Subject's Self-Assessment Questionnaire

The baseline mean values for the Subject's Self-Assessment Questionnaire are presented in table 14. Based on an analog scale of 100mm in length, where the 0 point was labeled "not bothered/uncomfortable" and where the 100 point was labeled "extremely bothered/uncomfortable, the mean baseline scores for all six self-assessment questions for subjects in both the eflornithine 15% cream and vehicle groups were over 80. General bother caused by facial hair for both treatment groups was over 88, indicating that at baseline the subjects in both groups had a very high degree of distress over their condition.

Table 14
Analysis of the Subject's Self-Assessment Questionnaire at Baseline
Protocol DE140-001

MULTIVARIATE STATISTIC: TREATMENT P=0.015

QUESTION	BMS203522 15%CRM N	MEAN	SD	BMS203522 VEHCRM N	MEAN	SD	P-VALUE
BOTHERED BY FACIAL HAIR?	186	88.42	13.0	95	88.62	12.6	0.887
UNCOMFORTABLE WHEN MEET NEW PEOPLE?	186	83.60	20.1	95	87.55	18.0	0.103
UNCOMFORTABLE AT WORK OR CLASS?	186	81.94	20.7	95	88.43	14.4	0.006
UNCOMFORTABLE AT SOCIAL GATHERINGS?	186	82.87	21.1	95	87.87	14.2	0.035
UNCOMFORTABLE IN EXCHANGES OF AFFECTION?	186	81.19	25.1	95	82.37	25.7	0.707
BOTHERED BY TIME SPENT REMOVING HAIR?	186	80.34	24.2	95	78.48	26.3	0.554

* Based on an analog scale of 0 (not bothered/uncomfortable) to 100 (extremely bothered/uncomfortable)

For the Subject's Self-Assessment performed after 24 weeks of treatment, results of the multivariate analysis of covariance indicated a significant difference between the vectors of treatment means (p=0.0297); therefore, the individual questions were examined for their statistical significance. The results of these analyses (see table 15) revealed significant treatment differences in all six questions favoring eflornithine 15% cream over its vehicle ($p \leq 0.0182$) indicating a decrease in the subjects level of bother and discomfort. General bother caused by facial hair was reduced an average of 24 points for the eflornithine 15% cream group and 13 points for the vehicle group with a mean rating of 65 in the eflornithine 15% cream group and 76 in the vehicle group.

Table 15
Analysis of the Subject's Self-Assessment Questionnaire at Week 24
End of Treatment
Protocol DE140-001

WEEK = 24: END OF TREATMENT
MULTIVARIATE STATISTIC: TREATMENT P=0.0297**

QUESTION	BMS203522 15%CRM N	MEAN	SD	BMS203522 VEHCRM N	MEAN	SD	UNIVARIATE P-VALUE
BOTHERED BY FACIAL HAIR?	159	64.91	30.1	87	75.83	24.1	0.0046
UNCOMFORTABLE WHEN MEET NEW PEOPLE?	159	64.10	31.5	87	77.72	22.7	0.0005
UNCOMFORTABLE AT WORK OR CLASS?	159	63.83	23.8*	87	74.41	23.9*	0.0011***
UNCOMFORTABLE AT SOCIAL GATHERINGS?	159	64.31	23.8*	87	74.22	23.9*	0.0022***
UNCOMFORTABLE IN EXCHANGES OF AFFECTION?	159	61.40	34.0	87	73.86	28.0	0.0045
BOTHERED BY TIME SPENT REMOVING HAIR?	159	59.40	32.6	87	69.57	29.2	0.0182

Based on an analog scale of 0-100
* Baseline-adjusted means and standard deviations
** Multivariate Analysis of Covariance: adjusted for baseline differences.
*** Analysis of Covariance: adjusted for baseline differences.

The mean scores for all six questions at week 8 for the subjects in the eflornithine 15% cream group were lower (ranging from 68.88 to 76.45) than the mean scores for the vehicle cream group (ranging from 73.59 to 82.94). At weeks 16, the mean scores were again lower for eflornithine 15% cream group (ranging from 62.80 to 69.61) than for the vehicle cream group (ranging from 70.90 to 80.14). The analysis of the week 32 subject self-assessment questionnaire, administered 8 weeks after treatment cessation, indicated no significant differences (p=0.46) demonstrating regression of the treatment effect.

Reviewer's Comment: *The results of the Subject's Self-Assessment Questionnaire at the primary evaluation time (week 24) supports physician's global assessment evaluation at that same time point. The results at the secondary evaluation times, weeks 8 and 16, are also parallel to the results obtained in the physician's global assessment and thus are supportive. The result at week 32 supports the findings at week 32 of the primary efficacy endpoint in that the treatment effect is lost.*

Subgroup Analysis

The effects of age, race, and prior hair removal technique upon the Physician's Global Assessment at week 24 were descriptively summarized (see tables 15-17). The proportion of success within the eflornithine 15% cream group remained much the same across categories (where sufficient sample sizes were present) within each characteristic, except for race in which the success rate for whites was 30.6% and 13.8% for non-whites.

Table 15
Age Effects on Physician's Global Assessment
Protocol DE140-001

AGE		TREATMENT				STUDY TOTAL	
		BMS203522 15%CRM		BMS203522 VEHCRM			
		N	PCTN	N	PCTN	N	PCTN
<65	SUCCESS	40	23.7	4	4.6	44	17.2
	FAILURE	129	76.3	83	95.4	212	82.8
	CATEGORY TOTAL	169	100.0	87	100.0	256	100.0
>=65	SUCCESS	3	50.0	0	0	3	27.3
	FAILURE	3	50.0	5	100.0	8	72.7
	CATEGORY TOTAL	6	100.0	5	100.0	11	100.0
TOTAL		175	100.0	92	100.0	267	100.0

Table 16
Race Effects on Physician's Global Assessment
Protocol DE140-001

RACE		TREATMENT					
		BMS203522 15%CRM		BMS203522 VEHCRM		STUDY TOTAL	
		N	PCTN	N	PCTN	N	PCTN
WHITE	SUCCESS	34	30.6	2	4.2	36	22.6
	FAILURE	77	69.4	46	95.8	123	77.4
	CATEGORY TOTAL	111	100.0	48	100.0	159	100.0
NON-WHITE	SUCCESS	9	13.8	2	4.5	11	10.1
	FAILURE	56	86.2	42	95.5	98	89.9
	CATEGORY TOTAL	65	100.0	44	100.0	109	100.0
TOTAL		176	100.0	92	100.0	268	100.0

Table 17
Prior Hair Removal Technique on Physician's Global Assessment
Protocol DE140-001

PRIOR HAIR REMOVAL		TREATMENT					
		BMS203522 15%CRM		BMS203522 VEHCRM		STUDY TOTAL	
		N	PCTN	N	PCTN	N	PCTN
SHAVING/CUTTING	SUCCESS	19	22.9	1	2.1	20	15.4
	FAILURE	64	77.1	46	97.9	110	84.6
	CATEGORY TOTAL	83	100.0	47	100.0	130	100.0
PLUCKING	SUCCESS	10	25.6	0	0	10	17.5
	FAILURE	29	74.4	18	100.0	47	82.5
	CATEGORY TOTAL	39	100.0	18	100.0	57	100.0
SHAVING & PLUCKING	SUCCESS	13	24.5	3	11.1	16	20.0
	FAILURE	40	75.5	24	88.9	64	80.0
	CATEGORY TOTAL	53	100.0	27	100.0	80	100.0
PLUCKING & OTHER	SUCCESS	1	100.0	0	0	1	100.0
	FAILURE	0	0	0	0	0	0
	CATEGORY TOTAL	1	100.0	0	0	1	100.0
TOTAL		176	100.0	92	100.0	268	100.0

11.2.1.4.3 Safety outcomes

Table 18 provides a summary of subjects reporting adverse events. This includes both adverse events considered related to study medication and those considered not related to study medication.

Table 18
Subjects Reporting Adverse Events
Protocol DE140-001

	TREATMENT					
	BMS203522 15%CRM		BMS203522 VEHCRM		TOTAL	
	n	%	n	%	n	%
SUBJECTS WITH NO ADVERSE EVENTS	26	14	8	8	34	12
SUBJECTS WITH ADVERSE EVENTS	164	86	89	92	253	88
SUBJECTS WHO DISCONTINUED DUE TO ADVERSE EVENTS	6	3	5	5	11	4
SUBJECTS WITH RELATED ADVERSE EVENTS	66*	35	29	30	95	33
SUBJECTS WITH UNRELATED ADVERSE EVENTS	154	81	80	82	234	82
SUBJECTS WITH UNASSESSABLE ADVERSE EVENTS	27	14	19	20	46	16
SUBJECTS WITH SERIOUS ADVERSE EVENTS	12	6	2	2	14	5
DEATHS	0	0	0	0	0	0

* includes one subject with an unrelated adverse event incorrectly entered into the database as probably related

In this study, there was a total incidence of 1097 AEs reported by 253 (88%) subjects. Seven hundred fifty-seven of these AEs were reported by 164 subjects (86%) in the eflornithine 15% treatment group and 3340 AEs were reported by 89 subjects (92%) in the vehicle group.

A total of 95 subjects (33%) reported adverse events that were considered related to treatment by the investigator. AEs of 66 subjects (35%) in the eflornithine 15% treatment group and 29 subjects (30%) in the vehicle group were considered related to treatment with study medication by the investigators.

Two hundred thirty-four subjects (82%) reported 839 adverse events that were considered unrelated to treatment by the investigator. Forty-six subjects (16%) had 90 AEs whose relationship to study treatment was evaluated by the investigators as either unassessable or unknown.

Overall, the greatest number of subjects reported treatment-related AEs in the skin and appendages body system classification [86 subjects (30%)]. The proportion of subjects experiencing these AEs was similar for the two treatment groups. Fifty-nine subjects (31%) reported a treatment-related AE in the skin and appendages body classification in the eflornithine 15% cream group compared to 27 subjects (28%) in the vehicle group (see table 19).

