Table 39
Race Effects on Physician's Global Assessment
Protocol DE140-002

RACE		TREATMENT					
		BMS203522 15%CRM		BMS203522 VEHCRM		STUDY TOTAL	
		N	PCTN	N	PCTN	N	PCTN
WHITE	SUCCESS	61	46.2	10	15.2	71	35.9
	FAILURE	71	53.8	56	84.8	127	64.1
	CATEGORY TOTAL	132	100.0	66	100.0	198	100.0
NON-WHITE	SUCCESS	26	39.4	3	8.6	29	28.7
	FAILURE	40	60.6	32	91.4	72	71.3
	CATEGORY TOTAL	66	100.0	35	100.0	101	100.0
TOTAL		198	100.0	101	100.0	299	100.0

Table 40
Prior Hair Removal Technique on Physician's Global Assessment
Protocol De140-002

PRIOR HAIR REMOVAL		TREATMENT					
		BMS203522 15%CRM		BMS203522 VEHCRM		STUDY TOTAL	
		N	PCTN	N	PCTN	N	PCTN
SHAVING/CUTTING	SUCCESS	38	40.4	4	8.3	42	29.6
	FAILURE	56	59.6	44	91.7	100	70.4
	CATEGORY TOTAL	94	100.0	48	100.0	142	100.0
PLUCKING	SUCCESS	21	42.9	2	6.5	23	28.8
	FAILURE	29	57.1	29	93.5	57	71.3
	CATEGORY TOTAL	49	100.0	31	100.0	80	100.0
SHAVING & PLUCKING	SUCCESS	27	50.9	7	33.3	34	45.9
	FAILURE	26	49.1	14	66.7	40	54.1
	CATEGORY TOTAL	53	100.0	21	100.0	74	100.0
PLUCKING & WAXING	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		197	100.0	100	100.0	297	100.0

Reviewer's Comment: Differences in success between whites and nonwhites were not as great in this study, with whites experiencing success 46% of the time, and non-whites experiencing success 39% of the time.

11.3.1.4.3 Safety outcomes

Table 41 presents 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 41
Subjects Reporting Adverse Events
Protocol DE140-002

	TREATMENT					
	BMS203522 15%CRM		BMS203522 VEHCRM		TOTAL	
	n	%	n	%	n	%
SUBJECTS WITH NO ADVERSE EVENTS	22	11	18	17	40	13
SUBJECTS WITH ADVERSE EVENTS	183	89	86	83	269	87
SUBJECTS WHO DISCONTINUED DUE TO ADVERSE EVENTS	5	2	1	1	6	2
SUBJECTS WITH RELATED ADVERSE EVENTS	114	56	51	49	165	53
SUBJECTS WITH UNRELATED ADVERSE EVENTS	162	79	75	72	237	77
SUBJECTS WITH UNASSESSABLE ADVERSE EVENTS	39	19	18	17	57	18
SUBJECTS WITH SERIOUS ADVERSE EVENTS	9	4	3	3	12	4
DEATHS	0	0	0	0	0	0

In this study, there was a total incidence of 1389 AEs reported by 269 (87%) subjects. Nine hundred twenty-two of these AEs were reported by 183 subjects (89%) in the eflornithine 15% treatment group and 467 were reported by 86 subjects (83%) in the vehicle group.

A total of 165 (53%) subjects reported 331 adverse events which were considered related to treatment by the investigator and 237 (77%) subjects reported 968 adverse events which were considered unrelated to treatment by the investigator. AEs of 114 subjects (56%) in the eflornithine 15% treatment group and 51 subjects (49%) in the vehicle group were considered related to treatment with study medication by the investigators. Fifty-seven subjects (18%) had 90 AEs whose relationship to study treatment was evaluated by the investigators as either unassessable or unknown.

Overall, the greatest number of treatment-related AEs occurred in the skin and appendages body system classification [153 subjects (50%)]. The proportion of subjects experiencing these AEs was similar for the two treatment groups. One hundred seven subjects (52%) reported a treatment-related AE in this body classification in the eflornithine 15% cream group compared to 46 subjects (44%) in the vehicle group (see table 42).

