CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-788

MEDICAL REVIEW(S)

NDA 20-788, Correspondence dated November 24, 1997
Date of submission: November 24, 1997
Date of review: December 17, 1997
Re: PSA and Propecia

Medical Officer Memorandum

Background:

In a submission dated November 24, 1997, Joel S. Mindel, M.D. Ph.D., a member of the Dermatologic and Opthalmologic Drug Products advisory committee, expressed some concerns related to the interpretation of serum PSA measurements in patients taking Propecia™(finasteride I mg). He previously had voiced these same concerns at the actual advisory committee meeting of November 13, 1997.

Review of the Submission:

The following list comprises selected areas of concern, taken directly from the correspondence, and addresses each concern individually:

1. **Merck eventually let the Committee know that the PSA level of patients on 1 mg of finasteride is reduced by approximately 50%, the same as the 5 mg dose. I am concerned about the consequences of the internist/family practitioner/general practitioner not multiplying the PSA test by 2 (or any other number).**-*continued in statement #2.*

   First, the sponsor clearly informed the committee that the mean PSA actually dropped from ng/ml to ng/ml at Week 48, not by 50%. Dr. John McConnell, a consultant for the sponsor, recommended doubling the PSA, as the most sensitive way to detect prostate cancers.

   Second, the label will clearly inform physicians and patients that the mean PSA did drop from ng/ml to ng/ml in clinical trials (see PRECAUTIONS section of proposed product circular) and that doubling the PSA is recommended as the most sensitive way of detecting prostate cancers. This recommendation, clearly provided in the label, should ensure safe and effective use of the product.

2. **This failure to multiply might occur because of any one of the following scenarios:**
   a. **The patient, not considering the finasteride used for hair growth to be "medication", fails to tell the general practitioner/family doctor/internist that it was ordered for him by a dermatologist or some other health care provider."**

First, Propecia™ (finasteride 1mg) is a compound obtained by prescription only. It is likely that all patients taking this drug will realize that it is a medication, obtained only by prescription.

Second, this particular concern has not appeared to prevent the detection of prostate cancer in men taking Proscar® (finasteride 5mg).[1]

b. **The patient is embarrassed to tell the general practitioner/family doctor/internist that he is taking a medication for a cosmetic reason, hair growth.**

This valid concern seems best managed by patient education, and enhancement of the doctor-patient relationship, rather than through regulatory action.

c. **The general practitioner/internist/family doctor is told by the patient that he is on finasteride but at the time the laboratory results arrive 48 hours later, the busy physician fails to remember to multiply the PSA by 2.**

The necessary information for safe and effective use of this product by a physician will be explicitly detailed in the product label.

3. **Therefore, the finasteride-induced reduction in the ultrasensitive PSA could delay radiation therapy by lowering the PSA below detection levels and potentially change a curable patient into a non-curable patient.**

In patients who have undergone radical prostatectomy with the intention for cure, the measurement of serum PSA may allow detection of local or distant tumor spread. Dr. Mindel refers to the adjuvant use of regional radiotherapy following radical prostatectomy in patients with presumed local residual disease as detected by postoperative serum PSA measurement.

First, the early detection of serum PSA following radical prostatectomy, in many cases, is indicative of occult distant spread of tumor and is not amenable to local treatments.[2]

However, in some instances, postoperative serum PSA measurement may alert the urologist to local residual tumor, and in those circumstances, therapeutic radiotherapy may be effective in providing effective local control and improved long-term

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[1] Stoner E, Round E, Ferguson D, Gormley GJ. The Finasteride Study Group. Clinical experience of the detection of prostate cancer in patients with benign prostatic hyperplasia treated with finasteride. J Urol 1994;151:1296-1300.

[2] Patel A, Dorey F, Franklin J and deKernion JB. Recurrence patterns after radical retropubic prostatectomy: clinical usefulness of prostate specific antigen doubling times and log slope prostate specific antigen. J Urol 1997;158:1441-1446.

progression-free survival[3,4]. Under these circumstances, Dr. Mindel's theoretic concern is valid. Therefore, the label should be amended to account for this possibility. An example of such a revision follows:

In patients undergoing radical prostatectomy for cancer, the use of Propecia™ may adversely affect the ability to detect recurrent or residual disease by its effect on postoperative serum PSA. In this circumstance, the use of Propecia™ should be discouraged.

4. **Furthermore, the urologist might not know that finasteride, under a name different from Proscar, had been given to the patient for cosmetic reasons.**

   The Division of Reproductive and Urologic Drug Products agrees with Dr. Mindel that Propecia ™(finasteride 1 mg) and Proscar® (finasteride 5 mg) should be named in a consistent manner. Further, we do not support the tradename, Propecia™ (finasteride 1 mg) for this product. Rather, we would prefer that the product be marketed as Proscar® (finasteride 1 mg) for consistency.

Reviewer conclusions:

In summary, Dr Mindel's concerns are valid, however, effective labeling of this product and patient/physician education should mitigate these theoretic concerns.

Recommended regulatory action:

1. The labeling revision proposed in concern # 3 will be conveyed to the reviewing medical officer.
2. The Division will again convey its concern about the tradename, Propecia™, to the reviewing division.

Mark S. Hirsch, M.D.
Medical Officer
DRUDP
Orig NDA 20-788
HFD-580 Div File
HFD-580/LRarick/HJolson/DShames

2/11/97

[3] Forman JD, Meetze, K, Pontes, E,,Wood Jr., DP, Shams, F, Rana, T and Porter AT. Therapeutic irradiation for patients with an elevated post-prostatectomy prostate specific antigen level. J Urol 1997;158:1436-1440.

[4] Crane CH, Rich TR, Read PW, Sanfillipo NJ, Gillenwater JY and Kelly MD. Preirradiation PSA predicts biochemical disease-free survival in patients treated with postprostatectomy external beam irradiation. Int J Rad Onc 1997;39:681-686.

Medical Officer's Review of NDA 20-788 DEC 19 1997

1. General Information

NDA #20-788
Original

Submission date: December 20, 1996
Received date: December 21, 1996
Assigned date: January 7, 1997
Review completed: September 26, 1997
Review revised: October 20 and
December 11, 1997

Drug name: finasteride 1 mg tablets

Generic name: finasteride

Proposed trade name: PROPECIA™

Chemical name : *N*-(1,1-Dimethylethyl)-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide

Applicant: Merck Research Laboratories
Sumneytown Pike
P.O. Box 4, BLA-20
West Point, PA 19486

Pharmacologic category: 5α-reductase inhibitor

Proposed Indication: male pattern baldness (MPB) in men

Dosage Form(s) and Route(s) of Administration: tablet, oral

NDA Drug Classification: 3 S

Related NDAs and INDs:
NDA 20-180 PROSCAR™ for the treatment of symptomatic benign prostatic hyperplasia (BPH)
IND
Studies done by the Applicant for NDA 20-788 were conducted under IND

Related Reviews: **Statistical Review dated:** 12/11/97
Biopharm Review dated: 10/22/97
Pharm/Tox Review dated: 9/29/97
Chemistry Review dated: 12/10/97

Table of Contents

3 Material Reviewed

This review is based on material submitted by the Applicant in volumes 1.1, 1.16 through 1.47 of NDA 20-788, which is also contained in CANDA with adobe acrobat format. Items 11 and 12 ("vol 1.61 and 1.62") are only provided in the CANDA. In addition, the Applicant amended the NDA with significant clinical information as follows:

120-day safety update	4/18/97
Justification of endpoints and data exclusion in pivotal studies	6/18/97
Executive summary of extension studies from pivotal studies	8/11/97
Changes to package insert	9/25/97
Details of extension studies data not submitted on 8/11/97	9/26/97
Estradiol and prolactin analysis at Week 48 of Study 094	9/30/97
Briefing Package for Advisory Committee meeting	10/10/97

4 Chemistry/Manufacturing Controls see review by Chemist.

PROPECIA™ has the following formulation:

Table 4 Formulation of PROPECIA™

Component	Reference	Role	mg per Tablet
Tablet Core Composition			
Finasteride	---		
Lactose Monohydrate	NF		
Microcrystalline Cellulose	NF		
Pregelatinized Starch	NF		
Sodium Starch Glycolate	NF		
Docusate Sodium	USP		
Magnesium Stearate	NF		
Total Uncoated Tablet Weight	---		mg
Tablet Coat Composition			
Total Coated Tablet Weight			mg
Tan Color Concentrate Composition for Finasteride Tablets, 1 mg Aqueous Coating Suspension (2)			
Hydroxypropyl Methylcellulose 2910, 6 cps	USP		
Hydroxypropyl Cellulose LF	NF		
Titanium Dioxide	USP		
Talc	USP		
Ferric Oxide (Yellow)	NF		
Ferric Oxide (Red)	NF		

(1) Used in the manufacture of tablets, but removed during processing.
(2) The tan color concentrate for finasteride tablets, 1 mg aqueous coating suspension is purchased from [redacted] An excess of the tablet coating suspension may be prepared to account for manufacturing loss. The quantities shown are theoretical quantities applied per batch. Quantities may be varied to account for process efficiencies during film coating.

5 Animal Pharmacology/Toxicology see Pharm/Tox review

This application is for a lower dosage formulation (1 mg) as compared to that in NDA 20-180 (PROSCAR™; 5 mg). Most of the information is cross-referenced to NDA 20-180. Additional studies since the submission of the marketing application for finasteride 5 mg have been conducted to understand the pharmacological effects of finasteride on genital differentiation in the fetal monkey and on prostatic hormonal changes in rats. The Pharm/Tox Reviewer, Dr. J. Avalos, considers this application approvable with

labeling changes.

6 Clinical Background

6.1 Relevant Human Experience

6.1.1 Finasteride

Finasteride is a 5α-reductase (5α-R) inhibitor which has been approved in the U.S. on 6/19/92 as 5-mg tablets (PROSCAR™) for the treatment of BPH. The most common drug-related adverse experiences in the clinical trials for BPH were impotence, decreased libido and decreased volume of ejaculate. Postmarketing experience has revealed the following additional adverse events which may be drug-related:- breast tenderness and enlargement and hypersensitivity reactions, including lip swelling and skin rash. It has never been marketed for the treatment of MPB and the pertinent human experience for this indication is contained within this NDA.

