9.3.1 Comparison of Protocol Designs

Two trials on hair loss on vertex (087 and 089) and one on the "frontal" area (092) constitute the phase 3 program. The studies on hair loss on vertex were the pivotal trials. The phase 2 Pilot and Dose-Range studies and these phase 3 studies were performed as double-blind, placebo-controlled, randomized, parallel-group, multicenter studies as outlined in Table 9. All used similar techniques to count scalp hair and obtain investigator and global photographic assessments of scalp hair. The hair growth questionnaire consisted of seven questions: four on treatment efficacy and three on satisfaction. In the frontal hair loss study, 092, one of the seven questions (change in size of the bald spot) was deleted and the target area for hair count was smaller (1 cm^2) than that used in the pivotal studies (087 and 089: 1-inch diameter circle, or 5.1 cm^2).

9.3.2 Baseline Comparability Between Studies

The pivotal studies 087 and 089 had patients showing similar demographic characteristics (Table 9). They were also similar to those in two phase 2 (047 and 081) and one other phase 3 (092) studies except for the degree and pattern of baldness, which were defined by inclusion criteria.

9.3.3 Pivotal Studies (087 and 089): Hair Count

As expected, there was a significant ($p < 0.010$) net decrease from baseline in hair count at Months 6 and 12 in patients treated with placebo in each pivotal study and in the combined analysis. At Month 12, the net decrease from baseline in hair count was 21.1 hairs in the combined analysis (mean baseline hair count = 877). This decrease represents a 2.7% loss of hair at the leading edge of the thinning area and is consistent with the natural history of male pattern hair loss. **In the combined analysis, at Month 12, 58% (390/672) of placebo patients demonstrated hair loss by a net decrease in hair count compared with only 14% (92/679) of finasteride patients.**

Table 9.3.3 Effect of Finasteride on Hair Count - Mean Changes From Baseline at Months 6 and 12 and From Month 6 to Month 12 Phase 3: Pivotal Studies Individually and Combined ITT Population

	Finasteride		Placebo		Between-Group Study
	N	Mean	N	Mean	Difference
Month 6					
087	402	69.5**	386	-13.6**	83.1 ###
089	266	58.4**	275	-22.9**	81.3 ###
Combined	668	62.4**	661	-20.1**	82.5 ###
Month 12					
087	407	91.3**	395	-15.0**	106.3 ###
087	272	83.7**	277	-23.7**	107.3 ###
Combined	679	86.0**	672	-21.1**	107.1 ###
Month 6 to Month 12					
087	377	23.5 ††	359	-1.1	24.5 ###
089	240	24.9 ††	249	-3.3	28.2 ###
Combined	617	25.1 ††	608	-0.3	25.4 ###

*,** Significant change from baseline at the $p < 0.050$ and $p < 0.010$ level, respectively #,##,### Significant between-group difference at the $p < 0.050$, $p < 0.010$ and $p < 0.001$ level, respectively †,†† Significant change from Month 6 at the $p < 0.050$ and $p < 0.010$ level, respectively

9.3.4 Pivotal Studies (087 and 089): Patient Self-Assessment

The primary analysis of patient self-assessment by the Applicant was the global test across all hair growth questions at Month 12. For the phase 3 pivotal studies, this global test showed significantly greater efficacy for the finasteride group vs placebo group at all time points, beginning with Month 3 (p=0.035 for 087 and <0.001 for 089) and persisting through Month 12 (p<0.001 in Months 6, 9 and 12 for both studies). When the studies were combined, improvement for the finasteride group was also seen at all times (p<0.001). Analysis for individual questions are shown below in Tables 9.3.4.

Table 9.3.4A Effects of Finasteride on Patient Self-Assessment - Summary Statistics at Month 12: Individual Phase 3 Pivotal Studies ITT Population

	087		089		Combined	
Question	Finasteride	Placebo	Finasteride	Placebo	Finasteride	Placebo
N	452	443-444	298-299	304-305	750-751	747-749
Q1: Bald Spot Getting Smaller	0.3**	-0.3**	0.1	-0.4**	0.2**	-0.4**
Q2: Appearance of Hair	1.0**	0.3**	0.8**	0.2**	0.9**	0.3**
Q3: Growth of Hair	0.8**	0.3**	0.7**	0.1	0.7**	0.2**
Q4: Slowing Down Hair Loss	0.6**	-0.1	0.2*	-0.4**	0.4**	-0.2**
Q5a: Satisfaction With Frontal Hairline	0.0	-0.2**	0.0	-0.4**	0.0	-0.3**
Q5b: Satisfaction With Hair on Top	0.2**	-0.2**	0.2**	-0.3**	0.2**	-0.2**
Q5c: Satisfaction With Hair Overall	0.2**	-0.1*	0.2**	-0.2**	0.2**	-0.2**

*,** Significant change from baseline at the $p < 0.050$ and $p < 0.010$ level, respectively, assuming baseline score=0. Between group comparisons gave p-values of <0.001 in all cases.

Table 9.3.4B Effects of Finasteride on Patient Self-Assessment - Mean Change From Month 6 to Month 12 Phase 3 Pivotal Studies: Individually and Combined Intention-to-Treat Population

	087			089			Combined		
Question	Fin	Placebo	Bet-Gp	Fin	Placebo	Bet-Gp	Fin	Placebo	Bet-Gp
N	380-386	368-375	p-value	242-248	242-250	p-value	623-634	613-625	p-value
Q1: Bald Spot Getting Smaller	0.2**	-0.1	<0.001	0.0	-0.1*	0.056	0.1*	-0.1**	<0.001
Q2: Appearance of Hair	0.3**	-0.1**	<0.001	0.1	-0.2**	<0.001	0.2**	-0.2**	<0.001
Q3: Growth of Hair	0.2**	-0.1**	<0.001	0.1*	-0.2**	<0.001	0.2**	-0.2**	<0.001
Q4: Slowing Down Hair Loss	0.2**	-0.1	0.007	0.0	-0.2**	0.091	0.1*	-0.1	0.002
Q5a: Satisfaction With Frontal Hairline	0.1*	-0.1	0.012	0.0	-0.1*	0.035	0.0	-0.1**	0.001
Q5b: Satisfaction With Hair on Top	0.1**	0.0	0.082	0.0	-0.1*	0.030	0.1*	0.0	0.008
Q5c: Satisfaction With Hair Overall	0.1**	0.0	0.061	0.0	-0.1*	0.059	0.1*	0.0	0.006

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

Table 9.3.4C Effects of Finasteride on Patient Self-Assessment - Percent of Patients With a Positive Self-Assessment at Month 12 Phase 3 Pivotal Studies: Individually and Combined ITT Population

	087		089		Combined	
	Fin	Placebo	Fin	Placebo	Fin	Placebo
Q1: Bald Spot Getting Smaller	44	22	39	19	42	21
Q2: Appearance of hair	60	36	54	32	58	35
Q3: Growth of Hair	58	38	52	26	56	33
Q4: Slowing Down Hair Loss	73	51	60	37	68	45
Q5a: Satisfaction With Frontal Hairline	29	17	28	16	29	17
Q5b: Satisfaction With Hair on Top	35	21	37	18	36	20
Q5c: Satisfaction With Hair Overall	40	23	37	20	39	22

9.3.5 Pivotal Studies (087 and 089): Investigator Clinical Assessment

Table 9.3.5A Effect of Finasteride on Investigator Assessment - Mean Scores and Changes from Month 3 to Month 12: Phase 3 Pivotal Studies Individually and Combined ITT Population

		087			089			Combined		
		Fin	Placebo	p	Fin	Placebo	p	Fin	Placebo	p
Month 3	N	441	433		297	299		738	732	
	Mean Score	0.6**	0.4**	0.2 ###	0.6**	0.4**	0.2 ###	0.6**	0.4**	0.2 ###
Month 6	N	451	443		297	302		748	745	
	Mean Score	0.9**	0.5**	0.4 ###	0.7**	0.5**	0.3 ###	0.8**	0.5**	0.3 ###
Month 9	N	451	444		297	303		748	747	
	Mean Score	1.0**	0.5**	0.5 ###	0.7**	0.3**	0.4 ###	0.9**	0.4**	0.5 ###
Month 12	N	451	444		297	303		748	747	
	Mean Score	1.1**	0.4**	0.7 ###	0.7**	0.2**	0.5 ###	1.0**	0.3**	0.6 ###
Change from Month 6 to Month 12										
N		392	371		257	267		748	745	
Change in Mean Score		0.2 ††	-0.1 †	0.3 ###	0.0	-0.3 ††	0.3 ###	0.1 ††	-0.2 ††	0.3 ###

*,** Significant change from baseline at the $p < 0.050$ and $p < 0.010$ level, respectively, assuming baseline score=0. #,##,### Significant between-group difference at the $p < 0.050$, $p < 0.010$, and $p < 0.001$ level, respectively †, †† Significant change from Month 6 at the $p < 0.050$ and $p < 0.010$ level, respectively.

Table 9.3.5B Effect of Finasteride on Investigator Assessment - Percent of Patients With a Positive Investigator Assessment Phase 3 Pivotal Studies: Individually and Combined Intention-to-Treat Population

	Percent Positive					
	087		089		Combined	
	Fin	Placebo	Fin	Placebo	Fin	Placebo
Month 3	50	40	43	31	47	36
Month 6	68	48	52	37	61	44
Month 9	72	49	55	31	65	42
Month 12	73	45	54	26	65	37

Comment Substantial placebo effect was shown with Investigator assessment.

9.3.6 Pivotal Studies (087 and 089): Global Photographic Assessment

Table 9.3.6A Effect of Finasteride on Global Photographic Assessment - Mean Scores and Changes from Month 6 to Month 12 Phase 3 Pivotal Studies: Individually and Combined ITT Population

		087			089			Combined		
		Fin	Placebo	p	Fin	Placebo	p	Fin	Placebo	p
Month 6	N	434	414		279	290		713	704	
	Mean Score	0.6**	0.1**	0.5 ###	0.6**	0.1**	0.5 ###	0.6**	0.1**	0.5 ###
Month 12	N	435	417		285	292		720	709	
	Mean Score	0.7 **	0.0	0.7 ###	0.6 **	0.0	0.6 ###	0.7 **	0.0	0.6 ###
Change from Month 6 to Month 12										
N		380	363		245	261		631	624	
Change in Mean Score from Month 6		0.1 ††	-0.1 ††	0.2 ###	0.0	-0.2 ††	0.1 #	0.0	-0.1 ††	0.2 ###

*,** Significant change from baseline at the $p < 0.050$ and $p < 0.010$ level, respectively, assuming baseline score=0. #,##,### Significant between-group difference at the $p < 0.050$, $p < 0.010$, and $p < 0.001$ level, respectively †, †† Significant change from Month 6 at the $p < 0.050$ and $p < 0.010$ level, respectively.

Table 9.3.6B Effect of Finasteride on Global Photographic Assessment - Percent of Patients With a Positive Global Photographic Assessment Phase 3 Pivotal Studies: Individually and Combined Intention-to-Treat Population

	Percent Positive					
	087		089		Combined	
	Fin	Placebo	Fin	Placebo	Fin	Placebo
Month 6	46	11	47	13	46	12
Month 12	50	8	44	6	48	7

Comment Placebo consistently showed hair loss vs baseline count with Global photographic assessment.

9.4 Supportive Phase 3 Study on Frontal Hair Loss (092) [See Section 8.1.5]

9.4.1 Comparison of Protocol Designs with Other Efficacy Studies

This has been discussed in Sections 9.3.1 and 9.3.2 and shown in Table 9. The uniqueness of this study is in (1) its enrollment criterion with inclusion of frontal hair loss pattern, (2) one of the seven questions (change in size of the bald spot) being deleted from the self-assessment questionnaire, (3) the target area for hair count being smaller (1 cm^2) and (4) an additional assessment with the Savin scale. However, as shown in Table 9, over half of the patients (54%) had vertex patterns of balding. In addition, the study defined frontal hair loss as involving frontal and mid areas. Therefore, caution must be exercised in the interpretation of the data in this study.