Table 42
Subjects Reporting Adverse Events
By Body System And Relationship to Treatment
Protocol DE140-002

	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	114	55.6	162	79	39	19	51	49	75	72.1	18	17.3
Skin/appendages	107	52.2	69	33.7	12	5.9	46	44.2	31	29.8	5	4.8
Body as a Whole	12	5.9	117	57.1	19	9.3	6	5.8	55	52.9	5	4.8
Headache	9	4.4	54	26.3	15	7.3	5	4.8	28	26.9	4	3.8
Asthenia	0	0.0	8	3.9	0	0.0	1	1.0	7	6.7	0	0.0
Pain Abdomen	0	0.0	5	2.4	3	1.5	1	1.0	4	3.8	0	0.0
Nervous System	4	2.0	26	12.7	4	2.0	4	3.8	14	13.5	2	1.9
Dizziness	3	1.5	15	7.3	1	0.5	3	2.9	13	12.5	1	1.0
Vertigo	1	0.5	1	0.5	1	0.5	1	1.0	0	0.0	0	0.0
Digestive System	13	6.3	48	23.4	6	2.9	5	4.8	20	19.2	2	1.9
Dyspepsia	8	3.9	27	13.2	5	2.4	3	2.9	14	13.5	1	1.0
Anorexia	1	0.5	18	8.8	0	0.0	3	2.9	8	7.7	1	1.0
Diarrhea	4	2.0	7	3.4	2	1.0	0	0.0	5	4.8	0	0.0
Nausea	2	1.0	3	1.5	0	0.0	2	1.9	1	1.0	0	0.0
Vomiting	0	0.0	2	1.0	0	0.0	1	1.0	0	0.0	0	0.0
Heme/lymphatic System	2	1.0	12	5.9	0	0.0	1	1.0	3	2.9	1	1.0
Leukopenia	1	0.5	1	0.5	0	0.0	1	1.0	1	1.0	0	0.0
Metabolic System	2	1.0	25	12.2	1	0.5	1	1.0	16	15.4	1	1.0
Hyperuricemia	2	1.0	2	1.0	0	0.0	0	0.0	3	2.9	0	0.0
BUN Increased	0	0.0	0	0.0	0	0.0	1	1.0	1	1.0	0	0.0
Special Senses	2	1.0	11	5.4	2	1.0	0	0.0	5	4.8	0	0.0
Taste Perversion	2	1.0	0	0.0	1	0.5	0	0.0	0	0.0	0	0.0
Urogenital System	2	1.0	48	23.4	2	1.0	1	1.0	25	24.0	3	2.9
Abnormal Urine	1	0.5	11	5.4	1	0.5	1	1.0	6	5.8	0	0.0
Cardiovascular System	0	0.0	6	2.9	2	1.0	0	0	6	5.8	0	0.0
Endocrine System	0	0.0	9	4.4	1	0.5	0	0.0	6	5.8	0	0.0
Musuloskeletal System	0	0.0	12	5.9	3	1.5	0	0.0	9	8.7	1	1.0
Respiratory System	0	0.0	39	19.0	3	1.5	0	0.0	15	14.4	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.

Reviewer's Comment: *The majority of the adverse events are related to the skin and appendages. The specific categories of events will be delineated below. The remaining adverse events also are fairly comparable between drug product and vehicle. There is not a significant difference between the eflornithine arm and the vehicle arm regarding systemic adverse events.*

Reports of skin and appendages AEs judged to be related to treatment were similar for subjects in both treatment groups, with the exceptions of stinging skin, burning skin and tingling skin. While the absolute number of AEs was low, the percentage of subjects having it reported as a treatment-related AE was slightly higher in eflornithine 15% cream treated subjects: 9% vs. 4% for stinging skin, 6% vs. 4% for burning skin, and 3% vs. 1% for tingling skin (see table 43).