6.1.2 Male Pattern Baldness and 5α-Reductase Activity

MPB may be considered a physiologic condition as it occurs universally with only a difference in degree and onset. It is also present in subhuman primates such as the stumptail macaque. However, the occurrence of MPB may be associated with psychosocial disturbance, especially in younger individuals.

Testosterone is converted to an active metabolite, dihydrotestosterone (DHT), by 5α-R. Recent studies have established that there are two 5α-R isozymes (Type 1 and Type 2) in rat, monkey and man. In primates including humans, finasteride shows greater selectivity for the Type 2 isozyme. Distribution of the two isozymes is differential, with Type 1 5α-reductase being the only isozyme detected biochemically in scalp homogenates (*J Invest Dermatol* 105:209, 1995; *PNAS* 89: 10787, 1992). Recent studies, however, have identified the Type 2 isozyme in scalp hair follicles while the Type 1 isozyme is localized to sebaceous glands in scalp skin (*Br J Dermatol* 133: 371, 1995; NDA 20-788, pp D6191-D6207; see Figure in Appendix VIII).

It is generally believed that MPB is mediated by androgenic action. An androgen-mediated decrease in the ratio of anagen to telogen hair follicles and an increase in the proportion of vellus, or vellus-like, miniaturized follicles as compared with terminal follicles constitute the hallmark of MPB. Thus, inhibition of androgen-mediated effects on hair follicles may be a rational goal for treatment. Dependence of MPB on the androgenic action of DHT has been suggested by the observation that men with an inherited deficiency of Type 2 5α-R have a selective reduction in DHT and do not develop MPB. This hypothesis is strengthened by the promotion of hair growth by finasteride in an animal model, the stumptail macaque. Since finasteride is a selective Type 2 5α-R inhibitor and specifically inhibits DHT-mediated effects on target tissues without affecting testosterone-mediated effects, it is reasonable to study finasteride in

the treatment of MPB.

6.1.3 Methodology for Studying Male Pattern Baldness

Hair growth is a dynamic process which involves the increase in length and thickness of hair. Scalp hairs are a diverse population in different phases of the hair cycle and of different sizes and thickness. If the current theory that MPB represents an androgen-mediated miniaturization of terminal hair follicles without actual loss of the follicles is upheld, there is no change in the number of hairs in MPB, just a change in the state of the hairs and hair follicles. Thus, the study of hair growth ideally would require demonstration of increase in length and thickness of the existing hairs, which is related to the recruitment of hair follicles into the anagen phase, and the conversion of vellus or vellus-like hairs into terminal hairs. It would be misleading to speak of hair growth and hair loss in terms of a change in apparent static hair count.

Since hair growth is the end result of the combination of cell proliferation and maturation, it would require invasive techniques to demonstrate this conclusively. Such techniques, including mitotic index, labeling index and metaphase arrest, would not be suitable for routine clinical studies. Hair plucking is a less invasive procedure, but introduces a variable lag in growth until the shaft has grown through the skin, and animal studies suggest its altering linear growth with synchronization of the random anagen growth phase for a while. The trichogram was developed to quantify the different mrophological parameters reflecting biology and pathology of the hair (J Invest Dermatol 44: 223, 1965) including the rate of growth (length increase/unit time), density (hair count/unit area) and, in conjuction with plucking, thickness, state of hair cycle and regeneration period. With advances in photographic technology, the phototrichogram is now available, which allows examination of thickness and state of hair cycle without plucking and may also help to eliminate time bias by maintaining blinding during a study.

The following methods have been used by the Applicant in the MPB studies in this NDA: (1) hair count, (2) patient self-assessment, (3) investigator assessment and (4) global photographic assessment. Details are given in the clinical trials in Section 8 of this review. Hair count over a preselected area is an objective method but measures an apparent net change over a defined time period without real regard to the real biologic paremeters of growth. The preselected area (leading edge of the "balding spot") may be variable between patients. The other three methods are subjective evaluations which may be open to bias. The Applicant has taken pains to validate the patient self-assessment questionnaire and the global photographic assessment. The patient Hair Growth Questionnaire appears to provide supportive evidence for the cosmetic importance of the objective changes in hair counts and these two parameters have therefore been chosen to be coprimary variables in the pivotal trials. As shown in the trials to be discussed, global photography appears to be giving least placebo effect among the subjective assessments. It also appears that the use of photographs for both

hair counts and global photographic evaluation do help to reduce time bias. The investigator assessment involves recall and, in contrast to hair count and global photography, is associated with substantial positive placebo effect.

Histologic evaluations were done in one center in one of the pivotal trials. Scalp biopsy with horizontal sections has been a standardized method in that center (Whiting) and has been used to study the changes in ratio of terminal vs vellus hairs (J Am Acad Dermatol 28: 755, 1993).

6.2 Important Information from related INDs and NDAs

As mentioned above, most of the Pharm/Tox data are cross-referenced to NDA 20-180. All the data from clinical studies in NDA 20-788 have been obtained through studies conducted under IND except for those from the phase 3 international study 089. Pertinent information from IND have also been submitted to NDA 20-788.

6.3 Foreign Experience

Finasteride 1 mg has not been marketed. Foreign experience in the use of finasteride 1 mg for the treatment of MPB has been derived from the international phase 3 study (089), which will be discussed in Section 8 of this review. Since 1992, the 5 mg product, PROSCAR™, has been marketed for the treatment of benign prostatic hyperplasia in over 100 countries and has not been withdrawn in any country.

6.4 Human Pharmacology, Pharmacokinetics and Pharmacodynamics

Human pharmacology and pharmacodynamics data have been submitted in the Clinical Section of this NDA and the information on safety and efficacy will be the subject of this review. Human PK data and PD studies on scalp and sebum DHT were also submitted in Item 6 (Human Pharmacokinetics and Bioavailability Section) of this NDA and reviewed by Biopharm. The Biopharm Reviewer, Dr. K. Kumi, considers this NDA approvable with labeling changes.

6.5 Other Relevant Background Information

6/7/94 The Division of Topical Drug Products, Division of Metabolism and Endocrine Drug Products, and Merck Research Laboratories (MRL) met to review the Male Pattern Baldness (MPB) clinical program: the program was to be transferred to DTDP and a new IND for finasteride MPB to be submitted.

6/29/94 IND submitted to DTDP for finasteride in the treatment of MPB

11/28/94 End-of-Phase 2 meeting to discuss the proposed Phase 3 clinical plan

3/14/95 Merck's understanding of commitments made at EOP2 meeting submitted

2/3/95 Telephone conference between Mr. S. Turtil of the FDA and Dr. L. Bell of

MRL - conclusion and subsequent agreement reached on use of two coprimary endpoints: Dr. Bell documented this decision in a letter to the Agency on 2/17/95.

4/20/95 Follow-up letter sent by Merck, at the request of the Agency, to provide information on whether serum finasteride levels were detectable in female partners exposed to semen of males taking finasteride 1 mg/d.

4/29/96 Pre-NDA meeting

11/15/96 In follow-up to the Pre-NDA Meeting, MRL sent a letter formally requesting a waiver allowing for the submission of electronic case report forms (CRFs) and case report tabulations (CRTs) without an archival hard copy for this NDA.

6.6 Directions for Use

In the proposed labeling,

7 Description of Clinical Data Source

Clinical studies presented in this NDA are summarized in the following Table:

Table 7 Summary of Database

Category	Short Study Title	Study Number	Finasteride Dose (mg)	Treatment Duration	Fin	Placebo	Total Number
Phase 3	U.S. Phase 3 Pivotal	087	1	1 yr	471	462	933
Controlled	International Phase 3 Pivotal	089	1	1 yr	308	312	620
	Phase 3 Frontal Hair Loss	092	1	1 yr	166	160	326
			Total		**945**	**934**	**1879**
Phase 2	Phase 2 Pilot	047	5	1 year	111	116	227
Controlled	Phase 2 Dose Range	081	1, 0.2, 0.01	6 months	349	117	466
	Safety	094	1	48 weeks	91	90	181
	Scalp DHT and Sebum	065	5, 1, 0.2, 0.05, 0.01	6 weeks	182	67	249
	Scalp DHT	031	5	4 weeks	9	9	18
	Semen Production #1	012	5	12 weeks	24	23	47
	Semen Production #2	056	5	24 weeks	70	68	138
			Total		**836**	**490**	**1326**
Phase 2	Extensions of the 047	047-10	5, 1	24 months	147#	N/A	147†
Uncontrolled		047-20					
	Extensions of the 081	081-10	1, 0.2, 0.01	1 year	343#	N/A	343†
		081-20					
	Multiple-Dose PK	102	1	2 weeks	12	N/A	12
			Total		**502**	N/A	**502†**

Subset of the Phase 2 Pilot and Phase 2 Dose-Range studies. † Cannot be added to other patient numbers. Overall number of patients = 3217.
N/A = Not Applicable

Studies 065, 031 and 102 are Clinical Pharmacology studies and are reviewed by Biopharm. The phase 2 pilot study using finasteride 5 mg and the dose-ranging study are discussed in Section 8 of this review, together with the phase 3 studies. The safety studies, 012, 056 and 094 are discussed in Section 10.

8. Controlled Clinical Studies for Efficacy and Safety

8.1 Indication #1. Treatment of MPB

8.1.1 Trial#1: Study#047 A Double-Blind, Randomized, Placebo-Controlled, Multicenter Study to Determine the Effect of Finasteride on Hair Loss in Male Patients with Androgenetic Alopecia (Male Pattern Baldness)

8.1.1.1 Objective/Rationale
This was designed to be a pilot study for the treatment of MPB with finasteride. The study lasted from 7/92 to 4/94. It used a dose of finasteride 5 mg/d for the treatment of MPB. The objectives were: (1) To determine if 12 months of finasteride treatment affects androgen-dependent scalp hair loss; and (2) To evaluate the safety and tolerability of finasteride in patients with MPB.

