

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-788

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology/Biopharmaceutics Review

NDA: 20,788

Submission Dates: 12/20/96

Generic Name, Strength, Formulation:

Finasteride 1 mg Tablets

Brand Name: Propecia

Date Assigned: 1/29/97

Applicant: Merck Research

Final Review: 10/17/97

Submission Code: 3S

Reviewer: Kofi A. Kumi, Ph.D.

SYNOPSIS:

The applicant submitted a new drug application (NDA) requesting approval of finasteride 1 mg (Propecia) tablet to be used to treat male pattern baldness (MPB), also known as androgenic alopecia. Finasteride 5 mg (Proscar) is approved for treating benign prostrate hypertrophy (BPH). One pivotal pharmacokinetics study and two supportive pharmacodynamic studies for MPB were submitted to section 6 (Human Bioavailability and Pharmacokinetics) of this application. The pharmacokinetic studies submitted to the previous application (NDA 20,180) are cross referenced in this study.

Finasteride is a synthetic structural analog of testosterone (T). Finasteride is an inhibitor of the human Type II 5 α -reductase enzyme which prevents the formation of dihydrotestosterone (DHT) from testosterone. Increases of DHT levels in scalp and serum is reported to be involved in the pathogenesis of MPB.

After daily administration of finasteride 1 mg for 17 days, a modest accumulation of 35% and 40% based on AUC and C_{max}, respectively is observed. Steady state was achieved in about 3 days. After daily administration of finasteride 1 mg to 12 healthy male volunteers for 17 days, the following pharmacokinetic parameters were observed.

Pharmacokinetic Parameters of Finasteride 1 mg after Daily Dosing for 17 Days

Pharmacokinetic Parameters	Day 1	Day 17
	Mean \pm SD (n=12)	
C _{max} (ng/mL)	6.53 \pm 1.64	9.20 \pm 2.63
AUC (0-24) ng*h/mL	38.2 \pm 17.4	53.2 \pm 33.8
T _{max} (h)	1.58 \pm 0.51	1.33 \pm 0.49
T $\frac{1}{2}$ (h)	4.49	4.79

The pharmacokinetics of finasteride 1 mg administered daily for 17 days were consistent with that reported for finasteride 5 mg administered daily for 17 days. Finasteride is metabolized by

The pharmacodynamic study demonstrated that men with MPB treated for 6 weeks with finasteride at doses from 0.01 to 5 mg demonstrated a dose related decrease in scalp skin and serum DHT levels. However, the effect on DHT produced by the 1 mg dose was similar to that observed with the 5 mg dose.

DISSOLUTION:

The following dissolution method and specification is recommended for finasteride 1 mg (Propecia) tablets;

Apparatus: USP 2 (paddle)
Media: 900 mL of deionized water at $37 \pm 0.5^\circ\text{C}$
Speed: 50 rpm
Q = % in mins

COMMENTS (To be Forwarded to Sponsor):

1) It is recommended that the sponsor conduct drug interaction studies with inhibitors of CYP 3A4 (e.g. ketoconazole, fluconazole), inducers of CYP 3A4 (e.g. rifampin) and other substrates of CYP 3A4 (eg. erythromycin).

2) Since a pharmacodynamic marker for MPB is known, it is recommended that in future pharmacodynamic/efficacy studies, the concentration-effect (PK-PD) relationship using the PD measures as surrogate markers be explored.

RECOMMENDATION:

The pharmacokinetic studies submitted to the Human Pharmacokinetics and Bioavailability Section of NDA 20,788 to fulfill sections 320 and 201.5 of 21 CFR are acceptable and support a recommendation for approval of the NDA.

10/17/97

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Concurrence: 10/22/97

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CC:	NDA 20,788 (original)	Division Files
	HFD-540	/MO/Hon-Sum Ko
		/CSO/SKummerer
	HFD-344	/Viswanathan
	HFD-880	/TLDPEIII/DBashaw
		/DPEIII/KKumi
		/DPEIII Drug Files ✓
	CDR	/BMurphy ✓

Draft 1: 10/17/97

Table of Contents

	Page
Synopsis	01
Comments	02
Recommendation	02
Background	04
Physicochemical Properties	05
Dissolution	06
Analytical Method	06
Overview of Studies	07
Protocol 102	07
Protocol 065	14
Protocol 031	25
In Vitro Metabolism	26

REVIEW

BACKGROUND:

The applicant submitted a new drug application (NDA) for the use of finasteride (Propecia) in treating male pattern baldness (MPB), also known as androgenic alopecia (AGA). The pharmacokinetics of finasteride, including the bioavailability of the 1-mg tablet-formulation (using multiple tablets), have been characterized by studies that were submitted in the approved application (NDA 20,180) of finasteride 5 mg (Proscar) for benign prostatic hyperplasia (BPH). This review focuses on the additional studies that were submitted to this NDA (20,788) to support the application of finasteride 1 mg to be used for the treatment of male pattern hair loss. The studies submitted under NDA 20,180 are cross-referenced in this application.

The pathophysiologic mechanism underlying male pattern hair loss involves a decrease in the ratio of anagen to telogen hair follicles and an increase in the proportion of vellus, or vellus-like, miniaturized follicles, compared with terminal follicles. Androgens act to alter the normal chronotropic cycle of hair follicles in androgen-sensitive regions of the body. The reported deleterious effect of androgens on scalp hair is due to a shortening of the anagen phase duration and progressive miniaturization of terminal hairs to vellus-like follicles, resulting in a decreased anagen to telogen ratio, an increased vellus to non-vellus ratio and, over time, a reduction in the absolute number of follicles.

Male subjects born with a genetic deficiency of Type II 5α -reductase are reported not to develop male pattern hair loss (androgenic alopecia) or benign prostatic hyperplasia (BPH). DHT is reported to be the predominant androgen involved in the pathophysiological changes that occur in scalp and prostate with age.

Finasteride, an inhibitor of the human Type II 5α -reductase enzyme, prevents the formation of the potent androgen dihydrotestosterone (DHT) from testosterone (T) in target tissues. Finasteride has no affinity for the androgen receptor and does not act as an antiandrogen, nor does it have androgenic, estrogenic, antiestrogenic, progestational, or other steroidal properties.

Finasteride is a synthetic, structural analog of T, the major circulating androgen in adult men that provides for normal male libido, muscle mass, and skeletal integrity. Finasteride inhibits conversion of T to the more potent androgen DHT, thus decreasing the formation of DHT systemically and in target tissues. Therefore, finasteride is reported to lower serum DHT and inhibits DHT-mediated effects on target tissues, such as the scalp, without lowering serum T or affecting T-mediated effects in tissues. This effect occurs by inhibition of the Type II 5α -reductase enzyme. Thus, male pattern hair loss is a target for treatment with 5α -reductase inhibitor.

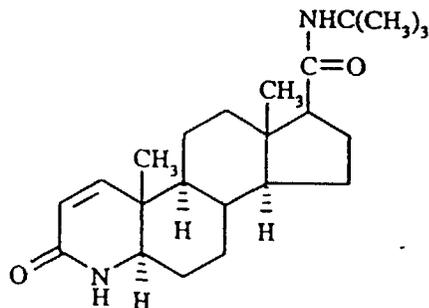
In the previous application for BPH (NDA 20,180), the absolute bioavailability of finasteride tablet was computed using a “ β -correction” method to adjust for intra subject variability in disposition between intravenous and oral treatments. Multiple units of the 1-mg dosage forms were used to accommodate assay sensitivity. The geometric mean (90% CI) bioavailability was 79.3% (68.7 to 91.5%) for 5 x 1-mg tablets. Absorption of finasteride occurred mostly 1 to 2 hours postdose and was essentially complete 6 to 8 hours postdose. The applicant did not conduct a new bioavailability study. From the pharmacokinetic review for NDA 20,180, there was not a significant difference in the pharmacokinetics of finasteride when it is taken following a fast or immediately prior to a standard breakfast. The proposed market formulation of finasteride for the treatment of male pattern hair loss is a 1-mg film-coated tablet. This formulation (with variation in colorants) was used in nearly all clinical studies and in the bioavailability and multiple-dose pharmacokinetics studies.

Physicochemical Properties:

Finasteride, *N*-(1,1-Dimethylethyl)-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide, has a molecular weight of 372.55 and chemical formula of C₂₃H₃₆N₂O₂.

Structure for finasteride is shown below:

Structural Formula:



Molecular Formula: C₂₃H₃₆N₂O₂

Molecular Weight: 372.55

Solubility: Finasteride is practically insoluble in water (about 0.05 mg/mL at room temperature) and in 0.1M hydrochloric acid. It is soluble in polar organic solvents such as methanol, ethanol, chloroform, acetonitrile, and dimethyl sulfoxide (DMSO) and is sparingly soluble in propylene glycol and in polyethylene glycol. The octanol/water partition coefficient exceeds 1200.

