CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-834

STATISTICAL REVIEW(S)

CLINICAL/STATISTICAL REVIEW AND EVALUATION

JUN 20 1997

NDA/Drug Class:	20-834
APPLICANT:	The Upjohn Company
NAME OF DRUG:	Rogaine Extra Strength for Men (Minoxidil topical solution 5%)
INDICATION(S):	Androgenetic Alopecia in Males and Females
TYPE OF REVIEW:	Clinical/Statistical
DOCUMENTS REVIEWED:	Volumes 1.1, 1.2, 1.181-1.280, Study# M/7415/0001 & Study# M/7410/0285
CLINICAL INPUT:	Dated December 22, 1995 Phillis Huene, M.D. (HFD 540)

I. INTRODUCTION

Rogaine Topical Solution 2% (2% minoxidil solution) was the first drug approved for the treatment of male pattern baldness in the United States in 1988 and for androgenetic alopecia in females in 1991. The sponsor claims that data from clinical studies that included minoxidil concentrations greater than 2% suggested that, dosing modifications (ie, applying higher concentrations of topical minoxidil solution) may enhance the therapeutic efficacy, which is the purpose of this new drug application.

The sponsor intends to demonstrate the safety and superiority of 5% Rogaine to 2% Rogaine and Placebo. The sponsor has submitted the results of two studies (studies M/7415/0001 and M/7410/0285) which are the basis for the approval of the new drug application of Rogaine Extra Strength for Men for the treatment of androgenetic alopecia to be approved for OTC purposes.

Study M/7415/0001 has used hair count as the sole primary endpoint to demonstrate the efficacy of Regain 5, whereas, study M/7410/0285 provides questionnaires to assess the satisfaction of the patients and global assessment of the investigator, in addition to hair count (total of three endpoints).

The FDA requires two **independent**, randomized, adequate and well-controlled, double blind, **multi center** studies for its approval. However, It was observed that study M/7415/0001 is a one center trial. Moreover, it was noted that a few of the investigators participated in more than one trial. In particular, center# 11917 participated in studies

M/7415/0001 and M/7410/0285 which are both male studies. These violations make the validity of these trials questionable. To resolve these problems in a certain extend, one of the centers which was in common in both studies was eliminated from study M/7410/0285 (n=100).

The table below summarizes the studies under review.

Table I, Overview of Pivotal Studies

Study #	Study Design	Treatment (n)	N	Treatment Duration	Endpoints	# of Centers
M/7415/0001 (Male)	Double Blind, PBO/Controlled	PBO (85) 2% (86) 5% (174)	345	32 Weeks	Hair Count	1
M/7410/0285 (Male)	Double Blind, PBO/Controlled	PBO (78) 2% (158) 5% (157)	393	48 Weeks	Hair Count Patient Questionnaire Investigator Questionnaire	6

In order to gain approval for the new formulation, the sponsor should show statistical superiority of the following: 1) Rogaine 5% to placebo, and 2) Rogaine 5% to Rogaine 2% at a two-sided, 5% significance level. The sponsor has performed Analysis of Variance test in their data analyses.

The main focus of this review is on patient's hair growth at the end of the treatment period on the evaluable population.

For study M/7410/0285 two different approaches were made. First, the analyses were performed on the data set based on all randomized subjects whose end of treatment hair count was available. This data set will be referred to as FDA-Evaluable (FDA_Eval) data. Second, in order to maintain the integrity of the randomization, an intent-to treat analysis was done. For the subjects who did not finish the 48-week treatment, the baseline hair count value was carried forward to replace their missing week 48 hair count value. In other words, subjects with missing hair count at the end of 48 weeks will show no change from the baseline. Because of the non-linearity of the hair count distribution throughout the 48 weeks, we found it inappropriate to attempt to carry the last observation forward.

II. REVIEW OF STUDIES,
EFFICACY

Study No. M/7415/0001 (Male):

Objectives, Design, Patient Enrollment and Statistical Methods:

The objective of this study was to evaluate the safety and efficacy of 5% Topical Minoxidil Solution (TMS) for the treatment of androgenetic alopecia and to compare results with those obtained with Rogaine Topical Solution 2% and PBO (vehicle for 5% solution) after thirty-two weeks of treatment in males.