Table 19
Subjects Reporting Adverse Events
By Body System And Relationship to Treatment
Protocol DE140-001

	Related to Treatment											
	BMS203522 15% Cream						BMS203522 Vehicle Cream					
	Yes		No		Unassessable*		Yes		No		Unassessable*	
Body System	n+	%	n	%	n	%	n	%	n	%	n	%
Total All Systems	66	34.7	154	81.1	27	14.2	29	29.9	80	82.5	19	19.6
Skin/appendages	59**	31.1	71	37.4	18	9.5	27	27.8	42	43.3	13	13.4
Body as a Whole	7	3.7	115	60.5	7	3.7	6	6.2	54	55.7	4	4.1
Headache	6	3.2	60	31.6	2	1.1	5	5.2	28	28.9	2	2.1
Asthenia	0	0.0	15	7.9	1	0.5	1	1.0	4	4.1	1	1.0
Nervous System	6	3.2	30	15.8	2	1.1	1	1.0	14	14.4	1	1.0
Dizziness	3	1.6	13	6.8	2	1.1	0	0.0	7	7.2	1	1.0
Digestive System	5	2.6	43	22.6	4	2.1	2	2.1	20	20.6	1	1.0
Dyspepsia	2	1.1	25	13.2	3	1.6	1	1.0	7	7.2	0	0.0
Anorexia	3	1.6	11	5.8	1	0.5	1	1.0	6	6.2	1	1.0
Respiratory System	2	1.1	39	20.5	3	1.6	0	0.0	18	18.6	1	1.0
Cough increased	2	1.1	8	4.2	1	0.5	0	0.0	4	4.1	1	1.0
Cardiovascular System	1	0.5	8	4.2	0	0.0	0	0.0	6	6.2	2	2.1
Musculoskeletal System	1	0.5	5	2.6	0	0.0	0	0.0	8	8.2	0	0.0
Special Senses	1	0.5	8	4.2	1	0.5	0	0.0	2	2.1	0	0.0
Endocrine System	0	0.0	5	2.6	1	0.5	0	0.0	2	2.1	1	1.0
Hemic/lymphatic System	0	0.0	4	2.1	0	0.0	0	0.0	3	3.1	0	0.0
Metabolic System	0	0.0	16	8.4	2	1.1	0	0.0	7	7.2	1	1.0
Urogenital System	0	0.0	39	20.5	3	1.6	0	0.0	15	15.5	1	1.0

+Within any body system category a subject may be included in more than one relationship category.
*UNASSESSABLE includes adverse events where relationship to study treatment is unknown.
**includes one subject with an unrelated adverse event incorrectly entered into the database as probably related.

Reviewer's Comment: *The sponsor suggests that the incidence of systemic events under "body as a whole", digestive system, and nervous system, might be due to the direct questioning by the investigator for events that are related to the systemic formulation of eflornithine. After reviewing the data presented, the investigator was able in the majority of these cases to ascertain that these symptoms were not related to treatment with eflornithine. In the cases that were deemed related to eflornithine, there was not an appreciable difference between the treatment arm and vehicle. This suggests that there was not any appreciable absorption of eflornithine hydrochloride into the systemic circulation to account for these symptoms.*

Reports of skin and appendages AEs described by the investigator as related to treatment were similar for subjects in both treatment groups and are summarized in table 20. In the stinging skin, tingling skin and burning skin categories, the absolute number of AEs was low but the percentage of subjects reporting treatment-related AEs was slightly higher in the eflornithine 15% cream group: 6% vs. 1% for stinging skin, 4% vs. 2% for tingling skin, and 3% vs. 0% for burning skin, respectively.

Table 20
Most Frequent Treatment-Related Skin and Appendages AEs
Protocol DE140-001

Adverse Events	BMS-203522 N=188 n*(%)	Vehicle N=97 n (%)
Acne	26 (14%)	14 (14%)
Pseudofolliculitis Barbae	21 (11%)	11 (11%)
Stinging Skin	12 (6%)	1 (1%)
Tingling Skin	8 (4%)	2 (2%)
Burning Skin	5 (3%)	0 (0%)
Alopecia	3 (2%)	3 (3%)
Pruritus	4 (2%)	2 (2%)
Papular Rash	2 (1%)	0 (0%)
Rash	2 (1%)	0 (0%)
Ingrown Hair	1 (0.5%)	2 (2%)
Dry Skin	1 (0.5%)	2 (2%)

*n=number of subjects

The greatest number of treatment-related AEs were acne and pseudofolliculitis barbae which were specifically evaluated as required by the protocol. A similar proportion of subjects in the two treatment groups had these AEs judged as treatment related by the investigators (acne 14% in both groups; PFB, 11% in both groups). Most of the treatment-related acne and PFB AEs in both treatment groups were rated as mild in severity. One case of PFB reported as possibly related to eflornithine 15% cream was defined as severe. Most acne (23% for eflornithine 15% cream and 21% for vehicle) and PFB (15% for eflornithine 15% cream and 19% for vehicle) AEs were deemed by the investigators to be unrelated to treatment. No subject was discontinued from the study for either of these AEs. Two subjects in the eflornithine 15% cream and one subject in the vehicle group had their study medication doses reduced or interrupted due to acne AEs while no PFB AEs resulted in a reduction or interruption of study medication doses.

Most subjects experienced adverse events that were classified as mild that were related to study treatment (77% for eflornithine and 66% for vehicle). Adverse events were mild to moderate for those assessed as unrelated to study medication (41% and 44%, respectively for eflornithine and 49% and 39% for vehicle). The majority of unassessable adverse events were also mild to moderate (44% and 41%, respectively for eflornithine and 53% and 37% for vehicle).

The majority of subjects who reported a skin-related event had that event classified as mild (see table 21). There were 2 patients in the eflornithine 15% cream arm who discontinued treatment secondary to a skin related adverse event. Both were due to a dermatitis, one mild in intensity and one moderate. Both were classified as possibly being related to study medication. In the vehicle arm, one patient discontinued secondary to an allergic skin reaction that was classified as unrelated to study medication and was mild in intensity. In the eflornithine 15% cream group, 2 subjects reported 5 treatment-related adverse events that resulted in dose reduction or interruption and in the vehicle group there were 3 subjects who reported treatment – related adverse events that resulted in dose reduction or interruption.

Table 21
Subjects Reporting at Least One Skin-Related Adverse Event by Severity
Protocol DE140-001

	TREATMENT					
	BMS203522 15%CRM		BMS203522 VEHCRM		TOTAL	
	N	%	N	%	N	%
NONE	67	35.3	29	29.9	96	33.4
MILD	94	49.5	52	53.6	146	50.9
MODERATE	23	12.1	15	15.5	38	13.2
SEVERE	4	2.1	1	1.0	5	1.7
NEVER TREATED	2	1.1	0	0	2	0.7
TOTAL	190	100.0	97	100.0	287	100.0

Reviewer's Comment: *There were 3 adverse events that appear to be related to the active ingredient, eflornithine hydrochloride, as they did not occur in the vehicle group: burning skin, papular rash, and rash. These events occurred in 3%, 1%, and 1% of the population, respectively. One subject discontinued from the rash category because of a pruritic eruption over lips and cheeks at week 12. It is not stated in the CRF whether this was felt to be secondary to allergy or irritancy. The patient was treated with Elocon cream. It is probably safe to say, that as shown in the topical dermal studies, the drug is capable of causing at least a contact irritant dermatitis in a small proportion of patients (1%).*

The time to onset of these events was about week 8 for the eflornithine 15% cream group and week 12 for the vehicle group. The results of the effects on race on the proportion of subjects with skin-related adverse events is presented in table 22.

Table 22
Effects of Race on the Proportion of
Subjects with Skin-Related Adverse Events
Protocol DE140-001

RACE		TREATMENT				STUDY TOTAL	
		BMS203522 15%CRM		BMS203522 VEHCRM			
		N	PCTN	N	PCTN	N	PCTN
WHITE	NO	35	29.9	12	23.5	47	28.0
	YES	82	70.1	39	76.5	121	72.0
	CATEGORY TOTAL	117	100.0	51	100.0	168	100.0
NON-WHITE	NO	32	45.1	17	37.0	49	41.9
	YES	39	54.9	29	63.0	68	58.1
	CATEGORY TOTAL	71	100.0	46	100.0	117	100.0
TOTAL		188	100.0	97	100.0	285	100.0

A total of 18 serious adverse events (SAEs) were reported in 14 subjects. All SAEs were judged to be unrelated to study treatment. By treatment group, 12 subjects (6%) in the eflornithine 15% cream group reported 15 SAEs compared to 2 subjects (2%) in the vehicle group who reported 3 SAEs. There were not any deaths reported during the study.

Reviewer's Comment: After reviewing each case reported, it is agreed that the serious adverse events that occurred in this study were not related to eflornithine 15% cream or its vehicle.

The results for laboratory parameters taken at baseline and end of treatment (for those subjects that completed both) did not reveal consistent out-of-range values or trends that could be attributed to test drug usage. Shifts in laboratory test values from baseline to Week 24 (end of treatment) showed that most subjects in both treatment groups had laboratory values within normal range at baseline and at the end of treatment.

For those subjects with both baseline and end of treatment laboratory tests, only the parameters presented in table 23 were observed to have shifts (increase or decrease) in greater than 2% of the subjects. Evaluation of these parameters did not reveal any trend considered to be associated with the study medications as the proportion of subjects experiencing shifts were comparable between the eflornithine 15% cream and vehicle cream groups.