Dissolution:

The dissolution test was conducted in 900 mL of water at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ using USP Method II with paddle agitation at 50 rpm. During product development, dissolution profiles of samples were taken at 15, 30, and 45 minutes. Samples were assayed by

In the previous application for finasteride 5 mg (Proscar) tablet, the sponsor proposed a dissolution specification of not less than $\bullet\bullet\bullet\%$ or $\bullet\bullet\bullet\%$ dissolved in $\bullet\bullet\bullet$ mins and the PK reviewer recommended $Q = \bullet\bullet\bullet\%$ in $\bullet\bullet\bullet$ mins.

The dissolution profile provided for the clinical and biopharmaceutics batches for this application (see appendix for dissolution profile) support the following dissolution specification for finasteride 1 mg (Propecia) tablet and is proposed by the applicant. This reviewer supports the applicant's proposal.

Apparatus: USP 2 (paddle)
Media: 900 mL of deionized water at $37 \pm 0.5^{\circ}\text{C}$
Paddle Speed: 50 rpm
 $Q = \bullet\bullet\bullet\%$ in $\bullet\bullet\bullet$ mins

Analytical Method:

OVERVIEW OF PHARMACOKINETICS STUDIES

Protocol 102: An Open-Label, Multiple-Dose Study to Investigate the Pharmacokinetics of Finasteride 1mg Administered Orally in Healthy Adult Male Subjects (Volume 13 page 1048)

Introduction: Dihydrotestosterone (DHT) is reported to play a role in the development of male pattern baldness (MPB), also known as androgenic alopecia (AGA). Finasteride, a 4-aza steroid inhibitor of Type 2 5- α -reductase, inhibits the conversion of testosterone (T) to DHT. Finasteride was therefore studied as a potential therapy for AGA. In a previous multiple dose study of daily 5 mg oral doses over 17 days, the area under curve (AUC(0- ∞)) on day 17 was 1.2 to 1.3 times higher than AUC(0- ∞) on day 1. In addition, mean trough plasma concentrations increased slowly over the 17 days and steady state was not achieved. This study investigated the single and multiple dose pharmacokinetics of finasteride 1 mg after daily dosing for 17 days.

Objective: 1) To assess the accumulation by estimating the plasma day 17 AUC(0-24hr)/Day 1 AUC(0-24hr) geometric mean ratio (GMR) 2) To evaluate the plasma pharmacokinetic profile of finasteride after multiple daily 1 mg oral doses (Day 17), including the parameters AUC (0-24hr), C_{max}, time to reach peak plasma concentration (T_{max}) and terminal half-life (T_{1/2}) 3) To evaluate the plasma pharmacokinetic profile of finasteride after single 1 mg oral dose (day 1), including the parameters AUC (0-24hr), C_{max}, T_{max}, and T_{1/2} 4) To determine the finasteride plasma concentration trough levels on selected study days.

Design: This was an open-label, multiple-dose study of finasteride to determine the plasma pharmacokinetics of finasteride 1 mg given orally once a day for 17 days. Twelve healthy male subjects with a mean±SD age of 35.8±7.8 years and 167.8±21.8 lbs, respectively participated in the study. During the study, there were 17 clinic visits including a screening evaluation and poststudy visit on Day 20 after the 72-hour plasma collection. Subjects returned to the clinic every morning for observed dosing between 10:00 and 11:00 hours. On Days 1 and 17, subjects fasted overnight before receiving finasteride. Two hours after taking finasteride, subjects were given a liquid breakfast consisting of orange juice and a cup of tea or coffee. Four hours after taking the study drug they were given a light lunch provided by the investigator.

Plasma samples for determination of finasteride concentrations was collected on Days 1 and 17 at 0 (predose), 30 minutes, and 1, 2, 3, 4, 6, 8, 10, 12, 15, and 24 hours postdose. In addition, following Day 17 dosing, plasma specimens were also collected at 36, 48, and 72 hours postdose. Trough finasteride plasma concentrations (collected predose, approximately 5 minutes prior to administration of finasteride) were determined on specimens collected on Days 2, 3, 4, 5, 6, 9, 11, 12, 15, 16, 17, and 18. The formulation number for the lot of finasteride 1 mg used in this study was E-8488 and the control numbers were WP-B956 and WP-B957.

Analytical Methods:

Data Analysis: The following pharmacokinetic parameters were calculated for each subject on Days 1 and 17 following once-daily administration of finasteride 1 mg 1) Calculated plasma AUC(AUC_(0-24 hr), ng•hr /mL; Days 1 and 17) 2) Observed C_{max} (ng/mL), T_{max} (hours) and t_{1/2} (hours).

The primary endpoints in this study were plasma $AUC_{(0-24 \text{ hr})}$ and C_{max} for finasteride after multiple oral doses (Day 17), and the Geometric Mean Ratios (GMRs) of Day 17 versus Day 1 in $AUC_{(0-24 \text{ hr})}$ and C_{max} , respectively. For each of the two primary pharmacokinetic parameters, $AUC_{(0-24 \text{ hr})}$ and C_{max} , the Day 17 values were compared with those obtained on Day 1 using analysis of variance (ANOVA) with subject and day as factors in the model. To assess the extent of drug accumulation, the GMRs of Day 17 versus Day 1 in $AUC_{(0-24 \text{ hr})}$ and C_{max} , and the corresponding 90% CI, were calculated.

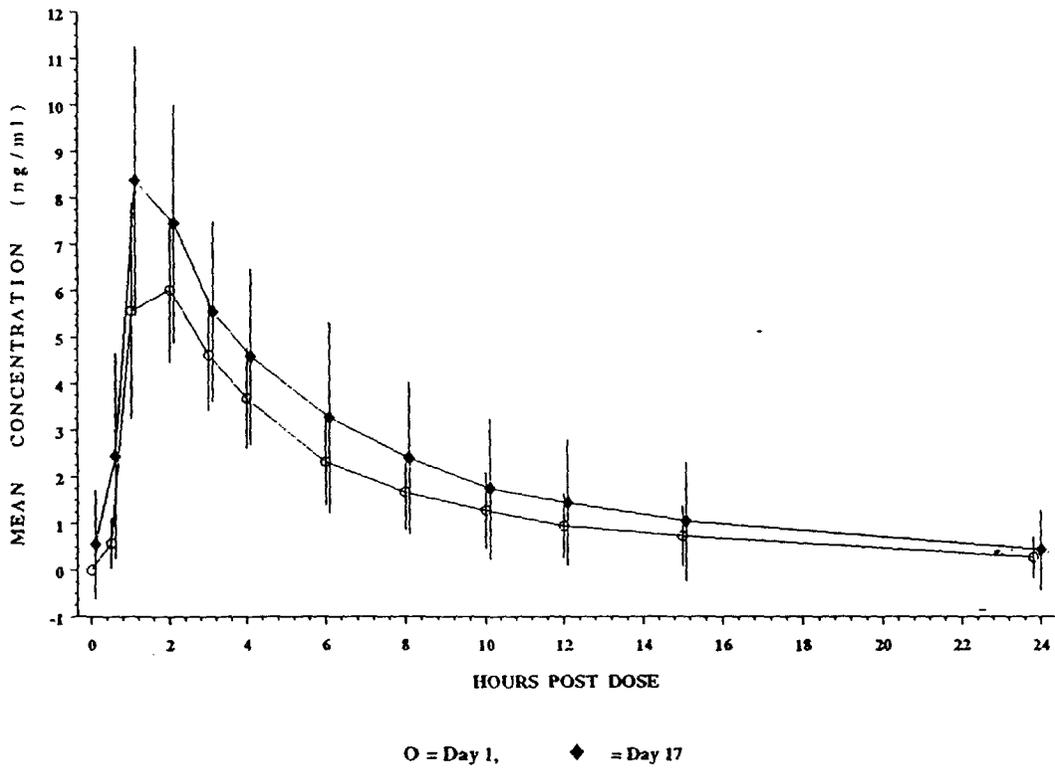
The secondary endpoints included T_{max} and $t_{1/2}$ of finasteride after multiple once-daily 1-mg oral doses (Day 17), and $AUC_{(0-24 \text{ hr})}$, C_{max} , T_{max} , and $t_{1/2}$ of finasteride after a single 1-mg oral dose (Day 1). The trough levels of finasteride over different study days were also explored as a secondary endpoint. For T_{max} and $t_{1/2}$, the Day 17 values were compared with the Day 1 values using a paired t-test. The analysis was performed on the rank transformed values of T_{max} and the inverse transformed values of $t_{1/2}$.

Finasteride trough levels were determined for Study Days 2, 3, 4, 5, 6, 9, 11, 12, 15, 16, 17, and 18. In an exploratory manner, a least-squares linear regression line was fitted to each subject's trough levels over time, and the mean slope over all 12 subjects was tested against zero using Student's t-test to determine if there was a linear time trend among the trough levels of finasteride.