This was a 32-week, double-blind, single-center, parallel design, phase III study of male patients with androgenetic alopecia. Patients were randomly assigned (approximately 2:1:1 ratio) to 5% TMS, 2% TMS and Placebo. Patients were instructed to apply 1.0 ml of the test solution to the affected area twice daily, 12 hours apart.

The primary endpoint for this study was nonvellus hair counts.

A total of three hundred and forty-five otherwise healthy male patients with androgenetic alopecia were randomly assigned to 5% TMS (n=174), 2% TMS (n=86), and placebo (n=85). Three hundred and twenty-one patients completed the entire 32 week study period.

A one-way analysis of variance statistical methodology was used to look at the difference among the three treatment groups in the primary endpoint variable, change in hair growth. The sponsor has used protected LSD (least significant difference) test for pairwise comparisons of the three treatment groups. In this review both the LSD method and the contrast method were used.

Evaluable Subjects:

A total of twenty-four subjects did not complete the 32-week treatment. Eleven (6%) of these patients had been assigned to the 5% TMS, 7 (8%) to the 2% TMS and 6 (7%) to the placebo arm. These subjects were eliminated from the analysis of efficacy.

Baseline Comparability:

The distribution of demographic and baseline characteristics were not statistically different among all three treatment groups. The FDA requires a multi-center studies for its approval. This was a single center study. For this reason there might be some potential bias in this trial. The demographic and baseline information are summarized in table II below:

Table II
Demographics and Baseline Characteristics of All Randomized Subjects
M/7415/0001 (Male)

	Whole Population (N=345)	5% TMS (n=174, 50%)	2% TMS (n=86, 25%)	Placebo (n=85, 25%)	P-Value
Age (Mean):	35	35	35	36	0.58
Race (n):					
White	314 (91%)	157 (90%)	78 (91%)	79 (93%)	0.57
Hispanic	24 (7%)	14 (8%)	5 (6%)	5 (6%)	
Black	2 (0.6%)	1 (0.6%)	1 (1%)	0 (0%)	
Oriental	1 (0.3%)	0 (0%)	0 (0%)	1 (1%)	
Other	4 (1%)	2 (1%)	2 (2%)	0 (0%)	
Baseline Hair Count (Mean):	105	107	103	105	0.80
Years of Hair Loss (Mean):	8	8	7	7	0.28
Duration of Hair Loss Category (n):					0.08
1 to <3	35 (10%)	20 (11%)	9 (10%)	6 (7%)	
3 to <5	60 (17%)	24 (14%)	20 (23%)	16 (19%)	
5 to < 10	144 (42%)	72 (41%)	29 (34%)	43 (51%)	
10 to < 15	69 (20%)	36 (21%)	23 (27%)	10 (12%)	
15 to <20	19 (6%)	9 (5%)	4 (5%)	6 (7%)	
>= 20	18 (5%)	13 (7%)	1 (1%)	4 (5%)	

Efficacy Analysis:
A total of 42 subjects lost hair in the 32-week study period.

Table III
Subjects with decrease hair count among three treatment groups
M/7415/0001 (Male)

Treatment	n	Mean (hair loss)	Range (hair loss)
5% TMS	7	17	
2% TMS	8	8	
Placebo	26	10	

Hair loss at the end of the study was not statistically different among the three treatment groups (p>0.2). (These results should be interpreted with caution, since the sample size being used is too small).

The table IV lists the mean hair count at baseline and mean hair count at week-16, week-32 and the mean changes for each treatment group.

Table IV
Comparison of change in hair count by treatment group (FDA_Eval)
M/7415/0001 (Male)

	5% TMS (Mean)	2% TMS (Mean)	Placebo (Mean)	P-Value (5% vs. 2% vs. PBO)	P-Value (5% vs. 2%)
Week_0	107	103	105	0.80	0.52
Week_16	142	129	110	0.0001	0.03
Week_32	145	133	110	0.0001	0.06*
Week_16 - Week_0	36	26	5	0.0001	0.002
Week_32 - Week_16	3	4	1	0.55	0.54
Week_32 - Week_0	39	30	5	0.0001	0.006

* At week 32, the average hair count is not statistically different between 5% and 2% solutions.