Table 23
Laboratory Shifts Greater than Two Percent From Baseline to End of Treatment
Protocol DE140—001

Laboratory Test		Change	TREATMENT			
			BMS203522 15%		Vehicle	
			N**	%*	N	%*
Chemistry	Potassium	Normal-Low	5	3.4	0	0
	Lactate dehydrogenase (LD)	High-Normal	3	2.0	5	6.8
	Uric acid	High-Normal	6	4.0	2	2.7
		Normal-High	8	5.4	1	1.4
	Alkaline phosphatase (ALP)	High-Normal	4	2.7	2	2.7
		Normal-High	3	2.0	3	4.1
	Alanine aminotransferase (ALT)	High-Normal	5	3.4	3	4.1
		Normal-High	5	3.4	3	4.1
	Aspartate aminotransferase (AST)	High-Normal	5	3.4	1	1.4
		Normal-High	2	1.4	2	2.7
	Blood urea nitrogen	Normal-Low	1	0.7	5	6.8
		Low-Normal	6	4.1	3	4.1
	Inorganic phosphorus	High-Normal	4	2.7	1	1.4
		Normal-High	10	6.8	4	5.4
		Low-Normal	5	3.4	2	2.7
		Normal-Low	3	2.0	1	1.4
	Prolactin	High-Normal	8	5.4	5	6.9
		Normal-High	6	4.0	1	1.4
	Dehydroepiandrosterone sulfate	High-Normal	9	6.8	4	5.8
		Normal-High	3	2.3	3	4.3
	Follicle stimulating hormone	High-Normal	2	1.9	4	7.4
		Low-Normal	0	0	4	7.4
		Normal-Low	0	0	3	5.6
Hematology	Hemoglobin	Normal-Low	4	2.7	1	1.3
		Low-Normal	4	2.7	2	2.7
	Hematocrit	High-Normal	6	4.1	0	0
	Erythrocytes	Normal-Low	5	3.4	1	1.3
		Low-Normal	9	6.2	5	6.7
	Eosinophils (absolute)	High-Normal	5	3.4	6	8.0
		Normal-High	2	1.4	2	2.7
	Lymphocytes (absolute)	High-Normal	4	2.8	3	4.0
	Monocytes (absolute)	High-Normal	5	3.4	1	1.3
		Normal-High	3	2.1	0	0
	Neutrophils (absolute)	High-Normal	5	3.4	4	5.3
		Normal-Low	4	2.8	2	2.7
		Low-Normal	4	2.8	0	0
	Leukocytes	High-Normal	4	2.8	1	1.3
		Normal-High	1	0.7	0	0
		Normal-Low	7	4.8	2	2.7
		Low-Normal	5	3.4	0	0

* Percentage of subjects with this shift out of all subjects in this treatment group who had baseline and Week 24 (end of treatment) values for the specific test.
**N= number of subjects

Four subjects reported pregnancies during the study. All four discontinued medication and withdrew from the trial. Three of the four subjects were treated with eflornithine 15% cream. Subject number 64 discontinued on day 18 and had a spontaneous abortion at four weeks gestation. The subject had a history of multiple spontaneous abortions. Subject number 247 stopped applying study medication at day 56 and delivered a healthy female infant at 40 weeks gestation. Subject number 321 had a positive urine βHCG on Day 103 and withdrew from the study on Day 107. The subject suffered preeclampsia during her pregnancy and at 33 weeks

delivered a female infant affected with Down's Syndrome. Subject 242 was in the vehicle arm of the study. She stopped applying medication on day 21 and withdrew from the study on day 23. The pregnancy ended with an induced abortion at eight weeks gestation.

11.2.1.5 Conclusions Regarding Safety

Eflornithine 15% cream is well tolerated. The greatest number of adverse events was skin-related. Adverse events that occurred in 3% or greater of the population were stinging skin (6%), tingling skin (4%), and burning skin (3%.). Events that occurred in less than 3% of patients but greater than 1% included alopecia, pruritus, papular rash, and rash. As stated earlier, the latter two events can be attributed to eflornithine hydrochloride as they did not occur in the vehicle arm of the trial. Even though alopecia was reported as related to eflornithine 2% of the time, it occurred 3% of the time in the vehicle arm and thus cannot be attributed to the study drug. The incidence of pruritus was the same for both arms of the study.

Only 1% of patients had to have the medication reduced or interrupted for a skin-related adverse event and all completed the study. It is in eflornithine's favor that by the time the majority of subjects began to experience topical side effects, a statistically significant number of patients were experiencing success with the drug product as compared to vehicle (p=0.007). The proportion of subjects between whites and non-whites, as it relates to adverse events involving the skin, is similar. It is interesting to note that both groups had a higher percentage of patients who experienced these adverse events in the vehicle arm of the study. The laboratory parameters did not reveal any area of concern that could reflect a drug effect from systemic absorption of eflornithine 15% cream. The outcome of the pregnancies in this trial does not appear to have a definitive relationship to use of eflornithine 15% cream.

Note: Pregnancy outcomes will be discussed in the overview of safety which incorporates all trials.

11.2.1.6 Conclusions Regarding Efficacy

This trial provides evidence that clearly demonstrates the efficacy of eflornithine 15% cream's ability to treat excessive facial hair in women. Evaluation of the primary efficacy measure, the Physician's Global Assessment, demonstrated that eflornithine 15% cream was statistically superior to vehicle and that this difference was clinically meaningful. The benefit of eflornithine 15% cream over vehicle was observed by week 4 (p=0.017) and increased through week 24 (p=0.001). Forty-three (22.9%) subjects receiving eflornithine 15% cream were rated as a clinical success (marked improvement or greater) by the PGA compared with four subjects (4.1%) in the vehicle cream group at the end of treatment (week 24). Additionally, at the end of treatment, 53% of subjects receiving eflornithine 15% cream were rated as having at least some improvement (or greater) in their condition.

The other efficacy measures, video image analysis and subject self-assessment questionnaire, supported the primary efficacy measure. In the video image analysis, a statistically significant decrease in spatial mass (hair area) favoring eflornithine 15% cream over vehicle was seen as early as week 2 (p=0.0003) and was maintained throughout the treatment phase to week 24 (p=0.0001). Although there was no statistically significant difference between the treatment groups for reduction in hair growth by our definition at the end of treatment (p=0.158), compared to vehicle there was statistical significance in reduction of

hair length (p=0.001). There was also a trend favoring the eflornithine group with 6.3% (8/128) of the subjects in the eflornithine 15% cream group considered a success in length reduction compared to 1.3% (1/77) of the subjects in the vehicle cream group. At week 24 the eflornithine 15% cream group showed a 16.8% mean percent reduction in hair length compared to a 1.3% mean reduction in the vehicle group.

The subject self-assessment questionnaire was consistent over time. The patients were able to assess more improvement with increasing duration of treatment and by week 24 the eflornithine 15% cream group's responses were statistically significant as compared to vehicle (p=0.0297). Their responses were also consistent with the primary efficacy measure, the physician's global assessment.

When evaluating the subgroup analysis by race, non-white subjects did not respond as well as white subjects. Thirty-one percent of white subjects were categorized as a success compared to only 14% of non-white subjects. Elfornithine 15% cream also lost its treatment effect by 8 weeks after cessation of drug therapy.

11.3 **Financial Disclaimer:** As per Form 3454, the sponsor has certified that no financial arrangements with investigators have been made where the outcome affects compensation, and that investigators have no proprietary, significant equity, interest, or any significant payments in this clinical study performed in support of this NDA.

Sponsor's protocol # DE140-002 **Title:** BMS-203522 Cream 15% Versus Its Vehicle in the Treatment of Women with Excessive Facial Hair Growth – A Randomized, Double-Blind Evaluation"

11.3.1 Investigators

1.	John E. Wolf, Jr., M.D.	002/Houston, TX
2.	Mark Lebwohl, M.D.	003/New York, NY
3.	Geoffrey P. Redmond, M.D.	004/Cleveland, OH
4.	David A Whiting, M.D.	005/Dallas, TX
5.	Elise A. Olsen, M.D.	006/Durham, NC
6.	Maria Hordinsky, M.D.	007/Minneapolis, MN
7.	Daniel Piacquadio, M.D.	008/LaJolla, CA
8.	Rodney Dawber, M.B.	009/United Kingdom
9.	Francisco Camcho, M.D.	012/Sevilla 41071 Spain
10.	Mary E. Sawaya, M.D., PhD.	014/Ocala, FL

11.3.1.1 Objective/Rationale

The objective of this study was to determine the efficacy and safety of BMS-203522 (eflornithine 15% cream) in the treatment of excessive facial hair growth in women by applying the cream bid to the affected area for 24 weeks. The study further attempted to access the duration of effect of the drug product with a four-week evaluation after treatment cessation.

11.3.1.2 Design

This was a double blind, randomized, vehicle-controlled study to evaluate the safety and efficacy of BMS-203522 15% cream in the treatment of women with excessive facial hair. Adult women of any race or skin type who removed facial hair at least twice per week and had an average hair density of at least five hairs per square centimeter on two facial areas (chin and upper lip), as determined by video image analysis, were eligible for enrollment. Subjects were randomized to receive BMS-203522 15% cream or vehicle cream in a 2:1 ratio, respectively. Study medications were applied to facial areas affected by excessive hair growth twice daily for 24 weeks, followed by an 8-week no-treatment phase. Visits to the study center were scheduled at baseline (Day 0), Day 2 and Weeks 2, 4, 8, 12, 16, 20, 24 and 32. On these visits, clinical evaluations were performed, self-assessments were obtained, video imaging was completed, photographs taken and safety data (physical examinations, laboratory tests and adverse events) evaluated as specified in the protocol (see table 24).

Table 24
Study Design and Procedures
DE140-002

	TIME ----END OF----									
ACTIVITY	Day 0	Day 2	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 32
Informed Consent	X									
History	X									
Physical Exam	X									
Peivic Exam	X									
Pregnancy Test	X		X	X	X		X		X	X
Clinical Lab Tests	X		X	X	X		X		X	
Hormone Panel	X								X	X
Photograph	X	X	X	X	X	X	X	X	X	X
Hair Removal	X		X	X	X		X		X	X
Video Analysis		X	X	X	X		X		X	X
Record Previous and Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Physician's Global Assessment			X	X	X		X		X	X
Adverse Events+		X	X	X	X	X	X	X	X	X
Dispense Rx		X	X	X	X	X	X	X	X	
Collect Rx			X	X	X	X	X	X	X	X
Subject Self-Assessment	X				X		X		X	X
Clinical Evaluations	X		X	X	X	X	X	X	X	X

+Includes adverse events from query of specific symptoms associated with the use of intravenous eflornithine.

11.3.1.3 Protocol

Inclusion Criteria

Adult women of legal age and capacity for consent.
Subjects of any skin type or race providing their hair/skin contrast did not prevent evaluation (by video image analysis) of hair growth.