9.4.2 Results on Efficacy

These have been presented in Section 8 and are summarized here:

Table 9.4.2 Efficacy at Months 6 and 12 Frontal Hair Loss Study Intention-to-Treat Population

	Month 6			Month 12		
	Fin	Placebo	p	Fin	Placebo	p
Hair Count in 1 cm^2 area (Mean Change From Baseline)	7.5**	-4.1**	<0.001	9.6**	-2.0	<0.001
(Finasteride N = 149; Placebo N = 139 to 142)						
Patient Self-Assessment: Global Test			<0.001			<0.001
(Finasteride N = 156; Placebo N = 153)						
Percent of patients with positive self-assessment (Mean score)						
Q1: Appearance of Hair	49 (0.7**)	27 (0.2*)		53 (0.8**)	30 (0.2*)	
Q2: Growth of Hair	49 (0.5**)	27 (0.2*)		49 (0.7**)	34 (0.2*)	
Q3: Slowing Down Hair Loss	60 (0.3*)	44 (-0.2)		65 (0.4**)	45 (-0.2*)	
Q 4a: Satisfaction With Frontal Hairline	29 (0.1)	12 (-0.2**)		33 (0.1)	16 (-0.2**)	
Q 4b: Satisfaction With Hair on Top	35 (0.3**)	22 (0.0)		42 (0.3**)	27 (0.0)	
Q 4c: Satisfaction With Hair Overall	38 (0.2**)	19 (0.0)		341 (0.3**)	25 (0)	
Investigator Assessment						
(Finasteride N = 156; Placebo N = 153 to 154)						
Mean Score:	0.6**	0.4**	<0.001	0.8**	0.3**	<0.001
Percent of patients with positive investigator assessment:	47	31		52	31	
Global Photographic Assessment						
(Finasteride N = 154 to 155; Placebo N = 150)						
Mean Score:	0.5**	0.1**	<0.001	0.4**	0.0	<0.001
Percent of patients with positive global photographic assessment:	45	16		37	7	

*,** Significant change from baseline at the $p < 0.050$ and $p < 0.010$ level, respectively. For subjective assessments (patient self-assessment, Investigator assessment and global photographic assessment), baseline scores are assumed to be 0.

Using the Savin scale, patients demonstrated significant between-group differences in mean scores in both hair pattern and density in all areas of the scalp at Months 9 and 12: "frontal", mid-area and vertex ($p<0.01$).

9.5 Effect on Serum Dihydrotestosterone

Treatment with finasteride leads to a rapid, marked reduction of serum DHT, which is sustained with 1 mg/d dosing ($p<0.010$). The median percent decrease in DHT in the

finasteride group at Month 12 was between 67.6 and 69.6 in Studies 087, 089, 092 and with all three studies combined. The differences between finasteride and placebo groups were significant (p<0.001).

9.6 Onset of Clinical Efficacy

In the three Phase 3 studies, significant efficacy was evident within 3 months in both patient self-assessment and investigator assessment, the only two efficacy measures obtained at this first efficacy time point (Month 3). Although hair counts were not obtained at Month 3 in the phase 3 studies, hair count data after 3 months of therapy are available from the phase 2 Dose-Range study (081), in which patients treated with finasteride 1 mg/day had a significant increase of 83.9 hairs at Month 3 vs a decrease of 7.5 for placebo patients (p<0.001). This increase was associated with significant improvements in patient self-assessment (p<0.050, global test) and investigator assessment compared with placebo (p<0.050) (Tables 9.6A and B and Section 9.3.5).

Table 9.6A Effects of Finasteride on Efficacy Endpoints at Month 3 Phase 2 Dose-Range and Phase 3 Studies

Study	Hair Count Difference From Placebo	Patient Self-Assessment Global Test p-Value	Investigator Assessment Difference From Placebo	Global Photo Assessment Difference From Placebo
081†	91.4***	0.037	0.2*	0.1 +
087	ND	0.035	0.2***	ND
089	ND	<0.001	0.2***	ND
092	ND	0.011	0.2**	ND

† Results for the finasteride 1-mg and placebo groups *,**,*** Significant between-group difference at the $p < 0.050$, $p < 0.010$, and $p < 0.001$ level, respectively. For subjective assessments (patient self-assessment, Investigator assessment and global photographic assessment), baseline scores are assumed to be 0. + p = 0.074 ND = not done

Table 9.6B Summary of Analysis of the Seven Hair Growth Questions at Months 3, 6, 9 and 12

	Month 3			Month 6			Month 9			Month 12		
	Mean Scores			Mean Scores			Mean Scores			Mean Scores		
Variable	Fin*	PBO		Fin*	PBO		Fin*	PBO		Fin*	PBO	
N	733-739	719-730	p-value	750-751	745-748	p-value	750-751	747-749	p-value	750-751	747-749	p-value
Q1	0.0	-0.3**	<0.001	0.1**	-0.3**	<0.001	0.2**	-0.3**	<0.001	0.2**	-0.4**	<0.001
Q2	0.6**	0.4**	<0.001	0.8**	0.4**	<0.001	0.9**	0.4**	<0.001	0.9**	0.3**	<0.001
Q3	0.5**	0.3**	0.008	0.6**	0.4**	<0.001	0.7**	0.3**	<0.001	0.7**	0.2**	<0.001
Q4	0.1	-0.2**	<0.001	0.3**	-0.1**	<0.001	0.5**	-0.2**	<0.001	0.4**	-0.2**	<0.001
Q5a	-0.1**	-0.2**	0.055	0.0	-0.2**	<0.001	0.0	-0.3**	<0.001	0.0	-0.3**	<0.001
Q5b	0.0	-0.2**	0.002	0.1**	-0.2**	<0.001	0.2**	-0.2**	<0.001	0.2**	-0.2**	<0.001
Q5c	0.0	-0.1**	0.022	0.1**	-0.1**	<0.001	0.2**	-0.2**	<0.001	0.2**	-0.2**	<0.001

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

Therefore, based on the Phase 2 and Phase 3 data, finasteride therapy may produce an increase in scalp hair count leading to significant cosmetic improvement within 3 months. These improvements may further increase through the first year of treatment.

9.7 Extension Studies

All five efficacy studies are in extension phases. Data for up to 3 years of treatment with finasteride in 047 and 081 were presented in the original submission (see Section 8). An Executive Summary of the combined data for 087 and 089 as well as those for 081 up to 24 months was submitted on 8/11/97 and more details updating 081 extension to 36 months and 092 to 24 months have been subsequently provided (submissions of 9/26/97 and 10/10/97).

Comment Patients entering into extension studies are a self-selected group who have not discontinued due to adverse events. In addition, the Applicant acknowledges that they generally had better response to finasteride than those who did not enter. Thus, data from these studies need to be studied with caution.

9.7.1 Extension from Pilot Study 047

In the original submission, the first 3-year experience from Study 047 showed treatment with finasteride 5 mg/d for 18 months followed by 1 mg/day for 18 months gave near **maximal increase in hair count by Month 12.** There was some fluctuation in hair count after this time point, with a **decrease of 13.4 hairs from Month 18 to Month 36.** Despite these fluctuations in hair count, maintenance of effect through 4 years of treatment was observed based on patient self-assessment, investigator clinical assessment, and global photographic assessment.

Table 9.7.1 Effects of Finasteride † on Efficacy Endpoints Efficacy at Months 12, 18, 24, 30, 36 and 48 in Phase 2 Pilot Open-Extension Study † (047-10 and 047-20)

	Months					
Endpoint	12	18	24	30	36	48
Hair Count (Mean Change From Baseline) (N = 33-56)	98.5**	80.5**	98.8**	62.1**	69.8**	74.4**
Patient Self-Assessment (N = 34-69) Mean Score:						
Q25: Bald Spot Getting Smaller	0.2	0.5**	0.6**	0.8**	0.8**	0.7**
Q29: Appearance of Hair	1.2**	1.5**	1.9**	2.0**	1.8**	2.0**
Q30: Growth of Hair	1.0**	1.4**	1.7**	1.8**	1.6**	1.7**
Q31: Slowing Down Hair Loss	0.9**	1.2**	1.5**	1.5**	1.6**	1.5**
Q32a: Satisfaction With Frontal Hairline	0.0	0.1	0.4*	0.2	0.2	0.5**
Q32b: Satisfaction With Hair on Top	0.3*	0.6**	0.8**	0.6**	0.6**	0.9**
Q32c: Satisfaction With Hair Overall	0.5**	0.5**	0.8**	0.6**	0.7**	0.7**
Investigator Assessment (N = 35-67) Mean Score:	1.6**	1.5**	1.6**	1.7**	1.6**	2.0**
Global Photographic Assessment (N = 34-61) Mean Score:	0.7**	1.0**	1.1**	1.0**	1.2**	0.8**

*, ** Significant change from baseline at the $p < 0.050$ and $p < 0.010$ level, respectively, assuming baseline=0 for the subjective assessments.
† Finasteride 5 mg/day for 18 months followed by finasteride 1 mg/day for 18 months for all patients who entered the open-extension study.

Comment The Applicant tried to explain the lack of additional response beyond Month 12 by arguing that this was likely due to normal biological variability combined with effects on hair dynamics due to therapy with finasteride, which appeared to recruit the majority of newly emerging hairs within 3 months of initiating therapy, thereby synchronizing their growth phase. Given the average anagen phase duration of approximately 3 years for scalp hair, a new hair count plateau above baseline would, therefore, be expected within 3 years of initiating therapy, and this plateau appeared to be reached in the extension to the Pilot study between Months 30 and 36. However, it is quite possible that, the follicles that were responsive had responded by Month 12 and no additional follicles could be recruited through the degree of DHT decrease provide by finasteride (60-70%).

9.7.2 Extension from Dose-Ranging Study 081

Results from patients using finasteride 1 mg/d in the extension phase are given in Tables 9.7.2A and 9.7.2B.

Table 9.7.2A Effects of Finasteride † on Efficacy Endpoints - Efficacy at Months 12 to 36 in Phase 2 Dose-Range Open-Extension Study (081-10 and 081-20)

	Months			
Endpoint	12	18	24	36
Hair Count (Mean Change From Baseline) (N = 50-51)	86.5**	85.0**	90.3**	69.2**
Patient Self-Assessment (N = 60-61) Mean Score:				
Q5: Bald Spot Getting Smaller	0.3*	0.3	0.5**	0.6**
Q24: Appearance of Hair	0.9**	1.0**	1.3**	1.4**
Q25: Growth of Hair	0.8**	0.9**	1.1**	1.2**
Q26: Slowing Down Hair Loss	1.0**	1.1**	1.2**	1.3**
Q27a: Satisfaction With Frontal Hairline	-0.2	-0.1	0.0	0.2
Q27b: Satisfaction With Hair on Top	0.2	0.3*	0.4**	0.5**
Q27c: Satisfaction With Hair Overall	0.1	0.2	0.3*	0.5**
Investigator Assessment (N = 60) Mean Score:	1.5**	1.6**	1.7**	1.7**
Global Photographic Assessment (N = 47-51) Mean Score:	0.7**	1.0**	0.9**	0.9**

*, ** Significant change from baseline at the $p < 0.050$ and $p < 0.010$ level, respectively, assuming baseline=0 for the subjective assessments. † Results for the finasteride 1-mg group for patients who entered the open-extension study

Table 9.7.2B Effects of Finasteride on Efficacy Endpoints - Efficacy at Month 24: Phase 2 Dose-Range Open-Extension Study (081-20)

	Patient Group			
Endpoint	1/1/1 mg	0.2/0.2/1 mg	0.01/0.01/1 mg	Pbo/Mix/1 mg
Randomized for 0-6 months to	Fin 1 mg	Fin 0.2 mg	Fin 0.01 mg	Pbo
6-12 months to	Fin 1 mg	Fin 0.2 mg	Fin 0.01 mg	Mixture of regimens
12-24 months (open extension) to	Fin 1 mg	Fin 1 mg	Fin 0.01 mg	Fin 1 mg
Month 24				
Hair Count (Mean Change From Baseline)	90.3**	81.1**	78.2**	59.5**
Patient Self-Assessment Mean Score:				
Q5: Bald Spot Getting Smaller	0.4**	0.7**	0.4*	0.1
Q24: Appearance of Hair	1.3**	1.5**	1.0**	0.9**
Q25: Growth of Hair	1.1**	1.3**	0.9**	0.7**
Q26: Slowing Down Hair Loss	1.2**	1.4**	1.1**	1.0**
Q27a: Satisfaction With Frontal Hairline	0.0	0.0	-0.2	-0.2
Q27b: Satisfaction With Hair on Top	0.4**	0.3*	-0.1	0.1
Q27c: Satisfaction With Hair Overall	0.2*	0.3**	0.1	0.1
Investigator Assessment Mean Score:	1.7**	1.9**	1.3**	1.5**
Global Photographic Assessment Median Score:	0.9**	0.7**	0.2*	0.4*
Change from Month 12 to Month 24				
Hair Count (Mean Change From Baseline)	-2.9	-10.9	100.3##	23.5
Patient Self-Assessment Change in Mean Score:				
Q5: Bald Spot Getting Smaller	0.1	0.2	0.5##	0.2
Q24: Appearance of Hair	0.3#	0.3##	0.4##	0.5##
Q25: Growth of Hair	0.3##	0.3##	0.2	0.3#
Q26: Slowing Down Hair Loss	0.2	0.3	0.3#	0.5##
Q27a: Satisfaction With Frontal Hairline	0.2	0.1	0.2	0.2
Q27b: Satisfaction With Hair on Top	0.2	0.1	0.2	0.4##
Q27c: Satisfaction With Hair Overall	0.1	0.1	0.2	0.4##
Investigator Assessment: Change in Mean Score:	0.2	0.3##	0.5##	0.6##
Global Photographic Assessment: Change in Median Score:	0.1	0.2	0.2#	0.1

*, ** Significant change from baseline at the $p < 0.050$ and $p < 0.010$ level, respectively, assuming baseline=0 for the subjective assessments.
#, ## Significant change from Month 12 to Month 24 at the $p < 0.050$ and $p < 0.010$ level, respectively. N varied between 42 and 54 depending on the group and endpoint. Pbo=placebo, Fin=finasteride.