8.1.1.2 Design Phase 2, 12-month, double-blind, randomized, placebo-controlled, multicenter study

8.1.1.3 Protocol After a 2-week, single-blind placebo run-in period, each patient was randomized to receive oral doses of finasteride 5-mg or placebo tablets qd before breakfast for 12 months. Patients were required to maintain use of the same shampoo (Neutrogena T/Gel™, supplied) and maintain the same hairstyle. A single dot tattoo was placed on the scalp at Week -2. Macrophotography and global photography were done at Week -2 and Months 6 and 12.

Study Plan

		Pbo Run-In	Treatment Period				
		Week	Month				
Procedure	Screening	-2	0	3	6	9	12
Visit:	1	2	3	4	5	6	7
Clinic visit	X	X	X	X	X	X	X
Physical examination (including occult blood)	X			X		X	
Scalp tattoo		X					
Macrophotography		X a	(X)a		X		X
Global photography		X			X		X
Medical history	X						
Testicular volume		X			X		X
Semen analysis	X b						
Vital signs c	X		X	X	X	X	X
Hematology d	X		X		X		X
Urinalysis d	X						X

Serum chemistry e	X		X	X	X	X	X
T/DHT e	X		X	X	X	X	X
LH/FSH e			X				X
TSH e	X						
PSA e	X		X		X		X
Sexual Function Questionnaire		X	X	X	X	X	X
Hair Growth Questionnaire (patient / investigator assessment of hair loss/growth)		X	X	X	X	X	X
Adverse experiences			X	X	X	X	X
Medication bottles f		I	II	III	IV	V	
Shampoo g		X	(X)	(X)	(X)	(X)	

a Week -2 macrophotography was repeated at the Month 0 visit if the Week -2 photographs were inadequate
b If semen analysis was abnormal or the sperm concentration was <40 x 10^6/mL, a second specimen was obtained at least 48 hours after the first specimen and the patient enrolled only if the second analysis was normal and the average sperm concentration of both samples was ≥40 x 10^6/mL
c Vital signs were pulse, blood pressure, temperature, and weight
d Performed in investigator laboratory
e Performed in the central laboratory
f Unused medication and bottles were returned before dispensing new medication
g Given at Week -2 and as needed at the appropriate time
Pbo=placebo

Comment The possiblity of Neutrogena T-gel shampoo affecting hair count should be addressed.

8.1.1.3.1 Population/Procedures

Patient Selection

Healthy men 18 to 35 years of age with Hamilton Grade III vertex or IV MPB with moderate vertex balding and progressive hair loss or recent onset of balding (within 3 years). A prostate-specific antigen (PSA) level >4 ng/mL and normal semen analysis with sperm concentration of >40 x 10^6/mL during the screening evaluation was required and the patient or his sexual partner(s) had to be willing to use adequate birth control. The following are exclusion criteria:

1) A history of any illness or condition that might confound results or pose additional risk, including multiple and/or severe allergies or incompetency.
2) A history of thyroid disease.
3) Significant abnormalities on screening clinical examination or laboratory measurements, including abnormal thyroid-stimulating hormone (TSH) or testosterone (T) level below normal range.
4) Patients with liver function tests >1.5 times upper limit of normal range.
5) Suspicion of malignancy, including prostate cancer.
6) History of varicocele.
7) History of infertility or difficulty fathering children.
8) Patients who wished to father children during the study or whose sexual partner(s) were pregnant.
9) Patients with light blond hair.
10) Patients with active seborrheic dermatitis.
11) Concurrent use of systemic corticosteroids, topical corticosteroids in the balding area studied, anabolic steroids, or over-the-counter "hair restorers."
12) Use of the following drugs with antiandrogenic properties within 6 months of study entry: flutamide, cyproterone acetate, estrogen, progesterone, cimetidine, spironolactone, or ketoconazole.
13) Patients who had been treated with any of the following drugs within the past year: minoxidil (topical or oral), zidovudine, cyclosporine, diazoxide, phenytoin, systemic interferon, psoralens, streptomycin, penicillamine, benoxaprofen, tamoxifen, phenothiazines, or cytotoxic agents.
14) Patients who had had hair transplant surgery or hair weaving.
15) History of drug or alcohol abuse.

Dosing Instructions and Restrictions during Trial

Patients were to take finasteride 5 mg or placebo once daily. They would continue their usual diet and maintain their usual hair style. Use of any medication in the exclusion criteria would result in discontinuation of the patient from the study. Compliance would be checked by counting tablets. Only the shampoo provided (Neutrogena T-gel shampoo) was allowed during study period.

Evaluations

a. Efficacy

Global Photography

Before taking photographs, the patient's hair was combed away from his bald spot so that the entire balding area could be viewed. Extraneous matter was eliminated. Global photographs were taken prior to macrophotography using a Nikon N-6000 camera with a Nikkor 60 mm f2.8 lens and two Nikon SB-23 flashes. Film emulsion, lighting, framing, exposure, and reproduction ratios were held constant. The lens had a fixed reproduction ratio of 1:6, and all photographs were taken at f/11. The patient's head was kept in a fixed position by placing it in a stereotactic device. Color slide film (Kodachrome KR-64 24 exposure) of a single emulsion lot number was used. Film was refrigerated at 4.4°C until 24 hours before use. Each patient's photographs at each session were taken using a separate roll of film. During each photographic session for a patient, the following exposures were shot in sequence:

a. One exposure of patient I.D. card and color card to insure quality control of color processing
b. Three exposures of patient's global photographs
c. A second exposure of patient I.D. card and color card

Each roll of film was shipped for processing the same day it was shot via overnight courier to
It was then processed at

Macrophotography

The hair count area on the patient was prepared as follows: A small (1 mm in diameter) dot tattoo was placed at Week -2 at the leading edge of the bald area directly anterior to the center of the vertex bald spot using either a commercial tattooing machine or needle and ink. The hair in an area approximately one square inch in size, centered at the tattoo at the leading edge of the balding area, was clipped to approximately 1 to 2 mm in length. Cut hairs were removed using tape, compressed air, and/or ethanol wipes.

Macrophotographs were taken using a Nikon N-6000 camera with a Nikkor 60 mm f2.8 lens and a Nikon SB-21B Macroflash. Film emulsion, lighting, framing, exposure, and reproduction ratios were held constant. The lens had a fixed reproduction ratio of 1:1.7, and all photographs were taken at f/22. A stereotactic device was attached to the camera. The lens was focused by correctly positioning the stereotactic device on the patient's head. Film for black and white prints (Kodak T-Max 100 24 exposure) of the same emulsion lot number was used. Film was refrigerated at 4.4°C until 24 hours before use. Each patient's photographs were taken using a separate roll of film.

During each session, the following exposures were shot in sequence:

a. One exposure at zero compensation of patient I.D. card
b. Three bracketed exposures (-2/3, 0, and +2/3 f-stop compensation) of hair count target area
c. A second exposure of patient I.D. card at zero compensation.

Each roll was shipped for processing the same day via overnight courier to ; where it was developed into prints within 48 hours of receipt. The clearest of the three macrophotographs for each patient was enlarged into an 8 x 10 inch black and white print for dot mapping. Each print was coded for blinding and sent to the central hair count reading site:

A trained technician placed a transparency over the photograph and, using a felt tip pen, placed a black dot over each visible hair. The dot map transparency was then counted using computer-assisted image analysis. Baseline and Month 6 photographs were dot mapped and counted and the data analyzed for an interim analysis at Month 6. At Month 12, the Baseline, Month 6 and Month 12 photographs were dot mapped and counted and the data analyzed for the final analysis.

Comments

1. The Applicant has not explained why an interim analysis at Month 6 was warranted, or why at month 12, dotmapping would need to be repeated for baseline and month 6. It is possible that the three photographs for baseline, Months 6 and 12 were dotmapped

together at Month 12 to maximize consistency by the same technician.
2. The methodology of hair counting counts total visible hair. This count therefore may include non-terminal hair if they are sufficiently thick and pigmented to be counted.

1. Hair count by Macrophotography see above for methodology

2. Patient Self-Assessment A Hair Growth Questionnaire was given to patients and was made up of two versions (HGB, the baseline questionnaire with 43 questions, and HGF, or the follow-up questionnaire, with 32 questions), seven questions of which were deemed valid for self-assessment. Six of the 7 questions were given only at Month 12; question 25 was given at all time points. The 7 questions used in analysis were:
Question 25--Since beginning the study, I can see my bald spot getting smaller.
Question 29--Because of the treatment I have received since the start of the study, the appearance of my hair is:
Question 30--Since the start of the study, how would you describe the growth of your hair?
Question 31--Since the start of the study, how effective do you think this treatment has been in slowing down your hair loss?
Question 32a--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 32b--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 32c--Compared to the beginning of the study, which statement best describes your satisfaction with the appearance of your hair overall?

Comment The questionnaire was not validated at the time of this study. Indeed, data derived from this study were used to validate the questionnaire (see Section 8.1.3).

3. Investigator Assessment Investigator assessment of hair growth/loss change from baseline was done 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 and 7 = Greatly Increased

4. Global Photography Three dermatologists (**Elise Olsen, Ron Savin, and David Whiting**) independently evaluated paired global photographs (Month 0 and Month 6 or Month 0 and Month 12) under identical lighting conditions for each patient. Each pair of global photographs were randomized so that the dermatologists were blinded to patient, treatment, and study center but not sequence. The procedure was performed twice, once after Month 6 and once after Month 12, with comparison between Month 0 and Month 6 or Month 0 and Month 12 global photographs. Each dermatologist rated the paired photographs separately based on a seven-point scale:
0 = Don't Know, 1 = Greatly Decreased, 2 = Moderately Decreased, 3 = Slightly Decreased, 4 = No Change, 5 = Slightly Increased, 6 = Moderately Increased and 7 = Greatly Increased.

Comments See Section 6.1.3 for comments on methodologies for studying hair growth.

5. Dihydrotestosterone , DHT were performed by
Investigators received baseline laboratory results and then were blinded to DHT levels.

b. Safety

1. Clinical Querying for AE and complete physical examination (including rectal for occult blood); testicular volume and a Sexual Function Questionnaire which consisted of 16 questions that had not been validated.

2. Laboratory Hematology, biochemistry and urinalysis

8.1.1.3.2 Subject Dispositions and Endpoints

Each subject would continue use of study drug for 12 months. The primary parameter in this study was hair count, and all other efficacy evaluations were secondary parameters.