Willingness and ability to apply study medication as directed, comply with study instructions and commit to all follow-up visits for the duration of the study.
Signed, written informed consent obtained
Clinical diagnosis of facial hirsutism.
Customary frequency of removal of facial hair of two or more times per week.
Chin hair density of at least 5 terminal hairs per square centimeter as measured by video image analysis. Chin hair density must be measured over an area of at least 2 square centimeters on each side.
Upper lip hair density of at least 5 terminal hairs per square centimeter as measured by video image analysis. Upper lip hair density must be measured over an area of at least one square centimeter on each side.
General good health, free of any disease state or physical condition which might impair evaluation of hirsutism or increase health risk to the subject by study participation.
Fertile subjects must agree to use an effective form of birth control for the duration of study (stabilized on oral contraceptives for at least 3 months, abstinence, IUD, foam, condom or diaphragm).

Exclusion Criteria

Previous participation in investigational studies of eflornithine hydrochloride.
Use of electrolysis, laser or epilation (waxing, Epilady®, sugaring, etc.) to remove hair within two months before the study.
Use of chemical depilatories to remove facial hair within two weeks before the study.
Use of bleaching as a treatment for facial hair within one week before the study.
Use of tweezing to remove facial hair within 48 hours before the study.
Use of shaving to remove facial hair within 24 hours before the study.
Use of systemic antiandrogens, spironolactone, growth hormone, immunostimulants, immunosuppressants, minoxidil, dehydroepiandrosterone (DHEA), estratest and other medications considered to have an effect on hair growth within six months before the study.
Facial conditions such as severe inflammatory acne for which the use of the study medication would be contraindicated.
History of hypersensitivity to any of the ingredients in the test formulations.
Concomitant therapy with any medication considered to be either a useful treatment for or considered to exacerbate hirsutism, including NORPLANT, finasteride, DEPO-PROVERA, flutamide, ketoconazole, and cyproterone acetate.
Subjects participating in an investigational study currently or within 4 weeks before the study.
Pregnant or nursing mothers.
Score of less than 20 (on an analog scale ranging from 0-100mm) for the question, "How much are you bothered by your facial hair?" on the Subject Self-Assessment Questionnaire (the investigator measured the distance between the mark made by the subject for this question and the extreme left side of the line in millimeters. Subjects who rated the level of bother as less than 20 millimeters were not eligible for enrollment.)

Study Procedures and Observations

Subjects were instructed to apply eflornithine 15% cream or its matching vehicle twice a day for 24 weeks. Each subject was instructed to apply a thin film of the assigned study medication to affected areas of clean, dry facial skin and rub in gently and completely. This initial application was demonstrated and observed by study staff who had been previously instructed on the proper dosing procedure. Written instructions were given to the subjects to follow.

Subjects shaved at the study site on day 0 the areas of the face affected by excessive hair growth. At a minimum, the upper lip and chin were shaved. They returned to clinic 48 hours later after being instructed not to remove facial hair by any means, to have video image analysis. This procedure was repeated at the end of weeks 2, 4, 8, 16, and 24 (end of treatment).

Subjects were queried at each visit regarding study medication usage. They were asked to apply a dose of study drug at the study site at subsequent visits. This provided the study staff with the opportunity to reinstruct subjects on the proper application technique. Subjects were dispensed two —g tubes of study medication per month. These two tubes were exchanged for two new tubes each month to ensure that subjects always had an adequate supply of study medication.

During the study, subjects were permitted to bleach facial hair or remove facial hair by shaving or other forms of cutting or plucking (tweezing). The restrictions for using these methods were that shaving could not be done within 24 hours, plucking within 48 hours, and bleaching within one week of a scheduled study visit. Depilatories, electrolysis, epilation (waxing, Epilady®, sugaring, etc.) or laser were not permitted.

Because reports concerning skin related adverse events (especially stinging, burning, tingling, itching, etc., immediately after application of study medication) could have provided clues to the identity of the blinded study medication, an individual other than the physician responsible for completing the Physician's Global Assessment queried subjects about adverse events at the day 2 visit and subsequent visits. If non-serious skin related adverse events were reported, an individual other than the physician responsible for completing the Physician's Global Assessment collected information about the events and completed the appropriate CRF (Please refer to Table 23 for flow chart).

11.3.1.3.1 Population

The population consisted of health adult women of any race or skin type who met the clinical diagnosis facial hirsutism and had a customary frequency of hair removal of two times or more per week.

11.2.1.3.2 Endpoints

Primary Efficacy Variable

Physician's Global Assessment (performed at weeks 2, 4, 8, 16, and 24)
Primary efficacy time point – week 24 (end of treatment)

The physician's global assessment scale is a static morphologic scale with 4 grades as follows:

GRADE 3- **CLEAR/ALMOST CLEAR** -- There is no or nearly no visible terminal hair on the treated areas of the face. There is no or nearly no darkening in the appearance of the facial skin due to terminal hair.

GRADE 2- **MARKED IMPROVEMENT** -- There is a considerable decrease in the visibility of terminal hair on the treated areas of the face. There is only minimal darkening in the appearance of facial skin due to terminal hair.

GRADE 1- **IMPROVED** --There is a clinically apparent decrease in visibility of terminal hair on the treated areas of the face. There is noticeable lightening in the appearance of the facial skin due to terminal hair.

GRADE 0- **NO IMPROVEMENT/WORSE** -- There is either no decrease or worsening in visibility of terminal hair on the treated areas of the face. Darkening of the facial skin due to terminal hair has not improved or has become worse.

Reviewer's Comment: Although the Physician's Global Assessment (PGA) labels each grade with an improvement category, the investigator was to evaluate the patient using the definition, which is a static assessment that does not require a referral to baseline. This was to decrease investigator variance between centers. However, in reality, because ——— photographs were taken at baseline and at subsequent visits for the video image analysis, investigators and subjects were allowed to use these as a tool in their global assessment.

Secondary Efficacy Variables

Video Image Analysis (assessed at day 2 and at weeks 2, 4, 8, 16, and 24)
Subject Self-Assessment (assessed at day 0 and at weeks 8, 16, and 24)
Secondary efficacy time point – week 32 (8 weeks post-treatment)

Video Image Analysis

A video fiber optic microscope was used to collect images of the skin including hair. Images were transferred to an image analysis system equipped with appropriate software on a personal computer.

The Image Analysis Hair Measurement System (IAHMS) consisted of a — personal computer (PC), two monitors and a ——— video microscope unit. One of the monitors was the display for the PC and the other was the display for the image from the ——— The ——— video microscope consisted of the power supply unit and a wand.

At the subject's first study visit, the subject's upper lip and chin areas were examined and depending on the shape of the hirsute area, one of the following video-imaging techniques was employed for each of the sites.

1. Video Imaging - Upper lip technique 1 – Downward

This technique started the acquisition of the images near the subject's nose and continues downward toward the corner of the lip. It was recommended to be used when the hirsute condition was more pronounced near the nose than toward the corner of the upper lip.

The upper lip was demarcated using a surgical marker (i.e.: ——— skin marker) with a pinpoint mark slightly inside the edge on the nose side of the upper lip. Photographs were taken to ensure that the same starting point for video imaging could be returned to at later video imaging sessions.

The ——— lens was placed, when video-imaging the right upper lip, so that the dot was centered on the right border of the video microscope frame. When the left upper lip was video-imaged the dot was centered on the left border of the video microscope frame.

Additional fields were acquired by moving the ——— lens downward one frame at a time toward the corner of the upper lip (the minimum number of fields per side was 4).

2. Video Imaging - Upper lip technique 2 – Upward

This technique started the acquisition of the images near the corner of the subject's lip and continues upward toward the nose. It was recommended to be used when the hirsute condition was more pronounced near the corner of the upper lip than toward the nose. All of the preparatory procedures outlined above for the Downward technique were employed when using the upward technique.

Figure 1 illustrates the two procedures described above.

Figure 1 **Video Imaging - Upper Lip Upward/Downward Techniques**
Protocol DE140-002

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3. Video Imaging - Upper lip technique 3 – Middle

Another suggested technique for the upper lip started the acquisition of the images in the middle of the hirsute region on the upper lip. Figure 2 illustrates this technique.

Figure 2 **Video Imaging - Upper Lip Middle Technique**
Protocol DE140-002

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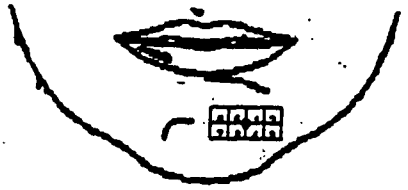
4. Video Imaging - Chin technique 1 – Center Wide

This technique was recommended to be used when the hirsute region resembled an oval area more horizontal than vertical on the chin. The lens movement is anchored to the skin demarcation spot in the lower left hand corner of frame 1 and moved in a clockwise direction to obtain image date for frames 2-4. The process was then repeated in a counterclockwise direction for frames 5-8. Video imaging data could also be obtained by anchoring to the skin demarcation spot for frames 1,4,5 and 8 and moving the wand one frame (left or right) at a time.

All of the preparatory procedures outlined above for the lip technique were employed when obtaining video imaging data on the chin. Figure 3 illustrates this technique.

Figure 3 **Video Imaging - Center Wide Chin Technique**
Protocol DE140-002



5. Video Imaging - Chin technique 2 – Center Tall

This technique was recommended to be used when the hirsute region resembled an oval area more vertical than horizontal on the chin. Figure 4 illustrates this technique.

Figure 4 **Video Imaging - Center Tall Chin Technique**
Protocol DE140-002

The video image analysis was conducted as close as possible to 48 hours after hair removal. A variation of ± 2 hours was allowable.

At the baseline visit, a ———————— camera was used to take duplicate photographs (standardized magnification of 2x) of demarcated facial sites which were to undergo treatment. The first set of photographs was referenced for demarcating the facial site, and the second set was used to reference the video imaging technique employed. The video-imaging technique employed at the first visit was to be employed throughout the study.

