Month 12 after all patients completed Month 6 or Month 12, respectively. Each dermatologist rated the paired photographs separately based on a 7-point scale:

0 = Don't know
1 = Greatly decreased
2 = Moderately decreased
3 = Slightly decreased
4 = No change
5 = Slightly increased
6 = Moderately increased
7 = Greatly increased

Safety Evaluation

At each visit, patients were asked whether they had any adverse experiences (AEs); none were suggested. The investigator was asked to evaluate all AEs as to their intensity and relation to test medication, to record the outcome and action taken, and to determine if they were serious.

A complete physical examination was done at screening and Month 12 and whenever a patient was discontinued from the study. Interim physical examinations were performed if clinically indicated.

A validated Sexual Function Questionnaire was given to patients at the Week -2 visit and at Months 0, 3, 6, 9, and 12 to evaluate any changes in sexual function and activity.

Statistical Planning and Analysis

1) Study Questions

Primary questions addressed by the analysis were:

Are there differences between the finasteride and placebo groups in hair growth/loss as measured by scalp hair counts at Month 12?

Are there differences between the finasteride and placebo groups in hair growth as

determined by the self-administered patient Hair Growth Questionnaire at Month 12?

Secondary questions addressed by the analysis were:

Are there differences between the finasteride and placebo groups based on safety and tolerability?
Are there differences between the finasteride and placebo groups in hair loss as determined by the self-administered patient Hair Growth Questionnaire at Month 12?

Are there differences between the finasteride and placebo groups in hair growth/loss at Month 12 as determined by:

Investigator clinical assessment of patient hair growth/loss change from baseline?

Independent global photographic assessment by a blinded panel of dermatologists?

2) Statistical Hypotheses and Power

The first primary efficacy hypothesis concerning **hair count**, was assessed by computing the change from baseline in hair count for each patient. The null hypothesis was that the mean changes from baseline in hair count at Month 12 were equal for the finasteride 1-mg and the placebo groups. The alternative hypothesis was that the mean changes from baseline were not equal.

To evaluate the **patient self-assessment of hair growth,** the sponsor used seven questions of the Hair Growth Questionnaire.

Reviewer's Comment: ***To evaluate the patient self-assessment of hair growth, this reviewer uses Questions 2 and 3 of the Hair Growth Questionnaire rather all seven questions of the Questionnaire.***

Question 2 is as follows: Because of the treatment I have received since the start of the study, the appearance of my hair is: (-3=a lot worse = = = = = > 3=a lot better).

Question 3 is as follows: Since the start of the study, how would you describe the growth of your hair? (-3 = greatly decreased = = = = = > 3 = greatly increased).

The null hypothesis for each of these two questions is that the distributions of scores at Month 12 were the same for the finasteride 1-mg and the placebo groups. The alternative hypothesis was that the distributions of scores were

different.

To determine whether treatment with finasteride prevents further hair loss, this reviewer uses patient's assessment of hair loss at Month 12 via Question 4 of the Hair Growth Questionnaire. Question 4 is as follows: Since the start of the study, how effective do you think this treatment has been in slowing down your hair loss? (-2 = not effective at all = = = > 2 = very effective). The null hypothesis is that the distributions of scores at Month 12 were the same for the finasteride 1-mg and the placebo groups. The alternative hypothesis was that the distributions of scores were different.

The study protocol called for 300 patients per treatment group. This was sufficient to detect a 24-hair difference in change from baseline in hair count between the two treatment groups with 95% power and alpha = 0.05, two-tailed.

3) Multiplicity

For finasteride to be statistically significantly superior to placebo, the Division requires it to be statistically significantly better than placebo relative to each of the co-primary endpoints at Month 12. Each co-primary endpoint involved only one treatment group comparison at only one time point, and thus no p-value adjustment was necessary.

4) Subgroup Analyses

In order to determine whether the treatment effect is different for various subgroups regarding the effect of therapy on hair count and patient self-assessment, the following subgroups were examined for change from baseline relative to hair count and individual questions at Month 12:

a) Baseline modified Norwood/Hamilton Classification as assessed by the investigator.

b) Positive family history (yes/no). Using the baseline Hair Growth Questionnaire, a "yes" response to Questions 5, 6, 8, or 9 indicated positive first degree family history (i.e., parents and/or siblings). A "yes" response to any part of Question 10 indicated a positive second degree family history (grandparents).

c) Race (Caucasian, Black, Asian, and Other).

d) Age (categorical, splitting into groups of 18 to 30 and 31 to 41).

e) Number of years a patient has been balding

f) Baseline hair count

5) Statistical Analyses

a) Populations Examined

Intent-to-Treat (ITT) Population

The primary patient set analyzed was the intent-to-treat population. All patients were included in the analyses as long as they had measurements both at baseline and on treatment. Dropouts were included by using the last observation on treatment for all time points subsequent to dropout. If a patient was not a dropout but had no data in the relative day range, the last observation prior to the time point being analyzed was used in the analysis.

Per Protocol Population

Analyses based on the per protocol population were also performed and used to corroborate the conclusions drawn from analyses of data based on the intention-to-treat population. These analyses excluded patients based on a set of pre-specified criteria (e.g., dropouts, noncompliant patients). The per protocol analyses did not carry data forward.

For the analyses of AEs, the denominator consisted of all patients who received at least 1 day of therapy during the double-blind period of the study.

Analytical Methods

Month 12 was a primary efficacy analysis time point.

ANOVA was used to compare treatment effects on hair count. For hair counts, change from baseline is the difference between the Month 12 value and the baseline value.

For the Questions 2, 3 and 4 of the patient Hair Growth Questionnaire, the investigator assessment and the global photographic assessment, the comparison between treatment groups was done using the Cochran-Mantel-Haenszel (CMH) test stratifying by center. SAS PROC FREQ was used to perform this test for the contingency table setting, adjusting for the center effect.

Following are the specifics of the analyses for some variable.

Investigator Assessment

The investigator assessment is the investigator's opinion regarding the patient's hair status. The investigator rated each patient on a 7-point scale, where 0 = don't know, 1 = greatly decreased, 4 = no change, and 7 = greatly increased. For analysis and interpretation purposes, this scale was centered on zero for "no change" by subtracting four from each score. Therefore, the baseline response represented a score of zero. This yielded a more intuitive view of the data, where positive changes indicated improvement in how a patient's hair looks, and negative changes indicated deterioration. "Don't know" was treated as missing. Thus, the scale for analysis and presentation of data was:

Missing = Don't know
-3 = Greatly decreased
-2 = Moderately decreased
-1 = Slightly decreased
0 = No change
1 = Slightly increased
2 = Moderately increased
3 = Greatly increased

Global Photographic Assessment

The global photographic assessment of the vertex area of the scalp was a rating given to each patient in which a panel of dermatologists independently and subjectively rated the patient's hair at Months 6 and 12 compared with baseline via photographs. For analysis and interpretation purposes, the "global photographic assessment" scale, where 0 = don't know, 1 = greatly decreased, 4 = no change, and 7 = greatly increased, was centered on zero for "no change" by subtracting four from each score. Therefore the baseline response represented a score of zero. This yielded a more intuitive view of the data, where positive changes indicated improvement in how a patient's hair looks, and negative changes indicated deterioration. "Don't know" was treated as missing. Thus, the scale for analysis and presentation of data was:

Missing = Don't know
-3 = Greatly decreased
-2 = Moderately decreased
-1 = Slightly decreased
0 = No change
1 = Slightly increased

2 = Moderately increased
3 = Greatly increased

Analyses of Adverse Experiences

Comparisons of treatment groups with respect to incidence of observed adverse events (AEs) were made using Fisher's Exact Test or Chi-Square test. No AE was tested for statistical significance unless that AE had an incidence rate across the two treatment groups of at least 1%.

III. RESULTS OF STUDY 087

Patient Characteristics

Patients were enrolled by the 33 centers in the US. Of the total of 933 patients (males aged), 471 patients were randomized to finasteride and 462 to placebo. The two treatment groups were similar with regard to age and race ($p \geq 0.05$). There were no significant differences ($p \geq 0.05$) between the two treatment groups relative to patients' family history of baldness, age at which patients began losing hair, baseline hair count, and other baseline characteristics. There was no difference ($p = 0.3$) between the two treatment groups relative to the number of patients who discontinued: 73 (15%) in the finasteride group and 83 (18%) in the placebo group. There was no difference between the two treatment groups relative to the proportion of patients included in the ITT analysis or Per protocol analysis at Month 12 ($p > 0.29$).

Hair Count

ITT POPULATION. Primary efficacy analysis was performed on the ITT population at Month 12 on change from baseline in hair count. Graph of the mean change in hair count across time for the two groups is shown in Figure 1A of Appendix. The summary of change from baseline analyses is presented in Table 1A of Appendix.

The change from baseline analysis showed a significant increase ($p < 0.010$) in hair count for the finasteride group at Month 12. The mean increase in hair count was 91.3 at Month 12 (see Figure 1A and Table 1A). The placebo group showed a significant mean decrease of 15.0 hairs ($p < 0.010$) from baseline at Month 12.

Comparing the finasteride group with placebo, there was a significant difference in favor of finasteride between the groups at Month 12 ($p < 0.001$). The estimated difference in the change from baseline between the two treatment groups at Month 12 was 106.3 hairs, with a 95% CI of (95.3, 117.3).

PER PROTOCOL POPULATION. Analysis based on the per-protocol population yielded similar results. The change from baseline analysis showed a significant increase ($p<0.010$) in hair count for the finasteride group at Month 12. The mean increase in hair count was 94.7 at Month 12. The placebo group showed a significant mean decrease of 14.4 hairs ($p<0.010$) from baseline at Month 12.

Comparing the finasteride group with placebo, there was a significant difference in favor of finasteride between the groups at Month 12 ($p<0.001$). The estimated difference in the change from baseline between the two treatment groups at Month 12 was 109.1 hairs, with a 95% CI of (97.6, 120.6).

Patient Self-Assessment of Hair Growth

Questions 2 and 3 from the Hair Growth Questionnaire were used as primary efficacy variable to evaluate patient self-assessment of hair growth. All responses were on scales such that positive changes were indicative of efficacy or improvement. Questions 2 and 3 and the responses used in the analysis are described below.

Question 2 -- Because of the treatment I have received since the start of the study, the appearance of my hair is: (-3 = a lot worse = = = = = > 3 = a lot better).

Question 3 -- Since the start of the study, how would you describe the growth of your hair? (-3 = greatly decreased = = = = = > 3 = greatly increased)

Figures 2A-(I) and 2A-(ii) of Appendix show percent of patients in the ITT population with positive self-assessment for Questions 2 and 3, respectively. Patient self-assessment was in favor of finasteride for both questions. Table 2A of Appendix summarizes distributions of scores for Question 2. The CMH test found a significant difference between the two treatment groups ($p<0.001$), favoring finasteride.

Table 3A of Appendix summarizes distributions of scores for Question 3. The CMH test found a significant difference between the two treatment groups ($p<0.001$), favoring finasteride.

Analysis based on the per protocol population yielded similar results for both Questions 2 and 3: the difference between the two groups was significant ($p<0.001$), favoring finasteride.

Investigator Assessment

Analysis was performed at Month 12 based on the investigator assessment of hair growth/loss evaluated as a change from baseline. Positive changes indicated improvement in a patient's hair and negative changes indicated deterioration. "Don't know" was treated as missing. The scale for analysis and presentation of the data ranged from -3 (greatly decreased) to 3 (greatly increased).

A graph of the percent of patients in the ITT population with positive investigator assessment is displayed in Figure 3A of Appendix. The CMH test showed that the distributions of scores at Month 12 were significantly different ($p<0.001$) for the two treatment groups in favor of finasteride group (Table 4A of Appendix). Analysis based on the per protocol population yielded similar results ($p<0.001$).

Global Photographic Assessment

Analysis was performed at Month 12 based on the median of the global photographic assessments of the three dermatologists. Positive changes indicated improvement in a patient's hair and negative changes indicated deterioration. "Don't know" was treated as missing. The scale for analysis and presentation of the data ranged from -3 (greatly decreased) to 3 (greatly increased).

A graph of the percent of patients in the ITT population with positive global photographic assessment is displayed in Figure 4A of Appendix. It shows better performance of finasteride compared to placebo. Analyses of the global photographic assessment for each individual dermatologist also supported better performance of finasteride compared to placebo.

Analysis of the global photographic assessment data (Table 5A of Appendix) indicated that the finasteride group in the ITT population was statistically superior to the placebo group at Month 12 ($p<0.001$ in the CMH test). Analysis based on the per protocol population yielded similar results ($p<0.001$).

Prevention of Further Hair Loss

The objective of this analysis was to assess whether treatment with placebo results in a decrease in hair count in men with male pattern hair loss compared with baseline to support the hypothesis that finasteride can be used to prevent further hair loss.

The hypothesis that finasteride would prevent further hair loss was supported at Month 12 as follows:

1) The placebo group showed a statistically significant ($p<0.01$) loss of hair, based on hair counts, as compared with baseline (Figure 1A and Table 1A of Appendix).

2) Finasteride showed a statistically significant ($p<0.001$) increase in hair counts compared with baseline (Figure 1A and Table 1A).

3) Question 4 from the Hair Growth Questionnaire addressed slowing in loss of hair. Questions 4 was as follows: Since the start of the study, how effective do you think this treatment has been in slowing down your hair loss? (-2 = not effective at all = = = > 2 = very effective). The CMH test has shown that relative to Question 4, finasteride was statistically significantly ($p<0.001$) better than placebo in the ITT population (Figure 5A and Table 6A of Appendix). Analysis based on the per protocol population yielded similar results ($p=0.007$).