The mean change hair count from baseline to the end of the 32-week period was still statistically significant when the results were adjusted for age, baseline hair count and years of hair loss among the three treatment groups, p<.001; pairwise comparison between 5%TMS vs. 2%TMS, yielded p<.05.

Conclusions:
The results of the male study, M/7415/0001 indicated a strong statistical superiority of 5% Rogaine to 2% Rogaine and placebo relative to hair growth in males (p=.001) after 32-weeks treatment period.

Study No. M/7410/0285 (Male):

Objectives, Design, Patient Enrollment and Statistical Methods:

The purpose of this study was to determine the safety and efficacy of 5% Topical Minoxidil Solution (TMS) for the treatment of androgenetic alopecia and to compare results with those obtained with Rogaine Topical Solution 2% and PBO (vehicle for 5% solution) after forty-eight weeks of treatment in males.

This was a 48-week, double-blind, randomized, placebo controlled, six-center, parallel design, phase III study of male patients with androgenetic alopecia. Patients were randomly assigned (approximately 2:2:1 ratio) to 5% TMS, 2% TMS and Placebo. Patients were instructed to apply 1.0 ml of the test solution to the affected area twice daily, 12 hours apart.

This study was designed to evaluate the nonvellus hair counts and also density ratings questionnaires from both the patient and investigator perspectives. The sponsor has selected three primary endpoints for the final results. These were: 1) Change in nonvellus hair count, 2) Change in scalp coverage (from the patient questionnaire), 3) Benefit from treatment (patient questionnaire). In this review, also three primary endpoints have been analyzed. However, instead of the 'Benefit from treatment, from the patient questionnaire', 'Change in scalp coverage from baseline from the investigator questionnaire' was chosen by the medical officer as the third primary endpoint. In order to gain approval, the sponsor should show statistical significance for all three primary endpoints, at a significance level of 0.05.

A total of 393 otherwise healthy male patients with androgenetic alopecia were randomly assigned to 5% TMS (n=157), 2% TMS (n=158), and placebo (n=78). Of these, a total of 346 subjects completed the entire 48 week.

A one-way analysis of variance statistical methodology was used to look at the difference among the three treatment groups in the primary endpoint variables, change in hair growth. The sponsor has performed a protected LSD (least significant difference) test for pairwise comparisons of the three treatment groups. In this review both the LSD method and the contrast method were used, but only the results from the contrast procedure will be reported. Questionnaire variables from visual analog scale, change in scalp coverage according to the patient and change in scalp coverage according to the investigator, were also treated as continuous variables and analyzed in the same manner.

Sample Size:

As was mentioned before in the introduction section, this study and study M/7415/0001 had investigator # 11917 in common. To maintain the independence of these two trials, this center was eliminated from the analysis of this study. A total of 100 subjects had been enrolled to this center. The entire population were removed from the data set. Therefore,

the number of subjects decreased from 393 to 293. This reduces the power of the study. Hence, the results of this trial should be interpreted with caution, since the analysis might not have enough statistical power.

Evaluable Subjects:

A total of thirty-five (12%) subjects did not complete their 48-week treatment. Of these, 14 (12%) had been assigned to the 5% TMS, 16 (14%) to the 2% TMS and 5 (9%) to the placebo arm. All of these patients were excluded from the 48-week FDA_Evaluable data for the purpose of efficacy analysis.