Comment(s): This was a pilot exploratory study. Hair count appears to be a suitable parameter for this "proof of concept" study.

8.1.1.3.3 Statistical Considerations

The hypotheses, specific statistical methodology, and expected results were exploratory rather than confirmatory for this study. The following gives an account of the special issues and methodology

Rescaling Responses from subjective assessments were re-scaled so that they were in the same direction as the change in hair count. Low values and negative changes were indicative of lack of efficacy for all endpoints.

Interim Analyses Data were collected and analyzed after the Month 6 time point for interim analysis of safety and efficacy as stated in the protocol. The study was planned to continue for the full 12 months regardless of the Month 6 results, unless there was a safety concern; therefore no p-value adjustments were made.

Populations Examined The primary patient set analyzed was the intention-to-treat population. All patients were included in the analyses as long as they had data both at baseline and on treatment. Data from last observation carried forward were used to substitute for missing data.

Analytical Methods

b) Safety Comparisons of treatment groups for incidence of observed AE were made using Fisher's Exact Test. Summary statistics were given for lab parameters. Sexual Function Questionnaire was analyzed according to individual questions in an ANOVA model except for 2 questions whose interpretation depended on factors external to the study (and not analyzed).

8.1.1.4 Results

8.1.1.4.1 Patient Disposition, Comparability

Investigators:

Investigator	Institution City and State

Dr. Wilma Bergfeld	Cleveland Clinic, Foundation Cleveland, OH
Dr. Richard DeVillez	University of Texas Health Science Center, San Antonio, TX
Dr. Virginia Fiedler	University of Illinois, Chicago, IL
Dr. Julianne Imperato-McGinley	Cornell University Medical College, New York, NY
Dr. Larry Millikan	Tulane Medical School, New Orleans, LA
Dr. Sigfrid Muller	Mayo Clinic, Rochester, MN
Dr. Elise Olsen	Duke University Medical Center, Durham, NC
Dr. Robert Rietschel	Oschner Clinic, New Orleans, LA
Dr. Janet Roberts	Private Practice in Dermatology, Portland, OR
Dr. Ronald Savin	Dermatology Center, New Haven, CT
Dr. Jerome Shupack	New York University Medical Center, New York, NY
Dr. Dowling Stough	The Stough Clinic, Hot Springs, AR
Dr. David Whiting	Baylor Hair Research and Treatment Center, Dallas, TX

Distribution of patients at entry by Investigator:

Investigator	Finasteride	Placebo	Total
Bergfeld, W.	4	4	8
DeVillez, R.	7	5	12
Fiedler, V.	14	14	28
Imperato-McGinley, J.	12	10	22
Millikan, L.	4	5	9
Muller, S.	5	3	8
Olsen, E.	12	11	23
Rietschel, R.	5	5	10
Roberts, J.	18	21	39
Savin, R.	4	6	10
Shupack, J.	9	13	22
Stough, D.	7	9	16
Whiting, D.	10	10	20
Total	111	116	227

Completion Status:

	Finasteride 5 mg	Placebo	Total
ENTERED: (age range)*	111 (18 to 36)**	116 (22 to 36)**	227 (18 to 36)**
COMPLETED:	80	86	166
DISCONTINUED: Total	31	30	61
Clinical adverse experience	4	1	5
Laboratory adverse experience	0	1	1
Other	27	28	55

* All patients were male. ** Thirty-six-year-old patients were 35 years old when screened for enrollment.

Patients Discontinued From Therapy:

	Finasteride 5 mg (N = 111)			Placebo (N = 116)		
Reason Discontinued	Up to 6 Months	7 to 12 Months	Total	Up to 6 Months	7 to 12 Months	Total
Clinical AE	3	1	4	1	0	1
Laboratory AE	0	0	0	1*	0	1*
Relocating	2	0	2	1	0	1
Wish to father children	0	0	0	2	1	3
Mate pregnant	3	0	3	1	0	1
Noncompliant	0	0	0	0	1	1
Lost to follow-up	11	1	12	10	2	12
Withdrew	4	0	4	3	0	3
Protocol violation	3	0	3	4	0	4
Lack of efficacy	2	0	2	2	0	2
Refused hair clipping	1	0	1	1	0	1

Total discontinued	29	2	31	26	4	30

* This patient's adverse experience occurred during the placebo run-in period and is not, therefore, reflected in the counts of laboratory adverse experiences.

Comment There was a large proportion of dropouts in the first 6 months in both groups (finasteride 29/111=26% and placebo 26/116=22%).

Comparability of Treatment Groups:

Patient Baseline Comparability

	Finasteride 5 mg	Placebo	Total
Age in Years	(N = 111)	(N = 116)	(N = 227)
Mean	30.3	30.3	30.3
Median	31.0	30.0	30.0
Range			
Race	(N = 111)	(N = 116)	(N = 227)
White	104	108	212
Asian	0	1	1
African-American	5	3	8
Hispanic	2	4	6
Number of Patients With Baseline Hamilton Classification			
	(N = 111)	(N = 116)	(N = 227)
Grade III Vertex	71	87	158
Grade IV	40	29	69
Hair Count	(N = 85)	(N = 116)	(N = 177)
Mean	861.6	953.9	909.6
SD	247.4	248.9	251.8
Age at Which Patients Began Losing Hair	(N = 95)	(N = 102)	(N = 197)
Mean	23.2	23.4	23.3
SD	4.1	4.1	4.1
Number of Patients With Family History of Baldness (First Degree--Parents and/or Siblings)			
	(N = 110)	(N = 115)	(N = 227)
Yes	87	95	182
No	23	20	43

* All patients were male. † Thirty-six-year-old patients were 35 years old when screened for enrollment.

Comment

1. Different patient numbers for different baseline parameters suggest incomplete data collection at baseline. Nevertheless, the two arms appear to be comparable.
2. Over 90% of the subjects were Caucasians.

8.1.1.4.2 Efficacy Parameters

1. Hair Count

Table 8.1.1.4.2 A Change From Baseline in Hair Count: ITT Population

	Finasteride 5 mg			Placebo		
	Baseline	Month 6	Change	Baseline	Month 6	Change
Month 0-6	N=83	N=83	N=83	N=88	N=88	N=88
Mean	864.1	933.5	69.3	960.7	943.8	-16.9
	Baseline	Month 12	Change	Baseline	Month 12	Change
Month 0-12	N=84	N=84	N=84	N=92	N=92	N=92
Mean	863.9	962.1	98.2	953.9	940.0	-13.9
	Month 6	Month 12	Change	Month 6	Month 12	Change
Month 6-12	N=72	N=72	N=72	N=78	N=78	N=78
Mean	920.2	953.3	33.1	933.9	936.6	2.8

Least Squares Summary Statistics and Confidence Intervals

	Finasteride 5 mg	Placebo	Difference +	p-Value
Month 0-6 Mean change +	65.7**	-20.0*	85.7	< 0.001
95% confidence interval	(45.7, 85.7)	(-39.5, -0.4)	(60.0, 111.3)	
Month 0-12 Mean change +	93.2**	-20.1*	113.3	< 0.001
95% confidence interval	(74.2, 112.2)	(-38.5, -1.8)	(89.1, 137.5)	
Month 6-12 Mean change +	30.0**	0.2	29.8	0.009
95% confidence interval	(12.4, 47.6)	(-16.8, 17.1)	(7.8, 51.8)	

Treatment-by-center interactions not significant (p>0.05); + : Adjusted for the treatment and center effects
*, ** : Significant change from baseline at the p < 0.050 and p < 0.010 level, respectively

2. Patient self-assessment Only the Month 12 measurement for all questions was used, since this was the only time when all questions were asked. The global test of treatment effect across all 7 questions at Month 12 showed significant (p<0.001) difference between arms. Treatment-by-center interaction was not significant (p=0.494).

Table 8.1.1.4.2B Summary of Analysis of the Seven Hair Growth Questions at Month 12

	Mean Scores				
Variable	Finasteride	Placebo	Between- Group Diff (Finasteride-Placebo)	95% Confidence Interval for Diff	Between-Group p-Value
Global test					<0.001
Q25	0.2	-0.4	0.6	(0.3, 0.9)	<0.001
Q29	1.2	0.3	0.9	(0.4, 1.3)	<0.001
Q30	1.0	0.3	0.7	(0.3, 1.1)	<0.001
Q31	0.9	0.0	0.9	(0.4, 1.4)	<0.001
Q32a	0.0	-0.3	0.3	(0.0, 0.6)	0.044
Q32b	0.4	-0.1	0.5	(0.2, 0.8)	0.003
Q32c	0.5	-0.1	0.6	(0.3, 0.9)	<0.001

Table 8.1.1.4.2C Distribution of Scores in Patient Self-Assessment Questionnaire at Month 12

	Finasteride 5 mg							Placebo						
	-3	-2	-1	0	1	2	3	-3	-2	-1	0	1	2	3
Q25	<----------Disagree-------- No opinion----Agree---------->							<----------Disagree-------- No opinion-----Agree---------->						
Pt No														
Percent		5%	29%	27%	28%	11%			8%	46%	32%	11%	2%	
Q29	<----------Worse---------- Same-----Better---------->							<----------Worsae-------- Same------Better---------->						
Pt No														
Percent	0	3%	10%	25%	19%	22%	21%	0	7%	20%	43%	15%	9%	7%
Q30	<----------Decreased-------- No Change-----Increased---------->							<----------Decreased-------- No Change------Increased---------->						
Pt No														
Percent	0	0	7%	5%	28%	19%	10%	0	4%	21%	45%	17%	8%	4%
Q31		<---Not Effective-			--Effective------>				<---Not Effective-			--Effective------->		
Pt No														
Percent		9%	18%		33%	40%			22%	32%		35%	11%	
Q32a		<---Dissatisfied--- Neutral----Satisfied------>							<---Dissatisfied--- Neutral----Satisfied------>					
Pt No														
Percent		6%	22%	42%	27%	3%			8%	39%	33%	20%	0	
Q32b		<---Dissatisfied--- Neutral----Satisfied------>							<---Dissatisfied--- Neutral----Satisfied------>					
Pt No														
Percent		0	19%	43%	27%	10%			4%	41%	35%	15%	5%	
Q32c		<---Dissatisfied--- Neutral----Satisfied------>							<---Dissatisfied--- Neutral----Satisfied------>					
Pt No														
Percent		0	21%	31%	37%	12%			7%	34%	38%	16%	5%	

Question 25--Since beginning the study, I can see my bald spot getting smaller.
Question 29--Because of the treatment I have received since the start of the study, the appearance of my hair is:
Question 30--Since the start of the study, how would you describe the growth of your hair?

