of hair growth, global photographic assessment

Safety: AE, clinical laboratory tests, sexual function questionnaire, body hair questionnaire, PSA and hormone levels.

Global Photography Methodology

Global photographs were taken prior to preparing the patient for macrophotography. Before taking the global photographs, the patient's hair was combed away from the vertex bald spot so that the entire balding area could be viewed. Extraneous matter was eliminated. The patient's head was kept in a fixed position. Films were taken using a Nikon N-6000 camera with a Nikkor 60 mm f2.8 lens and a CSI Twin Flash. Film emulsion, lighting, framing, exposure, and reproduction ratios were held constant. Color slide film (Kodachrome KR-64 24 exposure) from two emulsion lots matched for color consistency and a color card to ensure quality control of color processing was used.

The following exposures were shot in sequence: 3 exposures of the patient ID card and color card; 3 exposures of each position of the patient's global photographs (vertex, frontal, anterior and temporal); and again 3 exposures of the patient's ID and color cards. Film was sent to , and processed by set of baseline global prints was supplied for the Investigator's reference.

Macrophotography Methodology

Before taking the macrophotographs, hairs in a circular area slightly larger than the final target area (1 inch diameter circle, 5.1 cm^2) centered at the leading edge of the patient's bald spot were clipped to 1 mm in length. At the beginning of the study, a small (1 mm diameter) dot tattoo was placed in the center of the clipped area using a commercial tattooing machine.

Films were taken using a Nikon N-6000 camera with a Nikkor 60 mm f2.8 lens and a Nikon macro flash SB 21B. Film emulsion, lighting, framing, exposure, and reproduction ratios were held constant. A stereotactic device was attached to the camera for positioning. Film for color transparencies (Kodachrome KR-64 24 exposure) from two emulsion lots matched for color consistency was used.

The following exposures were shot in sequence: 3 exposures of the patient ID card; 3 exposures of the hair count target area: and again 3 exposures of the ID card. Film was sent to for processing by each macrophotograph was blinded to study center, patient, and time. A trained technician placed a transparency over the photograph and, using a fine-point black permanent pen, placed a black dot over each visible hair. The dot map transparency was then counted using computer assisted image analysis. All photographs were dot mapped and counted after patients completed Month 12.

Patient Self-Assessment

The Hair Growth Questionnaire was made up of two parts:

HGB, or the baseline questionnaire containing 14 questions, and

HGF, or the follow-up questionnaire, containing 7 questions.

The seven questions from the HGF questionnaire deemed valid for self-assessment and used in the analysis:

Question 1–Since the start of the study, I can see my bald spot getting smaller.

Question 2–Because of the treatment I have received since the start of the study, the appearance of my hair is:

Question 3–Since the start of the study, how would you describe the growth of your hair?

Question 4–Since the start of the study, how effective do you think this treatment has been in slowing down your hair loss?

Question 5a–Compared to the beginning of the study, which statement best describes your satisfaction with the appearance of the hairline at the front of your head?

Question 5b–Compared to the beginning of the study, which statement best describes your satisfaction with the appearance of the hair on top of your head?

Question 5c–Compared to the beginning of the study, which statement best describes your satisfaction with the appearance of your hair overall?

A global test across the 7 questions was used to compare treatment groups: **only patients who had responses to all 7 questions were included. Fewer than 3% of patients were excluded based on incomplete questionnaire at all time points.** Methodology was the generalized least squares procedure of , taking into account different scales of the questions and covariance among them.

Investigator Assessment

Investigator assessment of patient hair growth/loss, measured as a change from baseline, was based on opinion

regarding the patient's hair status using a 7-point scale as a response to the following question:
"As the investigator, how would you subjectively rate the patient's hair at this time point compared to baseline?" 0 = Don't know, 1 = Greatly decreased, 2 = Moderately decreased, 3 = Slightly decreased, 4 = No change, 5 = Slightly increased, 6 = Moderately increased, 7 = Greatly increased.

Global Photographic Assessment

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

Sexual Function Questionnaire

The Sexual Function Questionnaire was a "validated" instrument. Several domains were identified in the validation report. Total scores were computed for each domain and for each question that was not part of a domain. The primary analysis for this questionnaire was based on the domains:

Domain/Question Name	Question Numbers	Numbers Scale
Sexual interest	1, 2	(0 to 8)
Erections	3, 4, 5	(0 to 11)
Ejaculation	6, 7	(0 to 6)
Perception of problems	8, 9, 10	(0 to 12)
Global question	11	(0 to 4)
Morning erections question	12	(0 to 4)

Any response that did not fit into the order of the responses to a particular question was declared missing. Therefore, the last category in the responses to Questions 5, 6, and 7 were eliminated. The responses were then ordered such that smaller scores indicate worsening condition and larger scores indicate improvement.

Body Hair Assessment

This assessment is composed of 3 main questions (Questions 1a, 2a, and 3a) that address hair growth on chest, face, and extremities. There are 3 accompanying satisfaction questions (Questions 1b, 2b, and 3b). Each of the main questions was analyzed as a separate entity. The response was treated as a continuous variable and analyzed . The satisfaction questions were not analyzed.

Comments

1. The use of Neutrogena T-Gel shampoo was mandatory. Although its effects on hair growth, if any, may be controlled with the placebo arm, it presents a methodological problem with possible staining of non-pigmented, cosmetically unimportant hairs and thus confounding the hair count data. However, if it is assumed that the cosmetically unimportant hairs are greater in number in the placebo arm, this bias would not be in favor of the finasteride treatment group. Moreover, whether there is any synergistic effect between the tar-based shampoo and finasteride action is currently unknown.
2. See Section 6.1.3 for comments on the methodology and endpoints for hair growth studies.
3. The patient self-assessment instrument, Hair Growth Questionnaire, in this study was validated using data from Studies 047 and 081. It was derived from the initial questionnaire used in 047 through a process of item reduction to the current 7 questions. Apart from 2 questions that involved external factors, there were initially 11 global questions and the remainder grouped into 4 domains: satisfaction with appearance, hair loss, social and role functioning and balding experience. The domains were found not to correlate well with the global questions and were subsequently eliminated. Only 7 of the 11 global questions maintained internal consistency and were retained. They were then tested for (1) "responsiveness" by examining for differences between treatment groups in 047 and 081 and (2) correlation with hair count data in these two studies. Although there was only modest correlation with changes in hair counts, the "responsiveness" tests established these 7 global questions to be "valid" as the self-assessment instrument for cosmetic coverage of scalp. The correlation with

hair count changes (-0.09 to -0.27) was generally in the same low-to-moderate range as correlations between subjective and objective measurements as in other areas of medicine.

8.1.3.3.2 Subject Dispositions and Endpoints

Each subject would continue use of study drug for 12 months. Coprimary parameters in this study were hair count and patient's assessment. All other efficacy evaluations were secondary parameters.

8.1.3.3.3 Statistical Considerations

The primary analysis included all patients with a baseline and ≥1 on-treatment measurement, i.e., the intention-to-treat population. ANOVA was used for treatment group comparisons. The study protocol called for 300 patients/treatment group. This was sufficient to detect a 24-hair difference in change from baseline in hair count between treatment groups with 95% power (α= 0.05, 2-tailed). With 300 patients in a treatment group, any AE having an observed incidence of 2% would have a 95% upper bound of approximately 4%.

Intention-to-Treat Population The primary patient set analyzed was the ITT population. All patients were included in the analyses as long as they had measurements both at baseline and on treatment. Analysis was based on last observation carried forward for missing values. Data were not carried forward from baseline to the active phase or for any analyses of repeated measures.

Per-Protocol Population These analyses excluded patients based on a set of prespecified criteria (e.g., dropouts, noncompliant patients). The per-protocol analyses did not carry data forward.

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

8.1.3.4 Results

8.1.3.4.1 Patient Disposition, Comparability

Investigators:

Investigator	Institution, City and State
Richard G. Asarch, M.D.	Clinical Research Group of Colorado, Englewood, Colorado
Wilma Bergfeld, M.D.	Cleveland Clinic Foundation, Cleveland, Ohio
Denise M. Buntin, M.D.	Private Practice, Hermitage, Tennessee
Richard DeVillez, M.D.	University of Texas Health Science Center, San Antonio, Texas
Lynn Drake, M.D.	Massachusetts General Hospital, Boston, Massachusetts
Virginia Fiedler, M.D.	University of Illinois, Chicago, Illinois
David P. Fivenson, M.D.	Henry Ford Hospital, Detroit, Michigan
Toni Funicella, M.D.	Pharmaco Clinics, Austin, Texas
Christopher Gencheff, D.O.	Lakeview Medical Clinic, Madison, Wisconsin
Maria Hordinsky, M.D.	University of Minnesota, Minneapolis, Minnesota
Stephen N. Horwitz, M.D.	Horwitz & Weissmann, M.D., P.A., Miami Beach, Florida
Julianne Imperato-McGinley, M.D.	Cornell University Medical College, New York, New York
Irving Katz, M.D.	Minnesota Clinical Study Center, Fridley, Minnesota A.
Paul Kelly, M.D.	King-Drew Medical Center, Los Angeles, California
Mark R. Ling, M.D., Ph.D.	Emory University, Atlanta, Georgia
Nicholas Lowe, M.D.	Clinical Research Specialists, Santa Monica, California
Anne Lucky, M.D.	Dermatology Research Associates, Cincinnati, Ohio
Elise Olsen, M.D.	Duke Dermatopharmacology Study Center, Durham, North Carolina
Gary L. Peck, M.D.	Washington Hospital Center, Washington, DC

Vera Price, M.D.	University of California, San Francisco San Francisco, California R
Robert Rietschel, M.D.	Ochsner Clinic, New Orleans, Louisiana
Janet Roberts, M.D.	Private Practice, Portland, Oregon
Ronald Savin, M.D.	Savin Dermatology Center, P.C., New Haven, Connecticut J
Jerome Shupack, M.D.	New York University Medical Center, New York, New York
Daniel M. Stewart, D.O.	Midwest Cutaneous Research, Clinton Township, Michigan
Dowling Stough, M.D.	The Stough Clinic, Hot Springs, Arkansas
James Swinehart, M.D.	Colorado Medical Research Center, Denver, Colorado
Leonard J. Swinyer, M.D., P.C.	Private Practice, Salt Lake City, Utah
Gerald D. Weinstein, M.D.	University of California, Irvine, California
Darryl Weiss, M.D.	Plastic Surgery & Dermatology Associates, Fair Lawn, New Jersey
Jonathan S. Weiss, M.D.	Gwinnett Clinical Research Center, Snellville, Georgia
David Whiting, M.D.	Dallas Associated Dermatologists, Dallas, Texas
Elizabeth Whitmore, M.D.	Johns Hopkins Outpatient Center, Baltimore, Maryland

Distribution of Patients at Entry by Investigator:

Investigator	Finasteride	Placebo	Total
Bergfeld, Wilma	11	14	25
Buntin, Denise M.	9	9	18
DeVillez, Richard	7	7	14
Drake, Lynn A.	19	19	38
Fiedler, Virginia	13	16	29
Funicella, Toni	14	14	28
Gencheff, Christopher	8	8	16
Hordinsky, Maria	29	30	59
Imperato-McGinley, J.	16	8	24
Katz, Irving	10	10	20
Kelly, A. Paul	11	12	23
Ling, Mark R.	20	28	48
Lowe, Nicholas	16	13	29
Lucky, Anne	10	9	19
Olsen, Elise	22	19	41
Price, Vera	21	17	38
Rietschel, Robert	11	15	26
Roberts, Janet	31	29	60
Savin, Ronald	24	20	44
Shupack, Jerome	10	9	19
Stewart, Daniel	20	18	38
Stough, Dowling	4	9	13
Swinehart, James	19	17	36
Swinyer, Leonard J.	13	14	27
Weiss, Darryl	7	9	16
Weiss, Jonathan S.	15	14	29
Whiting, David	16	15	31
Asarch, Richard G.	14	15	29
Whitmore, Elizabeth	6	5	11
Horwitz, Stephen N.	13	10	23
Weinstein, Gerald D.	11	10	21
Peck, Gary L.	11	11	22
Fivenson, David	10	9	19
Total	471	462	933

Completion Status:

	Finasteride 1 mg	Placebo	Total
ENTERED: (age range)*	471 (19 to 41)	462 (18 to 41)	933 (18 to 41)
COMPLETED:	398	379	777

DISCONTINUED: Total	73	83	156
Clinical adverse experience	10	12	22
Laboratory adverse experience	0	0	0
Other	63	71	134

* All patients were male.