Baseline Comparability:

Eliminating center 11917 did not change the distribution of demographic and baseline characteristics among the three treatment groups. The demographic and baseline information are summarized in table IX:

Table IX
Demographics and Baseline Characteristics of All Randomized Subjects
M/7410/0285 (Male)

	Whole Population (N=293)	5% TMS (n=117, 40%)	2% TMS (n=118, 40%)	Placebo (n=58, 20%)	P-Value
Age (Mean):	37	36	37	37	0.56
Race (n):					
White	230 (79%)	86 (74%)	97 (82%)	47 (81%)	0.09
Hispanic	52 (18%)	27 (23%)	17 (14%)	8 (14%)	
Black	5 (2%)	1 (0.9%)	4 (3%)	0 (0%)	
Oriental	3 (1%)	2 (2%)	0 (0%)	1 (2%)	
Other	3 (1%)	1 (0.9%)	0 (0%)	2 (3%)	
Baseline Hair Count (Mean):	150	149	148	156	0.53
Years of Hair Loss (Mean):	10	10	10	10	0.95
Duration of Hair Loss Category (n):					0.59
1 to <3	11 (4%)	3 (3%)	4 (3%)	4 (7%)	
3 to <5	35 (12%)	15 (13%)	15 (13%)	5 (9%)	
5 to < 10	101 (34%)	42 (36%)	42 (36%)	17 (29%)	
10 to < 15	76 (26%)	32 (27%)	25 (21%)	19 (33%)	
15 to <20	44 (15%)	14 (12%)	23 (19%)	7 (12%)	
>= 20	26 (9%)	11 (9%)	9 (8%)	6 (10%)	
Investigator:					1.0
9225	55 (19%)	22 (19%)	22 (19%)	11 (19%)	
9677	60 (20%)	24 (21%)	24 (20%)	12 (21%)	
10225	62 (21%)	25 (21%)	25 (21%)	12 (21%)	
13470	55 (19%)	22 (19%)	22 (19%)	11 (19%)	
13471	61 (21%)	24 (21%)	25 (21%)	12 (21%)	

Efficacy Analysis:

1. Hair Count:

A total of 46 subjects lost hair in the 32-week study period.

Table X
Subjects with decrease hair count at week 32 among three treatment groups
M/7410/0285 (Male)

Treatment	n	Mean (hair loss)	Range (hair loss)
5% TMS	12	11	
2% TMS	19	11	
Placebo	15	11	

The mean hair loss at the end of the 32 weeks was not statistically different among the three treatment groups (p>0.99). (These results should be interpreted with caution, since the sample size being used is too small).

A total of 80 subjects lost hair in the 48-week study period.

Table XI
Subjects with decrease hair count at week 48 among three treatment groups
M/7410/0285 (Male)

Treatment	n	Mean (hair loss)	Range (hair loss)
5% TMS	28	12	
2% TMS	26	14	
Placebo	26	17	

Hair loss at the end of the 48 weeks was not statistically different among the three treatment groups (p>0.4).

Table XII illustrates the mean hair count at baseline and mean hair count at week-16, week-32, week-48 and the mean changes for each treatment group based on FDA_Evaluable subjects. This data represents subjects whose week 48 hair count was available (n=258). This approach interfered with the randomization scheme. The distribution of race was statistically different after removing non-compliant patients from the analysis (p=.03).

Table XII
Comparison of change in hair count by treatment group (FDA_Eval)
M/7410/0285 (Male)

	5% TMS (n=103) (Mean)	2% TMS (n=102) (Mean)	Placebo (n=53) (Mean)	P-Value (5% vs. 2% vs. PBO)	P-Value (5% vs. 2%)
Week_0	150	145	154	0.5	0.4
Week_16	183	173	166	0.09	0.1
Week_32	179	167	161	0.04	0.06
Week_48	166	155	155	0.18	0.1
Week_16 - Week_0	33	27	12	0.0001	0.06
Week_32 - Week_16	-4	-5	-5	0.8	0.5
Week_48 - Week_32	-13	-12	-6	0.09	0.6
Week_32 - Week_0	30	22	7	0.0001	0.02
Week_48 - Week_0	17	10	1	0.0004	0.04

From table XII, it is seen that the mean hair growth for the 5% Rogaine group and the 2% Rogaine group are not statistically different, at week_16 (p=0.1), week_32 (p=0.06), and week_48 (p=0.1).

The mean in change hair count from baseline, however, was highly statistically significant among the three arms at week_32 and week_48 ($p<0.001$) and statistically significant at point 0.05 between the 5% and 2% groups.

Adjusting for age yielded to a border-line significance between the 5% and 2% solutions ($p>.06$).