Question 31--Since the start of the study, how effective do you think this treatment has been in slowing down your hair loss?
Question 32a--Compared to the beginning of the study, which statement best describes your satisfaction with the appearance of the hairline at front of your head?
Question 32b--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 32c--Compared to the beginning of the study, which statement best describes your satisfaction with the appearance of your hair overall?

3. Investigator Assessment

Table 8.1.1.4.2D Investigator Assessment Intention-to-Treat Population at Month 12

	Finasteride 5 mg							Placebo						
	-3	-2	-1	0	1	2	3	-3	-2	-1	0	1	2	3
	<---------Decreased---------			No Change		Increased--------->		<---------Decreased---------			No Change		Increased--------->	
Pt No														
Percent	0	2%	21%	30%	30%	17%		0	0	13%	40%	27%	15%	4%

Least Squares Summary Statistics and Confidence Intervals

	Finasteride 5 mg	Placebo	Difference	p-Value
Mean score +	1.3**	0.4**	0.9	< 0.001
95% confidence interval	(1.1, 1.5)	(0.2, 0.6)	(0.6, 1.1)	

Treatment-by-center interaction: p-value = 0.444; + : Adjusted for the treatment and center effects *, ** : Significant change from baseline at the $p < 0.050$ and $p < 0.010$ level, respectively, assuming baseline score=0.

4. Global Photographic Assessment

Table 8.1.1.4.2E Global Photographic Assessment Intention-to-Treat Population at Month 12

	Finasteride 5 mg							Placebo						
	-3	-2	-1	0	1	2	3	-3	-2	-1	0	1	2	3
	<---------Decreased---------			No Change		Increased--------->		<---------Decreased---------			No Change		Increased--------->	
Pt No														
Percent	0	2%	49%	35%	12%	1%		0	0	12%	85%	3%	0%	0%

Least Squares Summary Statistics and Confidence Intervals

	Finasteride 5 mg	Placebo	Difference	p-Value
Mean score +	0.6**	0.0	0.7	< 0.001
95% confidence interval	(0.5, 0.8)	(-0.2, 0.1)	(0.5, 0.9)	

Treatment-by-center interaction: p-value < 0.001; + : Adjusted for the treatment and center effects *, ** : Significant change from baseline at the $p < 0.050$ and $p < 0.010$ level, respectively, assuming baseline score=0.

Comment As the scores for subjective assessments represent a change from baseline, it is not appropriate to further test for significance by comparing these scores with a "baseline" of zero. There was no baseline data collection for such assessments.

5. Dihydrotestosterone Levels

Table 8.1.1.4.2F Summary Statistics for Dihydrotestosterone (ng/dL) Intention-to-Treat Population

	Finasteride 5 mg				Placebo			
	N	Base-line	Level at Time	% Change	N	Base-line	Level at Time	% Change
Month 3	94	44.7	14.7	-66.7	103	44.8	44.2	1.6
Month 6	97	44.6	16.8	-61.4	104	44.7	46.1	5.0
Month 9	97	44.6	15.7	-64.7	104	44.7	46.3	5.4
Month 12	97	44.6	18.0	-59.5	104	44.7	44.7	2.0

Least Squares Summary Statistics and Confidence Intervals

Mean % change+ at	Finasteride 5 mg	Placebo	Difference	p-value
Month 3	-63.6**(-68.6, -58.5)	4.7 (-0.3, 9.6)	-68.2 (-74.7, -61.7)	< 0.001
Month 6	-60.5**(-65.7, -55.3)	5.8* (0.7, 10.9)	-66.3 (-73.1, -56.9)	< 0.001
Month 9	-63.4**(-68.5, -58.3)	7.3** (2.2, 12.4)	-70.7 (-77.4, -64.0)	< 0.001
Month 12	-57.2**(-63.2, -51.3)	4.5 (-1.4, 10.4)	-61.7 (-69.5, -53.9)	< 0.001

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

Subgroup analysis was performed on Month 12 data: by examining interaction with baseline Hamilton classification, positive family history, race and age. The treatment effect was the same (increase from baseline) for finasteride in each of the subgroups studied. However, the effect in nonwhites was much smaller (+36 hairs vs +4.3 hairs with placebo) than that in whites (102.1 vs -15.4 with placebo).

Comment The significance levels for between-race comparisons and those for between-treatment comparisons in the same race should be given. Nevertheless, these post-hoc analyses must be interpreted with caution, as the patient numbers were low among the non-white groups (finasteride 6 and placebo 7).

8.1.1.4.3 Safety Comparison

8.1.1.4.3.1 Adverse Events

Table 8.1.1.4.3.1A Adverse Experience Summary--Patient Counts (%)

	Finasteride (N = 111)	Placebo (N = 116)
Clinical AE	70 (63.1)	66 (56.9)
Drug-Related Clinical AE	9 (8.1)	10 (8.6)
Sexual AE	6 (5.4)	8 (6.9)
Serious Clinical AE	4 (3.6)	0
Discontinued Due to Clinical AE	4 (3.6)	1 (0.9)

There were no serious drug-related AE, serious laboratory AE or discontinuation due to laboratory AE.

Details of incidence of AE and drug-related AE - see Appendix I.

Table 8.1.1.4.3.1B Sexual Adverse Events--Patient Counts (%)

	Finasteride 5 mg (N = 111)		Placebo (N = 116)	
	ALL	Drug-related	ALL	Drug-related
Pt with one or more events	6 (5.4)	4 (3.6)	8 (6.9)	7 (6.0)
Libido decreased	3 (2.7)	3 (2.7)	7 (6.0)	5 (4.3)
Ejaculation disorder	2 (1.8)	1 (0.9)	1 (0.9)	1 (0.9)
Impotence	3 (2.7)	2 (1.8)	1 (0.9)	0
Semen viscosity increased	0	0	1 (0.9)	1 (0.9)

Table 8.1.1.4.3.1C Serious Clinical Adverse Events

Patient Number	Age /Sex	Dosage (mg)	Day of Onset	AE	Duration (Days)	Intensity	Drug Relation	Discon-tinuation	Outcome
Finasteride Group									
	34 M	5	314	Multiple trauma, head and abdomen	67	Severe	No	Yes	Still present
	28 M	5	14	Splenomegaly	87	Moderate	No	No	Still present
		5	72	Lipid storage disease	29	Severe	No	Yes	Still present
	35 M	5	130	Fracture, leg and ankle	141	Severe	No	No	Recovered
	30 M	5	259	Pneumonia	3	Severe	No	No	Recovered

Table 8.1.1.4.3.1D Discontinuation due to Adverse Events

Patient Number	Age /Sex	Dosage (mg)	Day of Onset	AE	?Serious	Duration (Days)	Intensity	Drug Relation	Day of Dis-continuation	Outcome
Finasteride Group										
	34 M	5	314	Multiple trauma, head and abdomen	Yes	67	Severe	No	314	Still present
	35 M	5	123	Impotence	No	74	Moderate	Possibly	170	Still present

31 M	5	36	Acne	No	16	Mild	Possibly	52		Recovered
28 M	5	72	Lipid storage disease	Yes	29	Severe	No	72		Still present
Placebo Group										
33 M		21	Prostatitis	No	87	Mild	?No	21		Recovered

There was no change in testicular volume in either treatment group.

8.1.1.4.3.2 Laboratory Studies There were no consistent significant clinical laboratory abnormalities. Special hormonal studies and PSA levels in the finasteride group:

Testosterone	Approximately 20% increase over baseline throughout treatment period.
PSA	Approximately 0.2 ng/mL decrease over baseline at Months 6 and 12 (from ng/mL).
LH	Not significantly different from baseline at Month 12.
FSH	Not significantly different from baseline at Month 12.

8.1.1.4.3.3 Sexual Function Questionnaire Except for Question 10, there were no significant differences between arms at Month 12 for any of the 16 questions. Analysis of Question 10 ("During the past month, how frequently have you awakened from sleep with a full erection?") showed that, on a scale of 0 to 6 (0 = Daily, 6 = Not at all), the mean baseline score was approximately 2 (two or three times per week) for both groups. The mean change from baseline in the finasteride and placebo groups respectively was +0.6 ($p<0.010$ vs baseline) and +0.3 at Month 12 ($p=0.034$), indicating small decreases in the average number of times they awoke from sleep with full erection.

Comment This questionnaire was not validated and not grouped into domains. The only significant difference between treatment groups was on the question of morning erections. The clinical relevance of this difference is unclear.

8.1.1.5 Conclusions

(1) Finasteride 5 mg/d for 12 months increased net scalp hair counts in men with MPB.
(2) Finasteride 5 mg/d for 12 months led to cosmetic improvement in men with MPB as determined by patient self-assessment of treatment efficacy and satisfaction with appearance of scalp hair, Investigator assessment and global photographic assessment.
(3) Finasteride 5 mg/d for 6 months was able to produce both objective and subjective improvements but 12 months of therapy provided greater improvement.
(4) Finasteride 5 mg/d was generally well tolerated by young men with MPB.

8.1.2 Trial#2: Study#081 A 6-Month, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study Followed by a 6-Month, Double-Blind, Randomized Study Extension to Determine the Effect of Low Doses of Finasteride on Hair Loss in Male Patients with Androgenetic Alopecia (Male Pattern Baldness)

8.1.2.1 Objective/Rationale

This was designed to be a dose-ranging study for the treatment of MPB with finasteride.

The study lasted between 12/93 and 10/94.
To determine whether 6 (and 12) months of finasteride treatment at 1, 0.2, or 0.01 mg/d would affect androgen-dependent scalp hair loss, and to evaluate the safety and tolerability of finasteride 1, 0.2, or 0.01 mg/d in patients with MPB.