Subgroup Analyses

Analysis was performed at Month 12 on change from baseline in hair count and on the hair growth questions for the following subgroups: age, race, baseline hair count, baseline modified Norwood/Hamilton classification as assessed by the investigator, number of years a patient has been balding, and positive family history of baldness. Finasteride was at least numerically superior to placebo in each of the subgroups examined. In subgroup analysis by race, there were 679 (84.7%) Caucasians, 81 (10.1%) blacks, and 42 (5.2%) others. In blacks, relative to mean change from baseline in hair count, there was a statistically significant ($p<0.01$) increase of 52.2 hairs in 31 patients on finasteride and a statistically significant decrease of 29.1 hairs in 50 patients on placebo ($p<0.01$). In others, relative to mean change from baseline in hair count, there was a statistically significant ($p<0.01$) increase of 58.0 hairs in 23 patients on finasteride and a non-significant increase of 4.2 hairs in 19 patients on placebo. In Caucasians, relative to mean change from baseline in hair count, there was a statistically significant ($p<0.01$) increase of 94.1 hairs in 353 finasteride patients on finasteride and a statistically significant decrease of 16.7 hairs in 326 patients on placebo ($p<0.01$).

Safety

Adverse Experiences—Clinical

Four hundred seventy-one finasteride patients and 462 placebo patients were evaluated for safety. The mean duration of therapy was 309.6 days for finasteride patients and 305.2 days for placebo patients.

Overall Assessment of Clinical Adverse Experiences

During the 12-month treatment period, clinical AEs were reported for 308 patients (65.4%) in the finasteride group and 288 patients (62.3%) in the placebo group ($p=0.3$). The clinical AE summary is presented in Table 7A of Appendix. Numerically greater number of finasteride patients reported total, sexual, and drug-related sexual AEs,but these difference between the two treatment groups were not statistically significantly different ($p>0.11$). The number of patients who withdrew from therapy due to a clinical AE was comparable between the two treatment groups ($p>0.05$).

Table 8A of Appendix summarizes the clinical AEs by body system. There was no significant difference between the two treatment groups relative to AEs by body system ($p>0.14$).

Table 9A presents number of patients with drug-related sexual AEs. Twenty-one patients on finasteride (4.5%) and 12 patients on placebo (2.6%) reported drug-related sexual AEs ($p=0.16$). Of these patients, 10 (48%) on finasteride and 3 (25%) on placebo reported resolution of the sexual AE while on therapy. Numerically there were more patients with sexual AEs in the finasteride group. But the difference between the treatment groups for any individual type of AE was not statistically significantly different ($p>0.45$).

Patients Discontinued Due to Clinical Adverse Experiences

Ten finasteride patients (2.1%) and 12 placebo patients (2.6%) discontinued therapy due to clinical AEs ($P=0.6$). The most common clinical AE that caused patients to be discontinued was impotence (5 on finasteride and 3 on placebo, $p=0.5$). All patients who discontinued the study due to a sexual AE (7 on finasteride and 6 on placebo, $p=0.8$) reported resolution of the sexual AE. Four of the 7 patients on finasteride reported that their sexual AE resolved on drug prior to discontinuation. The remaining 3 patients reported that their sexual AE resolved within 1 to 23 days once they stopped taking the study drug.

Adverse Experiences - Laboratory

Total of 439 finasteride subjects and 426 placebo subjects had at least one laboratory test after Month 0. Of them, 21 (4.8%) of finasteride subjects and 17 (4.0%) subjects had at least one laboratory AE ($p=0.6$). Three finasteride patients and 2 placebo patients had drug related laboratory AEs ($p=0.7$).

Sexual Function Questionnaire

A Sexual Function Questionnaire was used to examine the relationship betwen the use of finasteride and any occurrence of sexually related AEs. All questions were divided into six domains: Sexual interest, Erections, Ejaculation, Perception of problems, Global question and Morning erections. The total scores were computed for each domain. The responses were ordered such that smaller scores indicate worsening condiiton and larger scores indicate improvement. Table 10A of Appendix presents a summary of the total scores by the domain. There were significant differences ($p<0.001$) in favor of the placebo group relative to morning erections at all time points. There was a significant difference ($p\leq 0.039$) in favor of placebo group relative to the domain of perception of problems at Months 6 through 12. Relative to the domain of sexual interest, there was a significant difference ($p\leq 0.04$) in favor of the placebo group at the earlier months and a borderline significant difference at Month 12 ($p=0.062$). Relative to the domain of erection, there was a significant difference in favor of the placebo group at Months 6 and 12 ($p\leq 0.039$).

Reviewer's Conclusions on Study 087.

Of the total of 933 patients, 471 patients were randomized to finasteride and 462 to placebo. The two treatment groups were comparable ($p>0.05$) relative to baseline demographic characteristics and discontinuation rates. Efficacy analysis in the ITT population showed that finasteride was statistically better ($p<0.001$) than placebo relative to the change from baseline in hair count with the mean difference of 106.3 hairs between the two treatment groups. Finasteride was also statistically better ($p<0.001$) than placebo relative to patient's self-assessment of hair growth. The results for the Per protocol population supported the results for the ITT population. In the subgroup analysis, finasteride was numerically superior to placebo in each of the subgroups. Relative to the secondary efficacy variables, Investigator's assessment, Global photographic assessment by the panel of independent dermatologists, and assessment of slowing hair loss, finasteride was statistically better ($p<0.001$) than placebo also.

In the adverse events analysis, a markedly greater number of finasteride patients reported sexual and drug related sexual adverse events, but these differences between the two treatment groups were only marginally statistically significant ($p<0.12$).

Sexual Function Questionnaire was used to examine the relationship between the use of finasteride and any occurrence of sexually related AEs. There were statistically significant differences ($p<0.001$) in favor of the placebo group relative to morning erections at all time points. There was a significant difference

($p \leq 0.039$) in favor of placebo group relative to the domain of perception of problems at Months 6 through 12. Relative to the domain of sexual interest, there was a significant difference ($p \leq 0.04$) in favor of the placebo group at the earlier months and a borderline significant difference at Month 12 ($p = 0.062$). Relative to the domain of erection, there was a significant difference in favor of placebo at Months 6 and 12 ($p \leq 0.039$).

Overall, the efficacy analysis of Study 087 supports the sponsor's claim that finasteride is statistically better ($p < 0.001$) than placebo in treating subjects with androgenetic alopecia.

However, the safety analysis of Study 087 does not support the proposed label claim that the safety profiles of finasteride and placebo were similar. The Sexual Function Questionnaire showed that there were statistically significant differences ($p < 0.001$) in favor of placebo relative to morning erections at Months 3, 6, 9, and 12. There was a significant difference ($p \leq 0.039$) in favor of placebo relative to the domain of perception of problems at Months 6 through 12. Relative to the domain of sexual interest, there was a significant difference ($p \leq 0.04$) in favor of the placebo group at the earlier months and a borderline significant difference at Month 12 ($p = 0.062$). Relative to the domain of erection, there was a significant difference in favor of placebo at Months 6 and 12 ($p \leq 0.039$).

In the adverse events analysis, a markedly greater number of finasteride patients reported sexual and drug related sexual adverse events, but these differences between the two treatment groups were only marginally statistically significant ($p < 0.12$).

IV. RESULTS OF STUDY 089

Patient Characteristics

There were 27 centers in Canada, Europe, Israel, Mexico, New Zealand, South Africa, and South America. Of the total of 620 patients (males aged 308 patients were randomized to finasteride and 312 to placebo.The two treatment groups were similar ($p > 0.05$) with regard to baseline demographics: age, race, age at which patient began losing hair, baseline hair count, and other baseline characteristics. There was no difference between the two treatment groups relative to number of patients included in the ITT analysis or Per protocol analysis at Month 12 ($p > 0.63$). The two treatment groups were similar ($p = 0.69$) relative to the number of patients who discontinued: 48 (15.6%) in the finasteride group and 45 (14.4%) in the placebo group.

Hair Count

ITT ANALYSIS

Change from baseline in hair count at Month 12 in the ITT population was a primary efficacy variable. Graph of the mean change in hair count across time in the ITT population in the two treatment groups is shown in Figure 6A of Appendix. The summary of change from baseline is presented in Table 11A of Appendix.

The change from baseline analysis showed a significant increase ($p<0.01$) in hair count for the finasteride group at Month 12 (Table 11A). The mean change in hair count was 83.7 at Month 12. The placebo group showed significant ($p<0.01$) change from baseline of -23.7 at Month 12. Comparing the finasteride group with placebo, there was a significant difference in favor of finasteride between the two groups at Month 12 ($p<0.001$). The estimated difference and 95% CI for the difference in the change from baseline between the two treatment groups at Month 12 was 107.3 hairs, with a 95% CI of (93.6, 121.0).

The treatment-by-center interaction was significant ($P=0.028$) at Month 12. Gail and Simon's test for qualitative interaction and a plot of results by center were used to investigate the nature of the interaction at Month 12. It was found that the treatment-by-center interactions were quantitative in nature (Gail and Simon's test p-value>0.05) since the mean hair counts for the finasteride group at each center were consistently higher than the mean hair counts for the placebo group for all the centers.

PER PROTOCOL ANALYSIS

Per protocol analysis was a secondary efficacy analysis used to corroborate the results in the ITT population. The results in the Per protocol analysis were very close to that in the ITT analysis. The change from baseline analysis showed a significant increase ($p<0.01$) in hair count for the finasteride group at Month 12. The mean change in hair count was 85.6 at Month 12. The placebo group showed significant ($p<0.01$) change from baseline of -27.2 at Month 12. Comparing the finasteride group with placebo, there was a significant difference in favor of finasteride between the two groups at Month 12 ($p < 0.001$). The estimated difference and 95% CI for the difference in the change from baseline between the two treatment groups at Month 12 was 112.8 hairs, with a 95% CI of (98.2, 127.4).

Patient Self-Assessment of Hair Growth

Questions 2 and 3 from the Hair Growth Questionnaire were used to evaluate patient self-assessment of treatment effect. All responses were on scales such that positive changes were indicative of efficacy or improvement. Questions 2 and 3 and their responses used in the analysis are described below.

Question 2--Because of the treatment I have received since the start of the study, the appearance of my hair is: (-3 = A lot worse = = > 3 = A lot better)

Question 3--Since the start of the study, how would you describe the growth of your hair? (-3 = Greatly decreased = = > 3 = Greatly increased)

Figures 7A and 8A of Appendix show percent of patients with positive self-assessment for Questions 2 and 3, respectively. Patient self-assessment was in favor of finasteride for both questions. Table 12A summarized distribution of scores for Question 2. The CMH test showed a significant difference between the two tretament groups ($p<0.001$) in favor of finasteride.

Table 13A summarizes distribution of scores for Question 3. The CMH test found a significant difference between the two treatment groups ($p<0.001$) favoring finasteride. Per protocol analysis for Questions 2 and 3 agreed with the analysis using the ITT population (significant treatment differences with $p<0.001$).

Investigator Assessment

Analysis was performed at Month 12 based on the investigator assessment of hair growth/loss evaluation as a change from baseline. Positive changes indicated improvement in a patient's hair and negative changes indicated deterioration. The scale for analysis ranged from -3 (greatly decreased) to 3 (greatly increased).

A graph of the percent of patients with positive investigator assessment is shown in Figure 9A of Appendix. The CMH test showed that the distributions of scores at Month 12 were significantly different ($p<0.001$) for the two treatment groups in favor of the finasteride group (Table 14A of Appendix). Analysis of the Per protocol population agreed with that of the ITT population ($p<0.001$).

Global Photographic Assessment

Analyses were performed at Month 12 based on the median of the global photographic assessments of the three dermatologists. The baseline response was assumed to represent a score of zero. Positive changes indicated improvement in a patient's hair and negative changes indicated deterioration. "Don't know" was

treated as missing. The scale for analysis and presentation of the data ranged from -3 (greatly decreased) to 3 (greatly increased).

Figure 10A of Appendix displays the percent of patients with positive global photographic assessment. It shows better performance of finasteride compared to placebo. Analysis of the Global photographic assessment data (Table 15A) demonstrated that the finasteride group was statistically better than placebo group at Month 12 ($p<0.001$ in the CMH test). Analysis based on the Per protocol population yielded similar results with $p<0.001$.

Prevention of Further Hair Loss

The objective of this analysis was to assess whether treatment with placebo results in a decrease in hair count in men with male pattern hair loss compared with baseline to support the hypothesis that finasteride can be used to prevent further hair loss. The hypothesis that finasteride would prevent further hair loss was demonstrated at Month 12 as follows:

1) The placebo group showed a statistically significant loss of hair, based on hair counts, as compared with baseline (Figure 6A, Table 11A).

2) Finasteride showed a statistically significant increase in hair counts compared with baseline and placebo (Figure 6A, Table 11A).

3) Question 4 from the Hair Growth Questionnaire that addressed slowing in loss of hair. (Since the start of the study, how effective do you think this treatment has been in slowing down your hair loss?) was shown to be statistically significant with a positive effect of finasteride versus placebo (Figure 11A, Table 16A).

Subgroup Analyses

Analysis was performed at Month 12 on change from baseline in hair count and on the hair growth questions for the following subgroups: age, race, baseline hair counts, baseline modified Norwood/Hamilton classification as assessed by the investigator, number of years a patient had been balding, and positive family history of baldness. Subgroup analysis by race included only 2 subgroups: Caucasians and non-Caucasians, because there were only 2 black patients in the study. Finasteride was numerically superior to placebo in each of the subgroups examined.

Safety

Adverse Experiences—Clinical

Three hundred eight finasteride patients and 312 placebo patients were evaluated for safety. The mean duration of therapy was 315.6 days for finasteride patients and 316.9 days for placebo patients.

Overall Assessment of Clinical Adverse Experiences

During the 12-month treatment period, clinical AEs were reported for 185 patients (60.1%) in the finasteride and 178 patients (57.1%) in the placebo group ($p=0.45$). The clinical AE summary is presented in Table 17A. More patients in the finasteride group reported drug-related AEs, sexual AEs, and drug-related sexual AEs but these differences did not reach statistical significance ($p \geq 0.08$).