Results: The mean (\pm SE) plasma concentrations over time for Days 1 and 17 are presented in figure 1 on the following page. The maximum concentration was achieved within 2-4 hours after dosing. The individual trough concentrations are contained in figure 2. The trough concentrations for the subjects on the study days, except one patient ranged from ng/mL. For the trough values ranged from ng/mL, which were approximately 10 times the values observed for the other 11 subjects. This resulted in a large between-subject variation for trough values. Summary statistics of the observed trough levels of finasteride are contained in Table 1.

Figure 1

Mean Plasma Concentration of Finasteride (\pm SE)



~~Figure 1~~ Figure 2

Individual Trough Plasma Concentrations of Finasteride
in Healthy Male Subjects Receiving 1 mg Finasteride q.a.m. for 17 Days

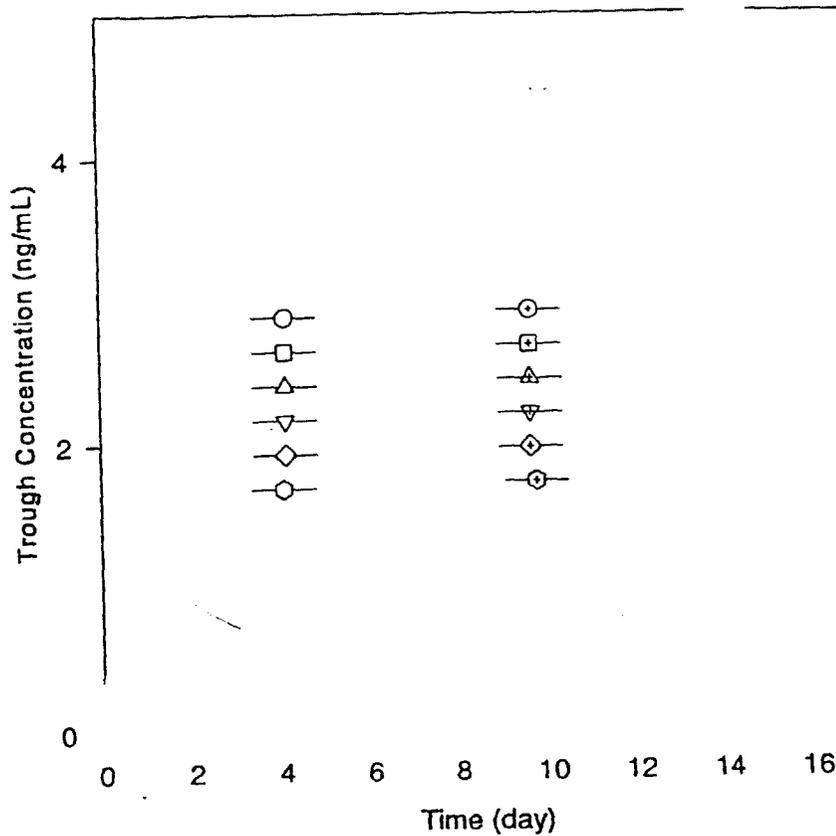


Table 1: Summary Statistics of Trough Levels of Finasteride

Day	N	Median	Mean	Minimum	Maximum	SD
2	12	0.17	0.26			0.45
3	12	0.24	0.54			1.07
4	12	0.23	0.53			1.10
5	12	0.21	0.50			1.07
6	12	0.24	0.54			1.17
9	12	0.28	0.48			0.90
11	12	0.27	0.56			1.24
12	12	0.25	0.54			1.10
15	12	0.25	0.56			1.13
16	12	0.25	0.58			1.26
17	12	0.22	0.55			1.17
18	12	0.20	0.43			0.87

Overall Mean slope = 0.00540 (SD= 0.0163), p-value for mean slope equal to 0 is p=0.276

Although the variation among subjects within each study day was large (due to ...), the trough levels were similar among the study days. The mean slope over the 12 subjects was computed as 0.005. There was no significant trend over time among the plasma trough levels ($p > 0.200$). To examine the effect of ... data on the estimation of the mean slope, the analyses were performed with this subject excluded. The same conclusion of no significant time trend among the trough levels was reached (mean slope = 0.001, $p=0.619$).

A summary of the pharmacokinetic parameters obtained on day 1 and day 17 are provided in the table below

Table 2: Pharmacokinetic Parameters of Finasteride 1 mg after Daily Dosing for 17 Days

Pharmacokinetic Parameters	Day 1	Day 17
	Mean \pm SD (n=12)*	
C _{max} (ng/mL)	6.53 \pm 1.64	9.20 \pm 2.63
AUC (0-24) ng*h/mL	38.2 \pm 17.4	53.2 \pm 33.8
T _{max} (h)	1.58 \pm 0.51	1.33 \pm 0.49
T _{1/2} (h)	4.49	4.79

*Arithmetic mean

T_{max} of finasteride was not altered significantly after 17 days of a 1-mg oral dose as compared with 1 day of dosing. The half-life ($t_{1/2}$) of finasteride on Day 17 was slightly longer than that observed on Day 1. However, the difference between the 2 study days was not statistically significant ($p > 0.200$).

Table 3: 90% Confidence Interval (CI) Based Upon the AUC₍₀₋₂₄₎ GMR of Day 17/Day 1

Day	N	Geometric Mean	GMR ^a	90% CI for GMR
1	12	35.0	1.35	(1.23, 1.47)
17	12	47.1		

^a Day 17/Day 1

Table 4: 90% Confidence Interval (CI) Based Upon the C_{max} GMR of Day 17/Day 1

Day	N	Geometric Mean	GMR ^a	90% CI for GMR
1	12	6.32	1.40	(1.28, 1.52)
17	12	8.83		

^a Day 17/Day 1

The Day 17/Day 1 GMR for AUC₍₀₋₂₄₎ was 1.35, which showed that there was an approximately 35% increase in AUC₍₀₋₂₄₎ from day 1 to day 17. The difference between the geometric mean AUC_(0-24 hr) values for Days 1 and 17 was significant ($p < 0.001$). The Day 17/Day 1 GMR for C_{max} was 1.40, which indicated that the mean C_{max} on Day 17 was approximately 40% greater than that on Day 1.

Day 17 versus Day 1 AUC_(0-24 hr) data from this study were compared with those observed in the finasteride 5 mg Multiple-Dose Pharmacokinetic/Effect of Age Study submitted to NDA 20,180. The AUC_(0-24 hr) Day 17/Day 1 GMR after multiple dosing of 5 mg (1.47) was divided by the AUC_(0-24 hr) Day 17/Day 1 GMR after multiple dosing of 1 mg (1.35). The following table summarizes the GMR comparisons for the two studies.

Table 5: Study Comparison of GMR of Day 17 AUC₍₀₋₂₄₎/Day 1 AUC₍₀₋₂₄₎

Finasteride Daily Dose	N	GMR ^a	Study Difference in GMR ^a	90% CI for Study Difference in GMR
1 mg	12	1.35	1.09	(0.99, 1.20)
5 mg	12	1.47		

^a Day 17/Day 1

^a Back transformed from log scale

The overall GMR, AUC 5 mg GMR/AUC 1 mg GMR, indicates that the accumulation of finasteride in the plasma after multiple doses of 1 mg was consistent with that observed after multiple doses of 5 mg.

Conclusion: The study revealed a modest accumulation of finasteride after once-daily 1-mg administration of 35% to 40% (based on $AUC_{(0-24 \text{ hr})}$ and C_{max} , respectively). These results were similar to those obtained with finasteride 5 mg (about 47% accumulation based on AUC). Analysis of the trough plasma concentrations suggests that steady state was approximated within 3 days of dosing. The present study was conducted in somewhat younger subjects (age range, years old) than those included in the 5 mg single and multiple dosing for 17 days pharmacokinetic study (age range, submitted to NDA 20,180. While this may account for numerical differences in some pharmacokinetic parameters, there were no clinically meaningful differences between the observations made after finasteride 1 mg versus 5 mg. There were no significant differences in T_{max} or $t_{1/2}$ after multiple-dose versus single dose administration of finasteride 1 mg.

One milligram finasteride was reported to be well tolerated in these healthy volunteers. No clinical AEs were noted. A single transient elevation in serum transaminases was reported in one subject, although there were no clinical sequelae.