Subject Self-Assessment

In the subject self-assessment evaluation, the study subject completed responses to questions concerning the impact of treatment on various aspects of her quality of life using a scale of bother and discomfort. The responses were recorded on a visual analog scale ranging from 0 mm (not bothered/uncomfortable) to 100 mm (extremely bothered/uncomfortable). To keep subjects aware of their appearance at the start of the study, baseline photos were reviewed by subjects at each subsequent visit. The investigator did not reveal to the subject his/her opinion of

the subject's status. The six questions that made up the Subject Self-Assessment Questionnaire were:

1. How much are you bothered by your facial hair?
2. How uncomfortable does your facial hair make you feel when you meet new people?
3. How uncomfortable does your facial hair make you feel when you go to work or class?
4. How uncomfortable does your facial hair make you feel when you to social gatherings, dine out in a public restaurant, go to a supermarket or other public place?
5. How uncomfortable does your facial hair make you feel in exchanges of affection (such as in an intimate situation with your partner)?
6. How much are you bothered by the time you spend removing, treating, or concealing your facial hair?

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Safety Measures

A complete physical examination was performed at the initial visit and at the termination of the study (week 32). Subjects were questioned concerning adverse events at each visit (day 2, week 2, 4, 8, 12, 16, 20, 24 and 32). This also included asking patients concerning specific events associated with the use of intravenous eflornithine. Patients were also examined at these visits for evidence of adverse events.

Reviewer's Comment: According to the protocol, an investigator other than the investigator assessing for efficacy, queried the subjects for adverse events in an attempt to keep the study medication blinded.

Laboratory tests

Blood and urine specimens were taken periodically during the study. Fasting blood collections were not required. Specimens were taken, processed and shipped according to procedures specified by the reference laboratory.

If Initial Visit (Day 0) baseline laboratory values, except hormones, were outside the normal ranges for the reference laboratory **and** were determined to be clinically significant by the investigator, an adverse event form was completed and the subject was informed of the abnormality. The subject was discharged from the study if, in the opinion of the investigator, the laboratory finding indicates the subject was no longer suitable for participation in the study or that continued participation represented an unreasonable hazard to the subject.

The following clinical laboratory tests or equivalent were conducted:

BLOOD CHEMISTRY: Glucose, Total Bilirubin, Alkaline Phosphatase, LDH, ALT (SGPT), AST(SGOT), Urea Nitrogen, Creatinine, Uric Acid, Phosphorous, Calcium, Total Protein, Albumin, Sodium, Potassium, Chloride

PREGNANCY TEST *(minimum sensitivity 25 IU/L of β-HCG)*

HORMONES: Free testosterone, Prolactin, Follicle Stimulating Hormone, Luteinizing Hormone, Dehydroepiandrosterone sulfate

HEMATOLOGY: Hemoglobin, Hematocrit, RBC, WBC, Neutrophils, Bands, Lymphocytes, Monocytes, Eosinophils, Basophils, Platelets, and Morphology

URINALYSIS: Specific Gravity, pH, Glucose, Ketones, Blood, Microscopic – reflexive

Clinically significant abnormal test values appearing during the study were followed until they returned to normal or had been satisfactorily explained. Results of these analyses were reported on the central laboratory report sheets. On receipt of these forms the investigator made appropriate entries on the Laboratory Test Log case report form, including a notation of whether or not any abnormal test values were clinically significant. Non-serious or Serious Adverse Event forms were completed for any abnormal value, which were determined to be clinically significant.

11.3.1.3.3 Statistical considerations

Data Set Descriptions

Two data sets were formed for the purpose of efficacy evaluation: the "all subjects randomized" or intent-to-treat (ITT) data set (primary data set) which comprises all subjects randomized into the study who were dispensed study medication; and the "evaluable data set" which consists of all subjects who were without significant protocol violations and received at least one dose of study medication. For both data sets, all subjects withdrawing from the study had their last observation carried forward through the end of treatment.

All efficacy and safety analyses were performed on the ITT data set. In addition, the analysis of the primary efficacy measure at the primary endpoint (Physician's Global Assessment at Week 24) was performed on the evaluable data set.

Statistical Analyses

Baseline Comparability

Statistical Analysis System (SAS) was used to summarize and analyze the verified and edited data (PROC GLM, FREQ, MEANS, LIFETEST, REG, CATMOD).

Demographic comparability between treatment groups was assessed for age, height and weight by a two-way analysis of variance (ANOVA) (SAS-PROC GLM) with investigator and treatment as effects in the model.

Differences between treatment groups in race (dichotomized into 'White'/ 'non-White') and hair removal methods were evaluated by the investigator-adjusted Cochran Mantel-Haenzel test for general association (SAS - PROC FREQ, CMH option) or Fisher's Exact test.

Differences between treatment groups in skin type were evaluated by an investigator-adjusted Kruskal-Wallis test (SAS- PROC FREQ, CMH option, scores=rank, 'ANOVA' statistic).

The Subject's Self-Assessment questionnaire administered at baseline comprised six questions that were expected to be intercorrelated. Therefore, a multivariate analysis of variance (MANOVA) was performed with treatment and investigator as effects in the model (SAS-PROC GLM, MANOVA option). Only if the multivariate analysis (Wilks's Criterion) was statistically ($p \leq 0.05$) significant would the univariate analysis for each question be evaluated.

Hair growth and spatial mass, evaluated by video image analysis, were analyzed using a two-way ANOVA with treatment and investigator as effects in the model (SAS-PROC GLM). If a baseline treatment difference in spatial mass was present, analyses at subsequent time periods were adjusted for baseline differences by analysis of covariance with baseline as the covariate.

Efficacy Analysis

The primary time period was Week 24 (end of treatment). All other evaluation periods were considered secondary.

The primary response measure was the Physician's Global Assessment (evaluated at the primary and secondary periods), dichotomized into 'success' (subjects who were assessed on the global scale as marked improvement or clear/almost clear) and 'failure' (subjects who were assessed as improved or no improvement/worse). Differences between treatments in the proportion of subjects achieving success were analyzed by a Cochran Mantel-Haenszel test for general association (or Fisher's Exact Test where appropriate), controlling for investigators (SAS - PROC FREQ, CMH option). The null hypothesis states that the treatment proportions are equal.

The Subject's Self-Assessment Questionnaire comprised six quality of life questions of bother and discomfort with facial hair measured on an analog scale. The questionnaire was administered at baseline, during treatment (Weeks 8 and 16), at the end of treatment (Week 24) and at the end of the study (Week 32). Since there were 6 questions administered to each subject, the responses to the various questions were expected to be intercorrelated. Therefore, a multivariate analysis of variance (SAS-PROC GLM, MANOVA option) was performed with treatment, investigational site and the interaction as effects in the model to test the null hypothesis that the treatment vectors of means are equal. If a significant interaction ($p \leq 0.05$) was not observed, the interaction term would be dropped from the model and the analysis re-run. Only if the multivariate analysis

(Wilks's Criterion) was statistically significant ($p \leq 0.05$) would the univariate analysis for each question be evaluated. The principal evaluation was at treatment cessation (Week 24) with a secondary evaluation performed at Week 32.

Reductions in hair growth and spatial mass (a measure of hair area per square centimeter of skin surface), evaluated by video image analysis, were regarded as secondary response measures. The primary evaluation time point was Week 24 (end of treatment), all other evaluations were secondary. The percentage of reduction in hair growth from baseline was dichotomized into 'success' (subjects with at least a 50% reduction in hair growth relative to baseline) and 'failure' (<50% reduction). Differences between treatments in the proportion of subjects achieving success were analyzed by a Cochran Mantel-Haenszel test (or Fisher's Exact Test if more appropriate) for general association, controlling for investigators (SAS - PROC FREQ, CMH option). The null hypothesis states that the treatment proportions are equal.

Analysis of Prognostic Factors

To examine the relationship of pre-existing characteristics of the study sample to the primary response measure (success rates of the Physician's Global Assessment at Week 24), descriptive subgroup summaries were presented. The effects of age (dichotomized at <65, ≥65), race (dichotomized into 'White', 'non-White') and hair removal methods prior to study upon success/failure in Physician's Global Assessment were summarized by a frequency distribution of success rates within each treatment and subgroup category.

Reviewer's Comment: *The sponsor has been asked to narrow the race analysis and look for any differences between Whites and African-Americans in terms of efficacy.*

Safety Analysis

Adverse events, observed or reported by subjects at each visit, were compiled. Adverse events were classified using a modified COSTART dictionary. Differences between treatments in the elapsed time to the first skin-related adverse event were evaluated by a non-parametric time-to-event analysis (SAS - PROC LIFETEST). Time-to-event was defined as elapsed time to the subject's first skin-related adverse event. Subjects not experiencing a skin-related adverse event during the study had their total time in the study recorded as right censored. The product-limit method was used to estimate the time-to-event distribution by treatment and the Wilcoxon statistic used to test for equality of the distribution curves between treatments.

For laboratory evaluations, shift tables were constructed to summarize the change from baseline to the end of treatment (Week 24) in the lab normal ranges. Subjects with out-of-range values were identified and their data presented.

Descriptive summaries were completed to determine the relationship of age and race with the proportion of subjects reporting at least one SKIN AND APPENDAGES adverse event. The number and proportion of subjects with at least one skin-related adverse event were presented within each subgroup level and treatment group.

Video Image Analysis

The novel video imaging system was implemented to obtain complementary information on efficacy. Issues arose with the video imaging technology, which were not anticipated prior to the initiation of the trial and affected the collection of images and processing of the data. The issues identified as having affected the data are discussed in this section. The primary effect of these factors was a reduction in the size of the data set and therefore the power for the analysis.

The video imaging system software used an algorithm that identified hair by the color contrast between hair and skin. It was known prior to the initiation of this study that this software did not identify all visible hairs in an image. It was expected that sufficient hairs would be identifiable for the entry criteria and the analysis of the rate of hair growth and spatial mass. On review, many files showed visible images of hairs that were identified either incompletely or not at all. Contrast problems included identifying gray hairs on light skin, light hairs on light skin, and dark hairs on darker or black skin.

In some instances the data files for the image analysis showed a many-fold excess of the expected numbers of hairs being identified by the software. A review of the data versus the images uncovered numerous artifacts that were being counted as hairs. The causes of these artifacts included: makeup; dry skin; oily skin; skin lesions (including hyperpigmented or hypopigmented areas in the imaged field); the orientation pen marking for the ——— and dirt, cleaning residue, or water on the lens of the ——— As a result, many hair measurements calculated by this software could not be used.