Table 18A lists the clinical AEs by body system. Relative to musculoskeletal disorders, finasteride group had significantly ($p=0.028$) more (12.7%) patient with AEs than the placebo group (7.4%). Relative to all other body systems, the difference between the finasteride and placebo groups was not significant ($p \geq 0.077$).

Table 19A presents number of subjects with drug related sexual AEs. Twelve finasteride patients (3.9%) and five (1.6%) placebo patients reported drug related sexual experiences ($p=0.09$). Of these, 5 finasteride patients (42%) and 1 (20%) placebo patient reported resolution of the sexual AEs while on therapy.

A total of 6 patients, 4 (1.3%) in the finasteride group and 2 (0.6%) in the placebo group, discontinued due to drug-related sexual AEs. These AEs resolved either prior to discontinuation therapy or after stopping therapy.

Laboratory AEs

Total 294 finasteride patients and 297 placebo patients had at least one laboratory test after Month 0. Of them, laboratory AEs were reported for 33 (11.2%) finasteride and 30 (10.1%) placebo patients ($p=0.66$). Drug related laboratory AEs were reported for 17 subjects in each group ($p=0.98$).

Sexual Function Questionnaire.

A Sexual Function Questionnaire was used to evaluate effect of finasteride on sexually related AEs. All questions were divided into six domains: Sexual Interest, Erections, Ejaculation, Perception of Problems, Global Question and Morning

erections. The total scores were computed for each domain. The responses were ordered such that smaller scores indicate worsening condition and larger scores indicate improvement. Table 20A of Appendix presents a summary of the total scores by the domain. There were significant differences ($p \leq 0.017$) in favor of placebo relative to Sexual Interest and Morning Erections at Months 3, 6, 9, and 12. Relative to Erections, significant differences were at Months 3, 9, and 12 ($p \leq 0.035$).

Reviewer's Conclusions on Study 089.

This was an international study with 27 centers in Canada, Europe, Israel, Mexico, New Zealand, South Africa, and South America. Of the total of 620 patients, 308 patients were randomized to finasteride and 312 to placebo. The two treatment groups were comparable ($p > 0.05$) relative to baseline demographic characteristics and discontinuation rates. Efficacy analysis in the ITT population showed that finasteride was statistically better ($p < 0.001$) than placebo relative to the change from baseline in hair count with the mean difference of 107.3 hairs between the two treatment groups. Finasteride was also statistically better ($p < 0.001$) than placebo relative to patient's self-assessment of hair growth. The results for the Per protocol population supported the results for the ITT population. The subgroup analysis showed that there was a similarity between the subgroups relative to the mean change in hair count and hair growth questions. Relative to the secondary efficacy variables, Investigator's assessment, Global photographic assessment by the panel of independent dermatologists, and assessment of slowing hair loss, finasteride was also statistically better ($p < 0.001$) than placebo.

In the adverse events analysis, a borderline significantly greater number of finasteride patients reported sexual and drug related sexual adverse events ($p = 0.097$ and 0.080, respectively). A significantly greater number of finasteride patients reported musculoskeletal adverse events ($p = 0.028$).

Sexual Function Questionnaire was used to examine the relationship between the use of finasteride and any occurrence of sexually related adverse events. The Sexual Function Questionnaire showed that there were significant differences ($p \leq 0.017$) in favor of placebo relative to Sexual Interest and Morning Erections at Months 3, 6, 9, and 12. Relative to Erections, significant differences were at Months 3, 9, and 12 ($p \leq 0.035$).

Overall, the efficacy analysis of Study 089 supports the sponsor's claim that finasteride is statistically better ($p < 0.001$) than placebo in treating subjects with androgenetic alopecia.

However, the safety analysis of Study 089 does not support the proposed label

claim that safety profiles of finasteride and placebo were similar. The Sexual Function Questionnaire showed that there were significant differences ($p \leq 0.017$) in favor of placebo relative to Sexual Interest and Morning Erections at Months 3, 6, 9, and 12. Relative to Erections, significant differences were at Months 3, 9, and 12 ($p \leq 0.035$).

In the adverse events analysis, a borderline significantly greater number of finasteride patients reported sexual and drug related sexual adverse events ($p = 0.097$ and 0.080, respectively).

V. RESULTS OF STUDY 092

Patient Characteristics

Study 092 was called a frontal baldness study, although actually the patients enrolled in Study 092 had frontal/mid area hair loss. Unlike Studies 087 and 089 which examined vertex area, in Study 092 a dot tattoo was placed on the frontal/mid area, a 1 square cm circular area was clipped, and Global photographs and microphotographs were taken in the frontal/mid area.

Patients were enrolled by the 15 centers in the US. Of the total of 326 patients (males aged 21 to 41), 166 patients were randomized to finasteride and 160 to placebo. The two treatment groups were similar with regard to age and race ($p \geq 0.05$). There were no significant differences ($p \geq 0.05$) between the two treatment groups relative to patients' family history of baldness, and age at which patients began losing hair, baseline hair count. There was no difference ($p = 0.53$) between the two treatment groups relative to the number of patients who discontinued: 19 (11%) in the finasteride group and 22 (14%) in the placebo group.

Hair Count

Before taking macrophotographs, a circular area of 1 square cm in a representative section of the frontal or mid area of the bald scalp was clipped. (Compare with the area of 5.1 square cm in Studies 087 and 089).

Primary efficacy analysis was performed on the ITT population at Month 12 on change from baseline in hair count. The change from baseline analysis showed a significant increase ($p < 0.01$) in hair count for the finasteride group at both Months 6 and 12. The mean increase in hair count was 7.5 hairs at Month 6 and 9.6 hairs at Month 12. The placebo group showed a significant decrease in change from baseline of -4.1 hairs at Month 6 ($p < 0.01$) and a non-significant decrease of -2.0 hairs from baseline at Month 12 ($p = 0.19$).

Comparing the finasteride group with placebo, there was a significant difference in favor of finasteride between the groups at both Months 6 and 12 ($p<0.001$). The estimated difference in the change from baseline between the two treatment groups at Month 12 was 11.6 hairs, with a 95% CI of (7.7, 15.5).

There were nonsignificant increases in hair count from Month 6 to 12 for both finasteride and placebo groups (mean increases of 2.2 and 2.4, respectively). The difference between the groups in change of hair count from Month 6 to Month 12 was not significant ($p=0.9$).

Patient Self-Assessment of Hair Growth

Question 4a from the Hair Growth Questionnaire was used by this reviewer as a primary efficacy variable to evaluate patient self-assessment of hair growth in the frontal/mid area. All responses were on scale such that positive changes were indicative of efficacy or improvement. Question 4 and the responses used in the analysis are described below.

Question 4a -- Compared to the beginning of the study, which statement best describes your satisfaction with the appearance of the hairline at the front of your head?: (-2 = I am very dissatisfied = = = = = > 2 = I am very satisfied).
At both Months 6 and 12, the mean score in Question 4a for the finasteride group was not significantly different from zero. The difference between the two treatment groups relative to Question 4a was significant and in favor of finasteride at Months 6, and 12 ($p<0.008$).

Investigator Assessment

Analysis was performed at Months 6 and 12 based on the investigator assessment of hair growth/loss evaluated as a change from baseline. Positive changes indicated improvement in a patient's hair and negative changes indicated deterioration. "Don't know" was treated as missing. The scale for analysis and presentation of the data ranged from -3 (greatly decreased) to 3 (greatly increased).

The finasteride group was significantly better than placebo at both Months 6 and 12 ($p<0.001$) relative to the Investigator's assessment. However, relative to change from Month 6 to Month 12, the difference between two groups was only marginally significant ($p=0.053$).

Global Photographic Assessment

Analysis was performed at Months 6 and 12 based on the median of the global photographic assessments of 3 dermatologists. Positive changes indicated

improvement in a patient's hair and negative changes indicated deterioration. "Don't know" was treated as missing. The scale for analysis and presentation of the data ranged from -3 (greatly decreased) to 3 (greatly increased).

Analysis of the global photographic assessment data indicated that the finasteride group in the ITT population was statistically superior to the placebo group at both Months 6 and 12 ($p<0.001$). However, relative to change from Month 6 to Month 12, the difference between two groups was not significant ($p=0.2$).

Safety

Adverse Experiences—Clinical

One hundred sixty-six finasteride patients and 160 placebo patients were evaluated for safety. The mean duration of therapy was 315.9 days for finasteride patients and 311.8 days for placebo patients.

Overall Assessment of Clinical Adverse Experiences

During the 12-month treatment period, clinical AEs were reported for 103 patients (62.0%) in the finasteride group and 94 patients (58.7%) in the placebo group ($p=0.54$). There was no significant difference between the two treatment groups relative to AEs by body system ($p>0.24$).

Reviewer's Conclusions on Study 092

Of the total of 326 patients, 166 patients were randomized to finasteride and 160 to placebo. The two treatment groups were comparable ($p>0.05$) relative to baseline demographic characteristics and discontinuation rates. Primary efficacy analysis showed that finasteride was statistically better ($p<0.001$) than placebo relative to the change from baseline in hair count with the mean difference of 11.6 hairs between the two treatment groups (95% CI: 7.7, 15.5).

To interpret the difference of 11.6 hairs between treatment groups, we need to take into account that the frontal/mid area baldness Study 092 used a smaller target area compared with vertex baldness Studies 087 and 089. Assuming that hair count is proportional to the geometric area of the target region and taking into account that 1 cm^2 circular area in Study 092 is approximately one fifth the size of the 1 inch diameter circle from the vertex area in Studies 087 and 089, it follow that the 11.6 hair difference seen in Study 092 is approximately equivalent to a 60 hair difference in a 1-inch diameter circle. Comparison of the 60 hair difference in the frontal area with the approximately 106 hair difference shown in vertex area Studies 087 and 089 leads to the conclusion that finasteride works better in the

vertex area than in the frontal/mid area.

Analysis of another primary efficacy variable - Patient's self-assessment using Hair Growth Questionnaire also shown that finasteride performed significantly better than placebo at both Months 6 and 12 ($p<0.008$).

Analysis of the secondary efficacy variables, Investigator's assessment and Global photographic assessment also demonstrated that finasteride was significantly better than placebo at both Months 6 and 12 ($p<0.001$).

Study 092 did not distinguish between frontal and mid areas. Therefore, it is not clear what was the efficacy of finasteride in frontal area alone. The following conclusions are on the efficacy in frontal/ mid area. The efficacy analysis of Study 092 supports the sponsor's claim that finasteride is statistically better ($p<0.001$) than placebo in treating subjects with androgenetic alopecia in the frontal/mid area. However, comparison of the results of Study 092 with vertex area Studies 087 and 089 shows that finasteride works in the vertex area better than in the frontal/mid area.

VI. INTEGRATED SAFETY ANALYSIS OF PHASE III STUDIES 087, 089, AND 092

1. Adverse events in Studies 087, 089, and 092 combined

Of the total of 1879 subjects enrolled in the three Phase III studies, 945 were in the finasteride group and 934 were in the placebo group. Integrated analysis of clinical adverse experiences in three Phase III studies showed that by the end of 12 months of treatment with finasteride, 36 (3.8%) of 945 men had reported one or more drug related sexual adverse experiences as compared to 20 (2.1%) of 934 men treated with placebo ($p=0.04$). In particular, the following drug related adverse experiences were reported: decreased libido (finasteride, 1.8%, vs. placebo, 1.3%), erectile disfunction (1.3%, 0.7%), and ejaculation disorder (1.2%, 0.7%).

2. Sexual Function Questionnaire in Studies 087 and 089 combined

A Sexual Function Questionnaire was administered in Studies 087 and 089 to detect more subtle changes in sexual function. The questionnaire consisted of four domains: sexual interest, erections, ejaculation, and perception of problems, and two other distinct questions: a global question addressing the overall satisfaction of the patient with his sex life, and a question addressing the occurrence of morning erections.

Comparisons at Month 12 on changes from baseline scores between treatment groups showed decreases in all parameters in patients treated with finasteride, while those treated with placebo did not or showed less decrease, as shown in the following

Table 1
Score Change from Baseline to Month 12 in Two Phase 3 Studies

Domains	Propecia	Placebo	P-values
Sexual interest	-0.2	0.1	<0.01
Erections	-0.2	0.1	<0.01
Ejaculation	-0.2	-0.1	0.184
Perception of problems	-0.5	-0.3	<0.05
Questions			
Overall satisfaction with sex life	-0.1	0.0	0.319
Morning erections	-0.1	0.1	<0.01

VI. SPECIALIZED STUDIES ON SEMEN PRODUCTION

Phase III studies did not include laboratory measurements of the semen production. Two specialized studies (protocols 012 and 056) showed that finasteride 5 mg produced a statistically significant decrease in ejaculate volume compared to placebo. Further, in Study 012, a -0.5 ml change from baseline ejaculate volume was still evident for finasteride 5 mg after approximately 12 weeks of discontinuation of treatment. In Study 056, there still was a clinically and statistically significant difference between finasteride 5 mg and placebo after 36 weeks of discontinuation of treatment.

Effect of finasteride 1 mg on semen production was evaluated in safety Study 094. 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% confidence interval. According to the Protocol, the minimal clinically important difference relatively to ejaculate volume is 10%.

Denote: Dif = true difference between finasteride 1 mg and placebo relative to median % change in ejaculate volume from Week 48 to baseline. Then:

H_0: Dif < -10% or Dif > +10% (There is a difference)

H_1: | Dif | < 10% (No difference)

In this case, the decision rule is as follows: If the 90% CI for the difference in median % change falls within +/-10%, then reject H_0 and accept H_1, i.e. conclude that there is no difference between finasteride and placebo relative to ejaculate volume.

However, if the 90% CI falls outside +/-10%, then the data support H_0 and we cannot reject H_0. In other words, the data failed to support the claim of no difference between treatment groups.