The greatest number of treatment-related AEs were acne and pseudofolliculitis barbae (PFB), which were specifically evaluated as identified in the protocol. A similar proportion of subjects in the two treatment groups had these AEs judged as treatment related by the investigators [acne, 28% both groups; PFB, 21% in the eflornithine 15% cream group and 19% in the vehicle group]. Most of the acne and PFB AEs in both treatment groups were rated as mild in severity with only a small number reported as moderate. Most acne and PFB AEs were deemed by the investigators to be possibly related to study treatment for the majority of subjects in both treatment groups. About one-quarter of each of these AEs in both treatment groups were considered unrelated to treatment with study medication, while a remaining small number were considered probably related to treatment. With the exception of one PFB AE in a vehicle treated subject which required a dose interruption, no other acne or PFB AE resulted in dose reduction or dose interruption and no subject was discontinued from the study for either of these AEs.

Table 43
Most Frequent Treatment-Related Skin and Appendages AEs
Protocol DE140-002

Adverse Events	BMS-203522 N=205 n*(%)	Vehicle N=104 n (%)
Acne	58 (28%)	29 (28%)
Pseudofolliculitis Barbae	43 (21%)	20 (19%)
Stinging Skin	19 (9%)	4 (4%)
Burning Skin	12 (6.0%)	4 (4%)
Pruritus	11 (5%)	6 (6%)
Tingling Skin	6 (3%)	1 (1%)
Dry Skin	6 (3%)	4 (4%)
Erythema	5 (2%)	0 (%)
Irritation Skin	4 (2%)	2 (2%)
Alopecia	3 (2%)	2 (2%)
Dermatitis	3 (2%)	1 (1%)
Ingrown Hair	0 (0%)	2 (2%)
Rash	2 (1%)	0 (0%)
Folliculitis	2 (1%)	0 (%)
Bleeding Skin	1 (1%)	1 (1%)
Rash Papular	2 (1%)	0 (0%)
Herpes Simplex	1 (1%)	1 (1%)

*n=number of subjects

Reviewer's Comment: *There were 4 adverse events that appear to be related to the active ingredient, eflornithine hydrochloride, as they did not occur in the vehicle group: erythema, rash, folliculitis, and papular rash. These events occurred in 2%, 1%, 1%, and 1% of the population, respectively. None resulted in discontinuation from the study.*

Overall, the majority of subjects with treatment-related AEs had them judged to be of mild intensity (127, 77%). The percentage of subjects with mild, treatment-related AEs was similar in the eflornithine 15% cream and vehicle groups (77% and 76%, respectively). The majority of subjects with AEs considered unrelated to study treatment had them judged to be of

moderate intensity (124, 52%). The percentage of subjects with AEs of moderate severity which were considered unrelated to treatment with study medication were also similar in the eflornithine 15% cream and vehicle groups (54% and 49%, respectively).

Only one subject discontinued because of an adverse event that was probably related to study medication. This patient had burning skin/pruritus of 126 days duration and was in the vehicle arm of the trial. Five other patients discontinued due to an adverse event. All were in the eflornithine 15% cream arm of the trial. Four of the five events were unrelated to study medication and one was recorded as unassessable.

Reviewer's Comment: *The patient deemed unassessable had folliculitis and requested to be removed from the study 4 days after beginning medication. On reviewing the CRF, the sites of folliculitis were on the upper extremity and lower extremity and not on the face. Patient elected to discontinue for personal reasons.*

There were only 6 AEs related to treatment reported by five subjects that required dose interruption, 4 in the eflornithine 15% cream group and 1 in the vehicle group. The only skin related AEs that required a dose interruption were rash reported in one subject in the eflornithine 15% cream arm and PFB reported by one subject in the vehicle group. These adverse events were moderate in intensity, resolved and both patients completed to the study.