Protocol 065: A Double Blind, Placebo-Controlled Study To Investigate the Effects of Finasteride on DHT and Testosterone in Scalp Skin and Sebum (Volume 13 page 1451)

Introduction: Finasteride is a 4-azasteroid inhibitor of the Type 2 5α -reductase enzyme. Inhibition of this enzyme blocks the conversion of testosterone (T) to the more potent androgen dihydrotestosterone (DHT). Many androgen target tissues including the prostate and the hair follicle are more responsive to DHT than T. Finasteride lacks affinity for the androgen receptor and is devoid of androgenic, estrogenic, antiestrogenic or progestational effects. Body hair growth in the pubic, axillary, and facial areas is androgen dependent. Scalp skin is reported to contain both the Types 1 and 2 5α -reductase enzymes. Many androgen target tissues including the hair follicle are more responsive to DHT than T. In a pilot study in men (Protocol No. 031) administration of finasteride 5 mg daily for 28 days produced a decrease in balding scalp skin DHT from a mean of 2.0 ng/g tissue at predose to 1.0 ng/g tissue on Day 28. Mean scalp skin T levels remained unchanged in the treated group (2.7 ng/g at predose and 3.0 ng/g on Day 28). Studies examining hormonal effects of different oral doses of finasteride demonstrated that 0.2 to 100 mg daily for 11 days produced maximal suppression of serum DHT levels. A lower dose study revealed rapid suppression of serum DHT levels and a dose-related rate of suppression at doses of 0.04, 0.12, 0.2 and 1 mg of finasteride for 14 days. DHT levels in 6 patients given 0.2 and 1 mg were maximally suppressed compared with those given 0.04 and 0.12 mg. The purpose of the present study was to describe the pharmacologic effects of lower doses of finasteride.

Objectives

- 1) To determine the effect of orally administered finasteride at 0.01, 0.05, 0.2, 1, and 5 mg daily versus placebo on scalp skin T and DHT.
- 2) To determine the amount of finasteride in semen of men taking 0.2, 1, or 5 mg for 6 weeks.
- 3) To determine whether sebum and/or serum DHT and 3-alpha-diol-glucuronide can be used as markers of finasteride's effectiveness in lowering scalp skin DHT.
- 4) To gain insight into androgenic control of sebum output.

Study Design: This was a 6-week, double-blind, randomized, placebo-controlled, multi center study in 249 healthy patients (mean age: 37.4 ± 7.6) who were candidates for hair transplantation or were willing to have scalp biopsies taken. Each patient was randomized to receive oral doses of either finasteride (0.01, 0.05, 0.2, 1.0, or 5 mg) once daily in the morning for 6 weeks. Balding scalp skin (500 mg or more) was obtained at baseline and after 42 days of treatment with either finasteride or placebo. During the study there were five visits: one screening visit, one baseline visit (Day 0), a follow-up visit for biopsy check after initiation of medication (Day 10), one posttreatment (efficacy) visit after 6 weeks of treatment (Day 42) and one follow-up visit on Day 49 to check the biopsy site. On Day 0 and 42 visits, the following samples were collected: scalp skin for measurement of DHT and T levels, semen for finasteride levels (except in the 0.05-mg group); serum for DHT, T, and 3-alpha-diol-glucuronide levels; scalp and facial sebum (except in the 0.01- and 0.05-mg groups). Scalp skin (500 mg or more) was collected from balding patients undergoing hair transplantation or volunteering for biopsies on Days 0 and 42 and was immediately frozen. The samples were shipped to Merck & Co., Inc. and the concentrations of DHT and T were measured. Sebum was collected from both the scalp, forehead and cheeks on or within 24 hours of Days 0 and 42. Semen was collected on or within 24 hours of Days 0 and 42 in patients receiving 0.01, 0.2, 1, and 5 mg of finasteride or placebo and analyzed for finasteride levels in finasteride patients. Patients were asked to produce semen samples prior to the first drug dose on Day 0 and within 2 hours following their final dose of drug on Study Day 42. Serum DHT, T, and 3-alpha-diol-glucuronide levels were measured at Days 0 and 42. Blood was drawn for laboratory safety tests, serum DHT, T, and 3-alpha-diol-glucuronide determinations were obtained on Days 0 and 42.

Data Analysis: Analyses of Pharmacological Effects

(1) Primary Endpoint: Scalp Skin Dihydrotestosterone: The main analysis was the percent change from baseline observed at Day 42. Baseline was defined as the last data collected before treatment initiation (Relative Day ≤ 1). Treatment effects were evaluated using the stepwise Tukey trend test, adjusted for multiplicity. Pairwise comparisons and the assessment of the overall treatment effect were performed using ANOVA. The ANOVA model only included the factor treatment.

(2) Secondary Endpoints: Serum Dihydrotestosterone, Scalp Skin and Serum Testosterone, and 3-Alphadiol-Glucuronide

Measures of serum DHT, scalp skin and serum T, and serum 3-alphadiol-glucuronide were evaluated based on the percent change from baseline observed at Day 42. Assessment of treatment effect proceeded in the same fashion as described above for scalp skin DHT.

(3) Other Endpoints: Finasteride Levels in Semen, Sebum Output, and Active Gland Counts:

The effect of 6 weeks of treatment on finasteride levels in semen was explored. Measurements reported as below the limit of detection (0.1 ng/mL) were assigned a value of zero for the analyses. Treatment effects were evaluated using the stepwise Tukey trend test, adjusted for multiplicity. This approach examined the dose-response relationship for the 0.2, 1, and 5-mg doses of finasteride. Pairwise comparisons and the assessment of the overall treatment effect were performed using ANOVA. Measures of sebum were evaluated based on the change from baseline observed at Day 42. Changes from baseline were analyzed for differences between the treatment groups.

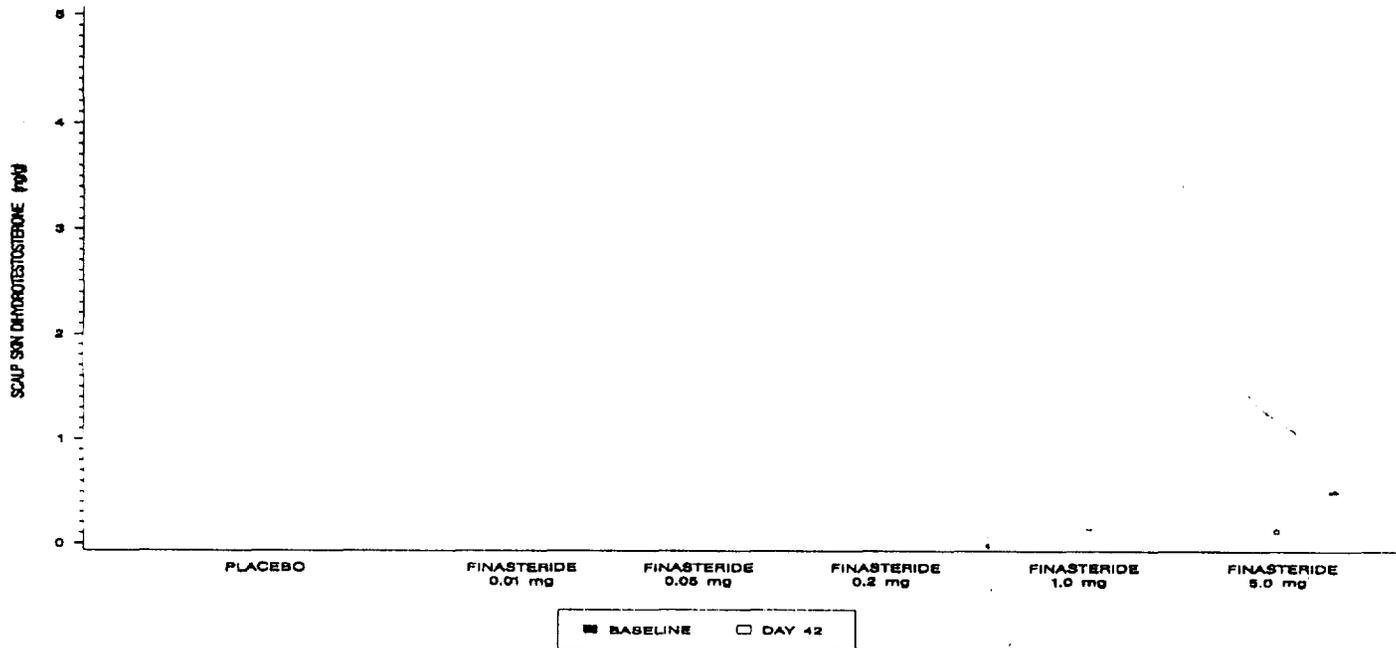
Results: Higher doses of finasteride (0.05, 0.2, 1, and 5 mg) provided greater reductions in scalp skin DHT than the lower dose (0.01 mg) and placebo. A significant linear trend was observed across the five active and placebo groups based upon scalp skin DHT expressed as percent change from baseline ($p < 0.001$). A significant linear trend was observed across the five finasteride dose groups (without the placebo group included) based upon scalp skin DHT percent change from baseline ($p < 0.001$). The linear trend remained significant among the 0.01, 0.05, 0.2 and 1-mg groups ($p < 0.001$), among the 0.01, 0.05 and 0.2-mg groups ($p < 0.001$), and among the 0.01 and 0.05-mg groups ($p < 0.001$). The results of a pairwise comparisons confirm that there was no significant difference between 0.01 mg of finasteride and placebo with respect to percent change from baseline in scalp skin DHT ($p = 0.124$) but that each differed significantly from the 4 higher dose groups ($p < 0.001$). The 0.05-mg group showed no significant difference from the 0.2 and 1-mg group ($p > 0.2$) and approached significance versus the 5-mg group ($p = 0.069$). The percent reductions in the 0.2-mg group were not different from those in the 1-mg group ($p > 0.2$) but were significantly smaller than those in the 5-mg group ($p = 0.032$). No significant differences existed among the two upper dosages ($p = 0.178$) regarding percentage change from baseline in scalp skin DHT. The pre versus posttreatment scalp skin DHT measurements of all patients by treatment group are displayed in figure 3. The median percent change from baseline DHT is provided in figure 4.