The results of Study showed that the 90% CI for the median difference was (-10.4%, 13.1%). This confidence interval includes +/-10% which was the minimal clinically important difference stated in the protocol. Therefore, it can not be concluded that the difference between the two treatment groups was less than the 10% clinically important difference.

All other analyses also failed to support the claim of no difference between finasteride and placebo relative to ejaculate volume. Table 2 shows that both at Week 24 and 48, in both Per Protocol and ITT populations, for both median and mean analyses, all the lower bounds in the 90% confidence intervals for the difference between finasteride and placebo fall beyond 10% which was a clinically important difference.

Table 2
90% Confidence Intervals for the difference between
finasteride 1 mg and placebo relative to percent change in ejaculate volume

Population	median/ mean	# finasteride patients	# placebo patients	Week	90% Confidence Interval
Per Protocol	median	38	33	24	(-12.2%, 5.7%)
Per Protocol	median	37	30	48	(-10.4%, 13.1%)
ITT	median	40	35	48	(-13.5%, 9.5%)
Per Protocol	mean	37	30	48	(-12.5%, 15.6%)
ITT	mean	40	35	48	(-15.5%, 9.9%)

Therefore, the data in Study 094 do not support the claim that the true difference between the treatment groups relative to ejaculate volume is less than 10%.

Unfortunately, this correct conclusion was not presented by the sponsor in the conclusions on safety. The safety conclusions in the NDA 20-788 do not mention the 90% confidence intervals as required by the protocol. Instead of the 90% CI, the sponsor mentioned a $p=0.9$ which alone is not appropriate for demonstrating no difference (or equivalence). The sponsor's conclusion throughout NDA 20-788 and in the "Adverse Reactions" section 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: The results of safety study 094 failed to support the claim that there was no difference between finasteride and placebo relative to ejaculate volume. This is due to an inadequate small sample size (37 patients on finasteride and 30 patients on placebo).

This reviewer did power calculations based on mean percent change and found that for the sample sizes of $37+30$ (placebo mean change = -6.3, SD = 35.5, and 1-sided alpha = 0.05), the power to detect a 10% difference was only 30% . Power analysis for medians can yield a slightly higher power, but still this power will be far less than the required 80%.

VII. OVERALL REVIEWER'S CONCLUSIONS

Three Phase III Studies, 087, 089, and 092, were submitted as an evidence to support the claim that finasteride (propecia 1mg tablets) once daily is safe and effective for treating androgenetic alopecia in males. Studies 087 and 089 were identical in design and examined vertex area. A frontal/mid area baldness Study 092 had a similar design with two major differences being that Study 092: a) included men with frontal/mid area baldness and b) did not use Sexual Function Questionnaire.

The primary efficacy population was the ITT population, primary efficacy timepoint was Month 12, primary efficacy variables were change in hair count from baseline and patient's self-assessment using Hair Growth Questionnaire. Subgroup analysis was performed at Month 12 on change from baseline in hair count and on the hair growth questions for the following subgroups: age, race, baseline hair count, baseline modified Norwood/Hamilton classification as assessed by the investigator, number of years a patient has been balding, and positive family history of baldness.

A Sexual Function Questionnaire was administered in Studies 087 and 089 to detect changes in sexual function. The questionnaire consisted of four domains: sexual interest, erections, ejaculation, and perception of problems, and two other

distinct questions: a global question addressing the overall satisfaction of the patient with his sex life, and a question addressing the occurrence of morning erections.

1. Study 087

The efficacy analysis of Study 087 supports the sponsor's claim that finasteride is statistically significantly better ($p<0.001$) than placebo in treating subjects with androgenetic alopecia in vertex area. Finasteride was numerically superior to placebo in each of the subgroups examined.

The safety analysis of Study 087 does not statistically support the proposed label claim that safety profiles of finasteride and placebo are similar. The Sexual Function Questionnaire showed that there was a statistically significant difference ($p<0.001$) in favor of placebo relative to morning erections at all times (Months 3, 6, 9, and 12). There was a statistically significant difference ($p\leq0.039$) in favor of placebo relative to the perception of problems at Months 6 through 12. Relative to sexual interest, there was a statistically significant difference ($p\leq0.04$) in favor of placebo at the earlier months and a borderline significant difference at Month 12 ($p=0.062$). Relative to erections, there was a statistically significant difference in favor of placebo at Months 6 and 12 ($p\leq0.039$).

In the adverse events analysis, a markedly greater number of finasteride patients reported drug related sexual adverse events, but the difference between the two treatment groups was only marginally statistically significant ($p=0.16$).

2. Study 089

The efficacy analysis of Study 089 supports the sponsor's claim that finasteride is statistically significantly better ($p<0.001$) than placebo in treating subjects with androgenetic alopecia in vertex area. Subgroup analysis by race included only 2 subgroups: Caucasians and non-Caucasians, because there were only 2 black patients in the study. Finasteride was numerically superior to placebo in each of the subgroups examined.

Safety analysis of Study 089 does not support the proposed label claim that safety profiles of finasteride and placebo were similar. The Sexual Function Questionnaire showed that there was a significant difference ($p\leq0.017$) in favor of placebo relative to sexual interest and morning erections at all times (Months 3, 6, 9, and 12). Relative to erections, significant differences in favor of placebo were reported at Months 3, 9, and 12 ($p\leq0.035$).

In the adverse events analysis, a markedly greater number of finasteride patients reported drug related sexual adverse events ($p=0.09$).

3. Study 092 (frontal/mid area baldness)

Study 092 did not distinguish between frontal and mid areas. Therefore, it is not clear what was the efficacy of finasteride in frontal area alone. The efficacy analysis of Study 092 supports the sponsor's claim that finasteride is statistically better ($p<0.001$) than placebo in treating subjects with androgenetic alopecia in the frontal/mid area. Comparison of results of the frontal/mid area baldness Study 092 with the vertex baldness Studies 087 and 089 shows that in the vertex area finasteride works better than in the frontal/mid area.

4. Integrated safety in Studies 087, 089, and 092

Integrated analysis of clinical adverse experiences in the three Phase III studies showed that by the end of 12 months of treatment with finasteride, 36 (3.8%) of 945 men had reported one or more drug related sexual adverse experiences as compared to 20 (2.1%) of 934 men treated with placebo ($p=0.04$). In particular, the following drug related adverse experiences were reported: decreased libido (finasteride, 1.8%, vs. placebo, 1.3%), erectile disfunction (1.3%, 0.7%), and ejaculation disorder (1.2%, 0.7%).

Comparisons between treatment groups at Month 12 on changes from baseline scores in the Sexual Function Questionnaire showed decreases in all parameters in patients treated with finasteride, while those treated with placebo did not or showed less decrease. There was a statistically significant difference in favor of placebo relative to the question on morning erections and relative to the domains of sexual interest and erections ($P<0.01$). Relative to the domain of perception of problems, the difference was statistically significant in favor of placebo with $p<0.05$.

5. Specialized studies on the effect of finasteride on semen production

Phase III studies did not include laboratory measurements of the semen production. Two specialized studies (protocols 012 and 056) showed that finasteride 5 mg produced a statistically significant decrease in ejaculate volume compared to placebo. Further, in Study 012, a -0.5 ml change from baseline ejaculate volume was still evident for finasteride 5 mg after approximately 12 weeks of discontinuation of treatment. In Study 056, there still was a clinically and statistically significant difference between finasteride 5 mg and placebo after 36 weeks of discontinuation of treatment.

The effect of finasteride 1 mg on ejaculate volume was evaluated in a specialized Study 094. The 90% CI for the median difference was (-12.2%, 5.7%) at Week 24 and (-10.4%, 13.1%) at Week 48. The lower bounds of these confidence intervals fall beyond 10% which was the minimal clinically important

difference stated in the protocol. Therefore, Study 094 failed to support the claim that there was no clinically important difference between finasteride 1 mg and placebo relative to ejaculate volume.

VII. REVIEWER'S CONCLUSIONS (WHICH MAY BE CONVEYED TO THE SPONSOR)

Overall, pivotal Studies 087 and 089, evaluating vertex baldness, support the sponsor's claim that finasteride is statistically significantly better ($p<0.001$) than placebo in treating subjects with androgenetic alopecia in vertex area.

Study 092 did not distinguish between frontal and mid areas. Therefore, it is not clear what the efficacy of finasteride was in frontal area alone.

The safety analysis does not support the proposed label claim that safety profiles of finasteride and placebo are similar. Integrated analysis of clinical adverse experiences in the three Phase III studies showed that by the end of 12 months of treatment with finasteride, 36 (3.8%) of 945 men had reported one or more drug related sexual adverse experiences as compared to 20 (2.1%) of 934 men treated with placebo ($p=0.04$). In particular, the following drug related adverse experiences were reported: decreased libido (finasteride, 1.8%, vs. placebo, 1.3%), erectile disfunction (1.3%, 0.7%), and ejaculation disorder (1.2%, 0.7%).

At Month 12, integrated analysis of changes from baseline scores in a Sexual Function Questionnaire showed decreases in all parameters in patients treated with finasteride, while those treated with placebo did not or showed less decrease. There was a statistically significant difference in favor of placebo relative to the question on morning erections and relative to the domains of sexual interest and erections ($p<0.01$). Relative to the domain of perception of problems, the difference was statistically significant in favor of placebo with $p<0.05$.

A specialized safety Study 094 failed to support the claim that there was no clinically important difference between finasteride 1 mg and placebo relative to ejaculate volume.

This is a matter of the clinical judgement of the reviewing medical division to decide whether finasteride (propecia 1 mg tablets) should be approved given the safety issues described above. A warning about possible sexual adverse experiences should be crafted into the label, if approved. An adequately powered Phase IV study is recommended to evaluate effect of finasteride on semen production and sexual function.

11.25.97

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12/11/97

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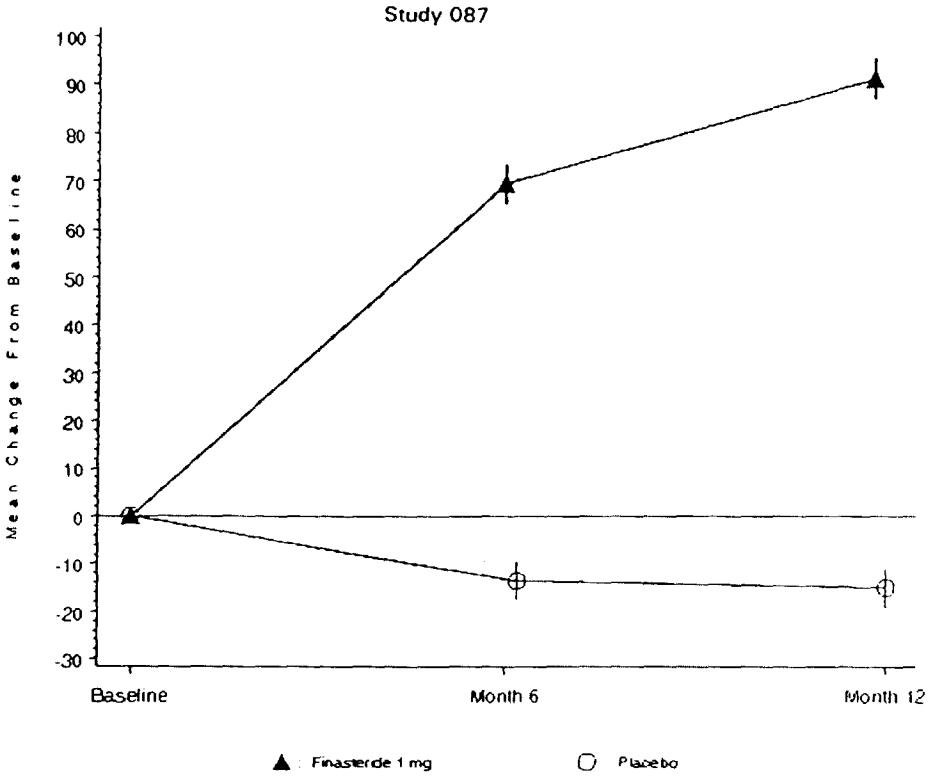
Archival NDA 20-788
HFD-540
HFD-540/Dr. Wilkin
HFD-540/Dr. Walker
HFD-540/Mrs. Kummerer
HFD-540/Dr. Hon-Sum Ko
HFD-725/Dr. Srinivasan
HFD-725/Dr. Freidlin
HFD-725/Dr. Huque
HFD-344/Dr. Carreras
Chron

This review contains 32 pages and Appendix with 20 Tables and 11 Figures.
WordPerfect 6.1/finaste1/propeci8.r8/11.25.97

Appendix
Figure 1A

Hair Count
Intention-to-Treat Population
Mean Change† (Hairs) ±1 SE



† Adjusted for the treatment and center effects

Appendix
Table 1A

Summary Statistics for Change From Baseline to Month 12 in Hair Count
Intention-to-Treat Population
Study 087

	Month 12					
	Finasteride 1 mg			Placebo		
	Baseline	Month 12	Change	Baseline	Month 12	Change
N	407	407	407	395	395	395
Mean	856.1	944.9	88.8	846.5	829.2	-17.3
SD	251.3	263.5	88.4	250.8	263.1	75.0
Lower quartile						
Median	848.0	939.0	81.0	837.0	821.0	-13.0
Upper quartile						

Least Squares Summary Statistics and Confidence Intervals

	Finasteride 1 mg	Placebo
Mean change+	91.3**	-15.0**
95% confidence interval	(83.3, 99.4)	(-23.2, -6.8)

	Difference+	95% CI	p-Value
Finasteride 1 mg vs placebo	106.3	(95.3, 117.3)	< 0.001