Patients Discontinued From Therapy:

Reason Discontinued	Finasteride 1 mg N = 471	Placebo N = 462	Total N = 933
Clinical AE	10	12	22
Laboratory AE	0	0	0
Lack of efficacy	1	6	7
Lost to follow-up	27	21	48
Withdrew	7	10	17
Relocating	7	6	13
Sexual partner pregnant	8	0	8
Protocol violation	1	1	2
Noncompliance*	11	23	34
Placebo run-in AE	1	2	3
Other	0	2	2
Total discontinued	73	83	156

* Includes noncompliance with hair clipping, visit schedule, or test drug, and patients who wished to father a child during the study.

Comparability of Treatment Groups:

Patient Baseline Comparability

	Finasteride 1 mg	Placebo	Total
Age in Years	(N = 471)	(N = 462)	(N = 933)
Mean	33.4	33.6	33.5
Median	34.0	35.0	34.0
Range			
Race	(N = 471)	(N = 462)	(N = 933)
White	405	380	785
Black	40	58	98
Asian	3	5	8
Hispanic	21	15	36
Other	2	4	6
Number of Patients With Baseline Hamilton Classification			
	(N = 471)	(N = 462)	(N = 933)
Grade II Vertex	63	63	126
Grade III Vertex	150	129	279
Grade IV	112	141	253
Grade V	146	129	275
Hair Count	(N = 470)	(N = 461)	(N = 931)
Mean	863.5	856.3	860.0
SD	248.5	250.7	249.5
Age at Which Patients Began Losing Hair	(N = 431)	(N = 426)	(N = 857)
Mean	24.4	24.7	24.5
SD	4.5	5.2	4.9
Number of Patients With Family History of Baldness (First Degree--Parents and/or Siblings)			
	(N = 465)	(N = 455)	(N = 920)
Yes	373	363	736
No	92	92	184

* All patients were male.

Comment The two arms were comparable. However, the majority of enrolled subjects were Caucasians.

8.1.3.4.2 Efficacy Parameters

Primary Parameters: Hair Count and Patient's Assessment

Hair Count

Table 8.1.3.4.2A Change From Baseline in Hair Count: ITT Population

	Finasteride 1 mg			Placebo		
	Baseline	Month 6	Change	Baseline	Month 6	Change
Month 0-6	N=402	N=402	N=402	N=386	N=386	N=386
Mean	854.6	921.9	67.3	846.5	830.9	-15.6
SD	251.1	254.0	80.9	252.0	253.0	74.0
	Baseline	Month 12	Change	Baseline	Month 12	Change
Month 0-12	N=407	N=407	N=407	N=395	N=395	N=395
Mean	856.1	944.9	88.8	846.5	829.2	-17.3
SD	251.3	263.5	88.4	250.8	263.1	75.0
	Month 6	Month 12	Change	Month 6	Month 12	Change
Month 6-12	N=377	N=377	N=377	N=359	N=359	N=359
Mean	918.2	941.1	22.9	832.2	831.0	-1.2
SD	250.1	260.8	74.3	251.5	263.3	70.9

Least Squares Summary Statistics and 95% Confidence Intervals

	Finasteride 5 mg	Placebo	Difference +	p-Value
Month 0-6 Mean change +	69.5** (61.6, 77.3)	-13.6**(-21.6, -5.6)	83.1 (72.4, 93.8)	0.001
Month 0-12 Mean change +	91.3** (83.3, 99.4)	-15.0**(-23.2, -6.8)	106.3 (95.3, 117.3)	< 0.001
Month 6-12 Mean change +	23.5** (16.2, 30.7)	1.1 (-8.4, 6.3)	24.5 (14.6, 34.4)	<0.001

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.

Patient Self-Assessment

The global test of treatment effect across all seven questions showed a significant (p < 0.005) difference between the two treatments from Month 3 onwards. There was a significant improvement from Month 6 to Month 12 for the finasteride group for all questions. The placebo group showed a significant decrease for Questions 2 and 3. The change from Month 6 to Month 12 was based on the cohort of patients that had data at both Month 6 and Month 12. Data on individual questions are shown in Table 8.1.3.4.2B, C and D.

Table 8.1.3.4.2B Summary of Analysis of the Seven Hair Growth Questions at Months 3, 6 and 12

	Month 3					Month 6				Month 12			
	Mean Scores			95% CI		Mean Scores			95% CI	Mean Scores			95% CI
Variable	Fin*	P.O.	Diff	for Diff	p-value	Fin*	P.O.	Diff	for Diff	Fin*	P.O.	Diff	for Diff
Global test					0.035								
Q1	-0.1	-0.3	0.2	(0.1, 0.3)	0.004	0.2	-0.2	0.4	(0.3, 0.5)	0.3	-0.3	0.6	(0.5, 0.7)
Q2	0.6	0.4	0.1	(0.0, 0.3)	0.058	0.8	0.5	0.3	(0.2, 0.4)	1.0	0.3	0.7	(0.5, 0.8)
Q3	0.5	0.4	0.1	(0.0, 0.2)	0.149	0.6	0.4	0.2	(0.1, 0.3)	0.8	0.3	0.5	(0.4, 0.6)
Q4	0.1	-0.1	0.2	(0.0, 0.4)	0.021	0.5	0.0	0.5	(0.3, 0.7)	0.6	-0.1	0.7	(0.5, 0.9)
Q5a	-0.1	-0.2	0.0	(-0.1, 0.1)	0.585	-0.1	-0.2	0.1	(0.0, 0.2)	0.0	-0.2	0.2	(0.1, 0.3)
Q5b	-0.1	-0.2	0.1	(0.0, 0.2)	0.060	0.0	-0.2	0.2	(0.1, 0.3)	0.2	-0.2	0.3	(0.2, 0.5)
Q5c	-0.1	-0.1	0.1	(0.0, 0.2)	0.279	0.1	-0.1	0.2	(0.1, 0.3)	0.2	-0.1	0.3	(0.2, 0.4)

p-values for global tests and between-group differences for individual questions at all time points from Month 6 were <0.001, except for Question 5a (satisfaction wit Front) at Month 6, which was 0.131. Month 9 differences between treatment groups (not shown) almost same as for Month 12 except for slightly lower values for Q2 and Q3 (0.5 and 0.4 respectively). Fin=finasteride, P.O.=placebo.

Question 1--Since beginning the study, I can see my bald spot getting smaller.

Question 2--Because of the treatment I have received since the start of the study, the appearance of my hair is:

Question 3--Since the start of the study, how would you describe the growth of your hair?

Question 4--Since the start of the study, how effective do you think this treatment has been in slowing down your hair loss?

Question 5a--Compared to the beginning of the study, which statement best describes your satisfaction with the appearance of the hairline at front of your head?
Question 5b--Compared to the beginning of the study, which statement best describes your satisfaction with the appearance of the hair on top of your head?
Question 5c--Compared to the beginning of the study, which statement best describes your satisfaction with the appearance of your hair overall?

Table 8.1.3.4.2C Summary Statistics for the Mean Change From Month 6 to Month 12: ITT Population

Question	Finasteride 1 mg	Placebo	Between-Group p-Value
Q1: Bald Spot Getting Smaller	0.2**	-0.1	<0.001
Q2: Appearance of Hair	0.3**	-0.1**	<0.001
Q3: Growth of Hair	0.2**	-0.1**	<0.001
Q4: Slowing Down Hair Loss	0.2**	-0.1	0.007
Q5a: Satisfaction With Front	0.1*	-0.1	0.012
Q5b: Satisfaction With Top	0.1**	0.0	0.082
Q5c: Satisfaction With Hair Overall	0.1**	0.0	0.061

*, **: Significant change from Month 6 at the $p < 0.050$ and $p < 0.010$ level, respectively

Table 8.1.3.4.2D Distribution of Scores in Patient Self-Assessment Questionnaire at Month 12

	Finasteride 1 mg							Placebo						
	-3	-2	-1	0	1	2	3	-3	-2	-1	0	1	2	3
Q1	<----------Disagree---------- No opinion-----Agree---------->							<----------Disagree---------- No opinion-----Agree---------->						
Pt No														
Percent		5%	17%	33%	31%	13%			15%	25%	38%	19%	3%	
Q2	<----------Worse---------- Same------Better---------->							<----------Worse---------- Same------Better---------->						
Pt No														
Percent	0	2%	5%	33%	26%	21%	13%	1%	4%	11%	47%	23%	9%	5%
Q3	<----------Decreased--------- No Change------Increased---------->							<----------Decreased--------- No Change------Increased---------->						
Pt No														
Percent	0	0	5%	36%	34%	17%	6%	0	3%	10%	48%	29%	7%	1%
Q4	<---Not Effective- --Effective------->							<---Not Effective- --Effective------->						
Pt No														
Percent		10%	17%		46%	27%			20%	29%		41%	10%	
Q5a	<---Dissatisfied--- Neutral----Satisfied------->							<---Dissatisfied--- Neutral----Satisfied------->						
Pt No														
Percent		5%	21%	45%	26%	3%			7%	26%	50%	15%	2%	
Q5b	<---Dissatisfied--- Neutral----Satisfied------->							<---Dissatisfied--- Neutral----Satisfied------->						
Pt No														
Percent		4%	20%	41%	27%	8%			8%	27%	45%	18%	3%	
Q5c	<---Dissatisfied--- Neutral----Satisfied------->							<---Dissatisfied--- Neutral----Satisfied------->						
Pt No														
Percent		2%	21%	37%	35%	5%			5%	27%	45%	20%	3%	

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

Secondary Parameters: Investigator Assessment, Global Photographic Assessment and Dihydrotestosterone Levels

Investigator Assessment

Table 8.1.3.4.2E Investigator Assessment Intention-to-Treat Population at Months 6 and 12

	Finasteride 1 mg							Placebo						
	-3	-2	-1	0	1	2	3	-3	-2	-1	0	1	2	3
	<----------Decreased--------- No Change------Increased---------->							<----------Decreased--------- No Change------Increased---------->						
Month 6														
Pt No														
Percent	0	0	1%	31%	41%	24%	3%	0	0	4%	47%	37%	10%	1%

Month 12													
Pt No	0	1	12	110	143	145	40	1	10	33	199	136	55	10
Percent	0	0	3%	24%	32%	32%	9%	0	2%	7%	45%	31%	12%	2%

Least Squares Summary Statistics and 95% Confidence Intervals

	Finasteride 5 mg	Placebo	Difference	p-Value
Month 6				
Mean score +	0.9**(0.8, 1.0)	0.5**(0.4, 0.6)	0.4 (0.3, 0.5)	< 0.001
Month 12				
Mean score +	1.1** (1.0, 1.2)	0.4**(0.3, 0.5)	0.7 (0.6, 0.8)	< 0.001
Between Months 6 and 12				
Mean change +	0.2** (0.2, 0.3)	-0.1*(-0.2, 0.0)	0.3 (0.2, 0.5)	< 0.001

Treatment-by-center interaction: p-value > 0.50 for both Months 6 and 12; + : 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.