In order to sustain the integrity of randomization, the baseline hair count value was carried forward for subject whose week 48 hair count was missing. This translates to no change in hair growth at week 48 for these subjects (n=293).

Table XIII shows the comparison of change in hair count by treatment group for the Intent-to-Treat population:

Table XIII
Comparison of change in hair count by treatment group (Intent - to - Treat)
M/7410/0285 (Male)

	5% TMS (n=117) (Mean)	2% TMS (n=118) (Mean)	Placebo (n=58) (Mean)	P-Value (5% vs. 2% vs. PBO)	P-Value (5% vs. 2%)
Week_0	149	148	156	0.5	0.9
Week_16	180	174	167	0.3	0.3
Week_32	179	166	161	0.05	0.06
Week_48	163	156	157	0.5	0.3
Week_16 - Week_0	33	27	13	0.0001	0.1
Week_32 - Week_16	-4	-6	-5	0.8	0.5
Week_48 - Week_32	-13	-12	-6	0.09	0.7
Week_32 - Week_0	29	21	7	0.0001	0.01
Week_48 - Week_0	15	9	1	0.0006	0.04

As can be seen from the tables XII and XIII, the results of the intent-to-treat analysis are not different from the results presented for evaluable subjects.

2. Change in Scalp Coverage Since Baseline, (Patient Questionnaire):
A total of 275 subjects, 112 (96%) in 5% TMS group, 109 (92%) in 2% TMS group and 54 (93%) in placebo group responded to the questionnaire regarding change in their scalp coverage at the 48th week since baseline. Each patient rated this change in scalp coverage from 0 to 100. An analysis of variance test was performed to compare these ratings.

Table XIV shows the means of change in scalp coverage at week 48 from baseline, based on the patients' questionnaires:

Table XIV
Comparison of Change in Scalp Coverage at Week 48 from Baseline According to the Patients
M/7410/0285 (Male)

	5% TMS (n=112) (Mean)	2% TMS (n=109) (Mean)	Placebo (n=54) (Mean)	P-Value (5% vs. 2% vs. PBO)	P-Value (5% vs. 2%)
Change in 48th Week from Baseline	62	57	52	0.0001	0.01

Patients in the 5% TMS group were satisfied with their scalp coverage more than the other treatment groups at the end of the treatment.

3. Change in Scalp Coverage Since Baseline, (Investigator Questionnaire):
A total of 365 responses were collected from the investigators regarding the change in scalp coverage of the subjects at the 48th week since baseline. Of these responses 147 (94%) were in 5% TMS group, 146 (92%) in 2% TMS group and 72 (92%) in placebo group. Each investigator rated the current scalp coverage. The change in scalp coverage was then calculated by subtracting the baseline scalp coverage from the current value. An analysis of variance test was performed to compare these changes.

Table XV shows the means of change in scalp coverage at week 48 from baseline based on the investigators' questionnaires:

Table XV
Comparison of Change in Scalp Coverage at Week 48 from Baseline According to the Investigators
M/7410/0285 (Male)

	5% TMS (n=147) (Mean)	2% TMS (n=146) (Mean)	Placebo (n=72) (Mean)	P-Value (5% vs. 2% vs. PBO)	P-Value (5% vs. 2%)
Change in 48th Week from Baseline	12	7	2	0.004	0.03

Investigators rated change in scalp coverage for patients in the 5% TMS group more favorably than the other treatment groups at the end of the treatment period.

In order to detect an investigator bias in this analysis, another test was run controlling for the investigator effect. The above results did not change.

Conclusions:

The results of the male study, M/7410/0285, indicated a strong statistical superiority of 5% Rogaine to 2% Rogaine and placebo in regards to hair growth in males (p=.001). Patients and the investigators noticed a significantly higher change in scalp coverage at week 48 from baseline with 5% Rogaine than the 2% (p<.05).

III. CONCLUSIONS (which may be conveyed to the sponsor):

Studies M/7415/0001 and M/7410/0285 provide a statistical evidence to the applicant's claim that 5% Rogaine induces more nonvellus hair increase in a male population in 48 weeks. However, it is not clear whether or not the hair growth effect will remain after the 48 week period.