Treatment-by-center interaction: p-value = 0.665

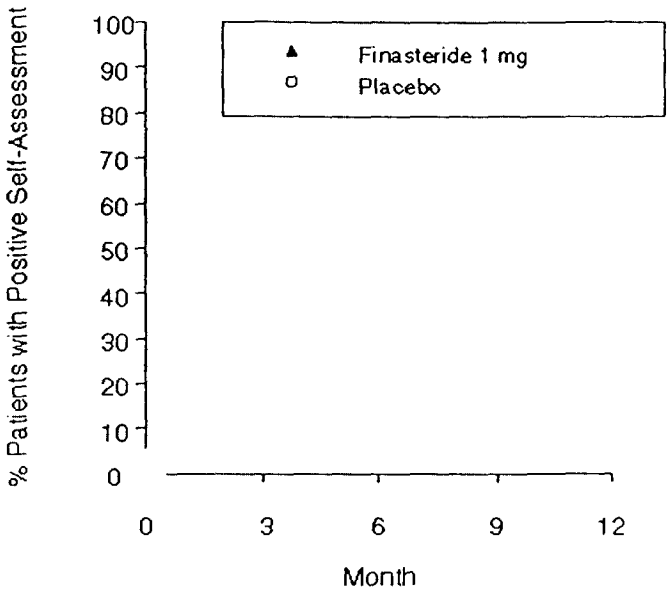
+ : Adjusted for the treatment and center effects

*, ** : Significant change from baseline at the $p < 0.050$ and $p < 0.010$ level, respectively

Appendix
Figure 2A

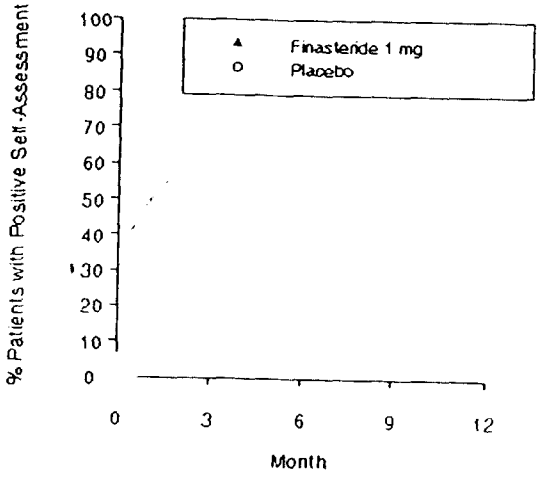
(i) Question 2 of the Patient Hair Growth Questionnaire.
Percent of Patients with Positive Self-Assessment.
Intent-to-Treat Population.

Study 087



(ii) Question 3 of the Patient Hair Growth Questionnaire.
Percent of Patients with Positive Self-Assessment.
Intent-to-Treat Population.

Study 087



Appendix
Table 2A

Summary Statistics for Question 2 at Month 12
Because of the Treatment I Have Received Since the Start of the Study, the Appearance of My Hair Is:
Intention-to-Treat Population
Study 087

	Month 12	
Question 2	**Finasteride 1 mg**	**Placebo**
-3: A lot worse	1 (0%)	4 (1%)
-2: Somewhat worse	9 (2%)	19 (4%)
-1: A little worse	22 (5%)	50 (11%)
0: Same	147 (33%)	210 (47%)
1: A little better	117 (26%)	101 (23%)
2: Somewhat better	96 (21%)	40 (9%)
3: A lot better	60 (13%)	20 (5%)
Total	452 (100%)	444 (100%)
Summary Statistics		
N	452	444
Mean	1.0	0.3
SD	1.2	1.1
Lower quartile		
Median	1.0	0.0
Upper quartile		

$P<0.001$ in the CMH test adjusting for investigator.

Appendix
Table 3A

Summary Statistics for Question 3 at Month 12
Since the Start of the Study, How Would You Describe the Growth of Your Hair?
Intention-to-Treat Population
Study 087

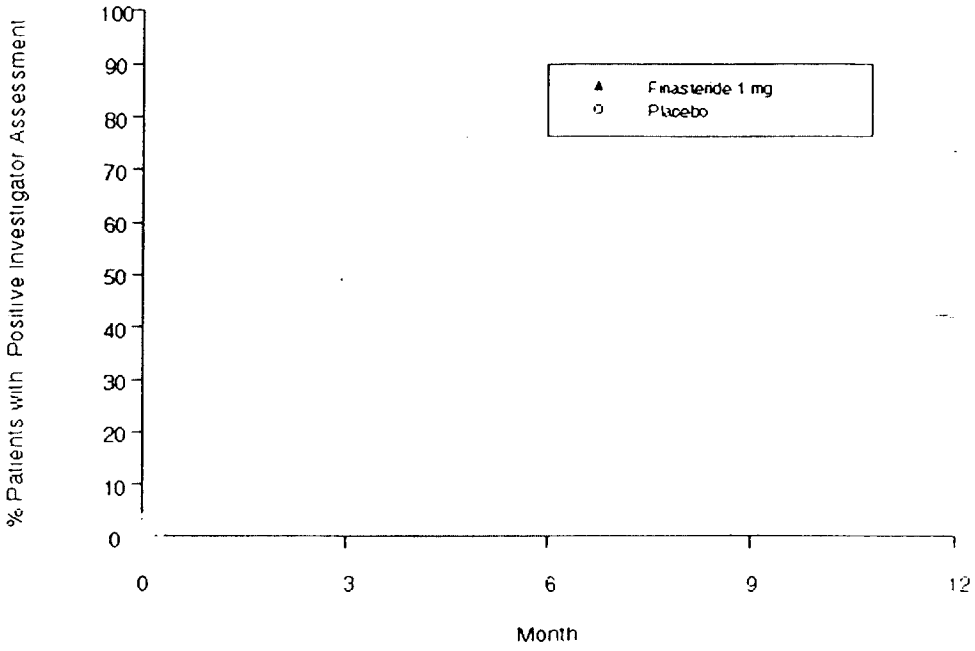
	Month 12	
Question 3	Finasteride 1 mg	Placebo
-3: Greatly decreased	1 (0%)	2 (0%)
-2: Moderately decreased	2 (0%)	15 (3%)
-1: Slightly decreased	24 (5%)	46 (10%)
0: No change	164 (36%)	214 (48%)
1: Slightly increased	155 (34%)	129 (29%)
2: Moderately increased	79 (17%)	32 (7%)
3: Greatly increased	27 (6%)	6 (1%)
Total	452 (100%)	444 (100%)
Summary Statistics		
N	452	444
Mean	0.8	0.3
SD	1.0	0.9
Lower quartile		
Median	1.0	0.0
Upper quartile		

$P<0.001$ in the CMH test adjusting for investigator.

Appendix
Figure 3A

Investigator Assessment
Percent of Patients With Positive Investigator Assessment
Intention-to-Treat Population

Study 087



Appendix
Table 4A

Summary Statistics for Investigator Assessment at Month 12
Intention-to-Treat Population
Study 087

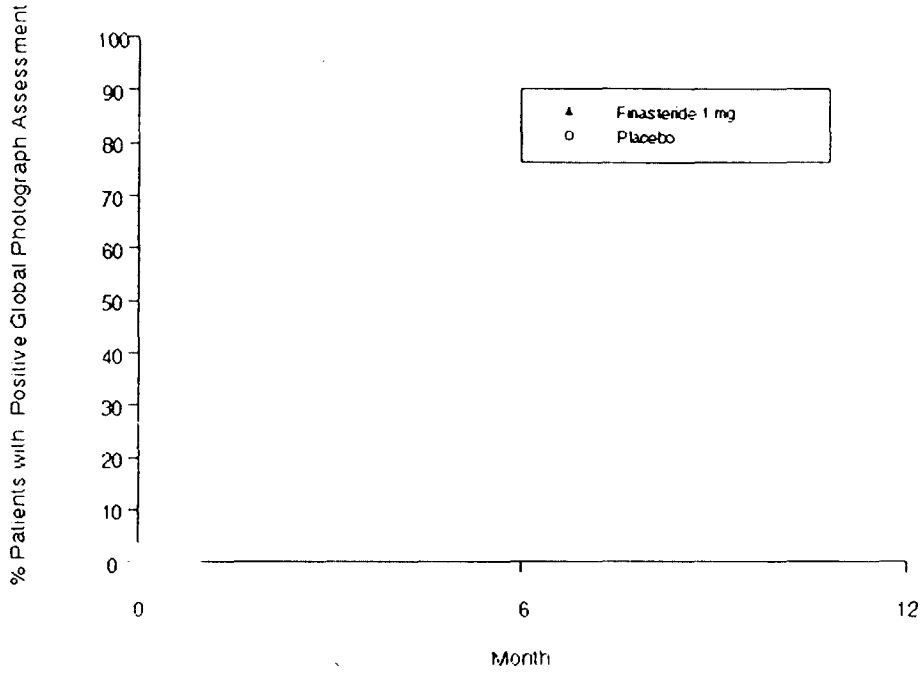
	Month 12	
Investigator Assessment	Finasteride 1 mg	Placebo
-3: Greatly decreased	0 (0%)	1 (0%)
-2: Moderately decreased	1 (0%)	10 (2%)
-1: Slightly decreased	12 (3%)	33 (7%)
0: No change	110 (24%)	199 (45%)
1: Slightly increased	143 (32%)	136 (31%)
2: Moderately increased	145 (32%)	55 (12%)
3: Greatly increased	40 (9%)	10 (2%)
Total	451 (100%)	444 (100%)
Summary Statistics		
N	451	444
Mean	1.2	0.5
SD	1.0	1.0
Lower quartile		
Median	1.0	0.0
Upper quartile		

$P < 0.001$ in the CMH test adjusting for investigator.

Appendix
Figure 4A

Global Photographic Assessment
Percent of Patients With Positive Global Photographic Assessment
Intention-to-Treat Population

Study 087



Appendix
Table 5A

Summary Statistics for Global Photographic Assessment at Month 12
Intention-to-Treat Population
Study 087

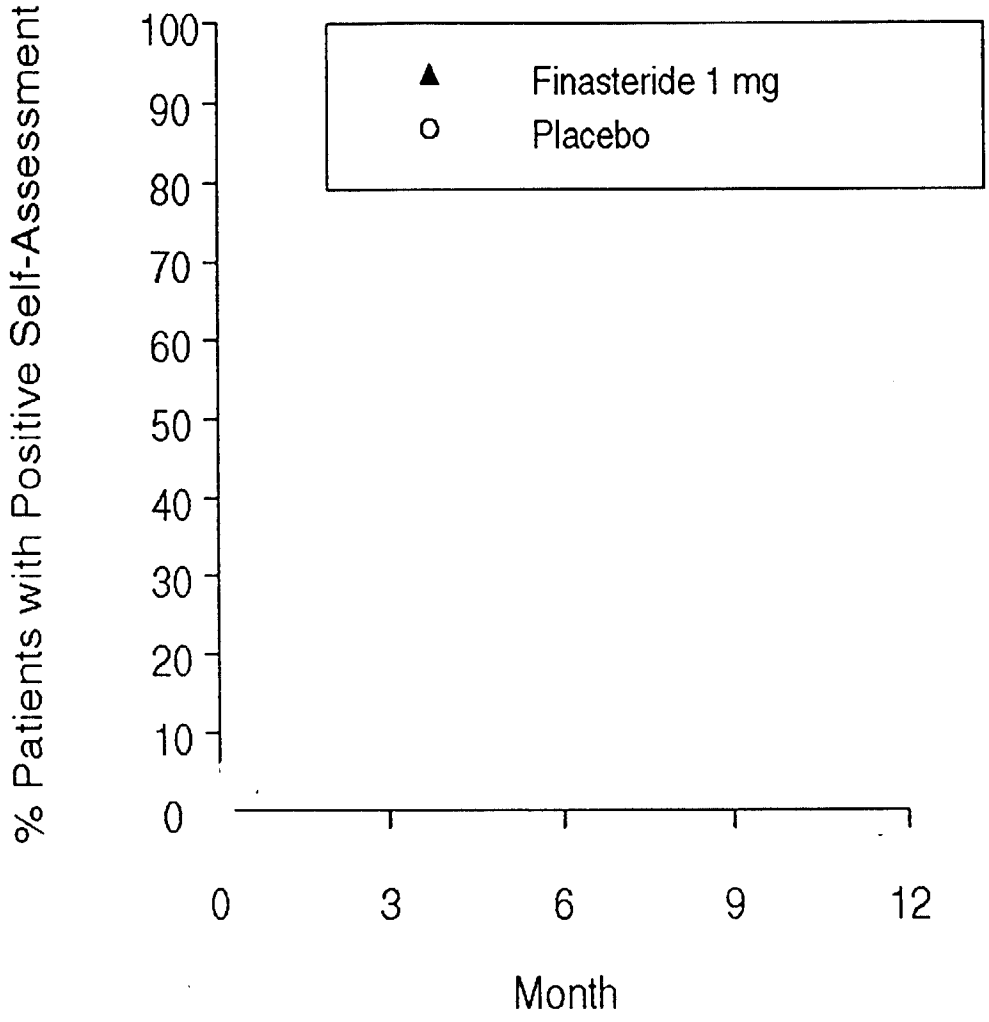
	Month 12	
Global Photographic Assessment	Finasteride 1 mg	Placebo
-3: Greatly decreased	0 (0%)	0 (0%)
-2: Moderately decreased	1 (0%)	4 (1%)
-1: Slightly decreased	4 (1%)	24 (6%)
0: No change	214 (49%)	357 (86%)
1: Slightly increased	138 (32%)	30 (7%)
2: Moderately increased	68 (16%)	2 (0%)
3: Greatly increased	10 (2%)	0 (0%)
Total	435 (100%)	417 (100%)
Summary Statistics		
N	435	417
Mean	0.7	0.0
SD	0.8	0.4
Lower quartile		
Median	0.0	0.0
Upper quartile		

$P<0.001$ in the CMH test adjusting for investigator.