Global Photographic assessment

Table 8.1.3.4.2F Global Photographic Assessment Intention-to-Treat Population at Months 6 and 12

	Finasteride 1 mg							Placebo						
	-3	-2	-1	0	1	2	3	-3	-2	-1	0	1	2	3
	<----------Decreased----------			No Change		Increased---------->		<----------Decreased----------			No Change		Increased---------->	
Month 6														
Pt No														
Percent	0	1%	53%	35%	10%	1%		0	1%	2%	86%	9%	1%	0
Month 12														
Pt No														
Percent	0	1%	49%	32%	16%	2%		0	1%	6%	86%	7%	0	0

Least Squares Summary Statistics and 95% Confidence Intervals

	Finasteride 5 mg	Placebo	Difference	p-Value
Month 6				
Mean score +	0.6**(0.5, 0.6)	0.1**(0.0, 0.2)	0.5 (0.4, 0.6)	< 0.001
Month 12				
Mean score +	0.7** (0.6, 0.7)	0.0 (-0.1, 0.1)	0.7 (0.6, 0.8)	< 0.001
Between Months 6 and 12				
Mean change +	0.1**(0.0, 0.2)	-0.1** (-0.2, 0.0)	0.2 (0.1, 0.3)	< 0.001

Treatment-by-center interaction: p-value=0.035 at Month 6 and 0.081 at Month 12 but 0.168 between Months 6 and 12; + : *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.

Comments

1. There are two statistical problems in the analysis: (a) 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. (b) Rescaling with center being zero for "no change" in the patient self-assessment questionnaire magnifies the treatment effect in question 4 because the original question gave a one grade change from "somewhat effective" to "not very effective" but after rescaling this as +1 and -1, the distance between these two grades is doubled. As the treatment effect mostly lie within these two grades, discrimination between the effects of finasteride and placebo become magnified.
2. Net "hair growth" by treatment with finasteride 1 mg/d for 12 months was established by (a) objective assessment - hair count and (b) subjective assessment - positive mean scores in questions in the Hair Growth Questionnaire. "Hair loss" by placebo treatment was also established by negative findings in both of these two parameters. The differences in hair count change and in scores to each of the 7 questions were significant between the two treatments at Month 12.
3. Although there was a 17% (Q.5a) to 51% (Q.4) positive response to the self-assessment questions for the placebo group at Month 12, the mean scores for 5 of the 7 questions at this time point were negative, suggesting hair loss in this arm. The lowest rate of positive response for the finasteride group was to Q.4 (73%) and all

the mean scores were positive except for a zero for Q5a (frontal hairline), suggesting subjective feeling of scalp hair growth.
4. The Applicant has not provided an analysis of the proportion of patients with positive vs negative changes in hair count in each treatment group with significance levels.
5. Substantial placebo effect is seen with Investigator assessment, in contrast to global photographic assessment.
6. The secondary parameters support results of the primary endpoints: hair count and patient's assessment, which indicate objective and subjective improvement in scalp hair coverage at vertex.

Dihydrotestosterone Levels There was a decrease of 61% and 63% in DHT levels at Months 6 and 12 respectively in the finasteride group but not in the placebo group.

Esploratory Parameter: Scalp Biopsy Study on Hair Follicles

Histological Changes in Scalp Biopsy At one center, 4 mm punch biopsies with horizontal sections were performed to examine for changes between Month 0 and Month 12 by counting the numbers of vellus and terminal hairs. The following data were provided by the Applicant in the submission of 6/18/97:

Table 8.1.3.4.2.G Histological Evaluation of Scalp Biopsies (Mean±SE)

	Finasteride N=14			Placebo N=12		
Hair Type	Baseline	Month 12	Change	Baseline	Month 12	Change
Terminal	15.5±1.6	20.9±1.9	5.4±1.8	17.3±1.8	18.3±2.3	1.0±1.7
Vellus	26.7±3.8	23.6±4.7	-3.4±3.6	21.3±2.9	20.3±3.4	-1.1±3.4
			Ratio of Month 12: Baseline			Ratio of Month 12: Baseline
Vellus/Terminal ratio	1.7±0.4	1.1±0.3	0.7±0.1	1.2±0.2	1.1±0.3	0.9±0.2

Comments
1. Significance levels of the findings have not been provided.
2. The baselines of the two treatment groups appear to be different especially with vellus hair count and the vellus/terminal ratio.
3. This study showed similar directions for finasteride and placebo groups differing only in degree: increase of terminal hair and decrease of vellus hair after 12 months of treatment. Thus, both resulted in a decrease in the vellus/terminal ratio, although that decrease was greater in the finasteride group.
4. This study also showed that there was a large number of hairs that were not countable with the macrophotography technique. The Applicant used this to support the counting with macrophotography as being of only cosmetically important hairs.

8.1.3.4.3 Safety Comparison

8.1.3.4.3.1 Adverse Events

Details of AE and drug-related AE are given in Appendix III.

Table 8.1.3.4.3.1A Clinical Adverse Experience Summary–Patient Count (%)

	Finasteride (N = 471)	Placebo (N = 462)
one or more AE	308 (65.4)	288 (62.3)
with drug-related AE	34 (7.2)	28 (6.1)
withdrawn from therapy		
due to an AE	10 (2.1)	12 (2.6)
due to sexual AE	7 (1.5)	6 (1.3)
due to a drug-related AE	8 (1.7)	9 (1.9)

due to a drug-related sexual AE	7 (1.5)	6 (1.3)
due to a serious AE	2 (0.4)	0
due to a serious drug-related AE	0	0

Table 8.1.3.4.3.1B Sexual Adverse Experiences--Patient Count (%)

	ALL AE		Drug-related AE	
	Finasteride (N = 471)	Placebo (N = 462)	Finasteride (N = 471)	Placebo (N = 462)
one or more sexual AE	24 (5.1)	14 (3.0)	21 (4.5)	12 (2.6)
Libido decreased	10 (2.1)	8 (1.7)	7 (1.5)	6 (1.3)
Ejaculation disorder	10 (2.1)	6 (1.3)	10 (2.1)	6 (1.3)
Impotence	8 (1.7)	5 (1.1)	8 (1.7)	5 (1.1)
Orgasm dysfunction	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
Priapism	1 (0.2)	0	1 (0.2)	0

Of the patients who reported drug-related sexual AE, 10/21 (48%) on finasteride and 3/12 (25%) on placebo reported resolution while on therapy. Thirteen patients discontinued therapy due to sexual AE (7 finasteride, 6 placebo), all reporting resolution. Four of 7 patients on finasteride reported resolution while still taking drug. The remaining 3 had AE resolved within 1 to 23 days after cessation.

Table 8.1.3.4.3.1C Serious Clinical Adverse Experiences

Number	Age/drug	Day of Onset	AE	Duration (Days)	Intensity	Drug Relationship	Discon-tinuation	Outcome*
	33 fin	75	Alcohol dependence	22	Severe	Definitely not	Yes	Recovered
	30 fin	301	Trauma	2	Moderate	Definitely not	No	Recovered
	36 fin	101	Trauma, brain	1	Severe	Definitely not	Yes	Death
	39 fin	50	Pain, abdominal	2	Moderate	Definitely not	No	Recovered
	35 fin	179	Neoplasm, skin, malignant	52	Mild	Definitely not	No	Recovered
	36 P	213	Hepatitis A	17	Severe	Definitely not	No	Recovered
	33 P	316	Urolithiasis	2	Severe	Definitely not	No	Recovered
	39 P	45	Pancreatitis	24	Severe	Probably not	No	Recovered
	32 P	172	Fracture, hand phalanx	84	Severe	Definitely not	No	Recovered
	33 P	126	Pain, abdominal	18	Severe	Definitely not	No	Recovered
		126	Pain, flank	18	Severe	Definitely not	No	Recovered
	28 P	285	Neoplasm, skin, malignant	67	Moderate	Definitely not	No	Still present
	36 P	341	Neoplasm, skin, malignant	8	Moderate	Definitely not	No	Recovered

*fin=finasteride, P=placebo

Table 8.1.3.4.3.1D Patients Discontinued From Therapy Due to Clinical Adverse Experiences

No.	Age/drug	Relative Day of Onset	AE	Relative Day Duration (Days)	Relative Day of Discon-tinuation	Intensity	Drug Relationship	Serious-ness	Outcome*
	33 fin	75	Alcohol dependence	22	76	Severe	Definitely not	Yes	Recovered
	36 fin	101	Trauma, brain	1	101	Severe	Definitely not	Yes	Still present*
	32 fin	78	Paresthesia	185	165	Mild	Possibly	No	Recovered
	34 fin	61	Impotence	17	69	Moderate	Probably	No	Recovered
	32 fin	1	Impotence	1	15	Mild	Possibly	No	Recovered
	28 fin	161	Impotence	47	185	Moderate	Probably	No	Recovered
	39 fin	68	Impotence	33	100	Moderate	Probably	No	Recovered
	37 fin	24	Impotence	29	54	Moderate	Probably	No	Recovered
	36 fin	1	Libido decreased	28	30	Moderate	Probably	No	Recovered
	41 fin	47	Ejaculation disorder	16	61	Moderate	Probably	No	Recovered
	36 P	45	Pain, abdominal[1]	23	44	Moderate	Probably	No	Recovered
	30 P	79	Depression	77	87	Moderate	Prob not	No	Still present
	30 P	15	Impotence	157	162	Moderate	Possibly	No	Recovered

41 P	143	Seizure disorder	56	143	Moderate	Possibly	No	Still present
35 P	175	Libido decreased	206	175	Severe	Probably	No	Recovered
40 P	86	Libido decreased	116	199	Moderate	Possibly	No	Recovered
39 P	9	Ejaculation disorder	14	17	Moderate	Probably	No	Recovered
28 P	56	Somnolence	26	62	Mild	Possibly	No	Recovered
33 P	245	Impotence	36	266	Moderate	Possibly	No	Recovered
34 P	8	Asthenia/fatigue	12	1	Moderate	Probably not	No	Still present
38 P	99	Impotence	61	153	Moderate	Possibly	No	Recovered
25 P	137	Emotional lability	39	147	Moderate	Probably not	No	Recovered

* Outcome is as of the latter of the day on which study drug was stopped, the patient's last clinic visit, or last contact with the patient, but subject [redacted] subsequently died; fin=finasteride, P=placebo.

8.1.3.4.3.2 Laboratory Findings There were no consistent significant clinical laboratory abnormalities or discontinuation due to laboratory adverse events. Special lab tests:

1. Testosterone Mean increases of 13.3% at Month 6 and 12.2% at Month 12 were noted in the finasteride group.

2. PSA Approximately 7% (59/838) of the patients had PSA measurements below the detectable limit of the assay (0.2 ng/mL) at Month 12. There were significant reductions ($p < 0.010$) in PSA for the finasteride group, -0.3 ng/mL at both Months 6 and 12. The change in placebo group was not significantly different from zero at either time point.

3. LH and FSH No significant difference between treatment groups.

8.1.3.4.3.3 Sexual Function Questionnaire

Table 8.1.3.4.3.3 Summary Statistics for the Domains/Questions of the Sexual Function Questionnaire Months 3, 6, 9, and 12 Intention-to-Treat Population

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

Month 9	451	0.0	443	0.0	0.0	0.607
Month 12	451	0.0	443	0.0	-0.1	0.223
Morning Erections (0 to 4)						
Month 3	450	-0.2**	438	0.0	-0.2	<0.001
Month 6	452	-0.2**	442	0.1	-0.3	<0.001
Month 9	452	-0.2**	442	0.1	-0.3	<0.001
Month 12	452	-0.1*	442	0.1**	-0.2	<0.001

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

Comments There were small but significant differences between the two groups for (a) the question on morning erections at all time points ($p<0.001$) and (b) the domain of perception of problems ($p<0.050$) at Months 6 through Month 12, (c) the domain of sexual interest at earlier time points ($p < 0.050$), but this difference disappeared at Month 12 and (d) the domains of erections only at Month 6 and Month 12 ($p<0.050$).