9.7.3 Extension from Phase 3 Pivotal Studies 087 and 089

The extension into second year was a blinded study with 10% of subjects in each group rerandomized into the opposite group. Combined data from 087 and 089 for up to 24 months were submitted on 8/11/97. Table 9.7.3 provides these combined data, with exception of the small group in which placebo subjects were rerandomized to receive finasteride 1 mg, as the data of this group primarily reflected those of the finasteride 1 mg group in the first year.

Table 9.7.3 Effects of Finasteride † on Efficacy Endpoints - Efficacy at Month 24 - Combined Data for Phase 3 Pivotal Studies: Double-Blind Extension Phase for 087-10 and 089-10

	Patient Group		
Endpoint	Fin 1/1 mg	Fin 1 mg/Pbo	Pbo/Pbo
Month 24			
Hair Count (Mean Change From Baseline)	87.8**	-13.5	-50.5**
Patient Self-Assessment % patients giving positive response/mean change			
Q1: Bald Spot Getting Smaller	58/0.5**	--/0.1	17/-0.4**
Q2: Appearance of Hair	71/1.2**	--/0.6**	30/0.2
Q3: Growth of Hair	69/1.0**	--/0.4**	27/0.1
Q4: Slowing Down Hair Loss	80/0.8**	--/0.5**	46/-0.2
Q5a: Satisfaction With Frontal Hairline	36/0.1**	--/0.0	12/-0.4**
Q5b: Satisfaction With Hair on Top	48/0.4**	--/0.0	17/-0.4**
Q5c: Satisfaction With Hair Overall	50/0.4**	--/0.1	26/-0.2
Investigator Assessment Mean Score:	1.3**	0.8**	0.4**
Global Photographic Assessment Mean Score:	1.0**	-0.1	-0.4**
Change from Month 12 to Month 24			
Hair Count (Mean Change between Month 12 and 24)	-4.2	-117.2##	-37.0##
Patient Self-Assessment Change in % patients giving positive response/mean change			
Q1: Bald Spot Getting Smaller	11/0.2##	--/-0.1	-10 /-0.1
Q2: Appearance of Hair	8/0.2##	--/-0.5##	-6 /-0.1
Q3: Growth of Hair	8/0.1##	--/-0.4##	-10 /-0.2
Q4: Slowing Down Hair Loss	5/0.2##	--/-0.1	5 /-0.2
Q5a: Satisfaction With Frontal Hairline	4/0.1#	--/-0.2	-3 /-0.1
Q5b: Satisfaction With Hair on Top	8/0.2##	--/-0.2#	-9 /-0.2#
Q5c: Satisfaction With Hair Overall	8/0.2##	--/-0.2	0 /-0.1
Investigator Assessment: Change in Mean Score:	0.3##	0.0	0.2
Global Photographic Assessment: Change in Median Score:	0.3##	-0.8##	-0.4##

*, ** Significant change from baseline at the $p < 0.050$ and $p < 0.010$ level, respectively, assuming baseline=0 for the subjective assessments. #, ## Significant change from Month 12 to Month 24 at the $p < 0.050$ and $p < 0.010$ level, respectively. --=Data not provided (% patients giving positive response to question in the Fin 1 mg/Pbo group). N varied between 42 and 54 depending on the group and endpoint. Pbo=placebo, Fin=finasteride.

Comments

1. Investigator assessment, but not global photographic assessment, showed a positive effect with placebo throughout the initial and extension phases.
2. Finasteride for an additional 12 months maintained the treatment effect without additional objective benefit. However, the subjective assessments: patient self-assessment, Investigator assessment and global photography suggested further improvement. This may be due to improved cosmetic coverage which cannot be addressed by hair number alone.
3. Placebo for 12 months following 12 months of finasteride treatment resulted in reversal of benefit. The mean global photographic score dropped to negative level (-0.1) while the Investigator assessment score remained high (0.8). This discrepancy may be attributed to either recall bias with the Investigator assessment or a possibility that the two endpoints are measuring some subtly different phenomena.

4. Placebo for 24 months resulted in progressive loss of hair.
5. For the change from Month 12 to Month 24, it may not be appropriate to directly compare the Fin 1 mg/fin 1 mg group with the Pbo/Pbo group, as the baselines (Month 12) were different. It appears adequate to compare within group between these time points to determine whether there is any additional positive or negative effect with the continued treatment.

9.7.4 Extension from Phase 3 Frontal Hair Loss Study (Study 092)

This is a study on frontal scalp baldness. The extension is an ongoing open study. The Applicant provided preliminary data on the Month 24 follow up of patients who took finasteride for 24 months in a submission on 9/26/97. At Month 24, there was (1) a slight net increase in hair count from Month 12 that was not significant (1.5 hairs), (2) significant subjective assessment improvement from Month 12 by patient with the 6 questions of the Hair Growth Questionnaire (all $p<0.01$), by Investigator ($p<0.01$) and by 5 out of the 6 scores in Savin's scale (all $p<0.01$, except for frontal pattern with $p<0.05$ and frontal density with $p>0.05$), but (3) no change in global photographic scores from Month 12.

Comment As the extension phase is an open study, it is uncertain whether the additional improvement from Month 12 to 24 is due to placebo effect or not, especially when the hair count and global photography indicated little to no improvement. With the Hair Growth Questionnaire, the question on satisfaction with frontal hairline showed the least additional improvement (mean +0.2) between Months 12 and 24.

9.8 Subset Analysis

Subgroup analyses were performed for hair count and patient self-assessment on **pooled** data from Studies 087 and 089. Patients were subgrouped by (1) baseline hair loss pattern (modified Norwood/Hamilton classification), (2) baseline hair count, (3) patient age, (4) number of years of hair loss, (5) family history of hair loss and (5) race. In all subgroups analyzed, finasteride treatment produced improvements in scalp hair and patient self-assessment that were superior to placebo.

- Efficacy as determined by hair count or patient self-assessment was comparable between the age groups and was not affected significantly by the number of years of hair loss.

- For hair count, the presence or absence of a family history of baldness did not affect efficacy. For patient self-assessment, although patients with a family history of baldness in their grandparents reported greater improvement for some of the hair growth questions, this effect was not seen for patients with a first degree family history of baldness.

- Analysis by hair loss pattern and by baseline hair count are shown in Tables 9.8A and 9.8B respectively. There appeared to be a greater increase in hair count with more severe hair loss pattern or lower baseline count. However, hair loss pattern (or baseline hair count) did not predict the degree of efficacy of

finasteride treatment from the patient's perspective, based on the Hair Growth Questionnaire.

Table 9.8A Effects of Finasteride on Hair Count and Patient Self-Assessment: Results at Month 12 Subgrouped by Modified Norwood/Hamilton Classification - 087 and 089 Combined

	Modified Norwood/Hamilton Classification			
Endpoint	Grade II Vertex	Grade III Vertex	Grade IV	Grade V
Hair Count				
Baseline [figures from per-protocol population]	1030.4 (N = 176)	940.3 (N = 341)	845.2 (N = 331)	762.4 (N = 366)
Mean change from baseline (finasteride-placebo)**	75.8 (N = 192)	100.9 (N = 380)	109.6 (N = 370)	124.4 (N = 409)
Patient Self-Assessment	(N = 229-230)	(N = 417-418)	(N = 403-404)	(N = 447-448)
Mean score (finasteride-placebo)				
Q1: Bald Spot Getting Smaller	0.4	0.7	0.5	0.6
Q2: Appearance of Hair	0.5	0.7	0.5	0.7
Q3: Growth of Hair	0.5	0.7	0.5	0.6
Q4: Slowing Down Hair Loss	0.5	0.8	0.5	0.8
Q5a: Satisfaction With Frontal Hairline	0.2	0.4	0.3	0.2
Q5b: Satisfaction With Hair on Top	0.4	0.6	0.5	0.3
Q5c: Satisfaction With Hair Overall	0.3	0.3	0.4	0.3

*,**,*** Significant subgroup by treatment interaction at the $p < 0.050$, $p < 0.010$, and $p < 0.001$ level, respectively

Table 9.8B Effects of Finasteride on Hair Count and Patient Self-Assessment: Results at Month 12 Subgrouped by Baseline Hair Count - Phase 3 Pivotal Studies Combined

	Baseline Hair Count Range				
Endpoint	112 to 666	667 to 811	812 to 928	929 to 1087	1088 to 1727
Hair Count	(N = 270)	(N = 268)	(N = 271)	(N = 272)	(N = 270)
Mean change from baseline (finasteride-placebo)	116.4	108.6	107.6	105.3	93.6
	112 to 673	674 to 820	821 to 940	941 to 1090	1091 to 1727
Patient Self-Assessment	(N = 297)	(N = 298-299)	(N = 297-299)	(N = 297-298)	(N = 297-298)
Mean score (finasteride-placebo)					
Q1: Bald Spot Getting Smaller	0.5	0.7	0.4	0.5	0.8
Q2: Appearance of Hair	0.7	0.8	0.4	0.5	0.9
Q3: Growth of Hair	0.5	0.7	0.4	0.4	0.8
Q4: Slowing Down Hair Loss	0.7	0.8	0.6	0.5	0.9
Q5a: Satisfaction With Frontal Hairline	0.2	0.4	0.2	0.2	0.4
Q5b: Satisfaction With Hair on Top	0.3	0.5	0.3	0.3	0.6
Q5c: Satisfaction With Hair Overall	0.3	0.5	0.2	0.2	0.5

Comment In general, patients with a more severe pattern of hair loss had lower baseline hair counts, as would be expected. It appears that patients with a more severe hair loss pattern (and to a lesser extent, those with a lower baseline counts) had a greater net increase in hair count with finasteride treatment than patients with a less severe hair loss pattern (or those with higher baseline counts). The Applicant postulates that such an effect may be related to a larger number of recruitable, dormant follicles in patients with more advanced hair loss. This hypothesis would require more work for substantiation, as (a) significance levels for comparisons between the various baseline patterns or counts have not been presented; and (b) hair loss pattern (or baseline hair counts) did not predict the degree of efficacy of finasteride treatment from the patient's perspective, based on the Hair Growth Questionnaire.

- Efficacy appears to be substantially lower in non-whites. Regardless, treatment with finasteride resulted in overall improvements compared with placebo and not necessarily translate into decreased efficacy from the patient's perspective even in "Asians" and Hispanics, although the scores on satisfaction with finasteride's

efficacy were low among Blacks.