Appendix
Figure 5A

Question 4 of the Patient Hair Growth Questionnaire.
Percent of Patients with Positive Self-Assessment.
Intent-to-Treat Population.

Study 087



Appendix
Table 6A

Summary Statistics for Question 4 at Month 12
Since the Start of the Study, How Effective Do You Think This Treatment Has Been in Slowing Down Your Hair Loss?
Intention-to-Treat Population
Study 087

	Month 12	
Question 4	Finasteride 1 mg	Placebo
-2: Not effective at all	43 (10%)	91 (20%)
-1: Not very effective	77 (17%)	127 (29%)
1: Somewhat effective	209 (46%)	180 (41%)
2: Very effective	123 (27%)	46 (10%)
Total	452 (100%)	444 (100%)
Summary Statistics		
N	452	444
Mean	0.6	-0.1
SD	1.3	1.4
Lower quartile		
Median	1.0	1.0
Upper quartile		

$P \leq 0.001$ in the CMH test adjusting for investigator.

Appendix
Table 7A

Clinical Adverse Experience Summary--Patient Count (%)*
Study 087

	Finasteride 1 mg (N = 471)	Placebo (N = 462)
Number (%) of patients with one or more AEs	308 (65.4)	288 (62.3)
with drug-related AEs	34 (7.2)	28 (6.1)
with sexual AEs	24 (5.1)	14 (3.0)
with drug-related sexual AEs	21 (4.5)	12 (2.6)
with serious AEs	5 (1.1)	7 (1.5)
with serious drug-related AEs	0	0
who died due to an AE	1 (0.2)	0
withdrawn from therapy due to an AE	10 (2.1)	12 (2.6)
withdrawn from therapy due to a sexual AE	7 (1.5)	6 (1.3)
withdrawn from therapy due to a drug-related AE	8 (1.7)	9 (1.9)
withdrawn from therapy due to a drug-related sexual AE	7 (1.5)	6 (1.3)
withdrawn from therapy due to a serious AE	2 (0.4)	0
withdrawn from therapy due to a serious drug-related AE	0	0

* Although a patient may have had two or more AEs, the patient was counted only once in "Number (%) of patients with one or more AEs.

P>0.11 in Chi-Square or Fisher's Exact test.

Appendix
Table 8A

Clinical Adverse Experiences by Body System--Patient Count (%)*
Study 087

	Finasteride 1 mg (N = 471)	Placebo (N = 462)
Body as a whole/site unspecified	43 (9.1)	45 (9.7)
Cardiovascular system disorders	8 (1.7)	5 (1.1)
Digestive system disorders	47 (10.0)	51 (11.0)
Endocrine disorders	0	0
Hematologic and lymphatic disorders	4 (0.8)	3 (0.6)
Metabolic, nutritional, immune disorders	12 (2.5)	16 (3.5)
Musculoskeletal disorders	75 (15.9)	59 (12.8)
Nervous system and psychiatric disorders	68 (14.4)	64 (13.9)
Respiratory system disorders	170 (36.1)	154 (33.3)
Skin and skin appendage disorders	75 (15.9)	58 (12.6)
Special sense disorders	17 (3.6)	15 (3.2)
Urogenital system disorders	33 (7.0)	23 (5.0)

* Although a patient may have had two or more AEs, the patient was counted only once in a particular body system.

P>0.14 in Chi-Square or Fisher's Exact test.

Appendix
Table 9A

Drug-Related Sexual Adverse Experiences--Patient Count (%)*
Study 087

	Finasteride 1 mg (N = 471)	Placebo (N = 462)	Between-Group p-Value	95% CIs for Between-Group Difference in Incidence (%) (1 mg—Placebo)
Number (%) of patients with one or more drug-related sexual AEs	21 (4.5)	12 (2.6)	0.156	(-1.0, 5.1)
Libido decreased	7 (1.5)	6 (1.3)	>0.999	(-1.9, 2.6)
Ejaculation disorder	10 (2.1)	6 (1.3)	0.451	(-1.4, 3.5)
Impotence	8 (1.7)	5 (1.1)	0.579	(-1.5, 3.1)
Orgasm dysfunction	1 (0.2)	1 (0.2)	>0.999	(-1.6, 1.5)
Priapism	1 (0.2)	0	>0.999	(-1.0, 1.8)

* Although a patient may have had two or more AEs, the patient was counted only once in "Number (%) of patients with one or more drug-related sexual AEs."

Appendix
Table 10A

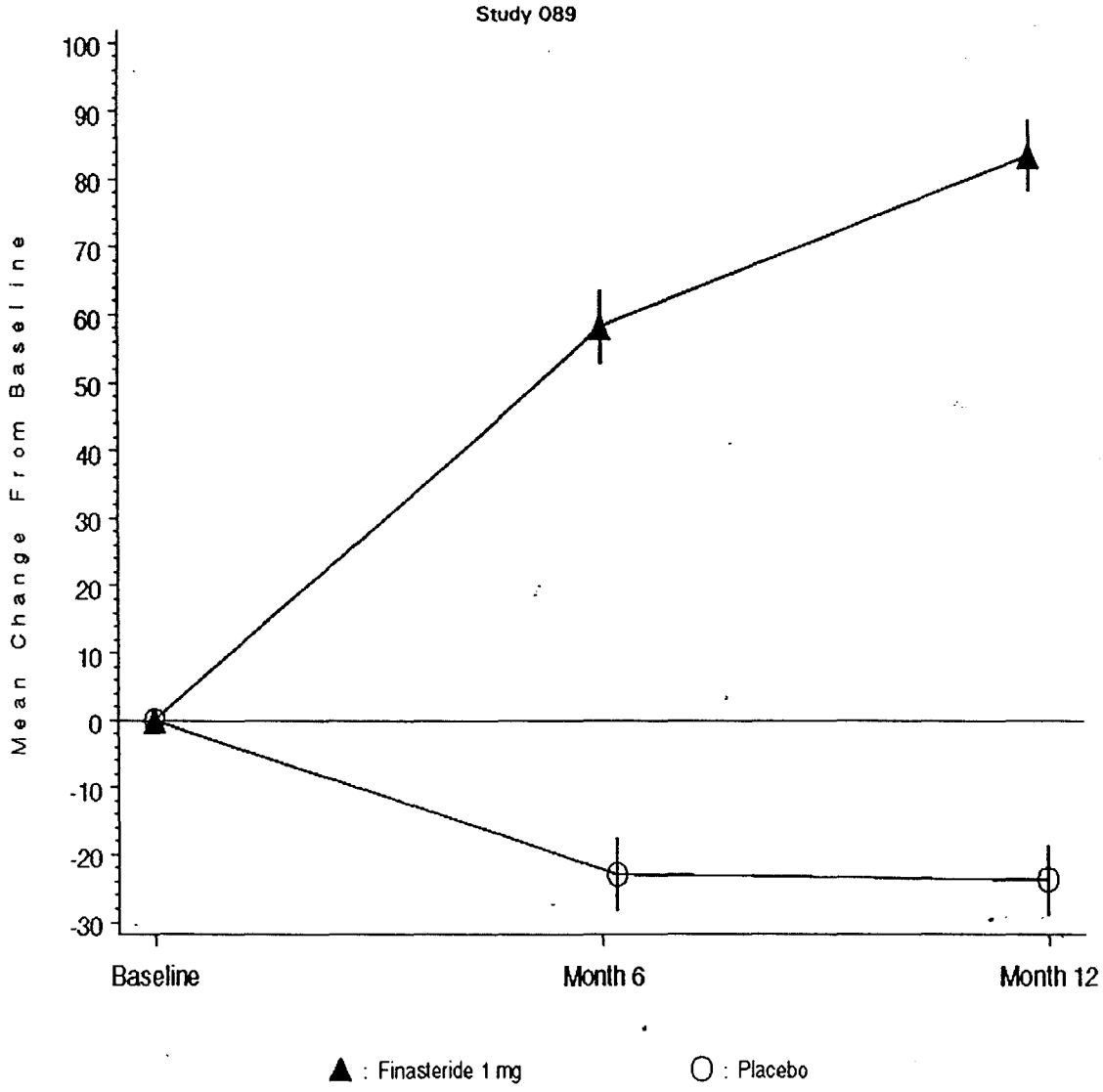
Summary Statistics for the Domains/Questions of the Sexual Function Questionnaire
Months 3, 6, 9, and 12
Intention-to-Treat Population
Study 087

Domain/Question (Scale)	Finasteride 1 mg		Placebo		Between-Group Difference+	Between-Group p-Value
	N	Mean Change+	N	Mean Change+		
Sexual Interest (0 to 8)						
Month 3	449	-0.2*	440	0.0	-0.2	0.037
Month 6	452	-0.2**	444	0.1	-0.3	<0.001
Month 9	452	-0.2*	444	0.0	-0.2	0.040
Month 12	452	-0.1	444	0.1	-0.2	0.062
Erections (0 to 11)						
Month 3	446	-0.2**	438	-0.1	-0.2	0.100
Month 6	452	-0.3**	441	0.1	-0.4	<0.001
Month 9	452	-0.2*	441	0.0	-0.2	0.090
Month 12	452	-0.2*	441	0.1	-0.3	0.039
Ejaculation (0 to 6)						
Month 3	440	-0.1**	433	-0.1**	0.0	0.664
Month 6	445	-0.2**	436	-0.1*	-0.1	0.015
Month 9	446	-0.2**	436	-0.1*	-0.1	0.050
Month 12	446	-0.2**	438	-0.1**	-0.1	0.337
Perception of Problems (0 to 12)						
Month 3	448	-0.5**	436	-0.3**	-0.2	0.224
Month 6	452	-0.6**	442	-0.2	-0.5	<0.001
Month 9	452	-0.6**	442	-0.3**	-0.3	0.039
Month 12	452	-0.7**	442	-0.3**	-0.4	0.006
Global Question (0 to 4)						
Month 3	448	0.0	440	0.0	0.0	0.783
Month 6	450	0.0	443	0.0	0.0	0.840
Month 9	451	0.0	443	0.0	0.0	0.607
Month 12	451	0.0	443	0.0	-0.1	0.223
Morning Erections (0 to 4)						
Month 3	450	-0.2**	438	0.0	-0.2	<0.001
Month 6	452	-0.2**	442	0.1	-0.3	<0.001
Month 9	452	-0.2**	442	0.1	-0.3	<0.001
Month 12	452	-0.1*	442	0.1**	-0.2	<0.001

\+ Adjusted for the treatment and center effects
*, **: Significant change from baseline at the $p < 0.050$ and $p < 0.010$ level, respectively

Appendix
Figure 6A

Hair Count
Intention-to-Treat Population
Mean Change† (Hairs) ±1 SE



† Adjusted for the treatment and center effects

Appendix
Table 11A

Summary Statistics for Change From Baseline to Month 12 in Hair Count
Intention-to-Treat Population
Study 089

	Month 12					
	Finasteride 1 mg			Placebo		
	Baseline	Month 12	Change	Baseline	Month 12	Change
N	272	272	272	277	277	277
Mean	902.8	988.4	85.5	919.4	898.1	-21.2
SD	255.2	265.3	89.1	246.5	262.5	76.4
Lower quartile						
Median	898.5	996.5	72.5	917.0	888.0	-18.0
Upper quartile						

Least Squares Summary Statistics and Confidence Intervals

	Finasteride 1 mg	Placebo
Mean change[+]	83.7**	-23.7**
95% confidence interval	(73.6, 93.7)	(-33.7, -13.7)

	Difference[+]	95% CI	p-Value
Finasteride 1 mg vs placebo	107.3	(93.6, 121.0)	< 0.001

Treatment-by-center interaction: p-value = 0.028

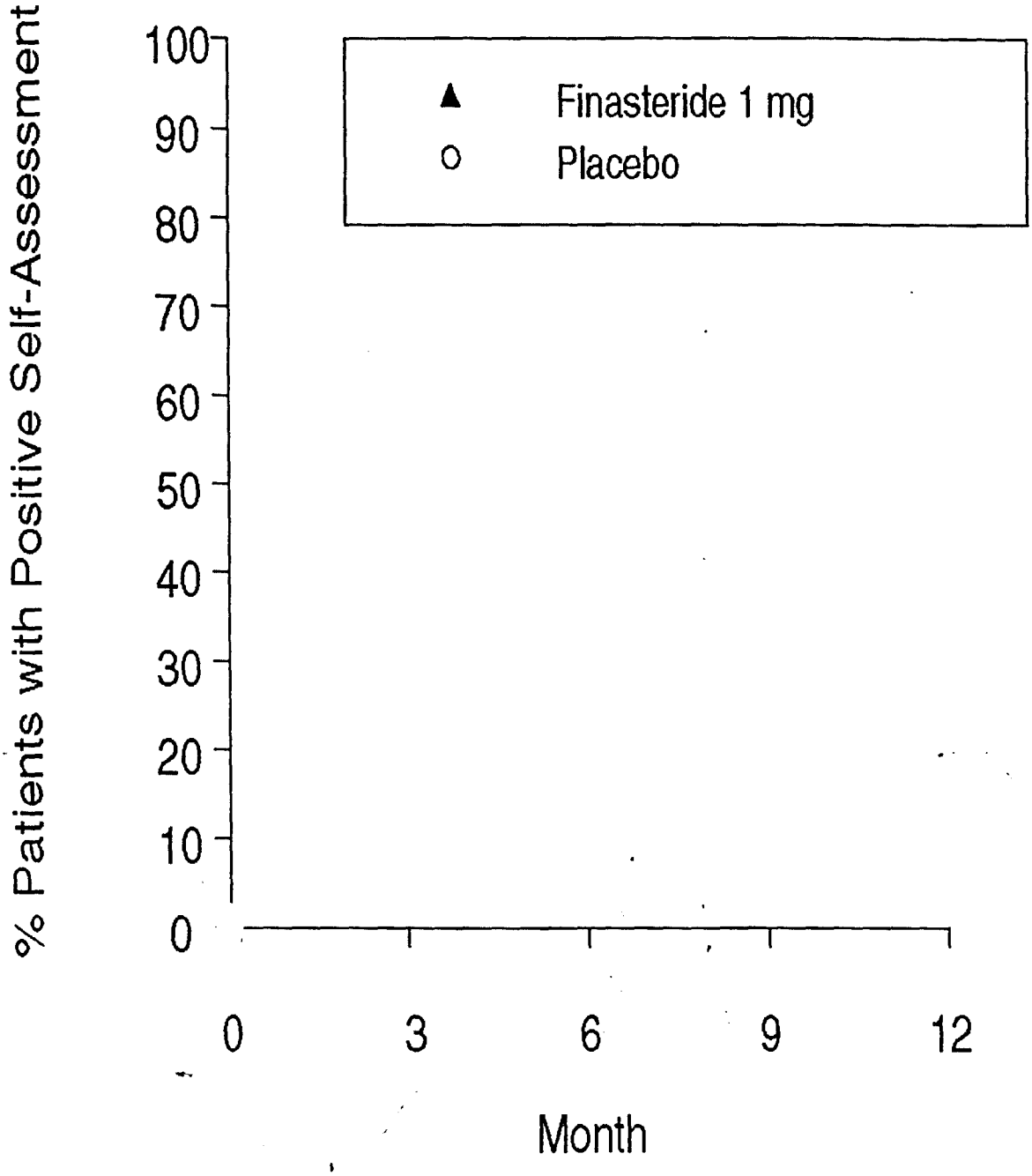
[+]: Adjusted for the treatment and center effects

*, **: Significant change from baseline at the $p < 0.050$ and $p < 0.010$ level, respectively

Appendix
Figure 7A

Question 2 of the Patient Hair Growth Questionnaire.
Percent of Patients with Positive Self-Assessment.
Intent-to-Treat Population.