A significant linear trend was observed across the five active and placebo groups based upon serum DHT percent change from baseline ($p < 0.001$). The linear trend remained significant among the placebo, 0.01, 0.05, 0.2 and 1-mg groups ($p < 0.001$), among the placebo, 0.01, 0.05, and 0.2-mg groups ($p < 0.001$) and among the placebo, 0.01, and the 0.05-mg groups ($p < 0.001$). A significant linear trend was also observed across the five finasteride dose groups (without the placebo group included) based upon serum DHT percent change from baseline ($p < 0.001$).

3. Pharmacologic Effects (Cont.)

Figure 3

Scalp Skin Dihydrotestosterone (ng/g)
Baseline Versus Day 42 for Placebo and Active Treatment Groups

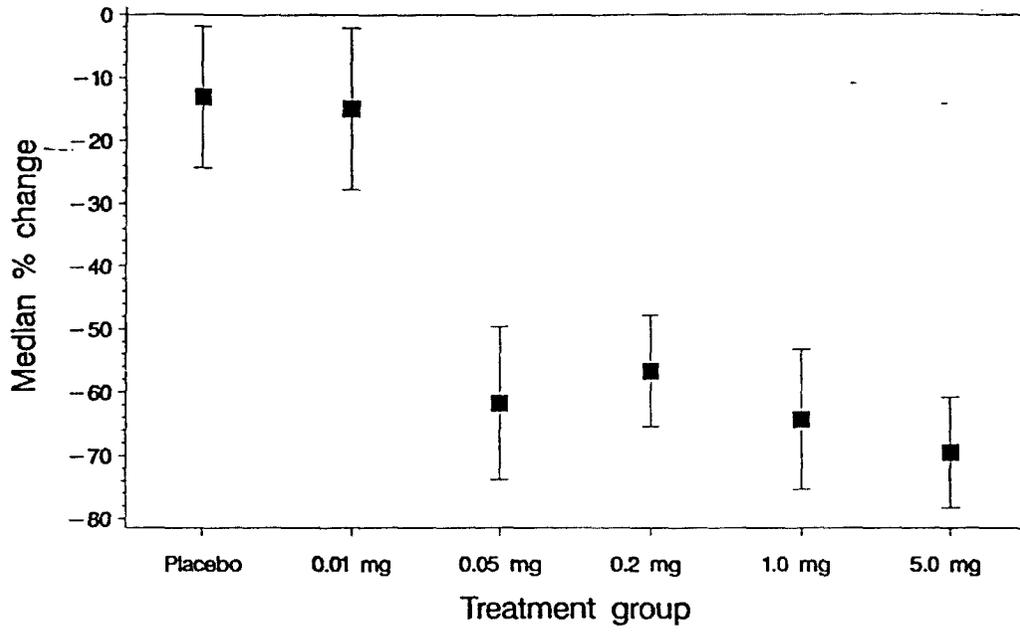


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Data Source: [4.1.12], [4.6]

Figure 4

Scalp Skin Dihydrotestosterone
Median Percent Change From Baseline and 95% Confidence Intervals



Data Source: [4.1.12], [4.6.1]

No significant differences existed among the 1 and 5 mg dose groups ($p > 0.2$) regarding percentage change from baseline in serum DHT. The median percent change from baseline is provided in figure 5.

Figure 6 provides a plot of median percent change from baseline of testosterone for each treatment group, with 95% confidence intervals around the median. Higher doses of finasteride (0.05, 0.2, 1 and 5 mg) provided greater increases in scalp skin T than the lower dose (0.01 mg) and placebo. Increases in scalp skin T were of comparable magnitude in the placebo and 0.01-mg group, in the 0.05 and 5-mg group, and in the 0.2 and 1-mg group. The 0.05-mg group showed no significant difference between the 0.2, 1 and 5-mg group ($p > 0.1$). No significant differences existed among the two upper dosages ($p = 0.172$) regarding percentage change from baseline in scalp skin T.

Figure 7 provides a plot of median percent change from baseline of serum T for each treatment group, with 95% confidence intervals around the median. Increases in serum T were of comparable magnitude in the placebo and 0.01, 0.2, 1 and 5-mg groups while the increase was larger in the 0.05-mg group.

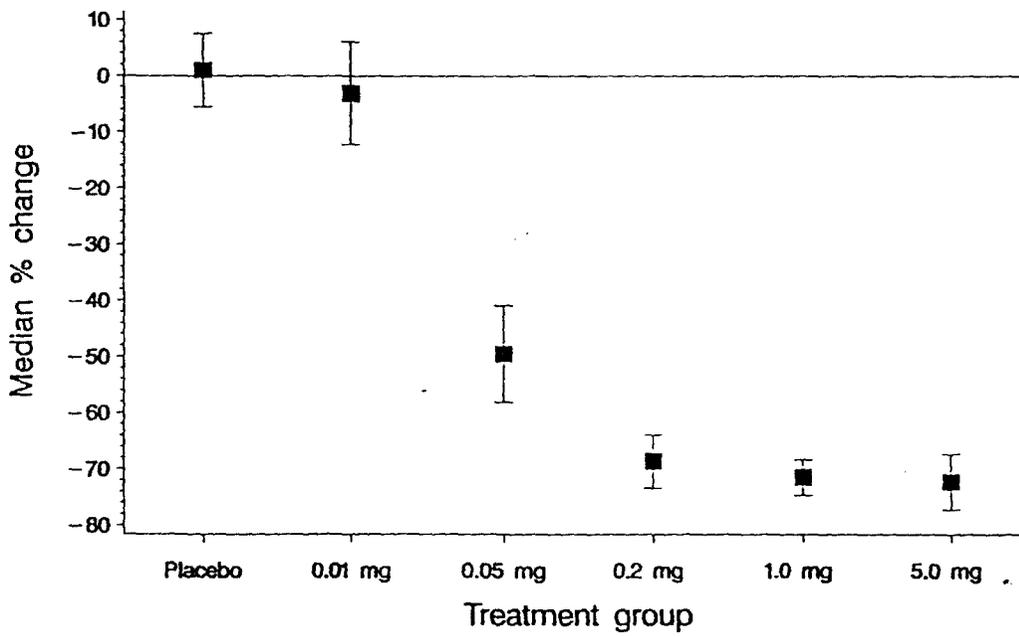
Figure 8 provides a plot of median percent change from baseline for serum 3-alpha-diol-glucuronide for each treatment group with 95% confidence intervals around the median. Higher doses of finasteride (0.05, 0.2, 1 and 5 mg) provided greater reductions in serum 3-alpha-diol-glucuronide than the lower dose (0.01 mg) and placebo.

The concentration of finasteride in semen was assessed in the 0.2, 1, and 5-mg groups. The finasteride levels in semen after 6 weeks of treatment for individual patients are displayed by treatment group in figure 9. After 6 weeks of treatment with finasteride, the maximum semen levels were 0.61 ng/mL in the 0.2-mg group, 1.52 ng/mL in the 1-mg group and 8.55 ng/mL in the 5-mg group. Finasteride levels in semen were significantly higher in the 5 mg group when compared to the 0.2 and 1 mg group ($p < 0.001$) and significantly higher in the 1 mg group compared to the 0.2 mg group ($p = 0.05$).

Conclusion: Serum concentrations of finasteride were not measured in this study. It appears that men with MPB treated for 6 weeks with finasteride at doses from _____ mg demonstrated a significant dose response in scalp skin and serum DHT levels. Greater reductions in scalp skin and serum DHT levels were observed with the 5 mg dose; however, there was no statistically significance difference in the 1 and 5 mg dose groups. Semen finasteride levels in men treated with 0.2, 1, and 5 mg finasteride for 6 weeks were dose dependent with greatest amount detected in patients on the 5 mg dose. This study demonstrated that, the effects on suffogate markers of MPB produced by the 1 mg dose were similar to that observed with the 5 mg dose.