Table 9.8C Effects of Finasteride on Hair Count and Patient Self-Assessment: Results at Months 12 Subgrouped By Race - Phase 3 Pivotal Studies Combined

	Racial Origin		
Endpoint	Caucasian	Black	Other
Hair Count	(N = 1185)	(N = 84)	(N = 82)
Mean change from baseline (finasteride-placebo)*	110.1	76.0	72.1
Patient Self-Assessment	(N = 1306-1308)	(N = 94-95)	(N = 96-97)
Mean score (finasteride-placebo)			
Q1: Bald Spot Getting Smaller	0.6	0.4	0.4
Q2: Appearance of Hair	0.6	0.5	0.7
Q3: Growth of Hair	0.5	0.7	0.5
Q4: Slowing Down Hair Loss	0.7	0.6	0.7
Q5a: Satisfaction With Frontal Hairline*	0.3	-0.2	0.3
Q5b: Satisfaction With Hair on Top*	0.5	0.0	0.6
Q5c: Satisfaction With Hair Overall	0.4	0.1	0.4

*,**,*** Significant by treatment- subgroup interaction at the $p < 0.050$, $p < 0.010$, and $p < 0.001$ level, respectively

Comments

1. The patient numbers in this Table refer to the sums of finasteride and placebo groups.
2. In the two pivotal trials, only 41 Blacks, 13 "Asians", 31 Hispanics and 6 "Others" received finasteride. In one of the pivotal studies (089), there were only 3 Blacks. The non-Caucasian, non-Black groups as a whole showed the least drug effect in terms of hair count, but their data had not been further analyzed with respect to individual racial groups because of the smaller numbers. As there is evidence of racial differences in 5α-reductase activity (*J Clin Endocrinol Metab* 72: 1242, 1991), analysis of efficacy in individual racial groups is necessary despite the small numbers.

9.9 Conclusions

1. Finasteride 1 mg/d for 12 months appeared to be effective in increasing hair count in MPB, leading to improved cosmetic perception. The cosmetic change was perceptible by patients after 3 months of treatment. The improvement was maintained with little further increase during an additional 12 month period of treatment using finasteride 1 mg/d, while cessation of treatment resulted in reversal of effect.
2. Treatment with placebo was associated with progressive hair loss.
3. The efficacy of finasteride has been established in men aged 18-41 with mild to moderate degrees of MPB.
4. The treatment effect of finasteride in racial subgroups other than Caucasians was smaller and the significance levels in the subgroups have not been presented.
5. The treatment effect of finasteride on the primary variables in the absence of Neutrogena T-gel shampoo has not been clarified.
6. 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.
7. There have been 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 (patient assessment for hair loss) 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.

10. Overview of Safety

10.1 Background and Methodology for Safety Review

The safety profile of finasteride for the treatment of male pattern hair loss in this NDA is derived from studies in three categories as shown in Table 10.1A. In addition, additional data were submitted in the 120-day safety update on the extension phases of the pivotal phase 3 trials 087 and 089 as well as on the reversibility phase of the safety study 094.

Table 10.1A Summary of Database

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

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

Table 10.1B and 10.1C summarize the overall patient exposure to finasteride and placebo therapy in the original submission. More than 1100 patients received finasteride 1 or 5 mg for greater than 300 days, and 250 patients received these doses for greater than 365 days. These figures are constantly increasing because of ongoing extension studies.

Table 10.1B Duration of Therapy by Study Category Range and Mean Duration

	Total Number of Patients		Range (Days)		Mean Duration (Days)	
Study Category	Finasteride	Placebo	Finasteride	Placebo	Finasteride	Placebo
Phase 3 Controlled	945	934			312.3	310.3
Phase 2 Controlled	836	490			165	194.4
Phase 2 Uncontrolled	502†	N/A#			480.1	N/A#

† Cannot be added to other patient numbers # Not applicable

Table 10.1C Patient Exposure by Therapy and Dose (in Original Submission)

	Days on Therapy						
	≥1	≥183	≥301##	≥366	≥549	≥732	≥1098
Any Finasteride Dose#	1953	1421	1299	392	158	50	4
Finasteride 1 or 5 mg	1721	1278	1118	250	117	50	4
Placebo	1424	1046	934	100	0	0	0

Finasteride 5, 1, 0.2, 0.05, or 0.01 mg ## This number corresponds to the minimum number of days on study for completion of Phase 3 studies.

Demographic and Other Characteristics of the Study Population

a. Baseline Demographics

Table 10.1D Summary of Baseline Demographics--Patient Count (%)#: Phase 3 Controlled Studies

	Finasteride 1 mg (N = 945)	Placebo (N = 934)	Total (N = 1879)
Age in Years			
18 to 30	318 (33.7)	304 (32.5)	622 (33.1)
31 to 41	627 (66.3)	630 (67.5)	1257 (66.9)
Mean	32.6	32.6	32.6
Range			
Racial Origin			
Caucasian	842 (89.1)	817 (87.5)	1659 (88.3)
Black	44 (4.7)	63 (6.7)	107 (5.7)
Other	59 (6.2)	54 (5.8)	113 (6.0)

All patients were male.

In Phase 2 controlled studies, the mean age was 32 and this is similar to Phase 3. The distribution of racial origins is similar to Phase 3 and similar between treatment groups, with 92% Caucasians, 3% Blacks and 5% "Others".

b. Secondary Diagnoses and Concomitant Medications

The finasteride and placebo groups were similar with respect to the prevalence of secondary diagnoses, as would be expected in large randomized studies. The use of concomitant therapy was balanced between the treatment groups. Approximately 0.6% of patients had an endocrine disorder as secondary diagnosis; however, about 6% in each treatment group received hormone or synthetic substitutes as concomitant therapy. Nevertheless, most of these hormone products were topical corticosteroids.

10.1.1 Deaths

A total of 3 patients died while participating in the clinical studies: 1 on finasteride, 1 on placebo, and 1 that remained blinded at the time of original submission. The Applicant updated information on fatal events in the 10/10/97 submission with one additional

subject. None of the AE were considered drug related.

Table 10.1.1 Fatal Serious Clinical Adverse Experiences Phase 3 Controlled, Phase 2 Controlled and Uncontrolled Studies

Study	Pt No	Age	Drug	Day/AE	AE	Relationship	Comments
056		33	Placebo	7	Suicide	Definitely not	Overdose of barbiturates and opiates
087		36	finasteride	101	Trauma	Definitely not	Motor vehicle accident, brain injury
087		40	Finasteride	489	Cardiomyopathy	Probably not	Autopsy suggested dilated cardiomyopathy
081		34	finasteride	984	Trauma	Definitely not	Motor vehicle accident, multiple trauma

10.1.2 Dropouts

10.1.2.1 Overall Pattern of Dropouts

Phase 3 Controlled Studies

In the Phase 3 studies 121 patients (12.8%) in the finasteride group and 127 patients (13.6%) in the placebo group discontinued for reasons other than an AE, while the corresponding figures for AE discontinuations were 16 (1.7%) and 20 (2.1%) respectively. The most common reason a patient discontinued was "Lost to Follow-Up." This was not unexpected due to the young age and mobility of patients participating in these studies.

Table 10.1.2.1A Discontinuations From Therapy -Patient Count (%): Phase 3 Controlled Studies

Reason	Finasteride (N = 945)	Placebo (N = 934)
Lack of efficacy	4 (0.4)	11 (1.2)
Lost to follow-up	46 (4.9)	41 (4.4)
Noncompliance#	33 (3.5)	36 (3.9)
Protocol violation##	10 (1.0)	5 (0.5)
Relocating	10 (1.0)	11 (1.2)
Withdrew	19 (2.0)	21 (2.2)
Other	1 (0.1)	2 (0.2)
Total non-AE discontinued	121 (12.8)	127 (13.6)
AE	16 (1.7)	20 (2.1)

Noncompliant with protocol requirements ## Violation of inclusion and/or exclusion criteria of the protocol.

Phase 2 Studies

In the Phase 2 controlled studies, 26 (2.0%) of 1326 patients discontinued due to AE and 170 (12.8%) discontinued for reasons other than an AE, with "Lost to Follow-Up" being the most prevalent reason. In the Phase 2 uncontrolled studies, 11 (2.2%) of 502 patients discontinued due to AE and 163 (32.5%) discontinued for non-AE reasons. The most common reason was also "Lost to Follow-Up."

Table 10.1.2.1B Discontinuations From Therapy - Patient Count (%): Phase 2 Studies

	Controlled						Uncontrolled
	Finasteride					Placebo	Finasteride
	5 mg (N = 252)	1 mg (N = 245)	0.2 mg (N = 151)	0.01 mg (N = 154)	0.05 mg (N = 34)	(N = 490)	(N = 502)
Lack of efficacy	2 (0.8)	0	0	0	0	2 (0.4)	10 (2.0)
Lost to follow-up	14 (5.6)	12 (4.9)	1 (0.7)	0 (6.6)	10 (6.5)	0 34 (6.9)	86 (17.1)
Noncompliance#	5 (2.0)	4 (1.6)	3 (2.0)	5 (3.2)	2 (5.9)	13 (2.7)	24 (4.8)
Protocol violation##	4 (1.6)	1 (0.4)	0	0	0	9 (1.8)	5 (1.0)
Relocating	4 (1.6)	1 (0.4)	1 (0.7)	1 (0.6)	0	3 (0.6)	12 (2.4)
Withdrew	4 (1.6)	5 (2.0)	2 (1.3)	6 (3.9)	1 (2.9)	11 (2.2)	26 (5.2)
Other	1 (0.4)	0	0	0	0	1 (0.2)	0
Total non-AE	34 (13.5)	23 (9.4)	16 (10.6)	22 (14.3)	3 (8.8)	73 (14.9)	163 (32.5)
AE	6 (2.4)	4 (1.6)	3 (2.0)	3 (1.9)	0	10 (2.0)	11 (2.2)

Noncompliant with protocol requirements. ## Violation of inclusion and/or exclusion criteria of the protocol

Comment The dropout rates are similar across studies, except that more patients tended to drop out due to "Lack of efficacy", "Lost to follow-up" or "Withdrew" in the open extension phase. It suggests that the treatment effect might have passed the maximal stage and patients were losing interest.

10.1.2.2 Adverse Events Associated with Dropout

In the initial phase 3 controlled studies, 16 patients (1.7%) in the finasteride group and 20 (2.1%) in the placebo group were discontinued due to a clinical adverse even. Four of the 36 patients (3 on finasteride and 1 on placebo) were discontinued due to a serious event. Eleven patients (1.2%) on finasteride and 8 patients (0.9%) on placebo discontinued due to a drug-related sexual adverse event. All of them had resolution of their sexual adverse events. The most common event resulting in discontinuation was erectile dysfunction, which occurred in 0.6% of finasteride patients and 0.5% of placebo patients.

Table 10.1.2.2 Discontinuations From Therapy Due to a Clinical Adverse Experience--Patient # Phase 3 Controlled Studies

	Finasteride (N = 945)	Placebo (N = 934)
One or more AE resulting in discontinuation	16 (1.7%)	20 (2.1%)
Body as a Whole	**0**	**4**
Asthenia/fatigue		087-2891*, 089-1137
Pain, abdominal		087-2204
Syncope##		089-1301
Musculoskeletal Disorders	**2**	**1**
Fracture, vertebra##	089-1657	
Myalgia		089-1777
Weakness, muscle	089-1017	
Nervous System and Psychiatric Disorders	**7**	**9**
Alcohol dependence##	087-2371	
Depression		087-3045
Emotional lability		087-2197
Headache		092-4218
Decreased libido	087-2223, 087-1430, 087-1035 087-1285	087-2169, 087-2704, 089-1367
Paresthesia	087-2897	
Seizure disorder		087-2774, 089-1230##

Somnolence		087-2316
Trauma, brain ##	087-2397	
Skin and Skin Appendage Disorders	**0**	**1**
Folliculitis		089-1029
Urogenital System Disorders	**7**	**6**
Ejaculation disorder	087-2234	087-2058
Erectile dysfunction 6 (0.6) 5 (0.5)	087-2998, 087-2629, 089-1136, 087-2712, 087-2417, 087-2587	087-2399, 087-3012, 087-2012 089-1507, 089-1367

Serious AE.*Patient numbers are given under individual adverse events. Patients may be counted twice because of more than one event leading to discontinuation.

In the phase 2 controlled studies 26 patients discontinued therapy due to a clinical adverse event. The most common event resulting in discontinuation in the finasteride 1-mg group was erectile dysfunction (0.8% in the finasteride group and 0.4% in the placebo group). In the phase 2 uncontrolled studies, 11 of 502 patients (2.2%) were withdrawn from therapy due to a clinical adverse event, one of the 11 discontinued due to a serious event. The most common drug-related AE resulting in discontinuation from the study was erectile dysfunction (0.8%), followed by decreased libido (0.6%). Of the 8 patients who discontinued due to decreased libido, erectile dysfunction, or ejaculation disorder, one patient with delayed ejaculation had not resolved his adverse event after discontinuation of therapy.