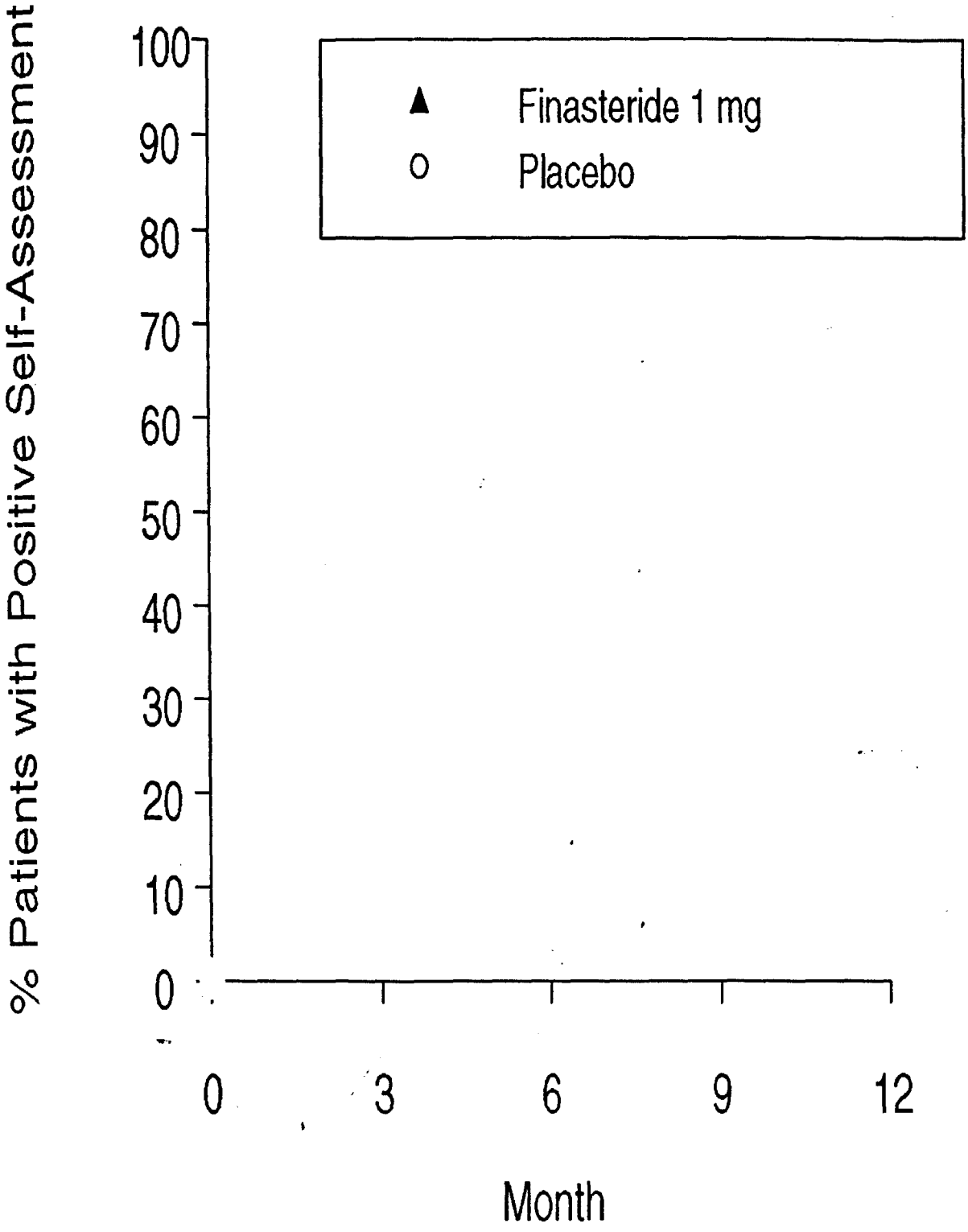
Study 089



Appendix
Figure 8A

Question 3 of the Patient Hair Growth Questionnaire.
Percent of Patients with Positive Self-Assessment.
Intent-to-Treat Population.

Study 089



Appendix
Table 12A

Summary Statistics for Question 2 at Month 12
Because of the Treatment I Have Received Since the Start of the Study, the Appearance of My Hair Is:
Intention-to-Treat Population
Study 089

	Month 12	
Question 2	Finasteride 1 mg	Placebo
-3: A lot worse	1 (0%)	7 (2%)
-2: Somewhat worse	5 (2%)	14 (5%)
-1: A little worse	20 (7%)	34 (11%)
0: Same	111 (37%)	151 (50%)
1: A little better	77 (26%)	64 (21%)
2: Somewhat better	49 (16%)	25 (8%)
3: A lot better	36 (12%)	10 (3%)
Total	299 (100%)	305 (100%)
Summary Statistics		
N	299	305
Mean	0.8	0.2
SD	1.2	1.1
Lower quartile		
Median	1.0	0.0
Upper quartile		

$P<0.001$ in the CMH test adjusting for investigator.

Appendix
Table 13A

Summary Statistics for Question 3 at Month 12
Since the Start of the Study, How Would You Describe the Growth of Your Hair?
Intention-to-Treat Population
Study 089

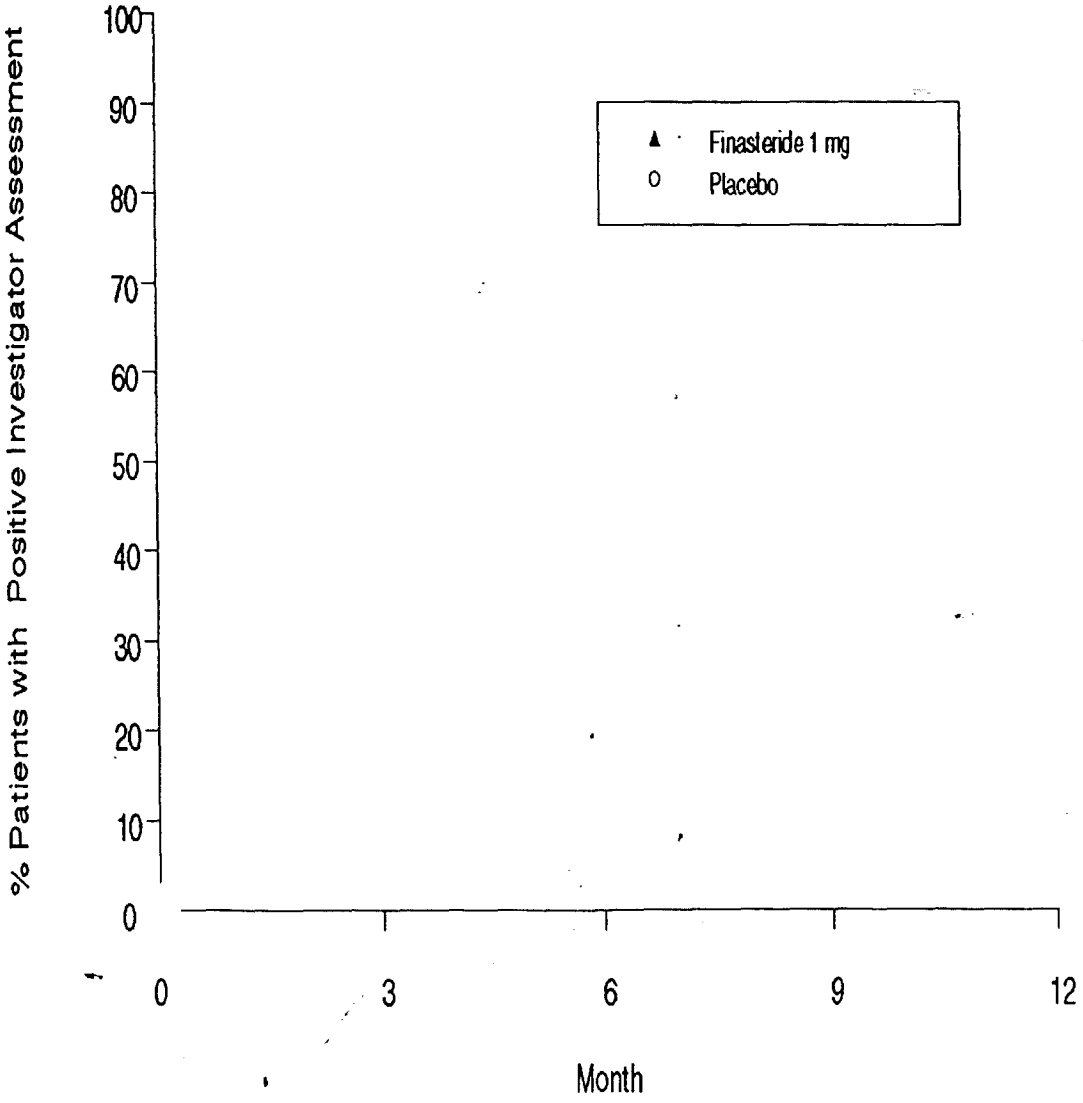
	Month 12	
Question 3	**Finasteride 1 mg**	**Placebo**
-3: Greatly decreased	2 (1%)	10 (3%)
-2: Moderately decreased	4 (1%)	14 (5%)
-1: Slightly decreased	25 (8%)	39 (13%)
0: No change	112 (37%)	162 (53%)
1: Slightly increased	96 (32%)	57 (19%)
2: Moderately increased	44 (15%)	19 (6%)
3: Greatly increased	16 (5%)	4 (1%)
Total	299 (100%)	305 (100%)
Summary Statistics		
N	299	305
Mean	0.6	0.0
SD	1.1	1.1
Lower quartile		
Median	1.0	0.0
Upper quartile		

$P<0.001$ in the CMH test adjusting for investigator.

Appendix
Figure 9A

Investigator Assessment
Percent of Patients With Positive Assessment
Intention-to-Treat Population

Study 089



Appendix
Table 14A

Summary Statistics for Investigator Assessment at Month 12
Intention-to-Treat Population