8.1.3.4.3.4 Body Hair Assessment

Table 8.1.3.4.3.4 Results in Body Hair Assessment Questionnaire at Month 12

	Finasteride 1 mg					Placebo				
	-2	-1	0	1	2	-2	-1	0	1	2
Q1a	<---Decreased-- No Change---Increased------->					<---Decreased-- No Change---Increased------->				
Pt No										
Percent	0	2%	77%	19%	2%	1%	2%	72%	23%	3%
Q2a	<---Decreased-- No Change---Increased------->					<---Decreased-- No Change---Increased------->				
Pt No										
Percent	0	1%	87%	11%	1%	0	1%	80%	18%	1%
Q3a	<---Decreased-- No Change---Increased------->					<---Decreased-- No Change---Increased------->				
Pt No										
Percent	0	2%	88%	9%	0	0	0	84%	15%	1%

Summary Analysis	Mean Scores			95% Confidence	
	Finasteride	Placebo	Between- Group Diff (Finasteride-Placebo)	Interval for Diff	p-Value
Q1a	0.2**	0.3**	0	(-0.1, 0.0)	0.220
Q2a	0.1**	0.2**	-0.1	(-0.1, 0.0)	0.003
Q3a	0.1**	0.2**	-0.1	(-0.2, 0.0)	<0.001

Q1a: Since the start of the study, how would you describe the growth of your hair on your face?
Q2a: Since the start of the study, how would you describe the growth of your hair on your chest?
Q3a: Since the start of the study, how would you describe the growth of your hair on your extremities?
*, **: Significant change from baseline at the $p < 0.050$ and $p < 0.010$ level, respectively.
Significant treatment-by-center interaction in all 3 questions ($p<0.001$).

Comments
1. As the scores for this assessment represent a change from baseline, it is not appropriate to further test for significance by comparing these scores with a "baseline" of zero. Although the protocol required answering this questionnaire at baseline, scores at baseline would be meaningless. It is unclear whether the Applicant used "zero" as baseline score for such analysis or used actual baseline data.
2. Both treatment groups perceived small increases in growth of hair on the face, chest and extremities at both time points. The placebo group perceived slightly more hair on the chest and extremities compared with the finasteride group.

8.1.3.5 Conclusions

(1) Twelve months of therapy with finasteride 1 mg/d in men with MPB produced net increases in scalp hair counts leading to cosmetic improvement as determined by patient self-assessment of both treatment efficacy and satisfaction with appearance.
(2) The net increases in scalp hair count and improvement in patient self-assessment

were supported by investigator assessment and global photographic assessment.
(3) Cosmetic improvement might be seen as early as 3 months. Scalp hair counts, patient self-assessment, and investigator and global photographic assessments showed additional improvements from Month 6 to Month 12, although most of the improvement took place in the first 6 months.
(4) Treatment with placebo led to a significant net decrease in scalp hair count and to perceptible continued balding based on patient self-assessment.
(5) The treatment effect of finasteride on the primary variables in the absence of Neutrogena T-gel shampoo has not been defined.
(6) Treatment with finasteride 1 mg/d was generally well tolerated. A small number of men report sexually-related AE. All patients who discontinued due to a sexual AE had resolution of the AE.

8.1.4 Trial#4: Study#089 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)

8.1.4.1 Objective/Rationale

8.1.4.2 Design

8.1.4.3 Protocol

This study is an international trial and is virtually identical to 087 including global photographic assessment by the same 3 dermatologists as in 087 (Elise Olsen, David Whiting and Ronald Savin). It is one of two pivotal studies. The modifications are:
1. Body hair assessment was eliminated.
2. The camera used for macrophotography and global photographic assessment was a Nikon N6006 instead of N-6000.

8.1.4.4 Results

8.1.4.4.1 Patient Disposition, Comparability

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Distribution of patients at entry by Investigator:

Study Number & Investigator	Finasteride	Placebo	Total
089040 Birchall, N	18	13	31
089041 Kerl, Helmut	14	17	31
089042 Plewig, G	2	2	4
089043 Fyrand, Ole	13	17	30
089044 Brenner Weintraub, SA	10	9	19
089045 Sher, Mary A	22	19	41
089046 Cilliers, Jacques	14	17	31
089047 Todd, Gail	21	21	42
089048 Steiner, Denise	13	14	27
089049 Jurado Santa Cruz, F	10	10	20
089050 Burg, G	11	11	22
089051 Rufli, Theo	12	11	23
089052 Rittmaster, R	15	14	29
089053 Unger, Walter P	12	12	24
089054 Shapiro, Jerry	20	25	45
089055 Gratton, David	8	6	14
089056 McDonagh, Andrew J	3	0	3
089057 Schmidt, Jolanta	8	10	18
089058 Reygagne, Pascal	10	8	18
089059 Saiag, Philippe	3	5	8
089060 Lachapelle, Jean-Marie	5	7	12
089061 Van Neste, Dominique	9	8	17
089062 Sanchez-Pedreno, Pal	14	11	25
089063 Cunliffe, William J	5	6	11
089064 Schuller, JL	12	14	26
089065 Lopez-Bran, Eduardo	12	13	25
089066 Prens, Errol Prosper	12	12	24
Total	308	312	620

Completion Status:	Finasteride 1 mg	Placebo	Total
ENTERED: (age range)*	308	312	620
COMPLETED:	260	267	527
DISCONTINUED: TOTAL	48	45	93
Clinical adverse experience	6	7	13
Laboratory adverse experience	1	0	1
Other	41	38	79

* All patients were male.

Patients Discontinued from Therapy:

Reason Discontinued	Finasteride 1 mg N = 308	Placebo N = 312	Total N = 620
Clinical AE	6	7	13
Laboratory AE	1	0	1
Lost to follow-up	13	14	27
Withdrew	7	6	13
Noncompliance*	8	4	12
Relocating	1	3	4
Protocol violation	8	3	11
Sexual partner pregnant	3	2	5
Lack of efficacy	1	5	6
Treated with drug in exclusion criteria	0	1	1
Total discontinued	48	45	93

* Includes noncompliance with hair clipping, visit schedule, or test drug, and patients who wished to father a child during the study.

Comparability of Treatment Groups:

Patient Baseline Comparability

	Finasteride 1 mg	Placebo	Total
Age in Years	(N = 308)	(N = 312)	(N = 620)
Mean	31.4	31.5	31.4
Median	31.0	32.0	32.0
Range			
Race	(N = 308)	(N = 312)	(N = 620)
White	283	283	566
Black	1	2	3
Asian	10	6	16
Hispanic	10	10	20
Other	4	11	15
Number of Patients With Baseline Hamilton Classification			
	(N = 308)	(N = 312)	(N = 620)
Grade II Vertex	56	59	115
Grade III Vertex	76	75	151
Grade IV	83	84	167
Grade V	93	94	187
Hair Count	(N = 305)	(N = 307)	(N = 612)
Mean	916.5	923.9	920.2
SD	257.7	244.4	250.9
Age at Which Patients Began Losing Hair	(N = 294)	(N = 293)	(N = 587)
Mean	23.7	23.8	23.8
SD	4.7	4.9	4.8
Number of Patients With Family History of Baldness (First Degree--Parents and/or Siblings)			
	(N = 308)	(N = 312)	(N = 620)
Yes	227	239	466
No	70	56	126
Unevaluable	11	17	28

* All patients were male.

Comments

1. The two arms were comparable. However, the majority of enrolled subjects were Caucasians (>90%).
2. In this international study, the only Asian country included was Israel, with all 19 subjects being Caucasians. It is not clear how many of the 16 "Asians" included were of Mongoloid origin. All of the patients in Brazil were "Caucasians" and all but

one of the 20 Mexican subjects were "Hispanic" (there were 20 "Hispanics" in the whole study). In addition, it is noted that there were only 3 Blacks in the study, despite an enrollment of 114 subjects among the South African investigators. Thus, this international study cannot be regarded as representative of the world's population at large and is heavily tilted towards collection of information on Caucasians.
3. As in 087, the restriction in age and degree/extent of balding will have implications on labeling. This study also required patients to use the tar-based shampoo from Neutrogena.

8.1.4.4.2 Efficacy Parameters

Primary Parameters: Hair Count and Patient's Self-Assessment

Hair Count

Table 8.1.4.4.2A Change From Baseline in Hair Count: ITT Population

	Finasteride 1 mg			Placebo		
	Baseline	**Month 6**	**Change**	**Baseline**	**Month 6**	**Change**
Month 0-6	N=266	N=266	N=266	N=275	N=275	N=275
Mean	903.5	966.9	63.4	919.4	899.7	-19.7
SD	254.8	262.0	91.9	247.4	262.4	83.3
	Baseline	**Month 12**	**Change**	**Baseline**	**Month 12**	**Change**
Month 0-12	N=272	N=272	N=272	N=277	N=277	N=277
Mean	920.8	988.4	85.5	919.4	898.1	-21.2
SD	255.2	265.3	89.1	246.5	262.5	76.4
	Month 6	**Month 12**	**Change**	**Month 6**	**Month 12**	**Change**
Month 6-12	N=240	N=240	N=240	N=249	N=249	N=249
Mean	965.4	990.0	24.6	899.4	898.2	-1.2
SD	261.2	263.7	71.2	262.6	263.8	81.3

Least Squares Summary Statistics and 95% Confidence Intervals

	Finasteride 5 mg	Placebo	Difference +	p-Value
Month 0-6 Mean change +	58.4** (47.8, 68.9)	-22.9**(-33.3, -12.5)	81.3 (67.0, 95.6)	< 0.001
Month 0-12 Mean change +	83.7** (73.6, 93.7)	-23.7**(-33.7, -13.7)	107.3 (93.6, 121.0)	< 0.001
Month 6-12 Mean change +	24.9** (15.3, 34.5)	-3.3 (-12.7, 6.2)	28.2 (15.1, 41.3)	<0.001

Treatment-by-center interactions significant for both Month 6 and Month 12 changes from baseline (p=0.028) but not significant for Month 12 changes from Month 6 (p=0.931); + : Adjusted for the treatment and center effects. *, ** : Significant change from baseline at the $p < 0.050$ and $p < 0.010$ level, respectively.

Patient Self-Assessment

The data are shown in Tables 8.1.4.4.2B, C and D. Treatment-by-center interaction was significant at Months 9 and 12 (p=0.003 and 0.011 respectively). Twenty-two out of 26 centers (after combining the 2 smallest centers, 089042 and 089056) demonstrated greater improvement for finasteride vs placebo. Four centers showed a greater effect for placebo. Gail and Simon's test was not significant: the interaction was quantitative.

Table 8.1.4.4.2B Summary of Analysis of the Seven Hair Growth Questions at Months 3, 6 and 12

	Month 3					Month 6				Month 12			
	Mean Scores			95% CI		Mean Scores			95% CI	Mean Scores			95% CI
Variable	**Fin***	**P.O.**	**Diff**	**for Diff**	**p-value**	**Fin***	**P.O.**	**Diff**	**for Diff**	**Fin***	**P.O.**	**Diff**	**for Diff**
Global test					<0.001								
Q1	0.0	-0.3	0.3	(0.1, 0.5)	<0.001	0.1	-0.3	0.4	(0.2, 0.6)	0.1	-0.4	0.5	(0.4, 0.7)
Q2	0.6	0.4	0.2	(0.1, 0.4)	0.003	0.8	0.4	0.3	(0.2, 0.5)	0.8	0.2	0.6	(0.4, 0.8)
Q3	0.5	0.3	0.2	(0.0, 0.3)	0.019	0.6	0.2	0.3	(0.2, 0.5)	0.7	0.1	0.6	(0.4, 0.8)
Q4	0.0	-0.3	0.3	(0.1, 0.5)	0.003	0.2	-0.3	0.5	(0.3, 0.7)	0.2	-0.4	0.6	(0.4, 0.8)
Q5a	0.0	-0.2	0.2	(0.0, 0.3)	0.013	0.0	-0.2	0.3	(0.1, 0.4)	0.0	-0.4	0.4	(0.2, 0.5)
Q5b	0.0	-0.2	0.2	(0.0, 0.3)	0.009	0.2	-0.2	0.4	(0.3, 0.5)	0.2	-0.3	0.5	(0.3, 0.6)
Q5c	0.1	-0.1	0.2	(0.0, 0.3)	0.020	0.2	-0.1	0.3	(0.2, 0.4)	0.2	-0.2	0.4	(0.2, 0.5)

p-vlaues for global tests were <0.001 throughout from Month 3 onwards, and p- values for between-group differences for individual questions at all time points from Month 6 onwards were also <0.001. Month 9 differences between treatment groups (not shown) similar to those for Month 12 except for slightly lower values for Q2, Q3, Q5a and Q5b (0.5, 0.4, 0.3 and 0.4 respectively).