10.1.3 Other Serious Adverse Events

In the original submission, 64 (2.0%) of a total patient population of 3217 had a nonfatal serious clinical AE; and none was considered drug-related. Ten were discontinued from therapy due to a nonfatal serious clinical AE (7 on finasteride and 3 on placebo; see above). In a submission dated 10/10/97, the Applicant updated this information, giving a total of 102 subjects with serious AE (Table 10.1.3A). Table 10.1.3.B lists these serious AE in the initial phase 3 controlled trials (087, 089 and 092); details of those in the extension periods are pending.

Table 10.1.3A Summary of Nonfatal Serious Clinical Adverse Experiences by Study Category

	Original Submission			Updated Figures		
Study Category	Fin*	Placebo	Total	Fin	Placebo	Total
Phase 3 Controlled (087, 089, 092)	16	20	36	16	20	36
Phase 3 Controlled Extensions (087, 089)	--	--	--	25	1	26
Phase 2 Controlled (012, 031, 047, 056, 065, 081, 094)	11†	5††	16	15#	6##	21
Phase 2 Uncontrolled	12	NA	12	19	NA	19
Total	39	25	64	75	27	102

NA = Not applicable † Two patients had serious AE during the off-drug period of the study; †† One patient had an AE during the off-drug period of the study. # Six patients had serious AE during the off-drug period of the study; ## Two patient had an AE during the off-drug period of the study. *Fin=finasteride.

Table 10.1.3B Nonfatal Serious Clinical Adverse Experiences by Body System--Patient Count (%)#: Phase 3 Controlled Studies

	Finasteride (N = 945)	Placebo (N = 934)
One or more serious AE	16 (1.7)	20 (2.1)
Body as a Whole	6	3
Pain, abdominal	087-2156*	087-2489
Pain, chest	092-4135	
Pain, flank		087-2489
Syncope		089-1301
Syncope, dizziness, anemia		089-1654
Trauma	087-2531, 089-1454, 089-1488, 089-1171	
Cardiovascular System Disorders	1	1
Atrial flutter		089-1771
Palpitation	089-1666	
Digestive System Disorders	1	3
Appendicitis	089-1443	
Gastroenteritis		089-1296
Hepatitis A		087-2976
Pancreatitis		087-2866
Metabolic, Nutritional, Immune Disorders	0	1
Dehydration		092-4093
Musculoskeletal Disorders	1	5
Fracture	089-1657	087-2487, 089-1147, 089-1310
Intervertebral disc disorder		089-1803, 089-1229
Nervous System and Psychiatric Disorders	1	2
Alcohol dependence	087-2371	
Cauda equina syndrome		089-1803
Neurological disorder		089-1803
Seizure disorder		089-1320
Respiratory System Disorders	0	1
Pneumonia		089-1703
Skin and Skin Appendage Disorders	4	4
Cellulitis		092-4279
Cyst, pilonidal	089-1512	
Neoplasm, skin, malignant	087-2127, 089-1731, 092-4366	087-2301. 087-2345, 092-4006
Urogenital System Disorders	2	1
Cyst, sebaceous, scrotum	089-1658	
Infection, urinary tract	092-4300	
Urolithiasis		087-2463

*Patient numbers given under individual adverse events. Patients may be counted twice because of occurrence of more than one serious event.

In the phase 2 controlled studies, a total of 16 patients among 1292 (1.2%) had a nonfatal serious clinical AE. The incidence was ≤1% in each treatment group except for the finasteride 5 mg/d group (3%; mostly musculoskeletal disorders). For the phase 2 uncontrolled studies, 12 of the 502 patients had a nonfatal serious AE. Like the phase 2 controlled studies, most serious AE were of the musculoskeletal system. None of the serious AE in phase 2 trials were considered treatment-related.

10.1.4 Other Search Strategies

10.1.4.1 Sexual Function Questionnaire A Sexual Function Questionnaire was incorporated into the phase 2 pilot study 047 and subsequently modified to be

included into the phase 3 program and in Study 094.

No effect on patients' overall satisfaction with their sex life (global question) was observed in the finasteride treatment group. Small but significant differences between treatment groups for three of the four domains and in the question addressing morning erections were observed. In order to determine whether these small changes were of any clinical significance, the questionnaire data were separately analyzed for those patients reporting a sexual AE. In each of the four domains, the change from baseline in both treatment groups for patients with a sexual AE was approximately 5 to 10 times greater than the difference between the finasteride and placebo patients for the entire study population.

Table 10.1.4.1 Sexual Function Questionnaire Domain Scores - Phase 3 Pivotal Trial Patients and Those With Sexual Adverse Experiences: Intention-to-Treat Population

		Finasteride 1 mg Mean ± SD				Placebo Mean ± SD				Fin vs Placebo	
		N	BL	Month 12	Change	N	BL	Month 12	Change	Diff	p-Value
Domain											
Sexual interest	All subjects	750	5.7 ± 1.4	5.5 ± 1.6	-0.2 ± 1.5*	746	5.6 ± 1.4	5.7 ± 1.5	0.1 ± 1.4	-0.2	<0.010
(9-point scale)	With sexual AE	34	5.5 ± 1.3	4.2 ± 1.7†	-1.3 ± 1.9	19	5.6 ± 1.8	4.5 ± 1.7†	-1.2 ± 1.6		
Erections	All subjects	749	9.4 ± 1.9	9.3 ± 2.1	-0.2 ± 1.9*	739	9.3 ± 1.8	9.5 ± 2.0	0.1 ± 1.8	-0.3	<0.010
(12-point scale)	With sexual AE	34	9.4 ± 1.9	7.6 ± 2.5 †	-1.7 ± 2.6	19	9.0 ± 2.2	7.1 ± 2.5†	-1.9 ± 2.8		
Ejaculation	All subjects	741	5.7 ± 0.7	5.5 ± 0.9	-0.2 ± 0.9**	737	5.7 ± 0.7	5.6 ± 0.9	-0.1 ± 0.9**	-0.1	0.184
(7-point scale)	With sexual AE	34	5.4 ± 1.0	4.9 ± 1.3†	-0.6 ± 1.3	18	5.7 ± 0.6	5.0 ± 1.5†	-0.7 ± 1.3		
Perception of problems	All subjects	749	11.3 ± 1.6	10.8 ± 2.3	-0.5 ± 2.3**	743	11.2 ± 1.7	11.0 ± 2.1	-0.3 ± 2.2**	-0.2	<0.050
(13-point scale)	With sexual AE	34	10.6 ± 2.4	7.9 ± 3.7†	-2.6 ± 3.5	18	11.2 ± 1.5	7.6 ± 3.8†	-3.6 ± 3.6		
Questions											
11. Global question	All subjects	749	2.8 ± 1.0	2.8 ± 1.0	-0.1 ± 1.1	746	2.9 ± 0.9	2.9 ± 1.0	0.0 ± 1.0	-0.1	0.319
(5-point scale)	With sexual AE	34	2.7 ± 1.0	2.2 ± 1.2†	-0.4 ± 1.3	19	2.4 ± 1.0	2.4 ± 1.0†	0.0 ± 1.2		
12. Morning erections	All subjects	750	1.9 ± 1.1	1.8 ± 1.0	-0.1 ± 1.0**	745	2.0 ± 1.1	2.0 ± 1.1	0.1 ± 0.9	-0.2	<0.010
(5-point scale)	With sexual AE	34	1.8 ± 1.2	1.3 ± 1.2†	-0.5 ± 1.0	19	1.7 ± 1.2	1.6 ± 1.0†	-0.1 ± 1.3		

*,** Significant change from baseline at the $p < 0.050$ and $p < 0.010$ level, respectively. † Subset of subjects who reported a sexual AE during the treatment period. Scores at the time of occurrence of the sexual AE.

Comment On the basis of the results of the four Domains, the Applicant concluded the effect measured by this questionnaire was small and of no clinical concern, that the small mean changes in the Sexual Function Questionnaire were well below the threshold for perceiving and reporting a sexual AE and that the findings were in agreement with the low frequency of sexual AE reported in the Phase 3 studies. However, the global question and the morning erections question (#11 and 12) showed marked differences in changes from baseline between subjects in the two treatment groups who had sexual AE. As the global question is a general measure of the sex life of the subject, this difference cannot be ignored. The Applicant should supply analysis of statistical significance of the answers for the subset having adverse sexual events.

10.1.4.2 Body Hair Assessment [See Section 8.1.3.4.3.4]

In the U.S. phase 3 pivotal study 087, an assessment of non-scalp body hair was obtained through a self-administered patient questionnaire. Both treatment groups reported small increases in body hair, with the placebo group perceiving slightly larger changes from baseline than the finasteride group.

Comment There is sparse body hair present in men with 5α-reductase deficiency. The finding in Study 087 is in contrast to reports in the literature where loss of body hair associated with finasteride use has been observed (N Engl J Med 330: 120, 1994). This may be due to the use of different dosage. Alternatively it is also possible that the perception that the studies were for hair growth could influence the answers: the finasteride group did perceive less increase from baseline vs placebo.

10.1.5 Adverse Event Incidence Tables

10.1.5.1 Clinical Adverse Experience Summary

A summary of AE in phase 3 controlled trials is given below (Table 10.1.5.1).

The phase 2 controlled population had a similar incidence of drug-related clinical AE reported in the finasteride 1-mg group (7.3%) compared with the placebo group (8.0%) and the phase 3 finasteride group (7.7%). The 5-mg group had an incidence of drug-related clinical AE that was higher than placebo (13.9 versus 8.0%) and higher than the incidence in the finasteride 1-mg group (7.3%) from both the phase 2 and phase 3 studies.

The majority of the patients included in the phase 2 uncontrolled study category are from extensions to the phase 2 Pilot study and Dose-Range study (047 and 081). Thirty-five patients (7.0%) experienced a drug-related clinical AE. Very few patients (1.6%) were discontinued due to a drug-related clinical AE. The clinical AE profile in the phase 2 uncontrolled studies was also similar to that in phase 3.

There was no additional AE data of interest in the 120-day safety update, apart from one case of unilateral gynecomastia (Patient) whose AE resolved off drug. The following is a summary of the clinical adverse events in phase 3 controlled trials and the extension periods of phase 2 and phase 3 studies to-date (submitted on 10/10/97):

Table 10.1.5.1 Clinical Adverse Experience Summary–Patient Count (%)# in Phase 3 Controlled Studies and their Extensions and in Phase 2 and Phase 3 Uncontrolled Extension Periods

	Phase 3 Controlled Fin* Studies (Year 1)		Phase 3 Controlled Extension Fin* Studies (Year 2)				Phase 2 & 3 Uncontrolled Extension Studies
	Fin N=945	Placebo N =934	Fin/Fin N=547	Pbo/Fin N=934	Fin/Pbo N= 65	Pbo/Pbo N= 60	Fin## N=746
one or more AE	596 (63.1)	560 (60.0)	304 (55.6)	318 (58.6)	31 (47.7)	30 (50.0)	431 (57.8)
with drug-related AE	73 (7.7)	65 (7.0)	18 (3.3)	29 (5.3)	0	4 (6.7)	43 (5.8)
with drug-related sexual AE	36 (3.8)†	20 (2.1)	8 (1.5)	14 (2.6)	0	1 (1.7)	29 (3.9)
with serious AE	17 (1.8)	20 (2.1)	11 (2.0)	15 (2.8)	0	1 (1.7)	20 (2.7)
with serious drug-related AE	0	0	0	0	0	0	0
who died due to an AE	1 (0.1)	0	1 (0.2)	0	0	0	1 (0.1)
withdrawn due to an AE	16 (1.7)	20 (2.1)	7 (1.3)	8 (1.5)	0	0	17 (2.3)
a drug-related AE	13 (1.4)	15 (1.6)	4 (0.7)	6 (1.1)	0	0	10 (1.3)
a serious AE	3 (0.3)	2 (0.2)	1 (0.2)	1 (0.2)	0	0	4 (0.5)
serious drug-related AE	0	0	0	0	0	0	0

Although a patient may have had two or more AE, the patient was counted only once in "Number (%) of patients with one or more AE."
† p = 0.041 versus placebo; *Fin=finasteride, Pbo=placebo; ##finasteride doses in uncontrolled extension studies included 5, 1, 0.2, 0.05 and 0.01 mg/d. Phase 3 controlled studies: 087, 089 and 092; phase 3 controlled extension studies: 087 and 089; phase 2 & 3 uncontrolled studies: 047, 081, 092 and 102.