8.1.2.2 Design After 2 weeks of single-blind placebo run-in period -
Initial study (first 6 months): double-blind, randomized, placebo-controlled, multicenter with 4 arms - finasteride 1, 0.2 or 0.01 mg and placebo once daily;
Extension (second 6 months): double-blind, randomized, multicenter with 3 arms - control (placebo) group rerandomized to active therapy so that patients who received active drug during the initial study continued on original dose while patients who previously received placebo were rerandomized in a blinded fashion to 1, 0.2, or 0.01 mg finasteride once daily.

Comment Ideally this study should have included doses above 1 mg/d so that the optimal dose is bracketed. As it is, only historical comparison with the 5 mg/d dose could be made, together with the pharmacodynamic data with the scalp DHT studies to affirm 1 mg/d as being optimal.

8.1.2.3 Protocol Study Plan:

		Placebo Run-In	Months				
Procedure	Screening	Week -2	0	3	6	9	12
Clinic visit	X	X	X	X	X	X	X
Physical	X				X		X
Scalp tattoo		X					
Global photography		X		X	X		X
Macrophotography		X	X	X	X		X
Medical history	X						
Vital signs	X		X	X	X	X	X
Urinalysis	X				X		X
Hematology	X		X		X		X
Serum chemistry & T	X		X	X	X	X	X
DHT			X	X	X	X	X
LH/FSH			X		X		X
TSH	X						
PSA	X				X		X
Sexual function questionnaire		X	X	X	X	X	X
Hair growth questionnaire		X	X	X	X	X	X
Investigator assessment				X	X	X	X
Hamilton classification	X				X		X
AE checking			X	X	X	X	X

8.1.2.3.1 Population/Procedures
Patient Selection Healthy men aged with PSA level ≤4 ng/mL and Hamilton Grade III Vertex or IV MPB, having moderate vertex balding and progressive hair loss or recent onset of balding (within 3 years). Subjects must be willing to have a dot tattoo on the scalp, maintain the same hairstyle throughout the study, use the Neutrogena

T/Gel® shampoo provided, use adequate contraception methods (if the patient's sexual partner(s) was/were of childbearing potential) and refrain from using hair enhancement products or procedures for during the study. In addition, he had to demonstrate good compliance during the single-blind placebo run-in phase by having taken at least 80% of the tablets they should have taken between the Week -2 and Month 0 visits.

Exclusions:

1) A history illness or condition that could confound results or pose additional risk, including multiple and/or severe allergies, or incompetency.
2) A history of thyroid disease.
3) Significant abnormalities on screening clinical examination or lab measurements, including subnormal TSH or T.
4) Liver function tests >1.5 times upper limit of the normal range.
5) History or suspicion of malignancy, excluding basal cell carcinoma.
6) History of varicocele.
7) History of infertility or difficulty fathering children.
8) Patients who wished to father children during the study or whose sexual partner(s) were pregnant.
9) Patients with hair color that contrasted insufficiently with scalp color such that there was inadequate contrast in macrophotographs for accurate hair counting.
10) Patients with active seborrheic dermatitis in the area of the scalp to be studied.
11) Concurrent use of systemic corticosteroids, topical corticosteroids in the balding area studied, anabolic steroids, or OTC "hair restorers."
12) Use of the following drugs with antiandrogenic properties within 6 months of entry: flutamide, cyproterone acetate, estrogen, progesterone, cimetidine, spironolactone, or ketoconazole.
13) Treatment with the following drugs within past year: minoxidil (topical or oral), zidovudine, cyclosporine, diazoxide, phenytoin, systemic interferon, psoralens, streptomycin, penicillamine, benoxaprofen, tamoxifen, phenothiazines, or cytotoxic agents.
14) Previous hair transplant surgery, scalp reduction surgery, or hair weaving.
15) Treatment with any other investigational drug during the previous 3 months.
16) Treatment with finasteride or any other 5α-reductase inhibitors in the past.
17) Baldness due to medical illness including alopecia areata, trichotillomania.
18) History of drug or alcohol abuse.

Patients were excluded from the extension study if they met any of the exclusion criteria for the initial study or if they had experienced a drug-related serious AE.

Dosing Instructions and Restrictions during Trial

Patients were to take study drug once daily. They would continue their usual diet and maintain their usual hair style. Use of medication in exclusion criteria would result in discontinuation of the patient from study. Compliance was checked by counting tablets. Only the shampoo provided (Neutrogena T-gel shampoo) was allowed in study period.

Evaluations Hair counts, patient hair growth questionnaire, investigator assessment of hair growth, global photographic assessment, laboratory tests, adverse events.

8.1.2.3.2 Subject Dispositions and Endpoints

Each subject would continue use of study drug for 12 months (placebo group rerandomized to take one of the three finasteride doses after Month 6). The primary parameter in this study was hair count. All other efficacy evaluations were secondary.

Comment . This was a dose-ranging study. Hair count appears to be a suitable objective parameter for comparing responses between dosing arms. It should be corroborated by the other subjective parameters.

8.1.2.3.3 Statistical Considerations

Statistical planning and analysis: The primary analysis for hair counts included all patients with a baseline measurement and at least one on-treatment result, i.e., intention-to-treat population. The primary analysis was Tukey's sequential trend test, which tested for dose response across all treatment groups. ANOVA was used for pairwise treatment group comparisons. Both absolute change and percent change from baseline were analyzed.

8.1.2.4 Results

8.1.2.4.1 Patient Disposition, Comparability

Enrollment by Investigator:

Study Number/Investigator	1 mg	0.2 mg	0.01 mg	Placebo	Total
081001 Bergfeld, Wilma	3	3	4	4	14
081002 DeVillez, Richard	3	4	5	4	16
081003 Fiedler, Virginia	5	3	3	5	16
081004 Imperato-McGinley, Julianne	5	3	5	5	18
081005 Hordinsky, Maria	7	9	8	6	30
081006 Price, Vera	3	3	4	3	13
081007 Olsen, Elise	4	4	3	3	14
081008 Rietschel, Robert	4	4	3	4	15
081009 Roberts, Janet	14	15	15	16	60
081010 Savin, Ronald	3	3	4	3	13
081011 Shupack, Jerome	3	3	3	5	14
081012 Stough, Dowling	4	4	3	3	14
081013 Whiting, David	5	4	5	5	19
081014 Carrington, Patrick	2	2	1	1	6
081015 Drake, Lynn	5	4	3	6	18
081016 Gencheff, Christopher	2	2	2	2	8
081017 Lucky, Anne	5	5	5	5	20
081018 Swinehart, James	14	13	16	16	59
081019 Weiss, Darryl	2	3	2	3	10
081020 Funicella, Toni	9	9	7	7	32
081021 Katz, Irving	5	5	6	4	20
081022 Lowe, Nicholas	7	8	8	4	27
081023 Whitmore, Elizabeth	3	2	2	3	10
Total	117	115	117	117	466

Completion Status:

PLACEBO-CONTROLLED INITIAL STUDY:

	1 mg	0.2 mg	0.01 mg	Placebo	Total
ENTERED: Total	117	115	117	117	466
Male (age range)	117	115	117	117	466
COMPLETED:	96	98	96	92	382
DISCONTINUED: Total	21	17	21	25	84
Clinical adverse experience (AE)	4	3	3	5	15
Laboratory AE	0	0	0	0	0
Other	17	14	18	20	69

EXTENSION STUDY:

	1 mg	0.2 mg	0.01 mg	Rerandomized Group¶	Total

ENTERED: Total	86	85	88	84	343
Male (age range)	86	85	88	84	343
COMPLETED:	73	65	69	71	278
DISCONTINUED: Total	13	20	19	13	65
Clinical AE	1	3	0	2	6
Laboratory AE	0	0	0	0	0
Other	12	17	19	11	59

** Thirty-six-year-old patients were 35 years old when screened for enrollment.
¶ Rerandomization: 28 subjects per group of 1 mg, 0.2 mg and 0.01 mg, with 25, 22 and 24 subjects completing study at Month 12 respectively. One from 1 mg and 1 from 0.2 mg groups discontinued due to clinical AE. All other discontinuations were due to "other".

Comment At the end of the 12-month period, only 278/466 (59.7%) completed the blind extension. Most of the dropouts were under "other", the commonest being "lost to follow-up".

Comparability of Treatment Groups: The groups were comparable in baseline characteristics including age (mean for entire study sample=30) and race (Caucasians 91.2%). The mean baseline hair count, however, was higher in the 1 mg finasteride group, whereas subjects in the 0.01 mg group who did not enter extension phase had the highest baseline hair counts.

Patient Baseline Comparability: Hair Count*

		1 mg	0.2 mg	0.01 mg	Placebo**	Total
Patients who entered initial study	N	101	99	97	96	393 †
	Mean	944.9	905.5	902.5	905.9	915.0
	Median	912.0	932.0	908.0	891.0	909.0
Patients who entered extension study	N	85	82	87	80	334
	Mean	942.0	896.2	876.0	902.5	904.1
	Median	907	915.5	860	866.5	894
Patients who did not enter extension study	N	16	17	10	16	59
	Mean	960.2	950.8	1133.1	923.1	976.7
	Median	984	933	1159	948.5	962

* For consistency of comparison between the patients who entered the extension study and patients who did not enter the extension study, the hair count baseline used in this table was the baseline count associated with the Month 3 dot mapping session. ** Patients in the placebo group were rerandomized to the three active doses during the extension study. † Only 393 patients had hair count data at both baseline and at least one follow-up time point (Month 3 or 6).

Comment Significance levels for these baseline hair count data have not been given. The Applicant states that the baseline hair counts were comparable.