To address these problems, it was determined that each image would be reviewed visually to manually select hairs. Measurement of hair length and spatial mass (hair area) by the software was not altered by the manual review. In order to implement the manual selection of imaged hairs, a new software package was developed by ——————— — in conjunction with ——————— A Standard Operating Procedure (SOP) was developed to document the operation and use of the system.

BMS staff were trained on how to operate the system and were fully blinded as to the identity of the subject, the study visit, and the treatment for each image. The original images obtained on the Write Once Read Many (WORM) disks were used with this new software and only allowed the reviewer to select those hairs that were originally identified by the software and stored on the WORM disk. In this way obvious artifacts would not be selected as hairs. The same algorithm that was originally used to select and measure hairs was maintained and produced the measurements that were used for the analysis. Due to a limitation in the software, if either the reviewer could not identify any hairs on the set of 24 images for a subject or bad images prevented the software from identifying hairs, no measurement could be recorded to the database. Therefore, data for subjects who had no actual identifiable hairs by video image analysis were not differentiated from data that the system could not record due to artifacts. This may have resulted in an underestimate in the reduction of the hair measurement data.

The large volume of data stored on the equipment in the latter stages of the study also affected the functioning of the equipment, as it slowed the operation and hindered the ability of the operator to view the collected data and images. This resulted in the redirection of image storage from the WORM drive to the hard drive of the unit and led to the loss of some images and data.

Although thorough instruction and training were given to investigational site personnel, the technical expertise and time required to operate the equipment may have been difficult for some individuals, and hindered the optimal implementation of the technology. Issues that affected collection of adequate data because of this factor included improper polarization, unclean lenses, lack of review for an adequate image, imaging the wrong location, and missing images. There was also a high turnover of operators (study staff) at investigational sites. This study was conducted over a long period (1½ years) and several changes in staffing occurred at many centers. Although supplemental training was provided, newly trained operators were not regarded as proficient as experienced users.

Because of these problems, complete image data for the baseline and final (week 24 or early discharge) visits (the primary evaluation period), were obtained for 74% of the subjects. This included 151 of 205 subjects (74%) in the eflornithine 15% cream group and 77 of 104 subjects (74%) in the vehicle cream group.

Reviewer's Comment: The sponsor has delineated a reasonable system to compensate for the shortcomings of the video image analysis technique. Given that this is a secondary efficacy variable, in this reviewer's opinion, collecting adequate data on almost ¾ of the enrolled population evenly distributed between the drug and vehicle arms will probably be adequate.

11.3.1.4 Results

11.3.1.4.1 Populations enrolled/analyzed

A total of 309 subjects were enrolled at nine investigational sites. Two hundred ninety-eight subjects were enrolled at eight centers in the U.S. and 11 subjects were enrolled in Europe (Spain). Two hundred five subjects were randomized to receive eflornithine 15% cream and 104 were randomized to receive vehicle cream. Table 25 describes the demographics of all subjects randomized (ASR) in the trial.

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Table 25
Demographic Characteristics
ITT Population
Protocol DE140-002

	BMS203522 15%CRM	BMS203522 VEHCRM	OVERALL	P-VALUE
AGE				0.410
n	204	103	307	
MEAN	41.2	42.5	41.7	
MEDIAN	40.0	40.0	40.0	
S.E.	0.96	1.17	0.75	
RANGE	18 - 83	23 - 74	18 - 83	
HEIGHT (INCHES)				0.672
n+	205	103	308	
MEAN	64.5	64.6	64.5	
MEDIAN	64.8	64.1	64.6	
S.E.	0.19	0.27	0.15	
RANGE	56.0 - 71.0	57.5 - 72.7	56.0 - 72.7	
WEIGHT (LBS.)				0.753
n	204	103	307	
MEAN	194.2	196.2	194.9	
MEDIAN	188.1	184.1	186.1	
S.E.	3.51	5.62	3.00	
RANGE	106.0 - 399.9	110.0 - 401.0	106.0 - 401.0	
RACE*				0.906
WHITE	137 (67%)	69(66%)	206 (67%)	
BLACK	56 (27%)	30(29%)	86 (28%)	
HISPANIC/LATINO	8 (4%)	5(5%)	13 (4%)	
OTHER	4 (2%)	0(0%)	4 (1%)	
SKIN TYPE				0.677
I	7 (3%)	6(6%)	13 (4%)	
II	50 (25%)	24(23%)	74 (24%)	
III	67 (33%)	31(30%)	98 (32%)	
IV	28 (14%)	14(13%)	42 (14%)	
V	25 (12%)	14(13%)	39 (13%)	
VI	27 (13%)	15(14%)	42 (14%)	

+ Totals for "n" include only subjects for whom data were provided
* Analyzed after having dichotomized RACE into WHITE AND NON-WHITE

A total of 240 subjects (78%) completed the 24-week treatment phase of the study and 228 (74%) completed the full 32 weeks, which included the 8-week follow-up phase. A total of 75 patients were discontinued from the study. Only a small portion discontinued because of an adverse event, 5 (2%) in the eflornithine arm and 1 (1%) in the vehicle arm. A total of 30 subjects discontinued from the study to their request (Patient Request). Eighteen (9%) of these subjects were in the eflornithine 15% cream group and 12 (12%) were in the vehicle group. The reasons included unable to keep visit schedule (12), lack of efficacy (8), general (6), irritation from shaving (2), moving (1) and adverse event (1). Of the eight who requested to discontinue due to lack of efficacy, six (6%) were in the vehicle group and 2 (1%) were in the eflornithine 15% cream group. Table 26 provides a summary of subject disposition for those who were enrolled in the study.

Table 26
Subject Disposition
ITT Population
DE140-002

		TREATMENT					
		BMS203522 15%CRM		BMS203522 VEHCRM		TOTAL	
		n	%	n	%	n	%
REASON	Off Trt Reason BMS Use						
Discontinued-Other	Lost to Follow-up	17	8	10	10	27	9
	Patient request	17	8	12	12	29	9
	Pregnancy	1	0	1	1	2	1
	Non-compliance	4	2	0	0	4	1
	Physician's decision	1	0	0	0	1	0
	Other	4	2	2	2	6	2
Discontinued-AE	Patient request	1	0	0	0	1	0
	Physician's decision	1	0	0	0	1	0
	Adverse Event	3	1	1	1	4	1
Completed	Completed treatment	153	75	75	72	228	74
Not Reported	Not Reported*	3	1	3	3	6	2
TOTAL		205	100	104	100	309	100

*Six subjects were recorded as "not reported" because their End of Study CRF was not available at the time of database lock. These forms were subsequently received and it was identified that all six completed the study.

Reviewer's Comment: *There is only a small difference between arms in this study of 1-3% for the various categories and thus should not have a significant affect on the outcome of the study.*

Hair removal methods used two weeks prior to the study were comparable (p=0.510) for eflornithine 15% cream and its vehicle. The percentages using the methods of "shaving/cutting", "plucking", "shaving and plucking", and "plucking and waxing" were 47.6%, 27.2%, 24.3%, and 1.0%, respectively (see table 27).

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Table 27
Method of Hair Removal Used during the Two Weeks Prior to the Study
ITT Population (N=309)
Protocol DE140-002

METHOD OF HAIR REMOVAL	TREATMENT					
	BMS203522 15%CRM		BMS203522 VEHCRM		STUDY TOTAL	
	N	%	N	%	N	%
SHAVING/CUTTING	98	47.8	49	47.1	147	47.6
PLUCKING	51	24.9	33	31.7	84	27.2
SHAVING & PLUCKING	54	26.3	21	20.2	75	24.3
PLUCKING & WAXING	2	1.0	1	1.0	3	1.0
TOTAL	205	100.0	104	100.0	309	100.0

COCHRAN MANTEL-HAENSZEL TEST: P-VALUE = 0.510

No differences were seen between the two treatment groups with respect to the prior medical history or presenting conditions. A total of 5 subjects (2 active and 3 vehicle) presented with a medical history of polycystic ovary disease, 3 recorded under the genitourinary system and 2 under the endocrine system.

Most subjects were exposed to study medication for 20-28 weeks, 143 (79%) in the eflornithine 15% cream group and 73 (70%) in the vehicle cream group. The percentage of subjects exposed to the study medications for the weekly intervals was similar for the two treatment groups. The mean exposure time was 22.35 weeks for the eflornithine 15% cream group compared to 22.30 weeks for the vehicle group. It was noted that at one investigational site treatment was not discontinued at week 24 for some subjects as specified in the protocol. This site continued to dispense study medication at week 24 and subjects administered treatment until week 32.

Reviewer's Comment: The violation of the protocol after the primary efficacy evaluation time will not effect the outcome of the study results. Given that it only occurred at one center and was during the post-treatment time period, it also probably will not greatly affect the time to regression analysis.

There was complete product usage data for the study medications dispensed and retrieved from 180 of 240 subjects (75%) at week 24. These data are for subjects who completed 24 weeks of treatment and had complete tube weights at dispensing and return. An identical percentage of subjects (75%) in both treatment groups had complete data at week 24. These data are for subjects who completed 24 weeks of treatment and had complete tube weights at dispensing and return. An identical percentage of subjects (75%) in both treatment groups had complete data at week 24. The average weight of study medication used during the treatment phase for these subjects was 83.1 grams for those in the eflornithine 15% cream group and 87.9

grams for those in the vehicle group. This equates to a usage rate of approximate 0.5 gram/day/subject for subjects in both treatment groups.

11.3.1.4.2 Efficacy endpoint outcomes

All efficacy analyses were performed on the ITT data set (n=309). In addition, the analysis of the primary efficacy measure at the primary evaluation period (Physician's Global Assessment at week 24) was performed on the evaluable subject data set. Table 28 describes the protocol deviations that excluded some subjects from the evaluable data set.