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

Table 8.1.4.4.2C Summary Statistics for the Mean Change From Month 6 to Month 12: ITT Population

Question	Finasteride 1 mg	Placebo	Between-Group p-Value
Q1: Bald Spot Getting Smaller	0.0	-0.1*	0.056
Q2: Appearance of Hair	0.1	-0.2**	<0.001
Q3: Growth of Hair	0.1*	-0.2**	<0.001
Q4: Slowing Down Hair Loss	0.0	-0.2 **	0.091
Q5a: Satisfaction With Front	0.0	-0.1*	0.035
Q5b: Satisfaction With Top	0.0	0.1*	0.030
Q5c: Satisfaction With Hair Overall	0.0	0.1*	0.059

*, **: Significant change from Month 6 at the $p < 0.050$ and $p < 0.010$ level, respectively.

Table 8.1.4.4.2D Distribution of Scores in Patient Self-Assessment Questionnaire at Month 12

	Finasteride 1 mg							Placebo						
	-3	-2	-1	0	1	2	3	-3	-2	-1	0	1	2	3
Q1	<----------Disagree--------- No opinion-----Agree---------->							<----------Disagree--------- No opinion-----Agree---------->						
Pt No														
Percent		10%	18%	33%	30%	9%			22%	23%	37%	16%	3%	
Q2	<----------Worsae---------- Same------Better---------->							<----------Worsae---------- Same------Better---------->						
Pt No														
Percent	0	2%	7%	37%	26%	16%	12%	2%	5%	11%	50%	21%	8%	3%
Q3	<----------Decreased--------- No Change------Increased---------->							<----------Decreased--------- No Change------Increased---------->						
Pt No														
Percent	1%	1%	8%	37%	32%	15%	5%	3%	5%	13%	53%	19%	6%	1%
Q4		<---Not Effective-			--Effective------->				<---Not Effective-			--Effective------->		
Pt No														
Percent		18%	22%		43%	17%			26%	37%		28%	9%	
Q5a		<---Dissatisfied--- Neutral----Satisfied------->							<---Dissatisfied--- Neutral----Satisfied------->					
Pt No														
Percent		4%	23%	45%	25%	3%			12%	29%	43%	13%	2%	
Q5b		<---Dissatisfied--- Neutral----Satisfied------->							<---Dissatisfied--- Neutral----Satisfied------->					
Pt No														
Percent		4%	18%	40%	32%	5%			13%	28%	40%	17%	2%	
Q5c		<---Dissatisfied--- Neutral----Satisfied------->							<---Dissatisfied--- Neutral----Satisfied------->					
Pt No														
Percent		3%	19%	41%	33%	4%			9%	28%	43%	17%	3%	

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

Secondary Parameters: Investigator Assessment, Global Photographic Assessment and Dihydrotestosterone Levels

Investigator Assessment

Table 8.1.4.4.2E Investigator Assessment Intention-to-Treat Population at Months 6 and 12

	Finasteride 1 mg							Placebo						
	-3	-2	-1	0	1	2	3	-3	-2	-1	0	1	2	3
	<----------Decreased--------- No Change------Increased---------->							<----------Decreased--------- No Change------Increased---------->						
Month 6														
Pt No														
Percent 0	0	2%	47%	3%	14%	2%		0	1%	2%	60%	30%	7%	0
Month 12														
Pt No														
Percent 0	0	6%	40%	32%	19%	3%		0	1%	10%	63%	21%	4%	0

Least Squares Summary Statistics and 95% Confidence Intervals

	Finasteride 5 mg	Placebo	Difference	p-Value
Month 6				
Mean score +	0.7**(0.6, 0.8)	0.5** (0.4, 0.5)	0.3 (0.1, 0.4)	< 0.001
Month 12				
Mean score +	0.7** (0.6, 0.8)	0.2** (0.1, 0.3)	0.5 (0.4, 0.7)	< 0.001
Between Months 6 and 12				
Mean change +	0.0 (-0.1, 0.1)	-0.3* (-0.4, 0.2)	0.3 (0.2, 0.4)	< 0.001

Treatment-by-center interaction: p-value > 0.50 for both changes from baseline at Months 6 and 12 and for changes between Months 6 and 12; + : 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.

Global Photographic assessment

Table 8.1.4.4.2F Global Photographic Assessment Intention-to-Treat Population at Months 6 and 12

	Finasteride 1 mg							Placebo						
	-3	-2	-1	0	1	2	3	-3	-2	-1	0	1	2	3
	<----------Decreased--------- No Change------Increased---------->							<----------Decreased--------- No Change------Increased---------->						
Month 6														
Pt No														
Percent 0	0	0	53%	32%	14%	1%		0	0%	4%	83%	11%	2%	0
Month 12														
Pt No														
Percent 0	0	1%	55%	27%	16%	1%		0	0	9%	85%	5%	1%	0

Least Squares Summary Statistics and 95% Confidence Intervals

	Finasteride 5 mg	Placebo	Difference	p-Value
Month 6				
Mean score +	0.6** (0.5, 0.7)	0.1** (0.0, 0.2)	0.5 (0.4, 0.6)	< 0.001
Month 12				
Mean score +	0.6** (0.5, 0.7)	0.0 (-0.1, 0.1)	0.6 (0.5, 0.7)	< 0.001
Between Months 6 and 12				
Mean change +	0.0 (-0.1, 0.1)	-0.2** (-0.2, -0.1)	0.2 (0.0, 0.3)	0.018

Treatment-by-center interaction: p-value >0.05 at Month 6 and Month 12 as well as between Months 6 and 12; + : 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.

Comments

1. There are two statistical problems in the analysis: (a) 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. (b) Rescaling with center being zero for "no change" in the patient self-assessment questionnaire magnifies the treatment effect in question 4 because the original question gave a one grade change from "somewhat effective" to "not very effective" but after rescaling this as +1 and -1, the distance between these two grades is doubled. As the treatment effect mostly lie within these two grades, discrimination between the effects of finasteride and placebo become magnified.
2. Net "hair growth" by treatment with finasteride 1 mg/d for 12 months was established by (a) objective assessment - hair count and (b) subjective assessment - positive mean scores in questions in the Hair Growth Questionnaire. "Hair loss" by

placebo treatment was also established by negative findings in both of these two parameters. The differences in hair count change and in scores to each of the 7 questions were significant between the two treatments at Month 12.
3. Although there was a 15% (Q.5a) to 37% (Q.4) positive response to the self-assessment questions for the placebo group at Month 12, the mean scores for 5 of the 7 questions at this time point were negative, suggesting hair loss in this arm. The lowest rate of positive response for the finasteride group was to Q.4 (60%) and all the mean scores were positive except for a zero for Q5a (frontal hairline), suggesting subjective feeling of scalp hair growth.
4. The Applicant has not provided an analysis of the proportion of patients with positive vs negative changes in hair count in each treatment group with significance levels.
5. Substantial placebo effect is seen with Investigator assessment, in contrast to global photographic assessment.
6. The secondary parameters support results of the primary endpoints: hair count and patient's assessment, which indicate objective and subjective improvement in scalp hair coverage at vertex.

Dihydrotestosterone Levels There was a decrease of 57% in DHT levels at both Months 6 and 12 in the finasteride group but inconsistent small changes in the placebo group (8.7% at Month 6 and -3.4% at Month 12).

8.1.4.4.3 Safety Comparison

8.1.4.4.3.1 Adverse Events

Details of AE and drug-related AE are given in Appendix IV.

Table 8.1.4.4.3.1A Clinical Adverse Experience Summary--Patient Count (%)

	Finasteride (N = 308)	Placebo (N = 312)
one or more AE	185 (60.1)	178 (57.1)
with drug-related AE	32 (10.4)	27 (8.7)
withdrawn from therapy		
due to an AE	6 (1.9)	7 (2.2)
due to sexual AE	4 (1.3)	2 (0.6)
due to serious AE	1 (0.3)	2 (0.6)
due to a drug-related AE	5 (1.6)	5 (1.6)
due to a drug-related sexual AE	4 (1.3)	2 (0.6)
due to a serious drug-related AE	0	0

Table 8.1.4.4.3.1B Sexual Adverse Experiences--Patient Count (%)

	ALL AE		Drug-related AE	
	Finasteride (N = 308)	Placebo (N = 312)	Finasteride (N = 308)	Placebo (N = 312)
one or more sexual AE	13 (4.2)	6 (1.9)	12 (3.9)	5 (1.6)
Libido decreased	9 (2.9)	4 (1.3)	8 (2.6)	4 (1.3)
Ejaculation disorder	1 (0.3)	0	1 (0.3)	0
Impotence	3 (1.0)	3 (1.0)	3 (1.0)	2 (0.6)
Semen abnormality	0	2 (0.6)	0	2 (0.6)

For sexual AE leading to discontinuations, all resolved prior to or subsequent to the discontinuation.

Table 8.1.4.4.3.1C Serious Clinical Adverse Experiences

Number	Age/drug	Day of Onset	AE	Duration (Days)	Intensity	Drug Relationship	Discon-tinuation	Outcome*
30	fin	227	Appendicitis	4/Severe		Definitely not	No	Recovered

20 fin	132	Trauma	8/Severe	Definitely not	No	Recovered
30 fin	137	Fracture, rib	1/Severe	Definitely not	No	Still present
fin	137	Fracture, vertebra	1/Severe	Definitely not	Yes	Still present
22 fin	191	Cyst, genital	3/Moderate	Probably not	No	Recovered
26 fin	16	Trauma	83/Severe	Definitely not	No	Recovered
34 fin	125	Palpitation	65/Severe	Probably not	No	Recovered
28 fin	12	Neoplasm, skin, malignant	107/Mild	Probably not	No	Recovered
23 fin	325	Sprain, neck	14/Moderate	Definitely not	No	Recovered
fin	325	Strain, back	14/Moderate	Definitely not	No	Recovered
fin	325	Fracture, rib	14/Moderate	Definitely not	No	Recovered
fin	325	Spleen disorder	14/Severe	Definitely not	No	Recovered
fin	325	Atelectasis	14/Severe	Definitely not	No	Recovered
fin	325	Diaphragm disorder	14/Severe	Definitely not	No	Recovered
30 fin	302	Cyst, pilonidal	3/Mild	Definitely not	No	Recovered
40 P	Off 31 days					
	74	Pneumonia	12/Severe	Definitely not	No	Recovered
34 P	192	Syncope	5/Moderate	Definitely not	No	Recovered
P	192	Anemia	1/Moderate	Definitely not	No	Recovered
37 P	274	Intervertebral disc disorder	1/Severe	Definitely not	No	Recovered
P	274	Cauda equina syndrome	2/Mild	Definitely not	No	Recovered
P	239	Neurological disorder	35/Severe	Definitely not	No	Recovered
34 P	15	Seizure disorder	5 min/Severe	Definitely not	No	Recovered
P	216	Seizure disorder	5 min/Severe	Definitely not	Yes	Recovered
26 P	213	Intervertebral disc disorder	5/Severe	Definitely not	No	Recovered
39 P	186	Fracture, elbow, right	3/Severe	Definitely not	No	Recovered
32 P	34	Atrial flutter	2/Moderate	Probably not	No	Recovered
33 P	Off 3 days					
	89	Syncope	5 min/Severe	Probably not	Yes	Recovered
36 P	206	Fracture, knee, left	17/Moderate	Definitely not	No	Recovered
37 P	Off 1 day					
	87	Gastroenteritis	2/Severe	Definitely not	No	Recovered

*fin=finasteride, P=placebo.