Figure 15

Serum Dihydrotestosterone
Median Percent Change From Baseline and 95% Confidence Intervals



~~As shown~~

Figure 6

Scalp Skin Testosterone
Median Percent Change From Baseline and 95% Confidence Intervals

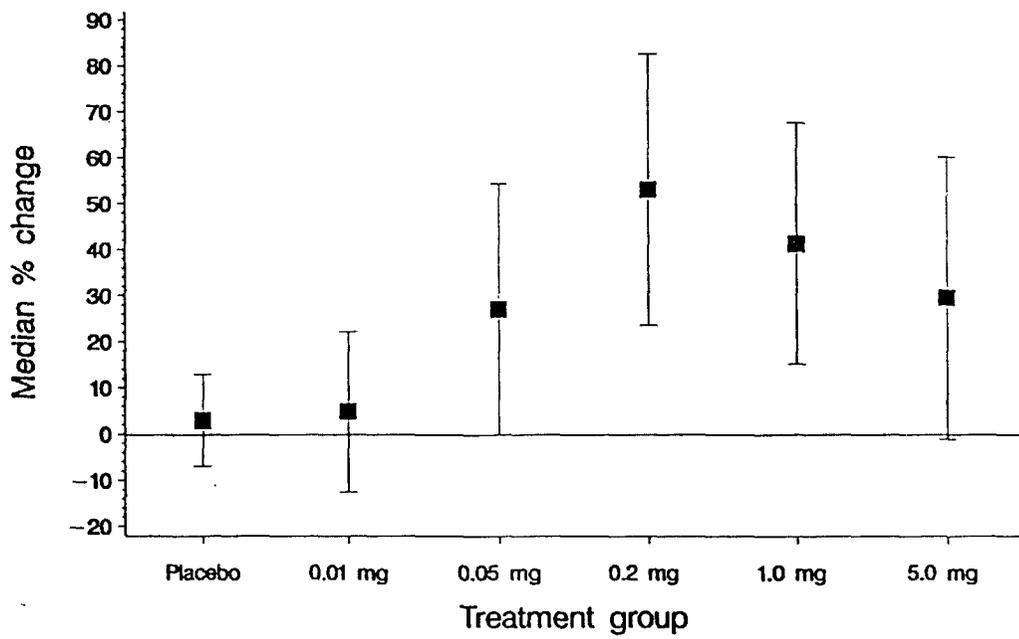


Figure 7

Serum Testosterone
Median Percent Change From Baseline and 95% Confidence Intervals

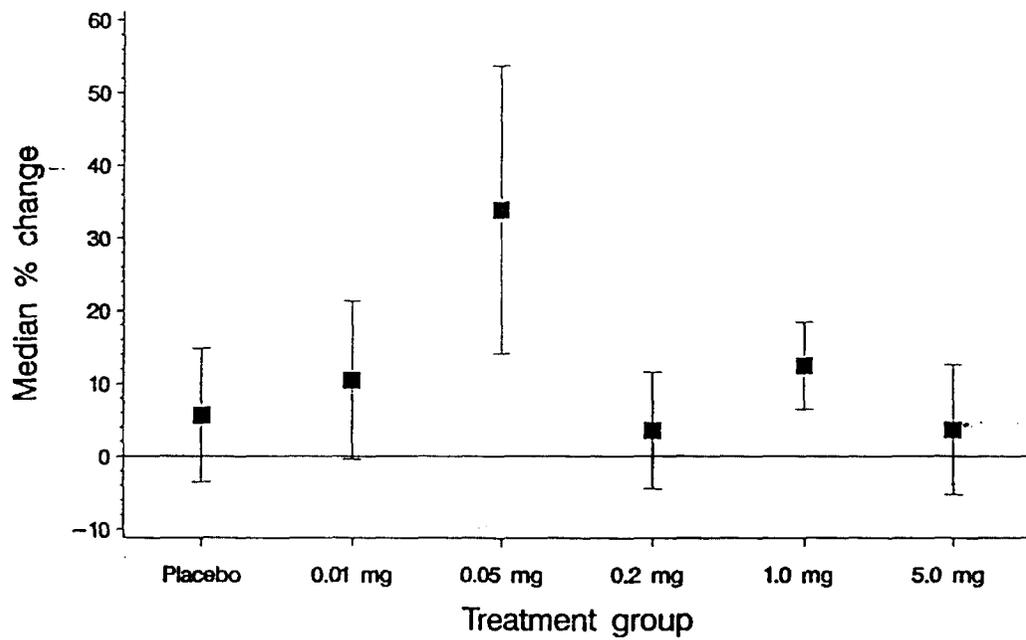
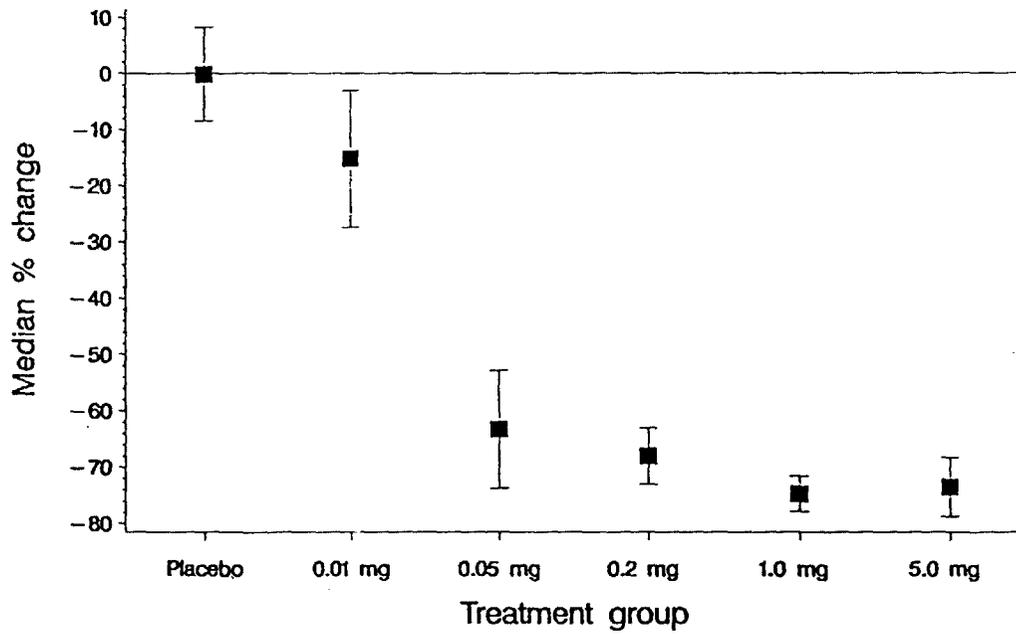


Figure 8

3-Alpha-diol-Glucuronide
Median Percent Change From Baseline and 95% Confidence Intervals



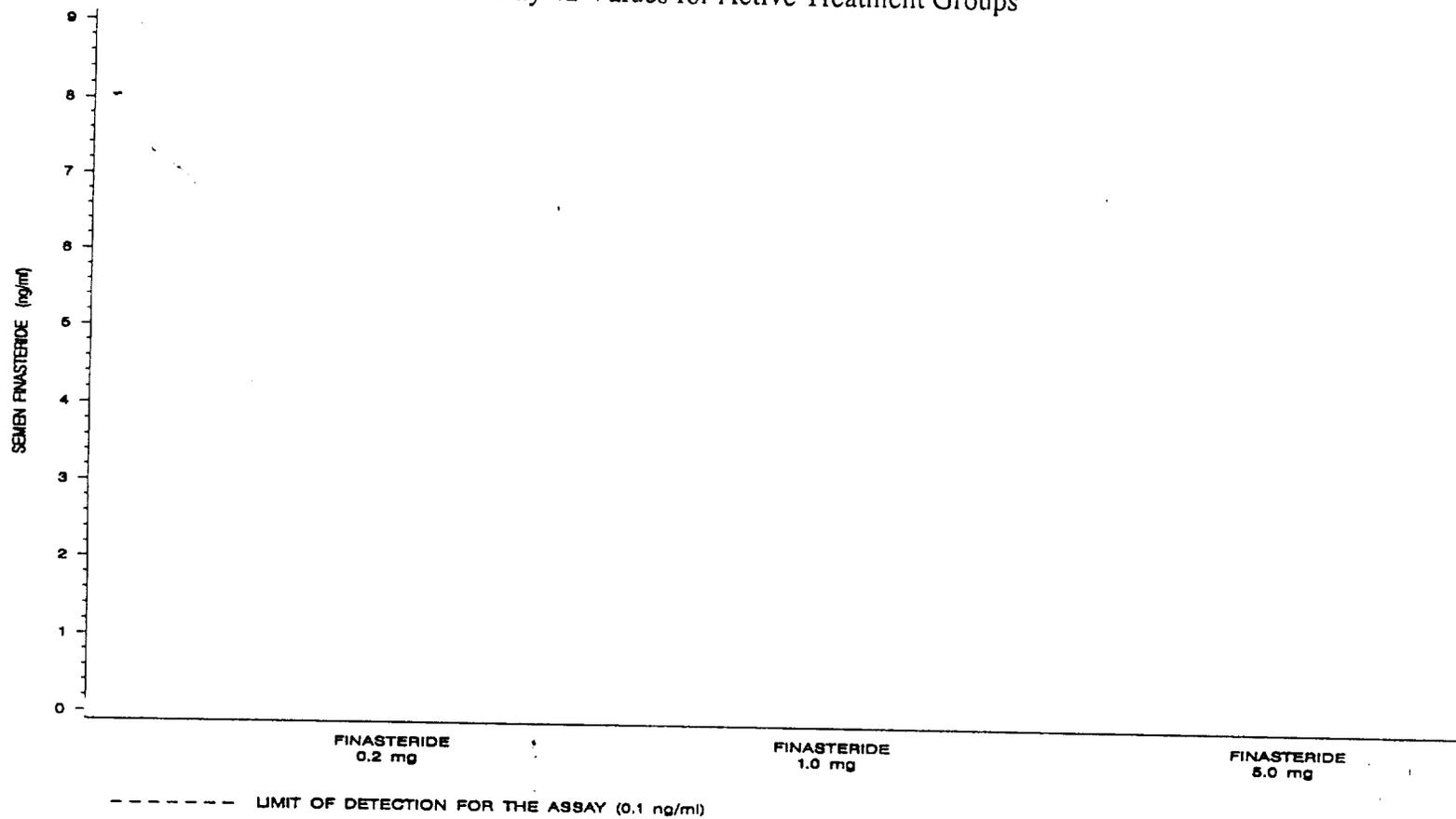
MK-0906 Prot. No. 065
Finasteride Scalp Skin DRF