Table 28
Protocol Deviations of Subjects Excluded from The Evaluable Dataset
Protocol DE140-002

REASON FOR EXCLUSION	BMS203522 15%CRM		BMS203522 VEHCRM		TOTAL	
	n	PCTN	n	PCTN	n	PCTN
SUBJECTS USING PROHIBITED MEDICATION CONCURRENTLY	7	3.4	4	3.8	11	3.6
SUBJECTS WITH LATE/EARLY VISITS	4	2.0	3	2.9	7	2.3
SUBJECTS WITH GLOBAL ASSESSMENTS NOT PERFORMED 48 HOURS AFTER SHAVING	3	1.5	3	2.9	6	1.9
NON-COMPLIANT SUBJECTS*	2	1.0	2	1.9	4	1.3

*Includes subjects within "dose change/improper application" category

Primary Efficacy Measure

The Physician's Global Assessment at 24 weeks was the primary response measure. The results indicate a statistical superiority of eflornithine 15% cream over its vehicle (p=0.001). Eighty-three subjects (41%) out of 198 treated with eflornithine 15% cream were classified successes compared with only 13% (13/101) of subjects treated with its vehicle. Results of the evaluable dataset show a similar statistical statistically superiority of eflornithine 15% cream over vehicle (p=0.001). Table 29 and 30 present these results.

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Table 29
Distribution of Physician's Global Assessment At Week 24
End of Treatment – ITT Population
Protocol DE140-002

	ASSESSMENT	TREATMENT BMS203522 15%CRM	TREATMENT BMS203522 VEHCRM	TOTAL
SUCCESS	CLEAR/ALMOST CLEAR	10 (4.9%)	0 (0.0%)	10
	MARKED IMPROVEMENT	73 (35.6%)	13 (12.5%)	86
	SUBTOTAL	83 (40.5%)	13 (12.5%)	96
FAILURE	IMPROVED	45 (22.0%)	28 (26.9%)	73
	NO IMPROVEMENT/WORSE	77 (37.6%)	63 (60.6%)	140
	SUBTOTAL	122 (59.5%)	91 (87.5%)	213
TOTAL		205	104	309

COMPARISON BETWEEN TREATMENTS

COCHRAN MANTEL-HAENSZEL TEST: P-VALUE = 0.001

Reviewer's Comment: In evaluating the success of eflornithine 15% cream , it was determined that the sponsor did not analyze the entire ITT population, which should have included all patients dispensed study medication. The sponsor had a total of 198 patients for the eflornithine arm and 101 for the vehicle arm instead of 205 and 104, respectively. Therefore, in constructing table 29, all patients who did not have an assessment at week 24, were considered failures. The modification did not change the overall assessment of eflornithine's success (statistical significance) compared to vehicle, but did decrease the percentages.

Table 30
Distribution of Physician's Global Assessment At Week 24
End of Treatment – Evaluable Subjects
Protocol DE140-001

	ASSESSMENT	TREATMENT BMS203522 15%CRM	TREATMENT BMS203522 VEHCRM	TOTAL
SUCCESS	CLEAR/ALMOST CLEAR	10 (5.4%)	0 (0.0%)	10
	MARKED IMPROVEMENT	71 (38.2%)	13 (13.7%)	84
	SUBTOTAL	81 (43.5%)	13 (13.7%)	94
FAILURE	IMPROVED	54 (29.0%)	29 (30.5%)	83
	NO IMPROVEMENT/WORSE	51 (27.4%)	53 (55.8%)	104
	SUBTOTAL	105 (56.5%)	82 (86.3%)	187
TOTAL		186	95	281

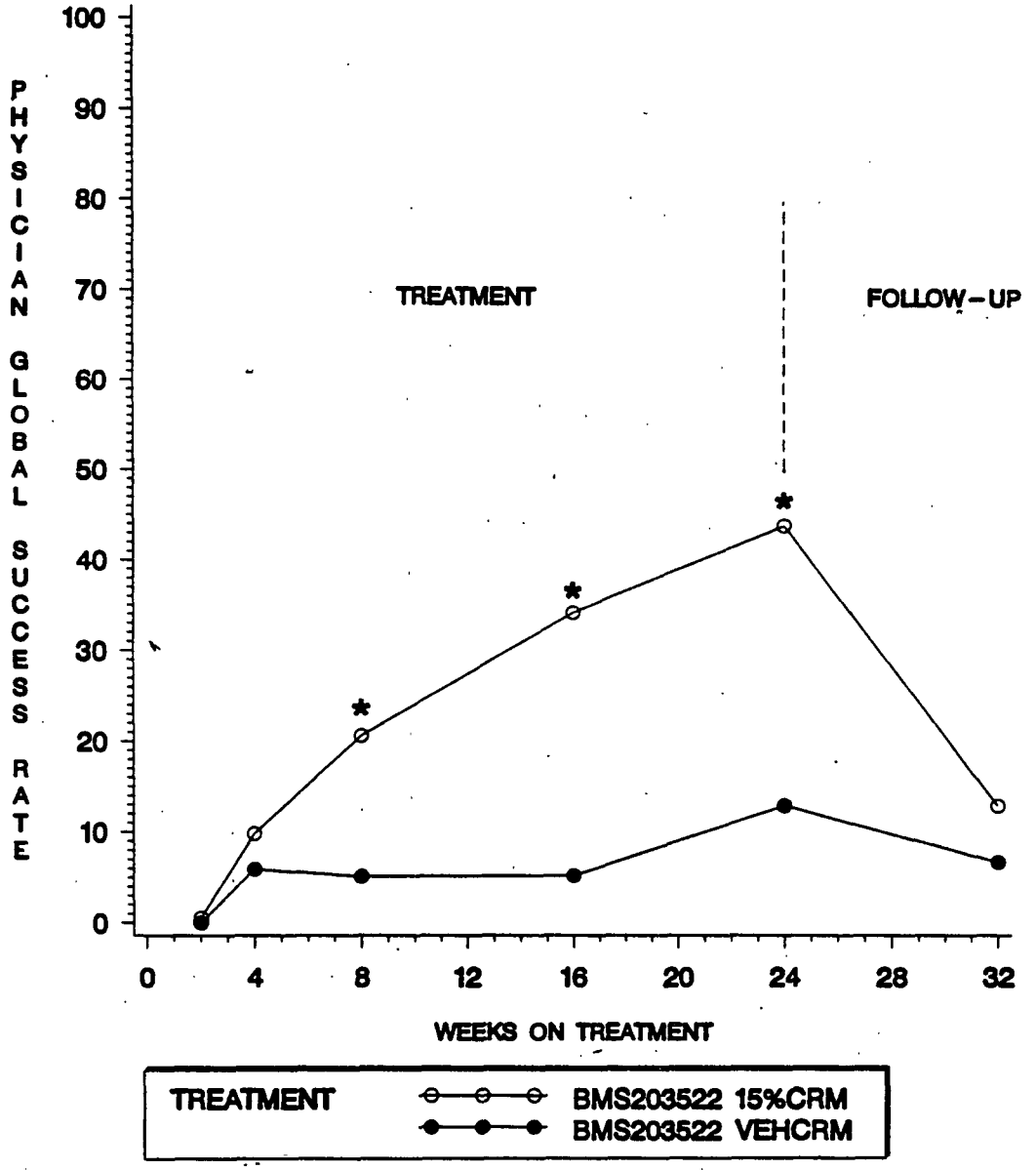
COMPARISON BETWEEN TREATMENTS

COCHRAN MANTEL-HAENSZEL TEST: P-VALUE = 0.001

Reviewer's Comment: *The sponsor evaluated several other time points during treatment to ascertain if there were points during the 24 week period where a statistically significant effect of eflornithine occurred over its vehicle. These will be called secondary time assessments of the physician's global assessment.*

Statistically significant differences in Physician's Global Assessment between treatment groups favoring eflornithine 15% cream were observed at weeks 8 and 16. At week 8, 19.5% (40/205) of subjects treated with eflornithine 15% cream were deemed successes compared with 4.8% (5/104) treated with the vehicle (p=0.001). By week 16, 31.2% (64/205) of subjects treated with eflornithine 15% cream were judged successes compared with 4.8% (5/104) treated with vehicle (p=0.001). Figure 2 demonstrates the Physician's Global Assessment over time.

Figure 2
Physician's Global Assessment – ITT Population
Protocol DE 140-002



***Indicates statistically significant treatment difference ($p \leq 0.05$)**

As shown in Figure 2, 8 weeks post-treatment (week 32), the difference between the two groups was no longer statistically significant ($p=0.151$), demonstrating regression of the treatment effect. Of those subjects treated with eflornithine 15% cream, 12.9% (20/155) were

categorized as successes while only 6.7% (5/75) of the vehicle-treated group were so judged (also see table 31).

Table 31
Distribution of Physician's Global Assessment at Regression Week 32 (8 weeks post-treatment) – ITT Population
Protocol DE140-002

		TREATMENT		
	ASSESSMENT	BMS203522 15%CRM	BMS203522 VEHCRM	TOTAL
SUCCESS	CLEAR/ALMOST CLEAR	1 (0.7%)	1 (1.3%)	2
	MARKED IMPROVEMENT	19 (12.3%)	4 (5.3%)	23
	SUBTOTAL	20 (12.9%)	5 (6.7%)	25
FAILURE	IMPROVED	57 (36.8%)	31 (41.3%)	88
	NO IMPROVEMENT/WORSE	78 (50.3%)	39 (52.0%)	117
	SUBTOTAL	135 (87.1%)	70 (93.3%)	205
TOTAL		155	75	230

COMPARISON BETWEEN TREATMENTS

COCHRAN MANTEL-HAENSZEL TEST: P-VALUE = 0.151

Table 32 presents a summary of subjects who had any improvement in their condition as indicated by the Physician's Global Assessment evaluation.

Table 32
Number of Subjects with Improvement* in Physician's Global Assessment
Protocol De140-002

Week	BMS-203522 15% Cream	Vehicle
2	73 (37%) n=205	22 (21%) n=104
4	113 (55%) n=205	36 (35%) n=104
8	129 (63%) n=205	37 (36%) n=104
16	123 (60%) n=205	36 (35%) n=104
24	128 (62%) n=205	41 (39%) n=104
32	77 (50%) n=155	36 (48%) n=75

*Improvement includes categories of Improved, Marked Improvement and Clear/Almost Clear; last observation was not carried forward

Reviewer's Comment: *Patients who showed improvement were not included in the dichotomization for success of eflornithine 15% cream. However, the category of "improved" on the physician's global assessment does state, "there is a clinically apparent decrease in visibility of terminal hair on the treated areas of the face. There is noticeable lightening in the appearance of the facial skin due to terminal hair." One can note from the table that when this*

category is added, from week 8 forward, the divergence of the treatment groups is greater than 20% and more than half the subjects have improved. For some women, this degree of improvement may be satisfactory.