Reviewer's Comment: *Subject 569 had leukopenia, which was reported as of moderate intensity and patient had a dose interruption. The onset was day 105 and it resolved on day 126 and patient completed the study.*

Forty-two subjects (14%) had 71 AEs related to study medication that required treatment intervention. The proportion of subjects requiring treatment intervention for treatment-related AEs was similar for the two treatment groups. In the eflornithine 15% cream group 27 subjects (13%) had 49 of these AEs that required treatment intervention compared to 15 subjects (14%) in the vehicle group who had 22 of these AEs that required treatment intervention. The most common AEs requiring treatment intervention were headache and acne. The incidence of these two AEs was similar for the two treatment groups.

The median time (time by which 50% of the subjects had experienced their first skin-related adverse event) was 9 weeks and 15 weeks for eflornithine 15% cream and vehicle, respectively. The results of the effects on race on the proportion of subjects with skin-related adverse events demonstrate that they are similar and are presented in table 44.

Table 44
Effects of Race on the Proportion of Subjects with Skin-Related Adverse Event
Protocol DE140-001

RACE		TREATMENT					
		BMS203522 15%CRM		BMS203522 VEHCRM		STUDY TOTAL	
		N	PCTN	N	PCTN	N	PCTN
WHITE	NO	45	32.8	29	42.0	74	35.9
	YES	92	67.2	40	58.0	132	64.1
	CATEGORY TOTAL	137	100.0	69	100.0	206	100.0
NON-WHITE	NO	26	38.2	16	45.7	42	40.8
	YES	42	61.8	19	54.3	61	59.2
	CATEGORY TOTAL	68	100.0	35	100.0	103	100.0
TOTAL		205	100.0	104	100.0	309	100.0

A total of 20 serious adverse events (SAEs) were reported in 12 subjects. All SAEs were judged to be unrelated to study treatment. By treatment group, 9 subjects (4%) in the eflornithine 15% cream group reported 16 SAEs compared to 3 subjects (3%) in the vehicle group who reported 4 SAEs.

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. There were not any deaths reported during the study.

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) show 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 45 were observed to have shifts (increase or decrease) in greater than 2% of the subjects. Evaluation of these parameters does not reveal any trend considered to be associated with study drug treatment as the percent of subjects experiencing shifts were comparable between active and vehicle treatment groups.

Table 45

Laboratory Shifts From Baseline to End of Treatment

Protocol DE140-002

(Table includes only parameters for which 2% or more of subjects who had a shift from baseline category.)

Laboratory Test		Change	TREATMENT			
			BMS203522 15%		Vehicle	
			n*	%	n	%
CHEMISTRY	Prolactin	High-Normal	6	3.9	1	1.3
		Normal – High	11	7.2	3	3.8
	Potassium	Normal- Low	1	0.7	5	6.6
		Low-Normal	6	3.9	0	0
	Alkaline Phosphatase (ALP)	High-Normal	4	2.6	0	0
		Normal-High	1	0.7	1	1.3
	Alanine Aminotransferase (ALT)	High-Normal	5	3.3	3	3.9
		Normal-High	5	3.3	3	3.9
	Blood Urea Nitrogen	Normal-Low	6	4.0	3	3.9
		Low-Normal	6	4.0	3	3.9
	Chloride, Serum	High-Normal	1	0.7	2	2.6
	Lactate Dehydrogenase (LD)	Normal-High	2	1.3	2	2.6
		High-Normal	3	2.0	0	0
	Phosphorous, Inorganic	High-Normal	7	4.6	0	0
		Normal-High	5	3.3	5	6.6
	Uric Acid	High-Normal	9	6.0	1	1.3
		Normal-High	4	2.6	4	5.3
	Dehydroepiandrosterone Sulfate	High-Normal	8	5.5	3	4.2
		Normal-High	6	4.1	2	2.8
	Follicle-Stimulating Hormone (FSH)	Normal-High	2	1.7	2	3.5
		Low-Normal	4	3.5	1	1.8
HEMATOLOGY	Hemoglobin	Normal-Low	4	2.6	5	6.5
		Low-Normal	0	0	1	1.3
	Hematocrit	Normal-Low	0	0	6	7.8
		Low-Normal	2	1.3	2	2.6
	Erythrocytes	Normal-Low	4	2.6	7	9.1
	Eosinophils (absolute)	High-Normal	5	3.3	2	2.6
		Normal-High	3	2.0	1	1.3
	Neutrophils (absolute)	Normal-High	3	2.0	0	0
		Low-Normal	5	3.3	0	0
	Platelet Count	High-Normal	1	0.7	0	0
		Normal-High	3	2.0	2	2.6
		Normal-Low	2	1.3	0	0
		Low-Normal	4	2.7	0	0
	Leukocytes	High-Normal	8	5.3	0	0
		Normal-High	2	1.3	2	2.6