8.1.2.4.2 Efficacy Parameters

Table 8.1.2.4.2A Least Squares Summary Statistics, Confidence Intervals, and Between-Group Comparisons for Endpoints at Month 6 Placebo-Controlled Initial Study

	1 mg	0.2 mg	0.01 mg	Placebo
Change From Baseline in Hair Count	N = 101	N = 99	N = 97	N = 96
Mean Change From Baseline+:	68.7**	54.9**	-8.6	-15.4
95% Confidence Interval	(51.4, 86.1)	(37.4, 72.5)	(-26.5, 9.3)	(-33.3, 2.4)
Investigator Assessment	N = 105	N = 105	N = 102	N = 102
Mean Score+	1.0**	1.0**	0.6**	0.5**
95% Confidence Interval	(0.8, 1.2)	(0.8, 1.1)	(0.4, 0.8)	(0.3, 0.7)
Global Photographic Assessment	N = 102	N = 103	N = 98	N = 98
Mean Score+	0.7**	0.4**	0.0	0.0
95% Confidence Interval	(0.5, 0.8)	(0.3, 0.6)	(-0.1, 0.2)	(-0.1, 0.1)

Patient Hair Growth Questionnaire Global Test Global test p values: see below	N = 105	N = 107	N = 103	N = 106

P values

	1 mg vs 0.2 mg	1 mg vs 0.01 mg	1 mg vs placebo	0.2 mg vs 0.01 mg	0.2 mg vs placebo	0.01 mg vs placebo
δ Hair Ct	0.252	<0.001	<0.001	<0.001	<0.001	0.577
Inv global	0.817	0.001	<0.001	0.002	<0.001	0.435
Ph global	0.017	<0.001	<0.001	<0.001	0.001	0.913
Pt ques	0.160	0.001	<0.001	0.118	0.025	0.479

+ Adjusted for the treatment and center effects. *, **: Significant change from baseline at the $p < 0.050$ and $p < 0.010$ level, respectively, assuming baseline score=0 for the subjective assessments: Investigator assessment, global photographic assessment and patient self-assessment.

Table 8.1.2.4.2B Least Squares Summary Statistics, Confidence Intervals, and Between-Group Comparisons for Endpoints at Month 12 Extension Study

	1/1 mg	0.2/0.2 mg	0.01/0.01 mg
Change From Baseline in Hair Count	N = 72	N = 58	N = 66
Mean Change From Baseline+:	85.0**	64.7**	-17.7
95% Confidence Interval	(63.1, 106.8)	(39.6, 89.7)	(-41.2, 5.8)
Investigator Assessment	N = 80	N = 73	N = 83
Mean Score+	1.4**	1.3**	0.6**
95% Confidence Interval	(1.2, 1.6)	(1.1, 1.5)	(0.4, 0.8)
Global Photographic Assessment	N = 68	N = 66	N = 67
Mean Score+	0.7**	0.4**	-0.1
95% Confidence Interval	(0.5, 0.9)	(0.2, 0.6)	(-0.3, 0.1)
Patient Hair Growth Questionnaire Global Test Global test p values: see below	N = 79	N = 75	N = 82

P-Values

	1 mg vs 0.2 mg	1 mg vs 0.01 mg	0.2 mg vs 0.01 mg
δ Hair Ct	0.175	<0.001	<0.001
Inv global	0.472	<0.001	<0.001
Ph global	0.025	<0.001	<0.001
Pt ques	0.230	<0.001	0.014

+ Adjusted for the treatment and center effects. *, **: Significant change from baseline at the $p < 0.050$ and $p < 0.010$ level, respectively, assuming baseline score=0 for the subjective assessments: Investigator assessment, global photographic assessment and patient self-assessment.

The following gives the data on patient self-assessment:

Table 8.1.2.4.2C Mean Score Change From Baseline for the Seven Hair Growth Questions

Variable	Placebo-Controlled Initial Study (Month 6)				Extension Study (Month 12)		
	1 mg	0.2 mg	0.01 mg	Placebo	1 mg	0.2 mg	0.01 mg
Q5	0.1	-0.1	-0.4**	-0.5**	0.2*	0.1	-0.3**
Q24	0.7**	0.5**	0.3*	0.2	0.9**	0.8**	0.2
Q25	0.6**	0.6**	0.2*	0.3**	0.8**	0.7**	0.3*
Q26	0.6**	0.3*	0.1	-0.2	1.0**	0.8**	0.5**
Q27a	-0.1	-0.3**	-0.4**	-0.4**	-0.1	-0.2	-0.6**
Q27b	-0.1	-0.1	-0.4**	-0.4**	0.2	0.0	-0.4**
Q27c	0.0	-0.1	-0.3**	-0.3**	0.1	0.1	-0.4**

*, ** Significant change from baseline at the $p < 0.050$ and $p < 0.010$ level, respectively, assuming baseline score=0.

Question 5--Since beginning the study, I can see my bald spot getting smaller.

Question 24-- Because of the treatment I have received since the start of the study, the appearance of my hair is:

Question 25--Since the start of the study, how would you describe the growth of your hair?

Question 26--Since the start of the study, how effective do you think this treatment has been in slowing down your hair loss?

Question 27a--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 27b--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 27c--Compared to the beginning of the study, which statement best describes your satisfaction with the appearance of your hair overall?

Table 8.1.2.4.2D Onset of Action: Data at Month 3

Least Squares Summary Statistics and 95% Confidence Intervals

	Finasteride 1 mg	Finasteride 0.2 mg	Finasteride 0.01 mg	Placebo
Hair Count Mean Change from Baseline+:	83.9** (67.8,100.0)	61.4** (45.1, 77.7)	-0.9 (-17.5, 15.8)	-7.5 (-24.0, 9.0)
Investigator Assessment Mean Score+	0.6** (0.5, 0.8)	0.8** (0.7, 0.9)	0.4** (0.3, 0.6)	0.4** (0.3, 0.6)
Global Photo Assessment Mean Score+	0.3** (0.2, 0.4)	0.3** (0.2, 0.4)	0.1 (0.0, 0.2)	0.1** (0.0, 0.2)

Between Group Comparisons	Difference+	95% C.I.	p-Value
Hair Count:			
Finasteride 1 mg vs Finasteride 0.2 mg	22.5	(0.7, 44.4)	0.044
Finasteride 1 mg vs Finasteride 0.01 mg	84.8	(62.8,106.8)	<0.001
Finasteride 1 mg vs Placebo	91.4	(69.5,113.4)	<0.001
Finasteride 0.2 mg vs Finasteride 0.01 mg	62.3	(40.1, 84.4)	<0.001
Finasteride 0.2 mg vs Placebo	68.9	(47.1, 91.1)	<0.001
Finasteride 0.01 mg vs Placebo	6.7	(-15.6, 28.9)	0.559
Patient Questionnaire Global Test:			
Finasteride 1 mg vs. Finasteride 0.2 mg			0.383
Finasteride 1 mg vs. Finasteride 0.01 mg			0.239
Finasteride 1 mg vs. Placebo			0.037
Finasteride 0.2 mg vs. Finasteride 0.01 mg			0.792
Finasteride 0.2 mg vs. Placebo			0.257
Finasteride 0.01 mg vs. Placebo			0.347
Investigator Assessment:			
Finasteride 1 mg vs. Finasteride 0.2 mg	-0.2	(-0.4, 0.0)	0.142
Finasteride 1 mg vs. Finasteride 0.01 mg	0.2	(0.0, 0.4)	0.021
Finasteride 1 mg vs. Placebo	0.2	(0.0, 0.4)	0.030
Finasteride 0.2 mg vs. Finasteride 0.01 mg	0.4	(0.2, 0.6)	<0.001
Finasteride 0.2 mg vs. Placebo	0.4	(0.2, 0.6)	<0.001
Finasteride 0.01 mg vs. Placebo	-0.0	(-0.2, 0.2)	0.888
Global Photographic Assessment			
Finasteride 1 mg vs. Finasteride 0.2 mg	0.0	(-0.2, 0.1)	0.736
Finasteride 1 mg vs. Finasteride 0.01 mg	0.2	(0.0, 0.3)	0.015
Finasteride 1 mg vs. Placebo	0.1	(0.0, 0.3)	0.074
Finasteride 0.2 mg vs. Finasteride 0.01 mg	0.2	(0.1, 0.3)	0.006
Finasteride 0.2 mg vs. Placebo	0.1	(0.0, 0.3)	0.034
Finasteride 0.01 mg vs. Placebo	0.0	(-0.2, 0.1)	0.503

+ Adjusted for the treatment and center effects. *, **: significant change from baseline at the p<0.050 and p<0.010 level, respectively, assuming baseline score=0 for the subjective assessments: Investigator assessment, global photographic assessment and patient self-assessment.

Comments

1. The 0.01 mg dose appears to be subtherapeutic. The 1 mg dose was superior to the 0.2 mg dose by hair count at Month 3 and by photographic global at Months 6 and 12.
2. Although the 1- and 0.2-mg groups were not significantly different for the global test or the seven individual questions of the hair growth questionnaire at any time, the mean scores for the seven individual questions showed that the 1-mg group consistently demonstrated superior or equal numerical efficacy over the 0.2-mg group at Months 6 and 12.
3. Multiplicity in this study has been properly addressed with Tukey's sequential trend test.
4. It is unclear why hair count data showed most of the increase by Month 3 while subjective assessments continue to improve over the next 9 months. It suggests inclusion of cosmetically unimportant hairs in the counting at Month 3. Alternatively, it is possible that increments in cosmetic coverage become more observable with time despite little additional increase in countable hair by macrophotography.

5. As the scores for subjective assessments represent a change from baseline, it is not appropriate to further test for significance by comparing these scores with a "baseline" of zero. There was no baseline data collection for such assessments.