Comment The incidence figures in the extension studies are slightly lower than, but not substantially different from, those in the initial phases. The lower figures must be interpreted with caution, as (1) those who had sexual AE earlier in the course might have exited from the study, thus making the remaining population less prone to such AE and (2) the subjects were followed up less frequently in the extension studies, thus introducing a difference in the recall bias in reporting.

10.1.5.2 Clinical Adverse Experiences by Body System

Table 10.1.5.2 gives the incidence of AE in phase 3 trials by body system. A complete Table of adverse events is provided in Appendix VII. The Phase 2 studies were similar to the Phase 3 controlled studies in the distribution of adverse events by body system.

Table 10.1.5.2 Clinical Adverse Experiences by Body System--Patient Count (%)# Phase 3 Controlled Studies.

	Finasteride (N = 945)	Placebo (N = 934)
Body as a whole/site unspecified	87 (9.2)	87 (9.3)
Cardiovascular system disorders	18 (1.9)	14 (1.5)
Digestive system disorders	94 (9.9)	104 (11.1)
Endocrine disorders	0	0
Hematologic and lymphatic disorders	7 (0.7)	4 (0.4)
Metabolic, nutritional, immune disorders	28 (3.0)	32 (3.4)
Musculoskeletal disorders	143 (15.1)†	107 (11.5)
Nervous system and psychiatric disorders	164 (17.4)	142 (15.2)
Respiratory system disorders	322 (34.1)	294 (31.5)
Skin and skin appendage disorders	127 (13.4)	113 (12.1)
Special sense disorders	36 (3.8)	26 (2.8)
Urogenital system disorders	50 (5.3)	35 (3.7)

Although a patient may have had two or more ASE, the patient was counted only once in a particular body system. † p = 0.021 versus placebo.

In the 120-day safety update, cumulative data including the update period subsequent to NDA submission were presented [Ref 5 of Safety Update]. Only data from the finasteride groups were given, without additional information on control groups and these results do not differ materially from those in the original submission.

10.1.5.3 Drug-Related Clinical Adverse Experiences

Drug-related AE in Phase 3 trials are given in Table 10.1.5.3.

Table 10.1.5.3A Drug-Related Clinical Adverse Experiences--Patient Count (%)# Phase 3 Controlled Studies

	Finasteride (N = 945)	Placebo (N = 934)
one or more drug-related AE	73 (7.7)	65 (7.0)
Body as a Whole	**5 (0.5)**	**5 (0.5)**
Asthenia/fatigue	3 (0.3)	3 (0.3)
Fever	1 (0.1)	0
Pain, abdominal	1 (0.1)	2 (0.2)
Cardiovascular System Disorders	**4 (0.4)**	**2 (0.2)**
Blood pressure decreased	0	1 (0.1)
Capillary disorder	1 (0.1)	0
Hypertension	0	1 (0.1)

Palpitation	1 (0.1)	0
Telangiectasia	2 (0.2)	0
Digestive System Disorders	**3 (0.3)**	**4 (0.4)**
Appetite increase	0	1 (0.1)
Constipation	1 (0.1)	0
Gastritis	0	1 (0.1)
Intestinal disorder, functional	0	1 (0.1)
Nausea	1 (0.1)	0
Tongue disorder	1 (0.1)	0
Ulcer, peptic	0	1 (0.1)
Metabolic, Nutritional, Immune Disorders	**7 (0.7)**	**6 (0.6)**
Weight gain	6 (0.6)	5 (0.5)
Weight loss	1 (0.1)	1 (0.1)
Musculoskeletal Disorders	**1 (0.1)**	**1 (0.1)**
Myalgia	0	1 (0.1)
Weakness, muscle	1 (0.1)	0
Nervous System and Psychiatric Disorders	**22 (2.3)**	**23 (2.5)**
Aggressive behavior	1 (0.1)	0
Depression	0	1 (0.1)
Depressive disorder	1 (0.1)	0
Emotional changes	0	1 (0.1)
Headache	2 (0.2)	6 (0.6)
Decreased libido	17 (1.8)	12 (1.3)
Paresthesia	1 (0.1)	1 (0.1)
Seizure disorder	0	1 (0.1)
Somnolence	0	2 (0.2)
Respiratory System Disorders	**1 (0.1)**	**1 (0.1)**
Infection, respiratory, upper	1 (0.1)	1 (0.1)
Skin and Skin Appendage Disorders	**18 (1.9)**	**15 (1.6)**
Acne	2 (0.2)	2 (0.2)
Alopecia	2 (0.2)	2 (0.2)
Body hair growth increased	7 (0.7)	7 (0.7)
Color change, hair	2 (0.2)	1 (0.1)
Dry skin	1 (0.1)	0
Folliculitis	0	1 (0.1)
Hyperpigmentation	0	1 (0.1)
Infection, skin	1 (0.1)	0
Lipoma	1 (0.1)	0
Neoplasm, skin, benign	2 (0.2)	1 (0.1)
Neurodermatitis	1 (0.1)	0
Nodule, cutaneous	0	1 (0.1)
Rash	1 (0.1)	1 (0.1)
Special Sense Disorders	**1 (0.1)**	**1 (0.1)**
Defect, visual field	0	1 (0.1)
Hemorrhage, retinal	1 (0.1)	0
Urogenital System Disorders	**27 (2.9)**	**18 (1.9)**
Dysuria	1 (0.1)	0
Ejaculation disorder	11 (1.2)	7 (0.7)
Erectile dysfunction	12 (1.3)	7 (0.7)
Infection, urinary tract	1 (0.1)	0
Orgasm dysfunction	1 (0.1)	1 (0.1)
Pain, breast	2 (0.2)	2 (0.2)
Pain, genitalia	0	1 (0.1)
Priapism	1 (0.1)	0
Prostatitis	0	2 (0.2)
Scrotum disorder	1 (0.1)	0
Semen abnormality	0	2 (0.2)

Table 10.1.5.3B Drug-Related AE with Incidence of ≥0.5%--Patient Count (%)# in Phase 3 Controlled Studies and their Extensions and in Phase 2 and Phase 3 Uncontrolled Extension Periods

	Phase 3 Controlled Fin* Studies (Year 1)		Phase 3 Controlled Extension Fin* Studies (Year 2)				Phase 2 & 3 Uncontrolled Extension Studies
	Fin N=945	Placebo N =934	Fin/Fin N=547	Pbo/Fin N=934	Fin/Pbo N= 65	Pbo/Pbo N= 60	Fin## N=746
Number (%) with drug-related AE	73 (7.7)	65 (7.0)	18 (3.3)	29 (5.3)	0	4 (6.7)	43 (5.8)
Weight gain	6 (0.6)	5 (0.5)	1 (0.2)	1 (0.2)	0	0	0
Headache	2 (0.2)	6 (0.6)	0	0	0	0	0
Libido decrease	17 (1.8)	12 (1.3)	6 (1.1)	7 (1.3)	0	1 (1.7)	11 (1.5)
Body hair growth increase	7 (0.7)	7 (0.7)	1 (0.2)	4 (0.7)	0	3 (5.0)	4 (0.5)
Ejaculation disorder	11 (1.2)	7 (0.7)	2 (0.4)	3 (0.6)	0	0	9 (1.2)
Erectile dysfunction	12 (1.3)	7 (0.7)	4 (0.7)	6 (1.1)	0	0	11 (1.5)
Urinary frequency	0	0	0	0	0	1 (1.7)	2 (0.3)

Although a patient may have had two or more AE, the patient was counted only once in "Number (%) of patients with one or more AE."
*Fin=finasteride, Pbo=placebo; ##finasteride doses in uncontrolled extension studies included 5, 1, 0.2, 0.05 and 0.01 mg/d.
Phase 3 controlled studies: 087, 089 and 092; phase 3 controlled extension studies: 087 and 089; phase 2 & 3 uncontrolled studies: 047, 081, 092 and 102.

Comment Table 10.1.5.3B incorporated information provided in a submission dated 10/10/97. The comments for Table 10.1.5.1 also apply here.

10.1.5.4 Additional Analyses and Explorations: Sexual Adverse Events

There were only 3 clinical AE reported as drug related that occurred in >1% of the phase 3 patients. These were: decreased libido (finasteride 1.8%, placebo 1.3%), erectile dysfunction (1.3 vs 0.7%), and ejaculation disorder (1.2 vs 0.7%). Ejaculation disorders consisted of two categories of related terms: (1) decreased volume of ejaculate and (2) changes in functional performance. The majority of patients with ejaculation disorder reported decreased volume of ejaculate (finasteride 8 patients, 0.8%; placebo 4 patients, 0.4%). Of the 6 patients with changes in functional performance, 3 were in the finasteride group and 3 were in the placebo group. Many of these AE resolved while patients continued on study drug. Table 10.1.5.4A further analyzes these sexual AE with the specific terms used by the Investigators.

Table 10.1.5.4A Drug-Related Sexual Adverse Experiences--Patient Count (%)# Preferred and Specific Terms Phase 3 Controlled Studies

	Finasteride N = 945	Placebo N = 934
one or more drug-related sexual AE	36 (3.8)	20 (2.1)
Libido Decreased	**17 (1.8)**	**12 (1.3)**
Lack of sexual desire	1 (0.1)	1 (0.1)
Libido decreased	10 (1.1)	9 (1.0)
Loss of libido	1 (0.1)	0
Sexual activity decreased	1 (0.1)	0
Sexual desire decreased	0	1 (0.1)
Sexual drive decreased	5 (0.5)	1 (0.1)
Sexual interest reduced	0	1 (0.1)
Ejaculation Disorder	**11 (1.2)**	**7 (0.7)**
Decreased Volume of Ejaculate	*8 (0.8)*	*4 (0.4)*
Decreased ejaculate	7 (0.7)	4 (0.4)
Semen volume decreased	1 (0.1)	0
Changes in Functional Performance	*3 (0.3)*	*3 (0.3)*
Delayed ejaculation	1 (0.1)	3 (0.3)
Ejaculation force decreased	1 (0.1)	0

Premature ejaculation	1 (0.1)	0
Erectile Dysfunction	**12 (1.3)**	**7 (0.7)**
Decreased morning erections	1 (0.1)	0
Erection difficulty	2 (0.2)	3 (0.3)
Erection dysfunction	1 (0.1)	2 (0.2)
Erection firmness decreased	3 (0.3)	1 (0.1)
Impotence	3 (0.3)	1 (0.1)
Impotence, intermittent	1 (0.1)	0
Incomplete erections	1 (0.1)	0
Potency weakened	1 (0.1)	0
Sexual dysfunction male	1 (0.1)	0
Sexual performance decreased	0	1 (0.1)

It is of interest to note that the incidences of sexual AE differ between the U.S. (087) and international (089) studies, with ejaculation disorder almost absent in 089:

Table 10.1.5.4B Drug-Related Sexual Adverse Experiences--Patient Count (%)# Phase 3 Controlled Studies

	087		089	
	Finasteride N = 471	Placebo N = 462	Finasteride N = 308	Placebo N = 312
Decreased libido	10 (2.1)	8 (1.7)	9 (2.9)	4 (1.3)
Ejaculation disorder	10 (2.1)	6 (1.3)	1 (0.3)	0
Erectile dysfunction	9 (1.9)	5 (1.1)	3 (1.0)	3 (1.0)

Like the incidence in the phase 3 studies, the overall incidence of AE reported as drug-related in phase 2 controlled studies was low:

- Decreased libido was the most common AE, occurring most frequently in the finasteride 0.2-mg group (4.6%). However, the incidence of decreased libido while on finasteride 1 mg was only 2.4 vs 2.7% in the placebo group.
- Ejaculation disorder was also reported more frequently in the placebo group (0.6%) when compared with the finasteride 1-mg group (0.4%).
- Erectile dysfunction was more frequently reported in the finasteride 0.2-mg (2.0%), 5-mg (1.6%) and 1-mg groups (1.6%) compared with placebo (0.4%).

Cumulative data of all subjects (1565) given finasteride in both controlled and open trials for the male pattern baldness program gave the following figures: decreased libido 2.2%, erectile dysfunction 1.9% and ejaculatory disorder 1.4%. In the 120-day safety update, lower figures were obtained in these AE, making the cumulative totals (among 2287 subjects: most of the additions being switches from placebo in the extension phases) also lower: decreased libido 1.9%, erectile dysfunction 1.5% and ejaculatory disorder 1.1%.