-56-

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1510

Figure 9
Semen Levels in Finasteride
Day 42 Values for Active Treatment Groups



Data Source: [4.6]

Protocol 031: A Double Blind, Placebo-Controlled Pilot Study to Investigate the Effects of Finasteride, 5 mg/day, on Scalp Skin DHT Content in Male Volunteers Undergoing Hair Transplantation for Male Pattern Baldness (Volume 13 page 1246)

Introduction: This supportive study was the initial evaluation of the effect of multiple oral doses of finasteride on scalp skin 5α -reduced metabolites. The inhibition of 5α -reductase activity in by finasteride has been demonstrated in prostate tissue. Therefore, if scalp skin DHT concentrations can be lowered by oral finasteride, this would constitute a solid basis for undertaking a clinical trial of prevention of male pattern baldness with this drug.

Objective: The objective of this study was to determine the effect of orally administered finasteride on T, DHT, and if possible, the content of other 5α -reduced metabolites in scalp skin of men with male pattern baldness. Only T and DHT determinations were evaluated for this report.

Design: This was a four-week, double-blind, randomized, placebo-controlled multicenter study in which 18 healthy male volunteers, mean age (range) was 31 scheduled to undergo hair transplantation provided scalp skin from a bald area and the hairline (500 mg or more from each site) at the time of their initial hair transplantation procedure (baseline) and after 28 days of treatment with finasteride 5 mg/day or placebo (Day 28) at the time of their second transplantation procedure. Subjects presented to the clinic on the morning of Day 1, i.e., 28 days prior to their second scheduled hair transplant to receive their bottle of medication. Subjects were instructed to take one tablet each morning, including Day 1 and each day for the following 14 days. Subjects were instructed to bring their bottle back to the clinic on Day 14 for assessment of compliance. On Day 14, a second bottle of medication was dispensed for the following two weeks of treatment. Serum T and DHT was obtained at screening, Day 1, Day 14, and Day 28. Scalp skin from a bald area and the hairline (500 mg or more from each site) was collected at the time of the hair transplantation procedures at baseline and Day 28, and scalp skin T and DHT content was determined. Blood (5 mL) was also obtained for serum T and DHT determinations at screening, Day 1, Day 14 and Day 28. Scalp skin samples were obtained at baseline and Day 28 from a bald area and, in selected subjects, from the hairline (500 mg or more from each site) by punch biopsy. Scalp skin specimens (approximately 30 punch biopsies) were flash frozen in liquid nitrogen and then stored at -20°C until assayed. No power was calculated before the study since no variability information on balding scalp DHT was available. However, a pilot study was done after the initiation of this study to determine T and DHT intra and intersubject variability in scalp skin of untreated male volunteers undergoing hair transplantation.

Results: Based on an evaluation of the statistical analysis conducted by the applicant, the following observations were made; the mean baseline level of DHT in bald scalp was significantly ($p = 0.002$) higher than that in hairy scalp (Table 6).

There was a significant ($p = 0.016$) decrease in balding scalp DHT from baseline to Day 28 for the MK-906 group, while there was no significant change for the placebo group. Mean percent change from baseline in balding scalp DHT for MK-906 was significantly ($p = 0.002$) different from that for placebo (Figure 10, Table 7). For the MK-906 group, all patients but one had bald scalp DHT decreased, whereas in the placebo group, bald scalp DHT increased in all patients except for one.

Day 28 serum DHT decreased significantly ($p = 0.004$) for the finasteride but insignificantly for the placebo group. The between-treatment comparison was significant ($p < 0.001$) (Table 8).

The change from baseline to Day 28 in balding scalp T for both treatments was not significant (Table 9). However, if two volunteers who had unusually high baseline values which resulted in larger variance at baseline are excluded, the percent change from baseline in balding scalp T for MK-906 was significantly different from placebo ($p = 0.026$).

A graphical representation of changes T after the two treatments are presented in figure 11. The baseline values for two volunteers were higher when compared to the other volunteers.

The change from baseline to day 28 in serum T for both treatments was not significant. The percent change from baseline in serum T for finasteride (MK-906) was not significantly different from placebo (Table 10).

Conclusion: In this study in which volunteers were treated with finasteride 5 mg/day for 28 days, the mean percent decrease of bald scalp DHT levels compared to that at baseline was 34.1%, while the mean percent increase in T levels was 43.5% from baseline. The placebo group showed little change in DHT and T levels when compared to that at baseline. The sponsor reported finasteride was well tolerated.

In Vitro Metabolism Studies (Volume 13 page 1036)

The applicant included in the application two published articles that provided evidence that finasteride metabolism is mediated by cytochrome P4503A (CYP3A). One of the articles (Ishii, Y et al, Drug Metab Dispos 1994; 22 (1): 79-84) used rat hepatic micromes to demonstrate that the metabolic reaction of finasteride was mediated by a mixed function oxidase involving cytochrome P450 (CYP) enzymes. The second article (Huskey, SW et al, Drug Metab Dispos 1995;23(10):1126-1135) identified the specific human cytochrome P450 enzyme involved in the metabolism of finasteride using human liver microsomes and recombinant CYP isozymes as the enzyme source. Each of the steps (finasteride and its consecutive metabolites ω -hydroxyfinasteride and ω -aldehyde finasteride) in the metabolism of finasteride was examined separately. Gestodene, a mechanism-based inhibitor of CYP 3A isozymes, showed a concentration dependent inhibition of the oxidative metabolism of ^{14}C -finasteride.

Table 6

Baseline Bald Scalp DHT Versus Baseline Hairy Scalp DHT

Baseline DHT (ng/g Tissue)	Sample Size	Mean ± S.E.
Bald scalp	10	2.14 ± 0.36
Hairy scalp	10	1.22 ± 0.19
Difference	10	0.92 ± 0.26*

* p-Value for bald versus hairy = 0.002

Table 7

DHT Concentration in Balding Scalp

Treatment	Sample Size	DHT (ng/g Tissue)		Percent Change From Baseline to Day 28		
		Baseline Mean ± S.E.	Day 28 Mean ± S.E.	Mean ± S.E.	95% C.I. (%)	Between-Group Comparison p-Value
Placebo	9	2.20 ± 0.39	2.36 ± 0.40	12.64% ± 7.64	(-9.03, 31.54)	