Table 8.1.4.4.3.1D Patients Discontinued From Therapy Due to Clinical Adverse Experiences

No. Age/drug	Relative Day of Onset	AE	Relative Day Duration (Days)	Relative Day of Discontinuation	Intensity	Drug Relationship	Seriousness	Outcome*
34 fin	Off 1 day							
	95	Libido decreased	160	192	Moderate	Definitely	No	Recovered
35 fin	61	Weakness, muscle	16	72	Severe	Possibly	No	Recovered
30 fin	137	Fracture, vertebra	1	137	Severe	Definitely not	Yes	Still present
34 fin	247	Impotence	22	255	Moderate	Possibly	No	Recovered
37 fin	92	Libido decreased	243	331	Mild	Possibly	No	Recovered
34 fin	200	Libido decreased	56	275	Moderate	Probably	No	Recovered
34 P	33	Libido decreased	49	79	Moderate	Probably	No	Recovered
P	33	Impotence	49	79	Moderate	Probably	No	Recovered
34 P	216	Seizure disorder	5 minutes	256	Severe	Definitely not	Yes	Recovered
38 P	177	Asthenia/fatigue	28	204	Moderate	Possibly	No	Recovered
25 P	298	Folliculitis	31	300	Moderate	Possibly	No	Recovered
27 P	Off 1 day							
	173	Myalgia	89	172	Moderate	Possibly	No	Recovered
33 P	Off 3 days							
	89	Syncope	5 minutes	86	Severe	Probably not	Yes	Recovered
33 P	115	Impotence	151	176	Severe	Probably	No	Recovered

* Outcome is as of latter of the day on which study drug was stopped, the patient's last clinic visit, or last contact with the patient.*fin=finasteride, P=placebo.

8.1.4.4.3.2 Laboratory Findings There were no consistent significant clinical laboratory abnormalities or discontinuation due to laboratory adverse events. Special lab tests:

1. Testosterone Mean increases of 18.4% at Month 6 and 16.0% at Month 12 were noted in the finasteride group.

2. PSA Approximately 10% (59/838) of the patients had PSA measurements below the detectable limit of the assay (0.2 ng/mL) at Month 12. There were significant reductions ($p < 0.010$) in PSA for the finasteride group, -0.2 ng/mL at Month 12. The change in placebo group was also significantly different from zero (-0.1 ng/mL). The difference between the two groups was significant ($p<0.001$).

3. LH and FSH No significant changes noted after finasteride treatment

8.1.4.4.3.3 Sexual Function Questionnaire

Table 8.1.4.4.3.3 Summary Statistics for the Domains/Questions of the Sexual Function Questionnaire Months 3, 6, 9, and 12 Intention-to-Treat Population

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

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

Comment There were significant between group differences ($p<0.05$) in the domains on sexual interest and erections as well as in the question on morning erections at all time points (except for erection domain at Month 6), with finasteride group showing less sexual interest, fewer erections and fewer morning erections.

8.1.4.5 Conclusions

This trial has replicated the results of 087 and identical conclusions can be drawn.

8.1.5 Trial#5: Study#092 A Double-Blind, Placebo-Controlled Multicenter Study to Determine the Effect of Finasteride in Men with Androgenetic Alopecia and Frontal Baldness

8.1.5.1 Objective/Rationale

8.1.5.2 Design

8.1.5.3 Protocol

This trial was very similar to the pivotal studies 087 and 089. However, the aim was to supplement those two studies on vertex balding with a study on frontal baldness. Thus, the area of interest for assessment was in the frontal and mid region (for the purpose of this study, "frontal" referred to both frontal and mid-areas of the scalp). Enrollment involved subjects having Norwood-Hamilton classification II, II vertex, IIa, III, or III vertex and active mild-to-moderate frontal and/or mid area hair loss/thinning. The power calculation was based on data obtained in the vertex area, which would be projected to yield 80% power to detect (at the $\alpha= 0.05$ level, 2-sided test) a 4.2% difference between the percent change from baseline in the finasteride 1-mg group and the placebo group for a sample size of 85 patients per treatment group.

Evaluation used the same four instruments for efficacy as in 087 and 089: hair count, patient self-assessment questionnaire, Investigator assessment and global photographic assessment; and for safety: AE, clinical laboratory tests, hormone and PSA levels. Differences in evaluation with the pivotal studies were:

1. For cosmetic reasons, hair count in the frontal or mid-area balding scalp was made on a smaller portion of the scalp: approximately larger than 1 cm^2 instead of 1 inch in diameter (5 cm^2) as in 087 and 089.
2. Patient self-assessment questionnaire removed the question on perception of change in size of the balding spot on vertex: only 6 questions remained.
3. Addition of the use of the Savin scale as an exploratory instrument (see Appendix X). Savin Scale assessments were performed at baseline and at Months 3, 6, 9, and 12. The investigator compared the patient's scalp to a standard set of photographs and separately evaluated the **pattern** and **density** of the frontal, mid, and vertex areas (thus 6 evaluations per subject per session). Lower numbers represent less thinning/balding than higher numbers.
4. Global photographic assessment was by a different panel of dermatologists: **Maria Hordinsky, Irving Katz, and Robert Rietschel.**
5. Similar to 089 but different from 087, no body hair assessment was made.
6. Sexual Function Questionnaire was not administered in this study.

An interim analysis at Month 6 was made.

Comment
1. This study includes both frontal and mid area balding subjects. It is well known that there are regional differences in hair cycle distribution. It is also not clear to what extent DHT exerts its effect on hair growth dynamics in different areas of the scalp. Such pooling of subjects is undesirable. It may be misleading to make a claim on frontal hair loss unless the data can be stratified to show efficacy of finasteride on frontal scalp. The applicant should analyze the data for hair count stratified according to location of the dot tattoo.
2. It is not clear why patterns IIIa, IVa and Va are not included, while II vertex and III vertex were studied.
3. Since this was not a pivotal trial and the study was designed to continue irrespective of the interim analysis, the Applicant did not adjust for p values.

8.1.5.4 Results

8.1.5.4.1 Patient Disposition, Comparability

Investigators:

Investigator	Institution	City and State
Dr. Hilary Baldwin, M.D.	TKL Research, Inc.	Paramus, NJ
Zoe Draelos, M.D.	Piedmont Research Associates	Winston-Salem, NC
Frank Dunlap, M.D.	Argus Research, Inc.	Tucson, AZ
Sewon Kang, M.D.	University of Michigan Medical Center	Ann Arbor, MI
Timothy Kelly, M.D.	Florida Pharmaceutical Research Corp	Palm Harbor, FL
Stephen J. Kraus, M.D.	Georgia Clinical Research Center, Inc	Atlanta, GA
Mark Lebwohl, M.D.	Mt. Sinai Medical Center	New York, NY
James Leyden, M.D.	University of Pennsylvania School of Medicine	Philadelphia, PA
Michael Markou, M.D.	Florida Pharmaceutical Research Corp	Palm Harbor, FL
Bruce Miller, M.D.	Dermatology Associates, P.C.	Portland, OR
David Pariser, M.D.	Virginia Clinical Research, Inc.	Norfolk, VA
Marvin Rapaport, M.D.	UCLA Medical Center	Beverly Hills, CA
Guy Webster, M.D.	College of Medicine, University Hospital, Hershey Med Ctr	Hershey, PA
Diane Thiboutot, M.D.	Thomas Jefferson University	Philadelphia, PA
Peter L.Winters, M.D.	Walker Information	Indianapolis, IN

Distribution of patients at entry by Investigator:

Investigator	Finasteride	Placebo	Total
Baldwin, H.	11	10	21
Draelos, Z.	10	10	20
Dunlap, F.	21	19	40
Kang, S.	9	9	18
Kraus, S.	11	11	22
Lebwohl, M.	13	12	25
Leyden, J.	6	5	11
Winters, P.	14	14	28
Miller, B.	20	19	39
Pariser, D.	8	9	17
Rapaport, M.	10	10	20
Thiboutot, D.	10	10	20
Webster, G.	4	3	7
Markou, M.	10	10	20
Kelly, T.	9	9	18
Total	166	160	326

Completion Status:

		Finasteride 1 mg	Placebo	Total
ENTERED: (age range)*		166	160	326
COMPLETED:		147	138	285
DISCONTINUED:	Total	19	22	41
	Clinical AE	0	1	1
	Laboratory AE	0	1	1
	Other	19	20	39

* All patients were male. ** Forty-one-year-old patients were 40 years old when screened for enrollment into the study.

Patients Discontinued From Therapy:

Reason Discontinued	Finasteride 1 mg (N = 166)	Placebo (N = 160)	Total (N=326)
Clinical AE	0	1	1
Adverse laboratory value	0	1	1
Lost to follow-up	7	6	13
Withdrew	5	5	10
Relocating	2	2	4
Lack of efficacy	2	0	2
Noncompliant, visit schedule	0	3	3
Sexual partner pregnant	2	1	3
Noncompliant	1	3	4
Total discontinued	19	22	41

Comparability of Treatment Groups:

Patient Baseline Comparability

	Finasteride 1 mg	Placebo	Total
Age in Years	(N = 166)	(N = 160)	(N = 326)
Mean	32.5	32.1	32.3
Median	33.0	33.0	33.0
Range			
Race	(N = 166)	(N = 160)	(N = 326)
White	155	154	309
Black	3	3	6
Asian	2	1	3
Hispanic	5	2	7
Other	1	0	1
Number of Patients With Baseline Hamilton Classification			
	(N = 166)	(N = 160)	(N = 326)
Grade II	30	40	70
Grade IIa	8	65	13
Grade II Vertex	30	39	69
Grade III	27	35	62
Grade III Vertex	71	41	112
Hair Count	(N = 166)	(N = 160)	(N = 326)
Mean	210.5	219.3	214.8
SD	48.7	51.6	50.2
Age at Which Patients Began Losing Hair	(N = 160)	(N = 157)	(N = 317)
Mean	25.9	25.0	25.4
SD	7.1	5.1	6.2
Number of Patients With Family History of Baldness (First Degree--Parents and/or Siblings)			
	(N = 164)	(N = 156)	(N = 320)
Yes	132	128	260
No	32	28	60

* All patients were male.

Comments

1. Most of the subjects were Caucasians (95%).
2. There were more patients having Grade III Vertex in Finasteride group (42% vs 25% in placebo).
3. Indeed, the majority of patients in this study (101/166 in finasteride group and 80/160 in placebo group) had II vertex or III vertex patterns. As the questions in the patient self-assessment instrument were not specifically directed at frontal hair loss except for one question (Question 4a), the validity of the questionnaire in this particular study is uncertain. The patient self-assessment data may need reanalysis with exclusion of those whose patterns were primarily vertex.

8.1.5.4.2 Efficacy Parameters

Primary Parameters: Hair Count and Patient's Self-Assessment

Hair Count

Table 8.1.5.4.2A Change From Baseline in Hair Count: ITT Population

	Finasteride 1 mg			Placebo		
	Baseline	**Month 6**	**Change**	**Baseline**	**Month 6**	**Change**
Month 0-6	N=149	N=149	N=149	N=139	N=139	N=139
Mean	212.0	219.3	7.2	218.9	214.8	-4.1
SD	46.5	47.2	20.0	49.0	45.6	17.0
	Baseline	**Month 12**	**Change**	**Baseline**	**Month 12**	**Change**
Month 0-12	N=149	N=149	N=149	N=142	N=142	N=142
Mean	212.0	222.7	10.6	218.7	218.1	-0.7
SD	46.5	47.7	19.2	48.6	48.3	18.0
	Month 6	**Month 12**	**Change**	**Month 6**	**Month 12**	**Change**
Month 6-12	N=140	N=140	N=140	N=128	N=128	N=128
Mean	219.1	222.7	3.6	216.2	220.0	3.7
SD	47.8	48.3	14.8	45.5	48.7	16.1

Least Squares Summary Statistics and 95% Confidence Intervals

	Finasteride 5 mg	Placebo	Difference +	p-Value
Month 0-6 Mean change +	7.5**	-4.1**	11.6	< 0.001
95% confidence interval	(4.7, 10.4)	(-7.0, -1.2)	(7.7, 15.5)	
Month 0-12 Mean change +	9.6**	-2.0	11.6	< 0.001
95% confidence interval	(6.8, 12.5)	(-4.9, 0.9)	(7.7, 15.5)	
Month 6-12 Mean change +	2.2	2.4	-0.2	0.903
95% confidence interval	(-0.3, 4.6)	(-0.1, 4.9)	(-3.6, 3.1)	

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.