Comment

1. The Applicant should do an inter-study analysis (087 and 089) of the incidence of sexual adverse events, giving significance levels. Whether the difference is due to biologic or social factors remains to be explained.
2. The lower cumulative figures in the safety update must be interpreted with caution, as (1) those who had sexual AE earlier in the course might have exited from the study, thus making the remaining population less prone to such AE and (2) the safety update

period was relatively short compared with the original study time-frame.

10.1.6 Laboratory Findings Clinical studies on finasteride in male pattern baldness all involved periodic testing with CBC, serum chemistry and urinalysis. There were no consistent clinically significant findings. Only 60 patients (6.7%) in the finasteride group had a laboratory AE in phase 3 trials, similar to the incidence in placebo group (6.1%). Twenty-three patients (2.6%) in the finasteride group had a laboratory AE considered drug-related, also similar to the incidence of 2.4% in the placebo group. There were only three laboratory AE reported that occurred in ≥1% of the patients who had a laboratory test postbaseline (increased ALT, AST, and total bilirubin).

Table 10.1.6A Most Common Laboratory Adverse Experiences–Patient Count (%)# (Incidence ≥1% in Any Treatment Group): Phase 3 Controlled Studies

	Finasteride (N = 945)	Placebo (N = 934)
At least one test postbaseline	889	873
One or more AE	60 (6.7)	53 (6.1)
Blood Chemistry		
ALT increased	20/880 (2.3)	12/870 (1.4)
AST increased	17/881 (1.9)	12/870 (1.4)
Total serum bilirubin increased	9/881 (1.0)	5/870 (0.6)

In the phase 2 controlled studies, increases in ALT were observed in 3.4% of patients in the finasteride 5-mg group, 2.6% in the 1-mg group, and 2.8% in the placebo group. AST elevations were the same in the finasteride 5-mg and placebo (2.6%) groups and was 0.9% in the finasteride 1-mg group. These incidences for the 1 mg/d dose are similar to those in the phase 3 trials for ALT and AST. In the uncontrolled phase 2 studies, only 2 laboratory AE were reported in >1% of patients: increased ALT (21 patients; 4.5%) and increased AST (17 patients; 3.6%). The absence of a placebo group makes the significance of this result difficult to interpret.

Table 10.1.6B Nonfatal Serious Laboratory Adverse Experiences–Listing of Patients: Phase 3 Controlled, Phase 2 Controlled and Uncontrolled Studies

Number/Age	Dosage	Day of Test	Laboratory AE	Value/Unit	Therapy Discon-tinuation	Drug Relation-ship	Comments/History
Phase 3 Controlled							
089-2976/36	Pbo	213	Urine nitrite ↑, urine bilirubin ↑	Positive	No	Definitely not	Associated with the serious clinical AE of Hepatitis A
Phase 2 Controlled							
012-7381/41	fin 5	63	Leukopenia	1.60 ths/μL	Yes	Probably not	Associated with fever, rash, myalgia, & possible septal infarction age undetermined
012-7384/33	fin 5	63	Leukopenia	2.10 ths/μL	Interrupted	Probably not	Associated with fever, lethargy,
	fin 5	63	Thrombocytopenia	100.00 ths/μL	Interrupted	Probably not	anorexia, rash & otitis media
	Off 3 d /fin 5	65	Leukopenia	1.40 ths/μL	Interrupted	Probably not	
Phase 2 Uncontrolled							
081-5242/30	Off 3 d /fin 1	460	Platelet count ↓	68.00 ths/mm³	No	Probably not	Associated with the serious AE of hepatitis & pneumonia
	Off 3 d /fin 1	460	Leukocytes ↓	2.100 ths/mm³	No	Probably not	

*Pbo=placebo, fin=finasteride (number after fin indicates dose in mg/d)

One patient in each treatment group discontinued due to a laboratory AE in the phase 3 controlled studies. Both AE were nonserious ALT increases reported as drug-related.

In phase 2 controlled studies, 3 patients (1.3%) in the finasteride 5-mg group and 5 (1.1%) in placebo group discontinued due to laboratory AE. None in the 1-mg group discontinued. One in the 5-mg group discontinued due to the serious AE of leukopenia. There were no discontinuations for laboratory AE in the phase 2 uncontrolled studies.

10.1.7 Vital Signs No evidence of adverse effect

10.1.8 ECGs Not studied

10.1.9 Special Studies

The clinical program for safety of finasteride in the treatment of male pattern baldness included one PK study (106) and one long-term reversibility-of-effect study (094). In addition, two studies on semen production have been conducted (012 and 056).

10.1.9.1 Pharmacokinetic Study

A PK study entitled "An Open-Label, Multiple Dose Study to Investigate the Pharmacokinetics of Finasteride 1 mg Administered Orally in Healthy Adult Male Subjects" (Protocol 102) has been submitted in this NDA. The following are conclusions from the Applicant:

(1) Once-daily administration of finasteride 1 mg for 17 days results in a modest accumulation of plasma concentrations (~35% based on $AUC_{0\text{-}24\ hr}$ on Days 1 and 17).
(2) C_{max} increases over the 17-day dosing interval by ~40%, consistent with findings based on $AUC_{0\text{-}24\ hr}$.
(3) There are no significant differences in T_{max} or t½ after multiple-dose vs single-dose administration of 1 mg.
(4) Examination of mean trough plasma concentrations over the course of the 17-day experiment suggests that near steady-state conditions are achieved in healthy adults within 3 days of once-daily dosing with finasteride 1 mg.
(5) Multiple once-daily 1-mg doses of finasteride are well tolerated (no clinical AE reported).

Comment This study enrolled 12 subjects: 8 Hispanics and 4 Caucasians. Caution should be exercised in interpretation of its findings, although they are in general agreement with previous findings using the finasteride 5-mg tablet.

10.1.9.2 Studies on Semen Production in Normal Male Volunteers

Studies 012 and 056 (same title): A Double-Blind, Placebo-Controlled, Multicenter Study to Determine the Effect of Finasteride on Semen Production in Male Volunteers

Both studies used a dose of finasteride 5 mg/d, which is different from the proposed dosing in this NDA. These studies had similarities and differences and their design findings will be briefly presented here.

Table 10.1.9.2 Design and Key Findings in Studies 012 and 056

	012		056	
Design	Double-blind, randomized, Pbo-controlled, 2-wk run-in, 12-wk dosing, 12-wk off-drug Dose= 5 mg/d		Double-blind, randomized, Pbo-controlled 24-wk dosing, 24-wk off-drug, additional 24-wk off-drug Dose= 5 mg/d	
Centers	4 U.S. sites		12 U.S. sites	
Results	Fin	Pbo	Fin	Pbo
Subjects number	24	23	70	68
Age	31-49	31-50	18-49	18-49
Ejaculate vol				
%Δ after 12 wk use	-29.8	-2.9 (p=0.009)	-7.8	4.9 (p=0.002)
%Δ after 24 wk use	Use only for 12 weeks		-18.0	1.2 (p<0.001)
%Δ after 12 wk off	-23.9	-5.1 (p=0.031)	-14.0	1.5 (p=0.001)
%Δ after 36 wk off			-7.2	5.1 (p=0.002)
%Δ after 60 wk off			-4.4	0.6 (p=0.151)
%Δ after 84 wk off			-3.2	4.0 (p=0.246)
Total sperm/ejaculate				
%Δ after 12 wk use	-46.9	-15.9 (p=0.227)	-17.5	-3.2 (p=0.039)
%Δ after 24 wk use	Use only for 12 weeks		-30.4	-3.0 (p<0.001)
%Δ after 12 wk off	-26.1	-6.6 (p=0.659)	-7.7	-3.0 (p=0.244)
Percent motile sperm				
%Δ after 12 wk use	-11.1	-2.8 (p=0.230)	-4.4	-1.5 (p=0.002)
%Δ after 24 wk use	Use only for 12 weeks		-3.9	0.5 (p=0.014)
%Δ after 12 wk off	-1.1	0 (p=0.891)	-1.1	-0.6 (p=0.917)
Sperm concentration & morphology	No meaningful differences between treatment groups in either study			
Semen pH	No meaningful differences between treatment groups in either study			
Semen Fin levels on drug	2.2-7.0 ng/mL	N/A	0-10.54 ng/mL	N/A
Sexual Function Questionnaire during treatment	No difference between groups except for question on ejaculation without full erection (placebo less)		No difference between groups except for question on morning erection (placebo more frequent)	
Volumes of sex organs	No differences between groups in testes, seminal vesicles and prostate volumes during treatment		Not measured	
Plasma testosterone	Significant ↓ (~5%) in finasteride group vs baseline during treatment; not significant vs placebo		Significant between group diff during treatment (↓ for finasteride group: 15% at wk 12 & 9% at wk 24 vs -25% & -5% for placebo)	
Plasma DHT	Significant ↓ (-45% to -65%) from baseline in finasteride group in both studies: this being significant vs placebo			
Plasma LH & FSH	No significant between group differences in changes seen in either study			
Serum PSA	Significantly different in change from baseline between groups during treatment (lower in finasteride group, p≤0.003) in both studies. In 056, this effect was still observed 12 weeks off drug but there was no significant difference between groups by 24 weeks off drug.			
Serum lipid profile	Not measured		No meaningful effects observed in finasteride group	
Adverse Events [Patient Numbers and (%)]				
Clinical AE	11 (45.8)	6 (26.1)	35 (50.0)	33 (48.5)
Drug-related clinical AE	3 (12.5)	0	12 (17.1)	6 (8.8)
Sexual AE			8 (11.4)	3 (4.4)
Serious clinical AE	1 (4.2)	0	1 (1.4)	1 (1.5)
Discontinued due to clinical AE	2 (8.3)	0	1 (1.4)	1 (1.5)

Serious AE: In 012, one subject [redacted]) on finasteride had laminectomy for displaced L5. In 056, Subjects [redacted] (finasteride) - severe back pain and [redacted] (placebo) - death by committing suicide.

AE discontinuations: In 012, subject [redacted] (viral infection) and subject [redacted] (hydrocele), both on finasteride. In 056, Subjects [redacted] on finasteride (libido decrease and rash) and [redacted] on placebo (death by committing suicide).

Oligospermia as a laboratory AE: In 012, one subject on finasteride developed oligospermia and in 056, 4 subjects in each group developed oligospermia. In 056, two consecutive evaluations showing sperm concentration < $2x10^7$/mL or total sperm count <$2x10^7$/ejaculate would result in "laboratory AE leading to

discontinuation": this occurred in 2 finasteride and 5 placebo subjects.

Comments
1. These two studies demonstrate the reversibility of finasteride effect on semen production after dosing at 5 mg/d for 12 or 24 weeks. Ejaculate volume took the longest time to return, while semen finasteride levels became undetectable within 72 hours of stopping dosing after 24 weeks of treatment. Hormonal levels (T, DHT, LH and FSH) returned to normal when tested 12 weeks after the last dose but serum PSA remained low until retested at 24 weeks off drug. As males with inherited deficiency of the 5α-reductase may have normal spermatogenesis in the absence of undescended testes, it appears that T is the hormone necessary for normal spermatogenesis, whereas DHT may have a minor role (as inhibition of 5α-reductase did impair testosterone-dependent restoration of spermatogenesis in adult rats; *Endocrinology* 137: 2703, 1996). The small differences in sperm concentration, motility and morphology between treatment groups in these two studies with the use of finasteride 5 mg/d tend to support this hypothesis.
2. The amount of finasteride in ejaculate [maximum of 11 ng/mL x 5 mL = 55 ng] during treatment is less than 0.6% of the no effect (oral) dose based on DHT suppression (0.01 mg/d; Study 081).

10.1.9.3 Long-Term Reversibility-of-Effect Study

Study 094: A Double-Blind, Randomized, Placebo-Controlled, Multicenter Study to Evaluate the Safety of Low-Dose Finasteride in Male Volunteers

OBJECTIVES:

(1) To evaluate the effect of 48 weeks of treatment with finasteride 1 mg/day in young male volunteers and the reversibility of such effects* on (a) prostate volume, (b) serum PSA; (c) sexual function; (d) plasma lipids; (e) semen production; and (f) bone density and indices of bone metabolism; and
(2) to further evaluate the safety and tolerability of finasteride 1 mg/day in young male volunteers.