*n= number of subjects

There were 4 pregnancies reported during the study, 3 patients were in the eflornithine arm and one in the vehicle arm. The patient in the vehicle arm was lost to follow-up. Two subjects had completed the treatment phase of the study (24 weeks) when pregnancy was confirmed. Subject 869 was confirmed pregnant on her week 24 visit. Treatment with study medication was discontinued when the results became known and the patient elected to have an abortion one month later. She completed the eight-week post-treatment phase of the trial. Subject number 616 had pregnancy confirmed at week 32. She had discontinued study medication at week 24. She experienced a spontaneous abortion about 3 weeks after pregnancy

confirmation and the fetus was 7 weeks gestation. The patient had had a previous spontaneous abortion in 1984. Subject number 736 had pregnancy confirmed 4 weeks after beginning medication. It was stopped and one month later (at 5 weeks gestation) patient had a spontaneous abortion. She reported no prior history of spontaneous abortions.

11.3.1.5 Conclusions Regarding Safety Data

Eflornithine 15% cream is well tolerated. The greatest incidence of adverse events was skin related. Those occurring at an incidence of 3% or greater were stinging skin (9%), burning skin (6%), tingling skin (3%), and dry skin (3%). The adverse events that occurred in less than 3% of subjects but greater than 1% included erythema, irritation skin, alopecia, dermatitis, rash, folliculitis, bleeding skin, rash papular, and herpes simplex. Of those adverse events, only erythema (2%), folliculitis (2%), rash (1%), and papular rash (1%) occurred only in the eflornithine arm and thus probably can truly be attributed to the drug product. The remaining adverse events occurred in the same percentages of patients in both arms except dermatitis where there was a 1% difference.

Only 2.0% of patients had to have the medication reduced or interrupted for skin-related adverse events and all completed the study. It is in eflornithine's favor that by the time half of the 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=0.001). The proportion of subjects between whites and non-whites, as it relates to adverse events involving the skin, is similar. The laboratory parameters did not reveal any area of concern that could reflect a drug effect from systemic absorption of eflornithine 15% cream.

11.3.1.6 Conclusions Regarding Efficacy Data

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 was clinically meaningful. The significant benefit of eflornithine 15% cream over vehicle was observed by week 8 (p=0.001) and was maintained to week 24 (p=0.001). Eighty-three subjects (40.5%) receiving eflornithine 15% cream were rated as a clinical success (marked improvement or greater) by the PGA compared with thirteen subjects (12.5%) in the vehicle cream group at the end of treatment (week 24). Additionally, at the end of treatment, 62% 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 ($p \leq 0.025$) and was maintained throughout the treatment phase to week 24 (p=0.0004). Although when dichotomized for success vs. failure in hair length (>50% reduction from baseline), there was no statistically significant difference between eflornithine 15% cream and vehicle (p=0.85), there was a statistically significant difference in reduction of hair length at end of treatment favoring eflornithine when compared to vehicle (p=0.001). By week 24, eflornithine 15% cream treated subjects had a 22% mean

percent reduction in hair growth compared to a 3.8% mean percent reduction in vehicle treated subjects.

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 ($p \leq 0.0003$). Their responses were also consistent with the primary efficacy measure, the physician's global assessment.

When evaluating the subgroup analysis by race and hair removal technique, the proportion of success remained fairly constant.