Patient Self-Assessment

Table 8.1.5.4.2B Summary of Analysis of the Six Hair Growth Questions at Months 3, 6 and 12

	Month 3					Month 6				
	Mean Scores			95% CI		Mean Scores			95% CI	
Variable	**Fin***	**P.O.**	**Diff**	**for Diff**	**p-value**	**Fin***	**P.O.**	**Diff**	**for Diff**	**p-value**
Global test					0.011					<0.001
Q1	0.5	0.4	0.3	(0.1, 0.5)	0.010	0.7	0.2	0.5	(0.2, 0.4)	<0.001
Q2	0.4	0.4	0.2	(0.0, 0.4)	0.069	0.5	0.2	0.3	(0.1, 0.3)	0.005
Q3	0.1	-0.1	0.5	(0.2, 0.8)	0.001	0.3	-0.2	0.5	(0.2, 0.7)	0.002
Q4a	-0.1	-0.2	0.1	(-0.1, 0.2)	0.248	0.1	-0.2	0.2	(0.1, 0.2)	0.008
Q4b	0.1	-0.2	0.1	(-0.1, 0.2)	0.342	0.3	0.0	0.3	(0.1, 0.3)	0.006
Q4c	0.1	-0.1	0.1	(0.0, 0.3)	0.100	0.2	0.0	0.3	(0.1, 0.3)	0.003
	Month 9					Month 12				
	Mean Scores			95% CI		Mean Scores			95% CI	
Variable	**Fin***	**P.O.**	**'Diff**	**for Diff**	**p-value**	**Fin***	**P.O.**	**Diff**	**for Diff**	**p-value**
Global test					<0.001					<0.001
Q1	0.9	0.2	0.6	(0.4, 0.9)	<0.001	0.8	0.2	0.6	(0.3, 0.9)	<0.001

Q2	0.7	0.2	0.5	(0.3, 0.7)	<0.001	0.7	0.2	0.4	(0.2, 0.7)	<0.001
Q3	0.5	-0.2	0.7	(0.4, 1.0)	<0.001	0.4	-0.2	0.6	(0.3, 0.9)	<0.001
Q4a	0.1	-0.2	0.3	(0.2, 0.5)	<0.001	0.1	-0.2	0.3	(0.1, 0.5)	0.004
Q4b	0.3	-0.1	0.4	(0.2, 0.5)	<0.001	0.3	0.0	0.2	(0.1, 0.4)	0.014
Q4c	0.3	-0.1	0.5	(0.3, 0.7)	<0.001	0.3	0.0	0.3	(0.1, 0.5)	0.007

Question 1--Because of the treatment I have received since the start of the study, the appearance of my hair is:
Question 2--Since the start of the study, how would you describe the growth of your hair?
Question 3--Since the start of the study, how effective do you think this treatment has been in slowing down your hair loss?
Question 4a--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 4b--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 4c--Compared to the beginning of the study, which statement best describes your satisfaction with the appearance of your hair overall?

Table 8.1.5.4.2C Summary Statistics for the Mean Change From Month 6 to Month 12 Intention-to-Treat Population

Question	Finasteride 1 mg	Placebo	Between-Group p-Value
Q1: Appearance of Hair	0.1	0.0	0.303
Q2: Growth of Hair	0.2*	0.0	0.128
Q3: Slowing Down Hair Loss	0.2	0.0	0.257
Q4a: Satisfaction With Front	0.1	0.0	0.500
Q4b: Satisfaction With Top	0.0	0.0	0.945
Q4c: Satisfaction With Hair Overall	0.0	0.0	0.774

*: Significant change from Month 6 at the $p < 0.050$ level, respectively

Table 8.1.5.4.2D Distribution of Scores in Patient Self-Assessment Questionnaire at Month 12

	Finasteride 1 mg							Placebo						
	-3	-2	-1	0	1	2	3	-3	-2	-1	0	1	2	3
Q1	<----------Worsae--------- Same------Better---------->							<----------Worsae--------- Same------Better---------->						
Pt No														
Percent	0	1%	13%	33%	22%	19%	12%	1%	8%	11%	49%	16%	10%	4%
Q2	<----------Decreased--------- No Change------Increased---------->							<----------Decreased--------- No Change------Increased---------->						
Pt No														
Percent	0	1%	13%	37%	26%	19%	4%	1%	4%	17%	44%	25%	8%	1%
Q3		<---Not Effective-			--Effective------->				<---Not Effective-			--Effective------->		
Pt No														
Percent		8%	27%		46%	19%			20%	35%		39%	6%	
Q4a		<---Dissatisfied--- Neutral----Satisfied------->							<---Dissatisfied--- Neutral----Satisfied------->					
Pt No														
Percent		6%	16%	46%	28%	5%			5%	26%	54%	14%	1%	
Q4b		<---Dissatisfied--- Neutral----Satisfied------->							<---Dissatisfied--- Neutral----Satisfied------->					
Pt No														
Percent		3%	17%	38%	33%	9%			1%	25%	46%	24%	3%	
Q4c		<---Dissatisfied--- Neutral----Satisfied------->							<---Dissatisfied--- Neutral----Satisfied------->					
Pt No														
Percent		3%	16%	40%	32%	9%			2%	24%	49%	22%	3%	

Question 1--Because of the treatment I have received since the start of the study, the appearance of my hair is:
Question 2--Since the start of the study, how would you describe the growth of your hair?
Question 3--Since the start of the study, how effective do you think this treatment has been in slowing down your hair loss?
Question 4a--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 4b--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 4c--Compared to the beginning of the study, which statement best describes your satisfaction with the appearance of your hair overall?

Comments

1. There appears to be little additional benefit on **hair counts** between Months 6 and 12. There were nonsignificant net increases in hair count from Month 6 to Month 12 for both the finasteride and placebo groups (mean increases of 2.2 and 2.4, respectively). The difference between the groups in change in hair count from Month 6 to Month 12 was

not significant (p=0.903). This is likely due to an increase in count in the placebo group.
2. The "global test" of treatment effect across all six questions in the Hair Growth Questionnaire showed a significant difference between the two treatments from Month 3 onwards. Although the Applicant contends that the finasteride group showed continuous improvement from Month 6 to Month 12 for four of the six questions which reached significance for one question (Question 2: Growth of Hair), it appears that the treatment effect of finasteride as assessed by the questionnaire peaked at Month 9.
3. More importantly, the question on satisfaction of frontal hairline (Q.4a) never achieved a mean score better than 0.1. However, at Month 12, 33% of the finasteride group had a positive response to this question vs 15% of the placebo group. This effect is significant by the Least Square Means comparison statistics provided by the Applicant, although significance level by CMH for this kind of inter-group comparison would be preferred.
4. As discussed above, the patient self-assessment data needs reanalysis with exclusion of patients with primarily vertex patterns and stratification in relation to frontal vs mid-area hair loss.

Secondary Parameters: Investigator Assessment, Global Photographic Assessment, Savin Scale and Dihydrotestosterone Levels

Investigator Assessment

Table 8.1.5.4.2E Investigator Assessment Intention-to-Treat Population at Months 6 and 12

	Finasteride 1 mg							Placebo						
	-3	-2	-1	0	1	2	3	-3	-2	-1	0	1	2	3
	<----------Decreased--------- No Change------Increased---------->							<----------Decreased--------- No Change------Increased---------->						
Month 6														
Pt No														
Percent	0	0	4%	49%	37%	6%	3%	0	0	8%	61%	27%	3%	1%
Month 12														
Pt No														
Percent	0	0	6%	42%	31%	18%	3%	0	3%	12%	54%	24%	7%	. 0

Least Squares Summary Statistics and 95% Confidence Intervals

	Finasteride 1 mg	Placebo	Difference	p-Value
Month 6				
Mean score +	0.6** (0.5, 0.8)	0.4** (0.3, 0.5)	0.3 (0.1, 0.4)	< 0.001
Month 12				
Mean score +	0.8** (0.7, 0.9)	0.3** (0.2, 0.4)	0.5 (0.3, 0.7)	< 0.001
Between Months 6 and 12				
Mean change +	0.2** (0.0, 0.3)	0.0* (-0.2, 0.1)	0.2 (0.0, 0.4)	0.053

Treatment-by-center interaction: p-value > 0.50 for both Months 6 and 12; + : Adjusted for the treatment and center effects *, ** : Significant change from baseline at the $p < 0.050$ and $p < 0.010$ level, respectively, assuming a baseline score of 0.

Global Photographic Assessment

Table 8.1.5.4.2F Global Photographic Assessment Intention-to-Treat Population at Months 6 and 12

	Finasteride 1 mg							Placebo						
	-3	-2	-1	0	1	2	3	-3	-2	-1	0	1	2	3
	<----------Decreased--------- No Change------Increased---------->							<----------Decreased--------- No Change------Increased---------->						
Month 6														
Pt No														
Percent	0	0	2%	53%	42%	4%	0%	0	0%	3%	81%	16%	0	0
Month 12														
Pt No														
Percent	0	0	1%	62%	34%	4%	0	0	0	7%	85%	7%	0	0

Least Squares Summary Statistics and 95% Confidence Intervals

	Finasteride 1 mg	Placebo	Difference	p-Value
Month 6				
Mean score +	0.5** (0.4, 0.6)	0.1** (0.1, 0.2)	0.3 (0.2, 0.5)	< 0.001
Month 12				
Mean score +	0.4** (0.3, 0.5)	0.0 (-0.1, 0.1)	0.4 (0.3, 0.5)	< 0.001
Between Months 6 and 12				
Mean change +	-0.1 (-0.2, 0.0)	-0.2** (-0.3, -0.1)	0.1 (0.0, 0.2)	0.191

Treatment-by-center interaction: p-value=0.035 at Month 6 and 0.081 at Month 12 but 0.168 between Months 6 and 12; + : Adjusted for the treatment and center effects *, ** : Significant change from baseline at the $p < 0.050$ and $p < 0.010$ level, respectively, assuming a baseline score of 0.

Comments

1. There are two statistical problems in the analysis: (a) 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. (b) Rescaling with center being zero for "no change" in the patient self-assessment questionnaire magnifies the treatment effect in question 3 because the original question gave a one grade change from "somewhat effective" to "not very effective" but after rescaling this as +1 and -1, the distance between these two grades is doubled. As the treatment effect mostly lie within these two grades, discrimination between the effects of finasteride and placebo become magnified.
2. Substantial placebo effect was seen with Investigator Assessment.
3. Global Photographic Assessment showed deterioration between Months 6 and 12.

Table 8.1.5.4.2G Summary Statistics of the Savin Scale Assessments Between-Group Difference + (95% Confidence Intervals for Differences and Least Square Statistics for Each Group)

Variable	Month 3	Month 6	Month 9	Month 12
Between-Group Differences:				
Frontal density	-0.1 (-0.3, 0.0)	-0.3* (-0.4, -0.1)	-0.5**(-0.6, -0.3)	-0.5** (-0.7, -0.3)
Frontal pattern	-0.2* (-0.3, 0.0)	-0.2* (-0.4, 0.0)	-0.3**(-0.5, -0.1)	-0.3** (-0.5, -0.1)
Mid-area density	0.0 (-0.2, 0.2)	-0.2* (-0.4, 0.0)	-0.3**(-0.5, -0.1)	-0.3** (-0.5, -0.1)
Mid-area pattern	-0.1 (-0.2, 0.0)	-0.1 (-0.3, 0.0)	-0.2**(-0.4, -0.1)	-0.2**(-0.4, -0.1)
Vertex density	-0.1 (-0.3, 0.0)	-0.4**(-0.6, -0.2)	-0.5**(-0.7, -0.3)	-0.4** (-0.6, -0.3)
Vertex pattern	-0.1 (-0.3, 0.0	-0.4**(-0.5, -0.2)	-0.4**(-0.6, -0.2)	-0.4** (-0.6, -0.2)

Least Squares Summary Statistics for Each Group:

	Finasteride				Placebo			
Variable	Mth 3	Mth 6	Mth 9	Mth 12	Mth 3	Mth 6	Mth 9	Mth 12
Frontal density	-0.2**	-0.4**	-0.6**	-0.7**	-0.1	-0.2*	-0.2*	-0.2**
Frontal pattern	-0.2*	-0.3**	-0.3**	-0.2**	0.0	-0.1	0.0	0.1
Mid-area density	0.0	-0.3**	-0.4**	-0.4**	0.0	-0.1	-0.1	-0.1*
Mid-area pattern	0.0	-0.1	-0.1	-0.1	0.1	0.0	0.1*	0.1*
Vertex density	-0.2*	-0.5**	-0.6**	-0.6**	0.0	-0.1	-0.2*	-0.2*
Vertex pattern	0.0	-0.4**	-0.3**	-0.4**	0.1	0.0	0.1	0.0

+: Adjusted for treatment and center effects *, **: Within-group p-value at the $p < 0.050$ and $p < 0.010$ level, respectively

Comments

1. Substantial placebo effect was observed at Month 12 especially with assessment of density.
2. The Savin scale measures hair loss by using higher scores for balding. Results using this scale indicate significant differences between treatment groups from Month 9 onwards for all 3 areas in pattern and density.
3. However, the frontal "pattern" for the finasteride group at Month 12 was less

favorable as compared to earlier time points (Months 6 and 9) despite improvement in density. It is possible that different evaluations were looking at types of hairs of different cosmetic importance. This issue cannot be resolved at the present stage. 4. Yet, the frontal "pattern" was the first to show significant difference between treatments (Month 3) and the difference was maintained throughout the study, possibly because of the continued hair loss in the placebo group.