Study 089

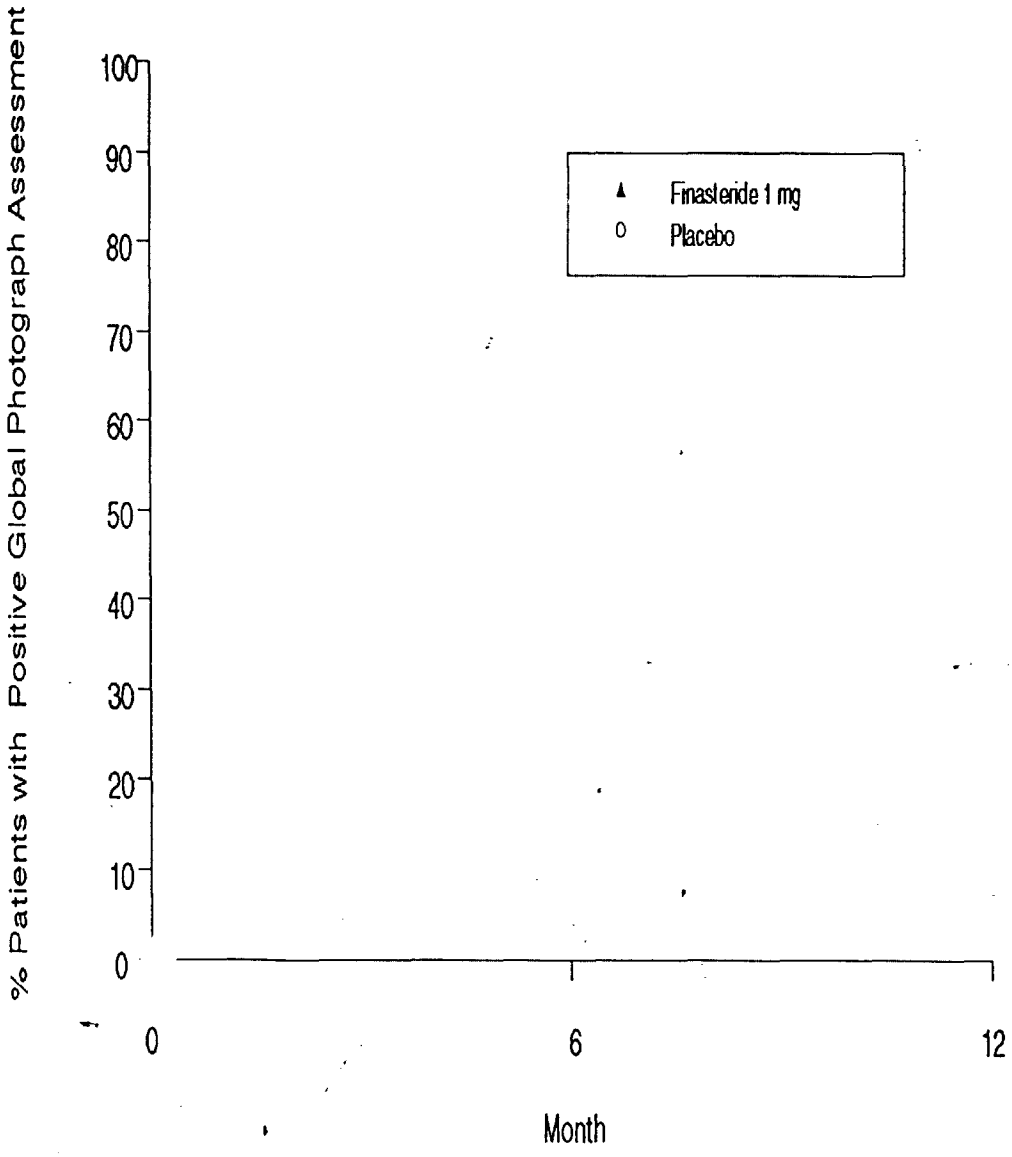
	Month 12	
Investigator Assessment	**Finasteride 1 mg**	**Placebo**
-3: Greatly decreased	0 (0%)	0 (0%)
-2: Moderately decreased	1 (0%)	4 (1%)
-1: Slightly decreased	18 (6%)	30 (10%)
0: No change	118 (40%)	191 (63%)
1: Slightly increased	96 (32%)	65 (21%)
2: Moderately increased	55 (19%)	13 (4%)
3: Greatly increased	9 (3%)	0 (0%)
Total	297 (100%)	303 (100%)
Summary Statistics		
N	297	303
Mean	0.7	0.2
SD	0.9	0.7
Lower quartile		
Median	1.0	0.0
Upper quartile		

P<0.001 in the CMH test adjusting for investigator.

Appendix
Figure 10A

Global Photographic Assessment
Percent of Patients With Positive Assessment
Intention-to-Treat Population

Study 089



Appendix
Table 15A

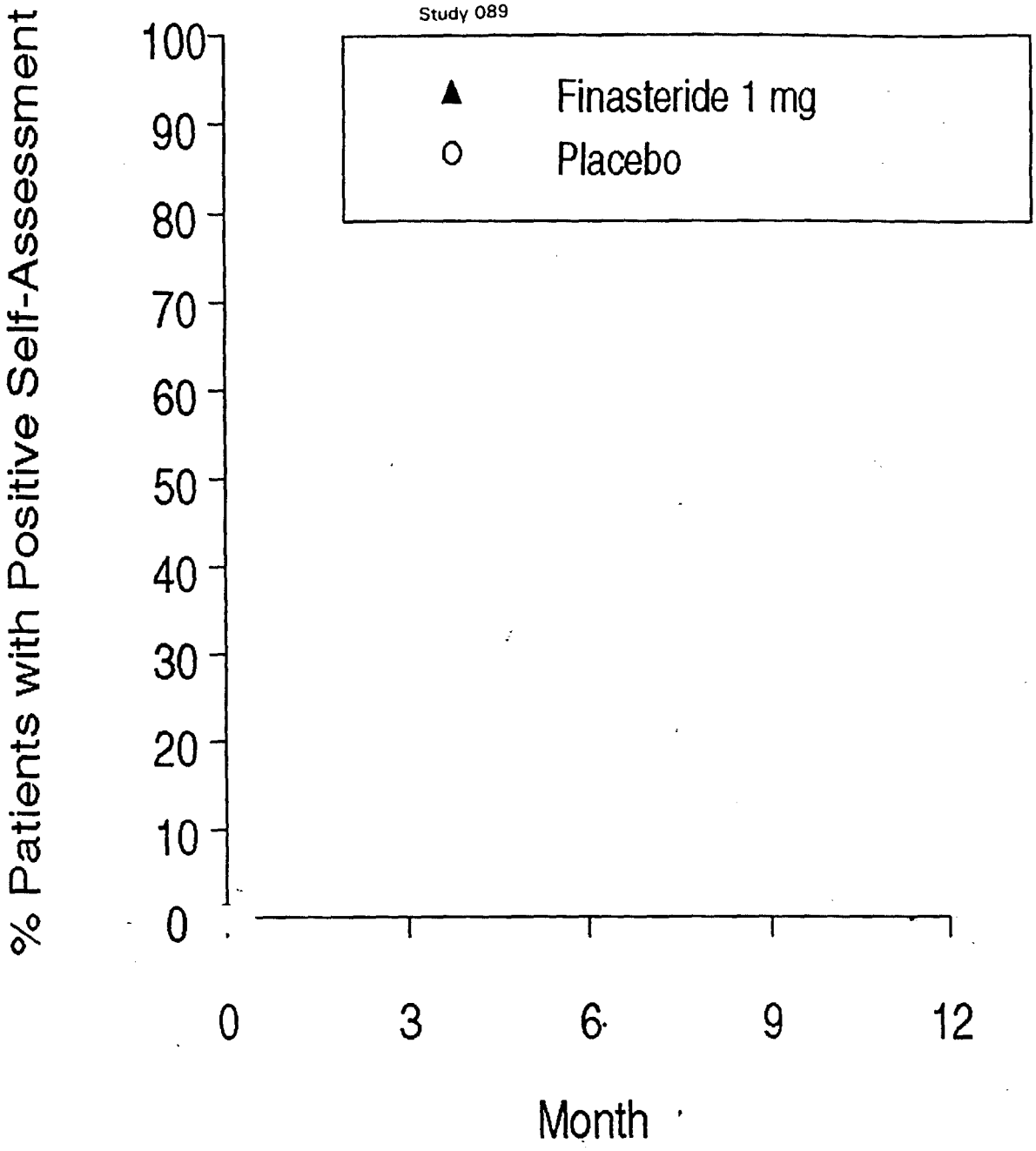
Summary Statistics for Global Photographic Assessment at Month 12
Intention-to-Treat Population

Study 089

	Month 12	
Global Photographic Assessment	**Finasteride 1 mg**	**Placebo**
-3: Greatly decreased	0 (0%)	0 (0%)
-2: Moderately decreased	0 (0%)	0 (0%)
-1: Slightly decreased	3 (1%)	26 (9%)
0: No change	156 (55%)	248 (85%)
1: Slightly increased	78 (27%)	14 (5%)
2: Moderately increased	45 (16%)	3 (1%)
3: Greatly increased	3 (1%)	1 (0%)
Total	285 (100%)	292 (100%)
Summary Statistics		
N	285	292
Mean	0.6	0.0
SD	0.8	0.5
Lower quartile		
Median	0.0	0.0
Upper quartile		

P<0.001 in the CMH test adjusting for investigator.

Appendix
Figure 11A
Question 4 of the Patient Hair Growth Questionnaire.
Percent of Patients with Positive Self-Assessment.
Intent-to-Treat Population.



Appendix
Table 16A

Summary Statistics for Question 4 at Month 12
Since the Start of the Study, How Effective Do You Think This Treatment Has Been in Slowing Down Your Hair Loss?
Intention-to-Treat Population
Study 089

	Month 12	
Question 4	**Finasteride 1 mg**	**Placebo**
-2: Not effective at all	53 (18%)	79 (26%)
-1: Not very effective	67 (22%)	114 (37%)
1: Somewhat effective	128 (43%)	84 (28%)
2: Very effective	51 (17%)	28 (9%)
Total	299 (100%)	305 (100%)
Summary Statistics		
N	299	305
Mean	0.2	-0.4
SD	1.4	1.4
Lower quartile		
Median	1.0	-1.0
Upper quartile		

$P<0.001$ in the CMH test adjusting for investigator.

Appendix
Table 17A

Clinical Adverse Experience Summary--Patient Counts (%)*

Study 089

	Finasteride 1 mg (N = 308)	Placebo (N = 312)
Number (%) of patients with one or more AEs	185 (60.1)	178 (57.1)
with drug-related AEs	32 (10.4)	27 (8.7)
with sexual AEs	13 (4.2)	6 (1.9)
with drug-related sexual AEs	12 (3.9)	5 (1.6)
who died due to an AE	0	0
with serious AEs	9 (2.9)	10 (3.2)
with serious drug-related AEs	0	0
who died due to an AE	0	0
withdrawn from therapy due to an AEs	6 (1.9)	7 (2.2)
withdrawn from therapy due to a sexual AE	4 (1.3)	2 (0.6)
withdrawn from therapy due to a serious AE	1 (0.3)	2 (0.6)
withdrawn from therapy due to a drug-related AE	5 (1.6)	5 (1.6)
withdrawn from therapy due to a drug-related sexual AE	4 (1.3)	2 (0.6)
withdrawn from therapy due to a serious drug-related AE	0	0

* Although a patient may have had two or more AEs, the patient was counted only once in "Number (%) of patients with one or more AEs."

P≥0.08 in Chi-Square or Fisher's Exact test.

Appendix
Table 18A

Clinical Adverse Experiences by Body System--Patient Counts (%)*

	Finasteride 1 mg (N = 308)	Placebo (N = 312)
Body as a whole/site unspecified	32 (10.4)	30 (9.6)
Cardiovascular system disorders	9 (2.9)	8 (2.6)
Digestive system disorders	37 (12.0)	36 (11.5)
Hematologic and lymphatic disorders	3 (1.0)	1 (0.3)
Metabolic, nutritional, immune disorders	13 (4.2)	12 (3.8)
Musculoskeletal disorders	39 (12.7)	23 (7.4)
Nervous system and psychiatric disorders	60 (19.5)	50 (16.0)
Respiratory system disorders	91 (29.5)	92 (29.5)
Skin and skin appendage disorders	35 (11.4)	38 (12.2)
Special sense disorders	15 (4.9)	7 (2.2)
Urogenital system disorders	11 (3.6)	9 (2.9)

* Although a patient may have had two or more AEs, the patient was counted only once in a particular body system.

P = 0.028 for musculoskeletal disorders and
P $\geq$ 0.077 for other comparisons in Chi-Square or Fisher's Exact test

Appendix
Table 19A

Drug-Related Sexual Adverse Experiences--Patient Count (%)*

	Finasteride 1 mg (N = 308)	Placebo (N = 312)	p-Value Between Groups	95% CI for Between-Group Difference in Incidence (%) (1 mg - Placebo)
Number (%) of patients with one or more drug-related sexual AEs	12 (3.9)	5 (1.6)	0.090	(-1.2, 6.1)
Libido decreased	8 (2.6)	4 (1.3)	0.259	(-1.9, 4.8)
Ejaculation disorder	1 (0.3)	0	0.497	(-1.7, 2.6)
Impotence	3 (1.0)	2 (0.6)	0.684	(-2.3, 3.1)
Semen abnormality	0	2 (0.6)	0.499	(-3.3, 1.3)

Although a patient may have had two or more AEs, the patient was counted only once in "Number (%) of patients with one or more drug-related sexual AEs."

Appendix
Table 20A

Summary of Statistics for Domains/Questions of the Sexual Function Questionnaire at Months 3, 6, 9, and 12
Intention-to-Treat Population

Domain/Question (Scale)	Finasteride 1 mg		Placebo		Between-Group Change+	Between-Group p-Value
	N	Mean Change+	N	Mean Change+		
Sexual Interest (0 to 8)						
Month 3	296	-0.3**	296	0.1	-0.4	<0.001
Month 6	298	-0.2*	301	0.1	-0.3	0.011
Month 9	298	-0.3**	302	0.2*	-0.4	<0.001
Month 12	298	-0.3**	302	0.1	-0.3	0.004
Erections (0 to 11)						
Month 3	292	-0.4**	291	0.0	-0.5	0.005
Month 6	297	-0.2	298	0.1	-0.3	0.082
Month 9	297	-0.3*	298	0.1	-0.4	0.035
Month 12	297	-0.2	298	0.2	-0.4	0.020
Ejaculation (0 to 6)						
Month 3	291	-0.2**	289	-0.1	-0.1	0.058
Month 6	295	-0.2**	297	-0.1	-0.1	0.293
Month 9	295	-0.2**	299	0.0	-0.1	0.065
Month 12	295	-0.2**	299	-0.1*	-0.1	0.326
Perception of Problems (0 to 12)						
Month 3	290	-0.4**	289	-0.3*	-0.1	0.592
Month 6	296	-0.3**	297	-0.1	-0.2	0.288
Month 9	297	-0.3*	300	0.0	-0.4	0.065
Month 12	297	-0.3*	301	-0.3	-0.1	0.771
Global Question (0 to 4)						
Month 3	293	-0.1	296	-0.1*	0.1	0.306
Month 6	298	-0.1	301	0.0	-0.1	0.285
Month 9	298	-0.1	303	-0.1	-0.1	0.570
Month 12	298	-0.1	303	-0.1	0.0	0.944
Morning Erections (0 to 4)						
Month 3	295	-0.2**	295	0.0	-0.2	0.001
Month 6	298	-0.2**	301	0.0	-0.2	0.001
Month 9	298	-0.2**	303	0.0	-0.2	0.006
Month 12	298	-0.2**	303	0.0	-0.2	0.017

+ Adjusted for the treatment and center effects
*, ** Significant change from baseline at the $p < 0.050$ and $p < 0.010$ level, respectively