Secondary Efficacy Measures

The secondary measures of response are the reduction in hair growth (length) and spatial mass (hair area) as assessed by video image analysis and the Subject's Self-Assessment Questionnaire. The primary evaluation time point is week 24 (end of treatment).

Video Image Analysis

The difference between treatments in baseline hair growth was evaluated by an analysis of variance. The results of the analysis indicated a statistically significant baseline treatment difference (p=0.11) with the vehicle mean (0.497mm) slightly lower than the active (0.535 mm). The transformation of the post-baseline data to a percent reduction from baseline, however, will essentially transform all subjects' baseline measures to zero percent. The analysis of the difference between treatments in baseline spatial mass (hair area per square centimeter of skin surface) indicated no statistically significant baseline treatment group difference (p=0.072).

The percent reduction in hair growth at post-baseline evaluations was dichotomized into "success" (subjects with at least a 50% reduction in hair growth relative to baseline) and "failure" (<50% reduction). The results of the analysis at the primary evaluation, week 24, showed no statistically significant treatment difference (p=0.085). Of the subjects treated with 15% eflornithine hydrochloride cream, 8.6% were deemed successes compared to 2.6% for those treated with the vehicle (see table 33).

Table 33
Video Image Analysis – Percent Success in Hair Growth at Week 24
End of Treatment
Protocol DE140-002

	TREATMENT		
PERCENT CHANGE FROM BASELINE	BMS203522 15%CRM N (%)	BMS203522 VEHCRM N (%)	TOTAL N
SUCCESS (>=50%)	13 (8.6%)	2 (2.6%)	15
FAILURE (< 50%)	138 (91.4%)	75 (97.4%)	213
TOTAL	151	77	228

COCHRAN MANTEL-HAENSZEL TEST P-VALUE=0.085

The results of the analysis at the secondary intermediate evaluation periods (weeks 2-16) revealed a statistically significant treatment difference at week 16 (p=0.039) but none for the other intermediate weeks (p=0.721). At week 16, 8.2% of subjects treated with eflornithine 15% cream were successes compared with 1.3% treated with the vehicle. As expected from these results, at week 32 (eight weeks after treatment cessation) the difference between treatments was

not statistically significant (p=1.000). Success rates were 4.2% for eflornithine 15% cream and 3.8% for the vehicle.

The results for mean spatial mass at the primary evaluation time (week 24) demonstrated a statistically significant treatment difference (p=0.0004), favoring eflornithine 15% cream over its vehicle. The mean spatial mass for the subjects treated with 15% eflornithine hydrochloride cream was 0.036 mm^2, while for those treated with the vehicle, mean spatial mass was 0.043 mm^2. Table 34 shows the results for mean spatial mass at 24 weeks and also for mean hair length. Table 35 gives the video image analysis for mean percent reduction in hair growth at the end of treatment (weeks 24).

Table 34
Video Image Analysis – End of Treatment
Week 24
Protocol DE140-002

	BMS203522 15%CRM	BMS203522 VEHCRM	OVERALL	P-VALUE
HAIR LENGTH				0.001
n	178	92	270	
MEAN	0.404	0.469	0.426	
S.E.	0.009	0.013	0.008	
RANGE				
SPATIAL MASS				0.0004
n	178	92	270	
MEAN	0.036	0.043	0.038	
S.E.	0.001	0.002	0.001	
RANGE				

Table 35
Video Image Analysis – End of Treatment
Mean Percent Reduction in Hair Growth
Protocol DE140-002

WEEK 24: END OF TREATMENT			
n	151	77	228
MEAN	22.0	3.8	15.8
S.E.	2.3	2.7	1.9

Reviewer's Comment: *Although the sponsor was unable to collect data for every subject (see section 11.3.1.33 – Video Image Analysis), the video image analysis was supportive of the physician's global assessment. The difference in spatial mass between eflornithine 15% cream and vehicle was statistically significant (p=0.0004) at the primary evaluation point (week 24). While there was not a statistically significant difference for success in reduction of hair growth by our definition (p=0.085, table 32), compared to vehicle there was statistical significance in reduction of hair length (p=0.001). There was also a trend favoring the eflornithine group over vehicle, 8.6% deemed success as compared to 2.6% for vehicle. The mean percent reduction in hair growth also favored the eflornithine group (22% reduction vs. 3.8%).*

Subject's Self-Assessment Questionnaire

The baseline mean values for the Subject's Self-Assessment Questionnaire are presented in table 36. Based on an analog scale of 100mm in length, where the 0 point was labeled "not bothered/uncomfortable" and where the 100 point was labeled "extremely bothered/uncomfortable", the mean baseline scores for tall the self-assessment questions for subjects in both the eflornithine 15% cream and vehicle groups were over 80. General bother caused by facial hair for both treatment groups was over 89, indicating that at baseline the subjects in both groups had a very high degree of distress over their condition.

Table 36
Analysis of the Subject's Self-Assessment Questionnaire at ~~Week 24~~ ~~End of Treatment~~ Baseline
Protocol DE140-002

/S/

MULTIVARIATE STATISTIC: TREATMENT P=0.908

QUESTION	BMS203522 15%CRM N	MEAN	SD	BMS203522 VEHCRM N	MEAN	SD	P-VALUE
BOTHERED BY FACIAL HAIR?	203	89.22	13.2	103	89.85	12.5	0.698
UNCOMFORTABLE WHEN MEET NEW PEOPLE?	203	85.25	19.9	103	84.48	20.4	0.724
UNCOMFORTABLE AT WORK OR CLASS?	203	83.61	20.2	103	83.84	18.9	0.943
UNCOMFORTABLE AT SOCIAL GATHERINGS?	203	83.99	19.5	103	85.10	18.4	0.642
UNCOMFORTABLE IN EXCHANGES OF AFFECTION?	203	82.82	23.1	103	83.76	21.9	0.747
BOTHERED BY TIME SPENT REMOVING HAIR?	203	83.24	21.2	103	81.96	23.0	0.599

Based on an analog scale of 0-100

For the Subject's Self-Assessment performed after 24 weeks of treatment, results of the multivariate analysis (Wilks's Lambda) indicated a significant difference between the vectors of treatment means (p=0.0027); thus the univariate analyses of the individual questions were examined for their statistical significance. The results of these analyses (see table 37) revealed significant treatment differences in all six questions favoring eflornithine 15% cream over its vehicle ($p \leq 0.0003$), indicating a decrease in subjects' level of bother and discomfort. General bother caused by facial hair was reduced an average of 37 points for the eflornithine 15% cream group and 16 for the vehicle group with a mean rating of 52 in the eflornithine 15% cream group and 74 in the vehicle group.

Table 37
Analysis of the Subject's Self-Assessment Questionnaire at Week 24
End of Treatment
Protocol DE140-002

MULTIVARIATE STATISTIC: TREATMENT P=0.0027 TREATMENT*INVESTIGATOR P=0.0021

QUESTION	BMS203522 15%CRM N	MEAN	SD	BMS203522 VEHCRM N	MEAN	SD	UNIVARIATE P-VALUE
BOTHERED BY FACIAL HAIR?	179	51.91	31.6	88	74.18	28.2	0.0001
UNCOMFORTABLE WHEN MEET NEW PEOPLE?	179	50.51	32.7	88	71.13	31.0	0.0002
UNCOMFORTABLE AT WORK OR CLASS?	179	48.46	32.6	88	68.81	30.9	0.0001
UNCOMFORTABLE AT SOCIAL GATHERINGS?	179	48.89	32.6	88	68.92	31.6	0.0003
UNCOMFORTABLE IN EXCHANGES OF AFFECTION?	179	50.14	34.1	88	69.67	32.2	0.0002
BOTHERED BY TIME SPENT REMOVING HAIR?	179	46.94	33.1	88	68.53	31.1	0.0001

Based on an analog scale of 0-100

The mean scores for all six questions for subjects in the eflornithine 15% cream group were lower (range, 63.93 to 67.61) than the mean scores for subjects in the vehicle group (range, 71.47 to 78.28). At week 16, the differences between the two groups were even larger, the lower mean scores for subjects in the eflornithine 15% cream group (55.90 to 59.17) compared to those in the vehicle group (range 68.32 to 75.71). Differences between treatment groups were no longer statistically significant when the questionnaire was administered 8 weeks after treatment cessation [week 32 (p=0.49)], demonstrating regression of treatment effect.

Reviewer's Comment: *The results of the Subject's Self-Assessment Questionnaire at the primary evaluation time (week 24) supports physician's global assessment evaluation at that same time point. The results at the secondary evaluation times, weeks 8 and 16, are also parallel to the results obtained in the physician's global assessment and thus are supportive. The result at week 32 supports the findings at week 32 of the primary efficacy endpoint in that the treatment effect is lost.*

Subgroup Analysis

The effects of age, race, and prior hair removal technique upon the Physician's Global Assessment at week 24 were descriptively summarized (see tables 38-40). The proportion of success within eflornithine 15% cream remained much the same across age, race, and hair removal technique classifications.

Table 38
Age Effects on Physician's Global Assessment
Protocol DE140-002

AGE		TREATMENT					
		BMS203522 15%CRM		BMS203522 VEHCRM		STUDY TOTAL	
		N	PCTN	N	PCTN	N	PCTN
<65	SUCCESS	77	43.0	12	13.0	89	32.8
	FAILURE	102	57.0	80	87.0	182	67.2
	CATEGORY TOTAL	179	100.0	92	100.0	271	100.0
>=65	SUCCESS	10	55.6	1	12.5	11	42.3
	FAILURE	8	44.4	7	87.5	15	57.7
	CATEGORY TOTAL	18	100.0	8	100.0	26	100.0
TOTAL		197	100.0	100	100.0	297	100.0