Dihydrotestosterone Levels There was a decrease of 61% in DHT levels at Month 6 and 64% at Month 12 in the finasteride group but inconsistent small changes in the placebo group (6% at Month 6 and -1% at Month 12).

8.1.5.4.3 Safety Comparison

8.1.5.4.3.1 Adverse Events

Details of AE incidences are given in Appendix V.

Table 8.1.5.4.3.1A Clinical Adverse Experience Summary--Patient Count (%)

	Finasteride (N = 166)	Placebo (N = 160)
one or more AE	103 (62.0)	94 (58.7)
with drug-related AE	7 (4.2)	10 (6.3)
withdrawn from therapy due to an AE	0	1 (0.6)
due to a sexual AE	0	0
due to drug-related AE	0	1 (0.6)
due to a drug-related sexual AE	0	0
due to a serious AE	0	0
due to a serious drug-related AE	0	0

Table 8.1.5.4.3.1B Sexual Adverse Experiences--Patient Count (%)

	Sexual Adverse Experiences--Patient Count (%)		Drug-related Sexual AE-- Count (%)	
	Finasteride (N = 166)	Placebo (N = 160)	Finasteride (N = 166)	Placebo (N = 160)
one or more sexual AE	3 (1.8)	3 (1.9)	3 (1.8)	3 (1.9)
Libido decreased	2 (1.2)	2 (1.3)	2 (1.2)	2 (1.3)
Ejaculation disorder	0	1 (0.6)	0	1 (0.6)
Impotence	1 (0.6)	0	1 (0.6)	0

Table 8.1.5.4.3.1C Serious Clinical Adverse Experiences

No	Age/drug	Day of Onset	AE	Duration (Days)	Intensity	Drug Relationship	Discon-tinuation	Outcome†
	31/fin	50	Infection, urinary tract	3	Mod	Probably not	No	Recovered
	30/fin	132	Pain, chest	7 hr	Mild	Probably not	No	Recovered
	39/fin	197	Neoplasm, skin, malignant	31	Mild	Definitely not	No	Recovered
	36/P	362	Dehydration	4	Severe	Definitely not	No	Recovered
	39/P	272	Neoplasm, skin, malignant	1	Mild	Definitely not	No	Recovered
	39/P	64	Cellulitis	35	Severe	Definitely not	No	Recovered

fin=finasteride, P=placebo

Patients Discontinued Due to Adverse Experiences

No finasteride patients and one placebo patient (0.6%) discontinued therapy due to a clinical AE (headache). One patient given placebo discontinued due to elevation of ALT (64 mU/mL; normal 5-25mU/mL).

8.1.5.4.3.2 Laboratory Findings

There were no consistent significant clinical

laboratory abnormalities. Special lab tests:
1. Testosterone Mean increases of 14.2% at Month 6 and 10.6% at Month 12 were noted in the finasteride group.

2. PSA Approximately 7% (21/302) of the patients had PSA measurements below the detectable limit of the assay (0.2 ng/mL) at Month 12. There were significant reductions ($p < 0.010$) in PSA for the finasteride group, -0.3 and -0.2 ng/mL at Months 6 and 12 respectively. The differences between the two treatment groups were significant ($p<0.001$) at both time points.

3. LH and FSH No significant differences between treatment groups at Months 6 or 12.

8.1.5.5 Conclusions
(1) Twelve months of therapy with finasteride 1 mg/d increased net scalp hair counts in men with MPB in the frontal/mid area.
(2) Twelve months of therapy with finasteride 1 mg/d led to cosmetic improvement in men with MPB in the frontal/mid area as determined by patient self-assessment of treatment efficacy and satisfaction with appearance of scalp hair, investigator clinical assessment, and global photographic assessment of scalp hair growth.
(3) In men with MPB in the frontal/mid area, significant improvements were seen for some endpoints as early as Month 3: self-assessment, Investigator assessment and Savin's frontal "pattern" assessment.
(4) Although improvement was shown in men with frontal/mid area hair loss, it remains to be demonstrated that treatment with finasteride for 12 months improves cosmetic coverage in the frontal area specifically, by stratification of responses with distinction of patients having frontal vs mid-area hair loss for the primary variables: hair count changes and patient self-assessment.
(5) Treatment with placebo for 12 months was associated with net decrease in hair count, perceived deterioration and less satisfaction in frontal hairline in patient assessment.
(6) The treatment effect of finasteride on the primary variables in the absence of Neutrogena T-gel shampoo has not been clarified.
(7) Treatment with finasteride 1 mg/d appears to be generally well tolerated by young men with frontal/mid area hair loss.

9. Overview of Efficacy
The principal focus of this overview section is the 1-year, placebo-controlled, multicenter U.S. and International phase 3 Pivotal studies (087 and 089). Their similar design and measures of efficacy and safety allow pooling of the data to more accurately estimate the treatment effects of finasteride on common endpoints. Relevant data from

the Frontal Hair Loss study (092) and phase 2 studies (047 and 081) will also be provided, as appropriate, to address specific aspects of dose-response, maintenance of efficacy beyond 1 year of treatment, consistency of effect among studies, and effect of finasteride in patients with hair loss other than at the vertex.

Table 9 Summary of Efficacy Studies

Study:	Phase 2 Pilot 047	Phase 2 Dose Range 081	Phase 3 Frontal Hair Loss 092	Phase 3 U.S. Pivotal 087	Phase 3 International Pivotal 089
Number randomized	227	466	326	933	620
Treatment	Pbo (116)	Pbo (117)	Pbo (160)	Pbo (462)	Pbo (312)
(N per group)	Fin 5 mg (111)	Fin 0.01 mg (117) Fin 0.2 mg (115) Fin 1 mg (117)	Fin 1 mg (166)	Fin 1 mg (471)	Fin 1 mg (308)
Age range					
mean	30	30	31	32	34
began losing hair (mean)	23	23	25	25	24
Baseline hair count (mean)**	910	915	215	860	920
Hair loss pattern*					
Grade II			70 (22%)		
Grade II a			13 (4%)		
Grade II vertex			69 (21%)	126 (14%)	115 (19%)
Grade III			62 (19%)		
Grade III vertex	158 (70%)	254 (55%)	112 (34%)	279 (30%)	151 (24%)
Grade IV	69 (30%)	212 (46%)		253 (27%)	167 (27%)
Grade V				275 (29%)	187 (30%)
Primary efficacy parameter(s)	Hair Count	Hair Count	Hair Count	Hair Count Patient Self-	Hair Count Patient Self-
Secondary efficacy parameters	Patient Self- Investigator Global Photo	Patient Self- Investigator Global Photo	Patient Self- Investigator Global Photo Savin Scale	Investigator Global Photo Hair Loss in Pbo Group	Investigator Global Photo Hair Loss in Pbo Group

* Hair loss pattern=Classifications of the modified Norwood/Hamilton Scale; Pbo=placebo, Fin=finasteride, Patient Self-=patient self-assessment questionnaire, Investigator=investigator assessment, Global Photo=global photographic assessment.
**Hair counts in a 1 inch diameter circular area in vertex scalp, except in 092, which was in a 1 sq cm area of the frontal/mid scalp.

9.1 Preliminary Pharmacodynamic Studies

9.1.1 Scalp DHT Studies (031 and 065)

A study evaluating the biochemical efficacy of finasteride on scalp androgens in balding men was performed early in development of this drug product (031). Mean baseline balding scalp DHT levels (2.14 ng/gm) were higher than those in hairy scalp (1.22 ng/gm) in the same subject (p=0.002). Treatment with finasteride 5 mg/day for 4 weeks produced significant mean reductions from baseline in balding scalp DHT compared with placebo (-34% vs +13%). Subsequent to this biochemical evidence of a local effect, a successful phase 2 pilot study (047) established the proof of concept for the efficacy of finasteride in the treatment of male pattern hair loss. Therefore, a second biochemical study evaluating the effects of finasteride on scalp DHT across a dose range from mg/day (065) was done and demonstrated that doses from 0.2 to

5 mg appeared to maximally suppress *both* (balding) scalp and serum DHT in balding men.

Table 9.1.1 Summary of Findings in Pharmacodynamic Dose-Ranging Study 065

Treatment Group	Day 42 Mean Change from Baseline (%)			Mean Level (ng/mL) of Semen Finasteride (D42)	Proportion of Patients with Semen Finasteride ≥0.1 mg/mL
	Scalp DHT	Scalp T	Serum DHT		
Placebo	-4	+12	+10	not done	not applicable
0.01 mg	-18	+13	+3	not done	not applicable
0.05 mg	-52	+46	-47	not done	not applicable
0.2 mg	-54	+71	-67	0.07	5/31 (16.1%)
1.0 mg	-58	+83	-71	0.26	14/35 (40.0%)
5.0 mg	-65	+66	-70	1.61	30/35 (85.7%)

Comment

1. The dose 0.05 mg/d also suppressed both scalp and serum DHT but the suppression in serum was significantly less than those for the 0.2, 1 and 5 mg doses even though suppression of scalp DHT level was comparable to those of other doses (see Table above). There was a dose-dependent detection of finasteride in semen: the 5 mg/d dose was associated with detectable levels of finasteride (>0.1 ng/mL) in most subjects.
2. Although it is difficult to make comparison across studies, it is noted that the mean reduction in scalp DHT was -34% by 4 weeks in Study 031 and -69% by 6 weeks in Study 065.

9.1.2 Pilot Efficacy Study (047) [See Section 8.1.1]

This study (047) involved placebo or finasteride 5 mg/d treatment in men 18 to 36 years of age with moderate vertex scalp hair loss. At the end of 12 months, patients had a hair count change of 93.2 and -20.1 for finasteride and placebo treatment groups respectively. Patients' self-assessment indicated significant differences between treatment arms for all seven pertinent questions on hair growth/loss and satisfaction favoring finasteride. This was further confirmed by data on Investigator assessment (patients assessed as showing positive hair growth: finasteride 77%, placebo 46%) and global photographic assessment (patients assessed as showing positive growth: finasteride 48%, placebo 3%).

9.2 Dose-Ranging Study (081) [See Section 8.1.2]

To fully characterize the dose-response relationship below 5 mg/d, doses of finasteride 1, 0.2, and 0.01 mg for 6 months were selected in a phase 2 Dose-Range study (081). The 1-mg dose was found to be optimal, based on superiority in hair counts and global photographic assessment and significant improvement compared with placebo for each of the seven pertinent questions in the hair growth questionnaire as early as Month 6 ($p<0.050$). The efficacy of the 1-mg dose was similar to that of the 5-mg dose used in the Pilot study (047), while the efficacy of the 0.2-mg dose was suboptimal. In this study, safety profiles of the 1 mg and 0.2 mg doses were comparable, and also by historic comparison, similar to that of the 5 mg dose. Thus, the 1 mg/d dose was chosen for further development.

9.3 Phase 3 Studies [See Sections 8.1.3 to 8.1.5]