8.1.2.4.3 Safety Comparison

8.1.2.4.3.1 Adverse Events Data

Table 8.1.2.4.3A Clinical and Laboratory Adverse Experiences--Patient Count (%)

Placebo-Controlled Initial Study	Clinical				Laboratory			
	1 mg N = 117	0.2 mg N = 115	0.01 mg N = 117	Placebo N = 117	1 mg N = 107	0.2 mg N = 108	0.01 mg N = 104	Placebo N = 109
Clinical AE	51 (43.6)	53 (46.1)	49 (41.9)	47 (40.2)	2 (1.9)	2 (1.9)	4 (3.8)	3 (2.8)
Drug-Related AE	8 (6.8)	9 (7.8)	6 (5.1)	6 (5.1)	0	0	1 (1.0)	1 (0.9)
Sexual AE	5 (4.3)	7 (6.1)	3 (2.6)	3 (2.6)				
Serious AE	0	0	1 (0.9)	1 (0.9)	0	0	0	0
Discontinued due to AE	4 (3.4)	3 (2.6)	3 (2.6)	5 (4.3)	0	0	0	0

Extension Study	1 mg N = 86	0.2 mg N = 85	0.01 mg N = 88	Rerandomized* N = 84	1 mg N = 80	0.2 mg N = 75	0.01 mg N = 83	Rerandomized* N = 82
Clinical AE	44 (51.2)	37 (43.5)	40 (45.5)	38 (45.2)	8 (10.0)	3 (4.0)	5 (6.0)	2 (2.4)
Drug-Related AE	3 (3.5)	6 (7.1)	0	4 (4.8)	2 (2.5)	1 (1.3)	0	0
Sexual AE	2 (2.3)	3 (3.5)	0	4 (4.8)				
Serious AE	0	0	1 (1.1)	1 (1.2)	0	0	0	0
Discontinued due to AE	1 (1.2)	3 (3.5)	0	2 (2.4)	0	0	0	0

* The cohort of patients on placebo during the initial study who were rerandomized to active therapy at Month 6 for the extension study.

Details of the incidences of AE are shown in Appendix II. Discontinuations due to AE and serious AE are given in the following Table:

Table 8.1.2.4.3B Patients (Identification Numbers) Discontinued due to AE

Placebo-Controlled Initial Study	1 mg	0.2 mg	0.01 mg	Placebo
Impotence	5432, 5294	5341	5457	
Pharyngeal discomfort	5265			
Epididymitis	5483			
Urinary frequency	5294			
Libido decrease		5642, 5115		5464
Hepatitis A			5399	
Appendicitis			5148*	
Trauma				5140*
Depression				5263
Arrhythmia				5395
Pituitary neoplasm				5537

Extension Study	1 mg	0.2 mg	0.01 mg	Rerandomized
Goiter	5195			
Impotence		5300, 5514		5641, 5437
Libido decrease				5641
Arrhythmia		5357		

*Serious AE in initial treatment period.

There were 2 serious AE in the extension phase: thoracic duct syndrome (0.01 mg finasteride; #5124) and skull fracture (Placebo rerandomized to 1 mg; #5108).

8.1.2.4.3.2 Laboratory Findings No consistent significant abnormalities in clinical laboratory tests. Special studies for LH and FSH levels showed no meaningful

changes vs baseline in any group, while testosterone and PSA levels did have dose-dependent changes from baseline:

	Month 6				Month 12		
	1 mg	0.2 mg	0.01 mg	placebo	1 mg	0.2 mg	0.01 mg
Testosterone (ng/dL)	19.4	18.1	7.6	4.1	20.3	29.9	8.0
PSA (ng/mL)	-0.2	-0.1	0	0	-0.2	-0.1	0.1

8.1.2.4.3.3 Sexual Function Questionnaire

Out of 14 questions analyzed in the Sexual Function Questionnaire, only two (rating of change in sexual drive and frequency of morning erections) showed any significant difference between placebo and finasteride:

Q2. Change in sexual drive in past month - both the 1-mg and 0.2-mg groups showed a 0.3 score difference with placebo (p=0.007 and 0.019 respectively), indicating decreased sexual drive in the initial treatment phase. No inter-group differences were noted in the extension phase.

Q10. Frequency of morning erections - during initial treatment phase: all finasteride groups showed decreased frequency with 0.6, 0.5 and 0.4 score differences with placebo for the 1 mg, 0.2 mg and 0.01 mg doses (p=0.002, 0.008 and 0.015 respectively), and in the extension phase, the 1 mg dose showed a 0.5 score difference with the 0.01 mg group (p=0.020).

Comments

1. In Study 047, there was also noted a decrease in frequency in morning erections by the Sexual Question Questionnaire in the finasteride 5 mg group vs placebo. The Applicant attributed this to over-sensitivity of the questionnaire. This is again demonstrated in Study 081.
2. There were no significant differences between the finasteride 1 mg and 0.2 mg groups for any of the questions in the questionnaire.

8.1.2.5 Conclusions

(1) Treatment with finasteride 1 or 0.2 mg/day produced increases in net scalp hair counts in men with MPB and led to cosmetic improvement as determined by patient self-assessment of efficacy and satisfaction with appearance of scalp hair, by investigator assessment, and by global photographic assessment of scalp hair growth.
(2) Three months of treatment with finasteride 1 or 0.2 mg/day might produce objective and subjective improvement in men with MPB; however, 6 months of therapy provided greater perceptible improvement, which was maintained with therapy through Month 12.
(3) Treatment with finasteride 1 mg/d provided greater efficacy than therapy with finasteride 0.2 mg/d without decrease in tolerability. The finasteride 0.01-mg dose was subtherapeutic.
(4) Although it is not optimal to study dose-ranging in the absence of a higher dose that brackets the optimal dose, the results of this study support the selection of finasteride 1 mg/d for further clinical evaluation, as it (a) is superior to 0.2 mg/d in efficacy and not worse in safety and (b) when compared to 5 mg/d in Study 047, appears to be similar to that dose in both efficacy and safety.
(5) Substantial placebo effect was seen in Investigator assessment.

8.1.3 Trial#3: Study#087 A Double-Blind, Randomized, Placebo-Controlled, Multicenter Study to Determine the Effect of Finasteride on Hair Loss in Men with Androgenetic Alopecia (Male Pattern Baldness)

8.1.3.1 Objective/Rationale

This was designed to be one of two pivotal studies for the treatment of MPB. The study lasted from 12/94 to 5/96.

Co-Primary Efficacy Objectives: To determine whether treatment with oral finasteride 1 mg/d, compared with placebo, (1) increases hair in men with male pattern baldness (MPB) and (2) improves MPB as shown by a self-administered Hair Growth Questionnaire.

Secondary Efficacy Objectives:

a. To determine whether treatment with oral finasteride 1 mg/d, 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.

Safety Objective: To evaluate the safety and tolerability of oral finasteride 1 mg/d in patients with MPB

8.1.3.2 Design

Double-blind, randomized, placebo-controlled, multicenter study with the following study plan:

		Placebo Run-In	Treatment Period				
		Week	Months				
Procedure	Screening	-2	0	3	6	9	12
Visit Number:	1	2	3	4	5	6	7
Medical history	X						
Physical examination	X						X
Vital signs and weight	X	X	X	X	X	X	X
Global photography	X	(X)*			X		X
Scalp tattoo		X					
Macrophotography		X	(X)		X		X
Hematology	X		X		X		X
Urinalysis	X		X				X
Serum chemistry	X		X		X		X
T/DHT			X		X		X
LH/FSH			X				X
PSA			X		X		X
Patient Hair Growth Questionnaire		X	X	X	X	X	X
Sexual Function Questionnaire		X	X	X	X	X	X
Patient body hair assessment			X		X		X
Investigator assessment of patient hair growth/loss				X	X	X	X
Modified Norwood/Hamilton classification by investigator	X				X		X
Adverse experiences			X	X	X	X	X

*Repeat photography if previous session unsatisfactory.

At one investigator site (Dr. Whiting), a 4-mm punch biopsy of the scalp was performed at Months 0 and 12. These biopsies were performed for exploratory purposes only.

8.1.3.3 Protocol

8.1.3.3.1 Population/Procedures

Patient Selection Healthy, ambulatory men aged 18 to 40, having modified Norwood/Hamilton Grade II vertex, III vertex, IV, or V MPB (see Appendix IX) with moderate vertex balding and progressive hair loss and/or recent onset of balding (within 3 years) and willingness to have a dot tattoo on scalp, maintain the same hairstyle throughout the study, use the shampoo provided (Neutrogena T/Gel®, Neutrogena Corp), and to refrain from dyeing hair or using any hair enhancement products or procedures. Patient's hair color must have adequate contrast against scalp color.

Exclusions:

1) A history of any illness or condition that might have confounded the results of the study or posed additional risk.
2) A history of thyroid disease.
3) Patients with liver function tests 1.2 times above the upper limit of the normal range (AST >26 mU/mL, ALT >30 mU/mL, total bilirubin >1.3 mg/dL).
4) History or suspicion of any malignancy, excluding basal cell carcinoma of the skin.
5) Patients whose sexual partner(s) was/were pregnant or planning pregnancy within the 12-month study period.
6) Patients who had had hair transplants, scalp reduction, or hair weaves.
7) Patients with seborrheic dermatitis in the area of the scalp to be studied.
8) Concurrent use of systemic corticosteroids, topical corticosteroids in the balding area studied or anabolic steroids.
9) Use of the following drugs with antiandrogenic properties within 6 months of study entry: [Casodex™, (bicalutamide, Zeneca, UK)], flutamide, cyproterone acetate, topical estrogen, progesterone, cimetidine, spironolactone or ketoconazole (ketoconazole topical cream, [Nizoral™, Janssen, Titusville, NJ] is acceptable).
10) Patients who had been treated with any of the following drugs within 1 year prior to entry: minoxidil (topical or oral), Accutane (isotretinoin, Roche Laboratories, Nutley, NJ), zidovudine, cyclosporine, diazoxide, phenytoin, systemic interferon, psoralens, streptomycin, penicillamine, tamoxifen, phenothiazines, or cytotoxic agents.
11) History of treatment with any other investigational drug during the previous 3 months.
12) History of treatment with finasteride or any other 5α-reductase inhibitor.
13) Scalp hair loss due to medical illness, alopecia areata, trichotillomania, or any form of pathologic alopecia other than AGA.
14) History of drug or alcohol abuse.

Comment This study included a restricted spectrum of patients showing MPB (Norwood-Hamilton Classes II vertex, III vertex, IV and V). More severe grades such as VI and VII have not been studied. In addition, the entry criteria regarding age and requirement to use Neutrogena T-Gel Shampoo will impact on eventual labeling.

Dosing Instructions and Restrictions during Trial

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. They would continue their usual diet and maintain their usual hair style. Use of medication(s) in the exclusion criteria would result in discontinuation. Compliance would be checked by counting tablets. Only Neutrogena T-gel shampoo was allowed during study period.

Evaluations

Efficacy: Hair counts, patient Hair Growth Questionnaire, investigator assessment