SAFETY

The adverse events considered in this review are, dryness, erythema, folliculitis, itching and stinging. These elements were reviewed for each one of the studies separately. In addition, the two studies were pooled together and analyzed as the integrated safety summary. The p-values for the Chi-Square statistics are reported in tables I, II and III.

Study No. M/7415/0001

The safety data for the total of 345 patients who had participated in this study was analyzed. Table I summarizes the number of subjects with adverse events, the percentages in each treatment group and the corresponding p-values for all treatment groups together and for 5% TMS vs. 2% TMS:

Table I
ADVERSE REACTIONS
MALE STUDY M/7415/0001

Adverse Events	5% TMS	2% TMS	PBO	p-value	
				All Trts.	5% vs. 2%
Dryness				*0.08*	*0.02**
None	*71 (41%)*	*51 (59%)*	*45 (53%)*		
Mild	*78 (45%)*	*30 (35%)*	*31 (36%)*		
Moderate	*23 (13%)*	*5 (6%)*	*9 (11%)*		
Severe	*2 (1%)*	*0 (0%)*	*0 (0%)*		
Erythema				*0.08*	*0.05**
None	*158 (91%)*	*85 (99%)*	*79 (93%)*		
Mild	*12 (7%)*	*1 (1%)*	*6 (7%)*		
Moderate	*4 (2%)*	*0 (0%)*	*0 (0%)*		
Severe	—	—	—		
Folliculitis				*0.89*	*0.78*
None	*161 (93%)*	*80 (93%)*	*80 (94%)*		
Mild	*12 (7%)*	*6 (7%)*	*5 (6%)*		
Moderate	*1 (0.6%)*	*0 (0%)*	*0 (0%)*		
Severe	—	—	—		
Itching				*0.10*	*0.21*
None	*121 (70%)*	*70 (81%)*	*72 (85%)*		
Mild	*32 (18%)*	*11 (13%)*	*10 (12%)*		
Moderate	*18 (10%)*	*4 (5%)*	*2 (2%)*		
Severe	*3 (2%)*	*1 (1%)*	*1 (1%)*		
Stinging				*0.71*	*0.57*
None	*160 (92%)*	*81 (94%)*	*80 (94%)*		
Mild	*12 (7%)*	*5 (6%)*	*5 (6%)*		
Moderate	*2 (1%)*	*0 (0%)*	*0 (0%)*		
Severe	—	—	—		

As it is shown in table I, more subjects in the 5% TMS arm suffered from dryness and erythema than the 2% TMS.

* Statistically significantly more adverse events were found in the 5% TMS arm.

Study No. M/7410/0285

The safety data for the total of 393 patients who had participated in this study was analyzed. The data for erythema and folliculitis were not collected for this study. Table II summarizes the number of subjects with adverse events, their percentages in each treatment group and the corresponding p-values for all treatment groups together and for 5% TMS vs. 2% TMS:

Table II
ADVERSE REACTIONS
MALE STUDY M/7410/0285

Adverse Events	5% TMS	2% TMS	PBO	p-value	
				All Trts.	5% vs. 2%
Dryness				*0.001*	*0.001**
None	*72 (46%)*	*119 (75%)*	*44 (56%)*		
Mild	*71 (45%)*	*34 (22%)*	*26 (33%)*		
Moderate	*12 (8%)*	*5 (3%)*	*8 (10%)*		
Severe	*2 (1%)*	*0 (0%)*	*0 (0%)*		
Itching				*0.001*	*0.001**
None	*86 (55%)*	*116 (73%)*	*79 (63%)*		
Mild	*42 (27%)*	*36 (23%)*	*22 (28%)*		
Moderate	*23 (15%)*	*4 (3%)*	*7 (9%)*		
Severe	*6 (4%)*	*2 (1%)*	*0 (0%)*		
Stinging				*0.42*	*0.47*
None	*128 (82%)*	*135 (85%)*	*71 (91%)*		
Mild	*22 (14%)*	*19 (12%)*	*6 (8%)*		
Moderate	*5 (3%)*	*4 (3%)*	*1 (1%)*		
Severe	*2 (1%)*	*0 (0%)*	*0 (0%)*		

It can be seen from table II that a statistically significant number of subjects suffered from dryness and itching in the 5% TMS group as compared to the 2% TMS.