* Within-group comparison p-value <0.05

Figure 10

Pre- and Posttreatment Plot for Balding Scalp DHT

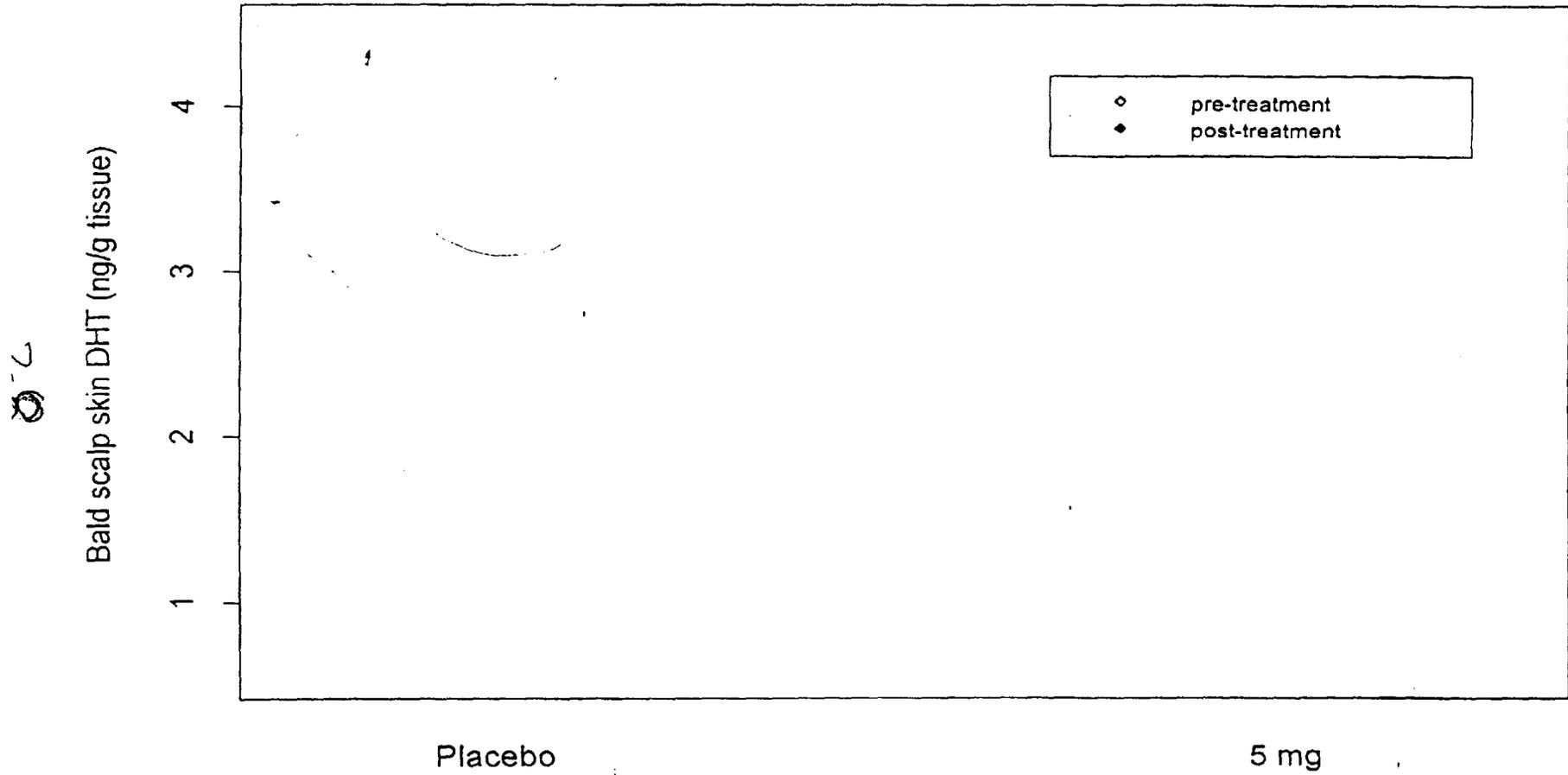


Table 8

DHT Concentration in Serum

Treatment	Sample Size	DHT (ng/dL)		Percent Change From Baseline to Day 28 (Transformed Back From Log Scale)		
		Baseline Mean ± S.E.	Day 28 Mean ± S.E.	Mean	95% C.I. (%)	Between-Group Comparison p-Value
		MK-906	9			
Placebo	9	37.89 ± 4.38	39.00 ± 4.88	1.53%	(-15.38, 24.79)	

* Within-group comparison p-value <0.05

Table 9

T Concentration in Balding Scalp

Treatment	Sample Size	T (ng/g Tissue)		Percent Change From Baseline to Day 28 (Transformed Back From Log Scale)		
		Baseline Mean ± S.E.	Day 28 Mean ± S.E.	Mean	95% C.I. (%)	Between-Group Comparison p-Value
		MK-906	8			
Placebo	9	1.29 ± 0.08	1.33 ± 0.06	4.39%	(-7.16, 18.14)	

Figure 11

Pre- and Posttreatment Plot for Balding Scalp T

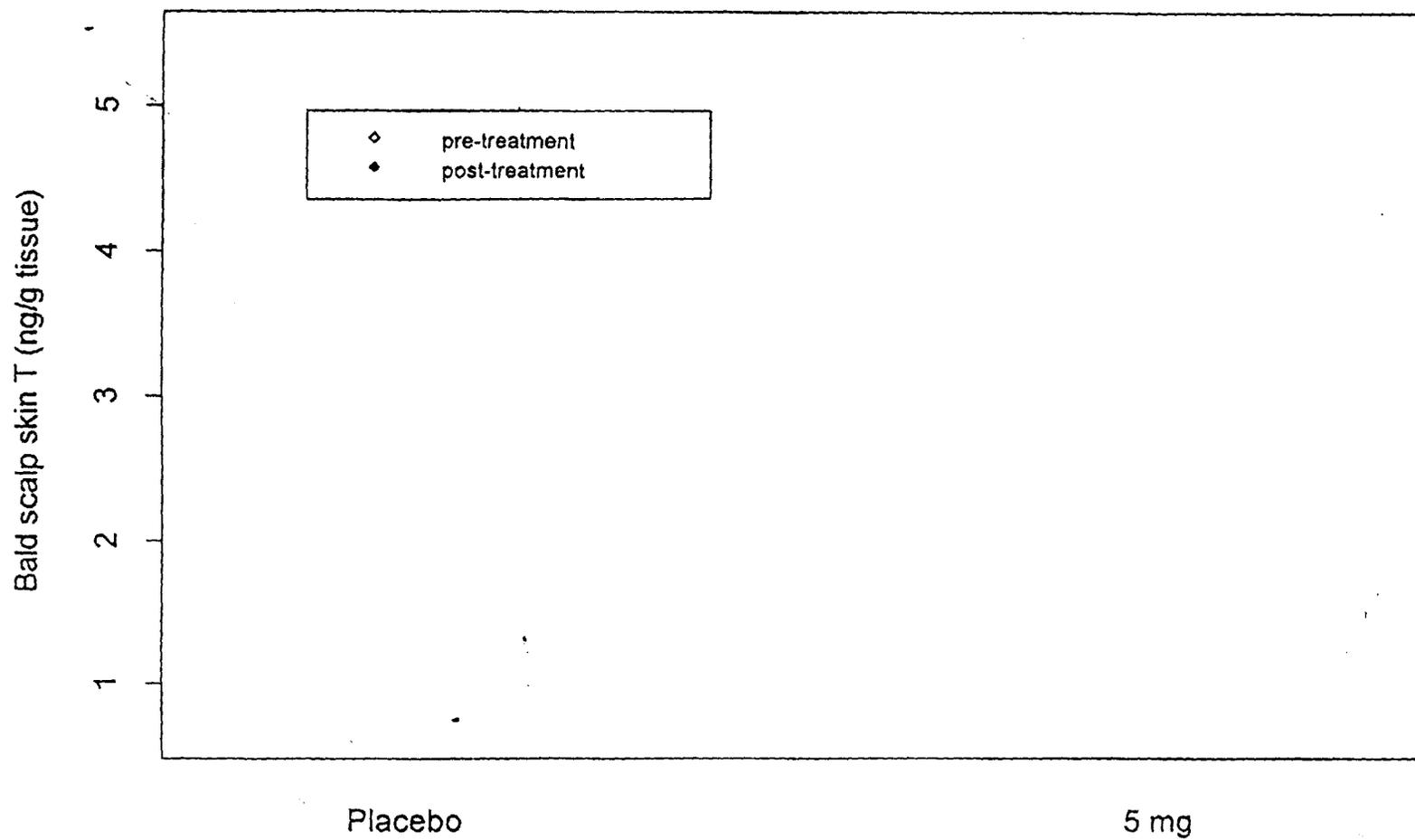


Table ~~18~~ 10

T Concentration in Serum

Treatment	Sample Size	T (ng/dL)		Percent Change From Baseline to Day 28 (Transformed Back From Log Scale)		
		Baseline Mean ± S.E.	Day 28 Mean ± S.E.	Mean	95% C.I. (%)	Between-Group Comparison p-Value
		MK-906	9			
Placebo	9	388.9 ± 49.2	391.6 ± 49.3	1.8%	(-15.2, 26.3)	

In addition, the respective ω -hydroxyfinasteride and finasteride- ω -oic acid, were generated by microsomes containing recombinant CYP 3A4. Other selective CYP inhibitors for CYP1A/2 (α -naphthoflavone), CYP2C8-10 (sulfaphenazole), CYP2D6 (quinidine), and CYP2E1 (diallylsulfone) showed minor or no inhibitory effects on finasteride metabolism.

GENERAL COMMENTS

1. The applicant did not conduct any additional drug interaction studies with inducers or inhibitors of CYP 3A4. It is recommended such studies be conducted to provide an quantitative evaluation of whether dose adjustment are needed when these drugs are administered concomitantly.
2. The sponsor did not conduct any pharmacodynamic-pharmacokinetic relationship studies. The pharmacodynamic studies evaluated dose response relationships but finasteride concentrations were not measured. MPB appears to have an excellent pharmacodynamic measure, DHT, which can be used as a marker. Such a study will be useful in optimizing therapy for these patients.

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