STUDY DESIGN: Phase 2, Double-blind, randomized, placebo-controlled, multicenter (13 U.S. centers) study with 48-week treatment period using finasteride at 1 mg/d followed by a 60-week reversibility phase in healthy male volunteers aged 18-40.
Evaluations included:

AE assessment/Sexual Function Questionnaire
laboratory safety tests/serum PSA/plasma lipids
prostate volume (by MRI)

In separate subsets of the study population:

Semen analysis:	ejaculate volume, total sperm per ejaculate, sperm concentration, semen pH, percentage of cells with normal morphology, and percentage of motile sperm; and
Bone metabolism:	bone densitometry (lumbar spine DXA)/urinary N-telopeptide (NTX)/serum bone-specific alkaline phosphatase (BSAP).

Semen slides were prepared and shipped to the laboratory , for measurement of percent of

sperm with normal morphology. acted as a central reading and coordination facility for the data. **A single blinded reader at** analyzed all scans, and final, blinded reports were submitted to Merck Research Laboratories.

Comment Qualification of should be submitted for review.

Preplanned Statistical Analyses:
The primary analysis for assessing the 48-week treatment effect was focused on the Week 48 data based on the Week 48 per-protocol population.

For prostate volume and ejaculate volume, where a minimal **clinically meaningful** difference of 10% was prespecified in the protocol, the decision rule for these two parameters was based on the 90% CI for the between-group difference. If the 90% CI was within (-10%, 10%), **regardless of whether zero was included, then the conclusion was that the treatment difference was less than 10%.** For all other parameters, the statistical approach was based on the 95% CI for the between-group mean difference and p-value.

Results:

Subject Accounting	Finasteride	Placebo	Total
ENTERED: (age range)	91	90	181
COMPLETED:	86	75	161
DISCONTINUED: Total	5	15	20
Clinical AE	0	2	2
"Other"	0	1	1
Lost to follow-up	1	7	8
Noncompliance	1	0	1
Relocating	0	1	1
Protocol violation	1	3	4
Wished to father child	1	1	2
Mate pregnant	1	0	1

Baseline Comparability The treatment groups were comparable. However, 89-93% in each group were Caucasians.

Key Findings
1. Prostate Volume, Semen Parameters, PSA, Bone Density Parameters and Lipid Profile Changes at Week 48.

Table 10.1.9.3A Changes From Baseline at Week 48 in Prostate Volume, Semen Parameters, PSA, and Bone Mineral Density Parameters and Lipid Profile in Study 094

	Mean or Median (N)		Difference + and CI for	Between-Group
	Finasteride	Placebo	Difference	p-Value
Prostate Volume				
Mean percent change + from baseline	-2.6* (82)	1.3 (71)	-3.9 (-6.3, -1.4) [90%]	0.010
Ejaculate Volume				
Median percent change from baseline	-10.9 (37)	-7.8 (30)	1.0 (-10.4, 13.1) [90%]	0.915
Sperm Concentration				
Median percent change from baseline	-5.6 (37)	-15.7 (30)	5.2 (-9.0, 20.8) [95%]	0.395
Total Sperm per Ejaculate				
Median percent change from baseline	-11.0 (37)	-20.3* (30)	6.3 (-13.9, 24.2) [95%]	0.583
Semen pH				
Median change from baseline	0.1* (37)	0.1 (30)	0.1 (-0.1, 0.2) [95%]	0.596
Percentage of Sperm With Normal Morphology				
Median change from baseline	-1.0 (37)	-0.3 (30)	0.0 (-2.0, 2.0) [95%]	0.990
Percentage of Motile Sperm				
Median change from baseline	-0.8 (37)	2.8 (30)	-3.5 (-7.7, 0.0) [95%]	0.059
PSA				
Mean change from baseline	-0.2** (80)	0.0 (70)	-0.2 (-0.3, -0.1) [95%]	<0.001
Bone Mineral Density				
Mean percent change + from baseline	0.7 (34)	-0.2 (29)	0.9 (-0.1, 2.0) [95%]	0.083
NTX				
Median percent change from baseline	-43.1** (34)	-11.3 (30)	-28.3 (-50.1, -5.9) [95%]	0.020
BSAP				
Median percent change from baseline	4.4 (34)	14.0** (31)	-9.7 (-17.8, -1.5) [95%]	0.021
Lipid Profile (Mean percent change from baseline)				
Total Cholesterol	4.7 ** (81)	4.2* (70)	0.5 (-4.0, 5.0) [95%]	0.826
Triglycerides	10.0 (81)	10.8 (70)	-0.8 (-22.0, 20.5) [95%]	0.944
HDL Cholesterol	6.2 ** (80)	4.8* (70)	1.4 (-3.3, 6.1) [95%]	0.550
LDL Cholesterol	5.8 ** (78)	3.2 (66)	2.6 (-3.4, 8.6) [95%]	0.395
VLDL Cholesterol	16.2 (78)	17.7 (66)	-1.5 (-27.7, 24.7) [95%]	0.909
Lipoprotein Lp (a)	11.8 * (80)	6.8 (70)	5.0 (-10.8, 20.9) [95%]	0.532
Apolipoprotein Al	4.2 * (80)	4.3* (70)	-0.1 (-4.5, 4.2) [95%]	0.956
Apolipoprotein All	6.4 ** (80)	6.2** (70)	0.2 (-5.3, 5.6) [95%]	0.954
Apolipoprotein B	6.3 ** (80)	5.8** (70)	0.5 (-4.5, 5.6) [95%]	0.836

+ : Adjusted for treatment and center effects, *: Significant change from baseline at the $p < 0.050$ level.
†: Median difference was computed using the Hodges-Lehmann procedure.

Comments

1. Since the 90% CI for the between-group differences was contained with ±10%, which was the predefined minimal clinically important difference, this was taken to mean that finasteride did not affect prostate volume by more than 10%, although the 3.9% mean difference in prostate volume percent change indicated that the finasteride group decreased significantly ($p = 0.010$) more than the placebo group.
2. The data on ejaculatory volume are inconclusive because of large variability. The median percent change in volume at week 48 (-10.9%) and the lower limit of the 90% confidence interval (-10.4%) both fell below the predefined limit of -10%.

2. Sexual Function Questionnaire at Week 48.

Table 10.1.9.3B Summary Statistics for Domains/Questions of the Sexual Function Questionnaire

	Finasteride		Placebo		Between-Group
	Mean		Mean		
Domain/Question (Total Score Range)	N	Change	N	Change	p-Value
Week 48					
Sexual interest (0 to 8)	72	-0.3	69	-0.3	0.898
Erections (0 to 11)	72	-0.4	69	-0.3	0.734
Ejaculation (0 to 6)	72	-0.2*	67	-0.2	0.886
Perception of problems (0 to 12)	72	-0.6**	67	-0.3	0.180
Global question (0 to 4)	72	-0.1	69	-0.2	0.515
Morning erections (0 to 4)	72	-0.2*	69	0.1	*0.021*

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

Comment There were no significant differences between treatment groups in changes from baseline for the Questionnaire's 4 Domains and 2 distinct Questions (Global question and Morning Erections) during the treatment period except for (1) Sexual Interest at week 36 (finasteride -0.5, placebo 0; p=0.023, data not shown in Table) and Morning Erections at week 48.

3. Hormone Levels at Week 48.

Serum Dihydrotestosterone: Median percent change from baseline in DHT in the finasteride group was -62.0% ($p< 0.010$) and in the placebo group -6.5% ($p < 0.010$). The difference between the two groups was significant ($p < 0.001$).

Serum Testosterone: Median percent change in the finasteride group was 15.6% ($p < 0.010$) and in the placebo group -7.5% ($p < 0.050$). The difference between the two groups was significant ($p < 0.001$).

LH and FSH: No significant difference between arms in the mean percent change from baseline in either parameter at Week 48.

4. Adverse Experiences.

Table 10.1.9.3C Adverse Experience Summary–Patient Count (%)

	Finasteride (N = 91)	Placebo (N = 90)		Finasteride (N = 89)	Placebo (N = 86)
Clinical AE	65 (71.4)	62 (68.9)	Laboratory AE	8 (9.0)	8 (9.3)
Drug-related clinical AE	7 (7.7)	6 (6.7)	Drug-related laboratory AE	2 (2.2)	1 (1.2)
Sexual AE	4 (4.4)	3 (3.3)	Serious laboratory AE	0	0
Serious clinical AE	1 (1.1)	3 (3.3)	Discontinued due		
Discontinued due to clinical AE	0	2 (2.2)	to a laboratory AE	0	0

There were no serious drug-related adverse experiences.

Details of adverse event incidences are provided in Appendix VI. The most common AE was decreased libido (finasteride 3.3% and placebo 2.2%).

Sexual AE were defined as untoward effects on sexual function and were all considered to be drug related. Their incidence is shown in Table 10.1.9.3D.

Table 10.1.9.3D Sexual Adverse Experiences–Subject Count (%)*

	Finasteride (N = 91)	Placebo (N = 90)
one or more sexual AE	4 (4.4)	3 (3.3)
Libido decreased	3 (3.3)	2 (2.2)
Ejaculation disorder	1 (1.1)	0
Impotence	1 (1.1)	2 (2.2)

Serious Adverse Events are shown in Table 10.1.9.3E.

Table 10.1.9.3E Serious Adverse Events in Study 094

Number	Age/drug	Relative Day of Onset	AE	Therapy Duration (Days)/Intensity	Drug Relation-ship	Discon-tinua-tion	Outcome
	34/fin	199	Early squamous cell carcinoma	23 hours/Mild	Definitely not	No	Recovered
	26/P	5	Trauma, cartilage	3/Severe	Definitely not	No	Recovered
	30/P	95	Hernia, inguinal	46/Severe	Definitely not	No	Recovered
	36/ Off 2 days P	202	Appendicitis	2/Severe	Probably not	No	Recovered

P=placebo, fin=finasteride

Two placebo subjects were discontinued from therapy due to clinical AE: impotence (subject and decreased libido and impotence (subject

5. Reversibility of Effect in Off-Drug Phase.

The original submission included data from the on-drug phase of this study (Week 0 to 48). The 120-day safety update provided data up to week 72. At the end of the on-drug phase, four parameters were significantly different between finasteride and placebo groups: prostate volume, PSA, NTX and BSAP. The Applicant did not consider the prostate volume change as being clinically significant and MRI has not been repeated beyond week 48. The following Table gives data of PSA, NTX and BSAP after week 48 (with figures corrected as in 10/10/97 submission).

Table 10.1.9.3F Changes From Baseline after Week 48 in PSA and Bone Metabolic Parameters

		Finasteride 1 mg				Placebo				
	Week	N	Baseline	Follow-up	Change	N	Baseline	Follow-up	Change	p-Value
NTX (median)	48	34	44.7	40.2	-18.3%*	30	33.9	36.0	-9.9%	0.047#
(nmol BCE/nmol Cr)	60	29	49.5	36.7	-15.5%*	28	33.9	33.0	0.9%	0.124#
	72	28	44.7	39.8	-14.%7	22	33.3	37.8	-14.1%	0.568#
BSAP (mean)	48	34	13.6	13.5	4.4%	31	10.8	11.6	14.0%*	0.021#
(ng/mL)	60	29	13.8	12.4	-10.3%**	29	10.6	10.2	-5.1%	0.211#
	72	30	14.0	12.7	-9.4%*	25	10.9	11.1	2.1%	0.030#
PSA (mean)	60	76	0.7	0.8	0.1	67	0.6	0.6	0	0.127
(ng/mL)	72	72	0.7	0.7	0.1	61	0.6	0.6	0	0.496

: Adjusted for treatment and center effects, *,**: Significant change from baseline at the p ≤0.050 and ≤0.01 levels respectively.

Comments

1. The present clinical study was conducted to determine whether finasteride 1 mg/day for 48 weeks affected prostate volume in young men without BPH. Finasteride for 48 weeks reduced mean prostate volume by 0.7 cc (mean percent change = -2.6%) vs 0.3 cc increase (+1.3%) with placebo. However, this was considered not clinically significant decrease based on the predefined criteria that effects on prostate volume less than 10% are not clinically important.
2. Serum PSA decreased slightly with finasteride. At Week 48, the serum PSA of subjects treated with finasteride had decreased by ng/mL from baseline, significantly different from placebo.
3. In contrast to data from Studies 012 and 056 which used finasteride 5 mg/d, finasteride 1 mg/d for 48 weeks had little effect on semen production. Median ejaculate volume at the end of the on-drug period (4 spermatogenic cycles) decreased by mL (median % decrease = 10.9%), not significantly different from changes with placebo (-0.2 mL, median % decrease = 7.8%). In comparison with Study 056, there appears to be a dose-dependent effect of finasteride therapy on ejaculate volume (-0.6