* Statistical significance indicating a higher number of subjects with adverse events in the 5% TMS arm.

Integrated Safety Summary (ISS):

The safety data for the total of 738 patients who had participated in the both pivotal male studies (study M/7410/0001 & study M/7410/0285) were pooled and analyzed. Table III summarizes the number of subjects with adverse events and their percentages in each treatment group and the corresponding p-values for all treatment groups together and for 5% TMS vs. 2% TMS:

Table III
ADVERSE REACTIONS
MALE STUDIES M/7415/0001 & M/7410/0285
(ISS)

Adverse Events	5% TMS	2% TMS	PBO	P-value			
				All Trts.	5% vs. 2%	5% vs. PBO	2% vs. PBO
Dryness				*0.001*	*0.001**	*0.05**	*0.003***
None	*143 (43%)*	*170 (70%)*	*89 (55%)*				
Mild	*149 (45%)*	*64 (26%)*	*57 (35%)*				
Moderate	*35 (11%)*	*10 (4%)*	*17 (10%)*				
Severe	*4 (1%)*	*0 (0%)*	*0 (0%)*				
Erythema				*0.08*	*0.05**	*0.37*	*0.05***
None	*158 (91%)*	*85 (99%)*	*79 (93%)*				
Mild	*12 (7%)*	*1 (1%)*	*6 (7%)*				
Moderate	*4 (2%)*	*0 (0%)*	*0 (0%)*				
Severe	—	—	—				
Folliculitis				*0.89*	*0.78*	*0.74*	*0.77*
None	*161 (93%)*	*80 (9336%)*	*80 (94%)*				
Mild	*12 (7%)*	*6 (7%)*	*5 (6%)*				
Moderate	*1 (0.6%)*	*0 (0%)*	*0 (0%)*				
Severe	—	—	—				
Itching				*0.001*	*0.001**	*0.02**	*0.66*
None	*207 (63%)*	*186 (76%)*	*121 (74%)*				
Mild	*74 (22%)*	*47 (19%)*	*32 (20%)*				
Moderate	*41 (12%)*	*8 (3%)*	*9 (6%)*				
Severe	*9 (3%)*	*3 (1%)*	*1 (1%)*				
Stinging				*0.43*	*0.64*	*0.22*	*0.35*
None	*288 (87%)*	*216 (89%)*	*151 (93%)*				
Mild	*34 (10%)*	*24 (10%)*	*11 (7%)*				
Moderate	*7 (2%)*	*4 (2%)*	*1 (1%)*				
Severe	*2 (1%)*	*0 (0%)*	*0 (0%)*				

A statistically significantly greater number of subjects suffered from dryness, erythema (The numbers and the percentages for erythema and folliculitis are the same as study

* Statistical significance indicating a higher number of subjects with adverse events in the 5% TMS arm.
** Statistical significance indicating a higher number of subjects with adverse events in the vehicle arm.

M/2415/0001, since these values were not collected for study M/7410/0285) and itching in the 5% TMS group as compared to the 2% TMS. Also, a higher number of people had dryness and itching in 5% TMS, as compared to placebo. Furthermore, it was observed that the subjects in the vehicle arm had more incidences of dryness and erythema than the patients in the 2% TMS group.

III. RESULTS:

Studies M/7415/0001 and M/7410/0285 indicated that 5% Rogaine induces more dryness (p=0.001), erythema (p=0.05) and itching (p=0.001) in subjects than the 2% TMS . In addition, more subjects suffered dryness (p=0.003) and erythema (p=0.05) in the vehicle treatment arm than the 2% TMS group.

IV. CONCLUSIONS (which may be conveyed to the sponsor):

Studies M/7415/0001 and M/7410/0285 provide statistical evidence that 5% Rogaine induces more dryness, erythema and itching than the 2% TMS. In addition, the vehicle used in these trials caused more dryness and erythema than the 2% TMS in patients.

Therefore, it can be concluded that according to these findings the 5% Rogaine is not as safe as the 2% Rogaine or the vehicle.

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