11.4 Sponsor's protocol #DE140-011 Title: Six- Month Safety Evaluation – Open Label Treatment of Women With Excessive Facial Hair with BMS-203522

11.4.1 Investigators

1.	Leslie Mark, M.D.	003/San Diego, CA
2.	Terry M. Jones, M.D.	004/Bryan, TX
3.	Carol H. Wysham, M.D.	005/Spokane, WA
4.	Ronald C. Savin, M.D.	006/New Haven, CT
5.	James Leyden, M.D.	007/Philadelphia, PA
6.	Daniel Stewart, M.D.	008/Clinton Township, MI
7.	Eduardo Tschen, M.D.	009/Albuquerque, NM
8.	Malcolm Sperling, M.D.	010/Fountain Valley, CA
9.	Denise Buntin, M.D., P.C.	011/Hermitage, TN
10.	Roger Anderson, M.D.	012/Pittsburgh, PA
11.	Ross D. Bright, M.D.	013/Palo Alto, CA
12.	Calvin McCall, M.D.	014/Atlanta, GA
13.	Janet Roberts, M.D.	015/Portland, OR
14.	David Tashjian, M.D.	016/Fresno, CA
15.	Christopher G. Nelson, M.D.	017/St. Petersburg, FL
16.	Alan H. Greenspan, M.D.	018/Paramus, NJ
17.	Jerold Powers, M.D.	019/Scottsdale, AZ
18.	Joseph G. Daddabbo, M.D.	020/Cincinnati, OH
19.	Rodney A. Sinclair, MBBS	021/Fiszroy, VIC Australia
20.	Peter Cowen, MBBS	022/Clayton, VIC Australia
21.	Louis Dubertret, M.D.	023/Paris Cedex 10 France
22.	Yorik Drouault, M.D.	024/Paris, France
23.	Jean-Paul Ortonne, M.D.	025/Nice Cedix 3 France
24.	Anders Johannesson, M.D.	028/Vallingby, Sweden
25.	Ids H. Boersma, M.D.	029/Dordrecht, Netherlands
26.	Jose Barba-Gomez, M.D.	030/ Jalisco, Mexico
27.	Oliverio Welsh, M.D.	031/Monterrey, Mexico
28.	Rocio Orozco, M.D.	033/Tlalpan, Mexico

29.	Alyson Layton, M.D.	036/NorthYorkshire, England
30.	Brian David Kramer, MBBCh	039/Parktown, South Africa
31.	Ray Moore, MBBS	040/Umhlanga Rocks, S.Af

11.4.1.1 Objective/Rationale

The objective of this study was to evaluate the long term safety of twice daily applications of BMS-203522 (eflornithine hydrochloride) 15% cream in the treatment of women with excessive facial hair for up to 26 weeks.

11.4.1.2 Design

This was an open-label study in which all subjects received eflornithine 15% cream. The study involved up to 26 weeks of twice daily treatment with a 4-week no treatment follow-up period. Study medication was to be applied to all affected areas of the face and anterior neck. Evaluations included physical examinations, clinical observations of adverse events, Global Assessment of improvement/worsening of the subject's facial hirsutism, and laboratory assessments. Subjects were evaluated on Day 1 and at weeks 2, 4, 8, 12, 16, 20, 26, and 30.

11.4.1.3 Protocol

Inclusion Criteria

Subjects who met the following criteria were eligible to enter the study:
Adult women of legal age and capacity for consent. Note: In most locations 18 years of age is the age of consent.
Women, including women of childbearing potential who had a negative urine or serum pregnancy test within 72 hours prior to the start of study medication.
Women of any skin type or race.
Willing and able to apply study medication as directed, comply with study instructions, and commit to follow-up visits for the duration of the study.
Signed a written informed consent.
Clinical diagnosis of facial hirsutism.
A customary frequency of removal of facial hair of two or more times per week.
The presence of a total of at least 20 terminal hairs on the upper lip and chin as determined by clinical observation.
Good general health and free of any disease state or physical condition which might have impaired evaluations or increased health risk to the subject by study participation.
Fertile subjects who agreed to use an effective form of birth control for the duration of the study (stabilized on oral contraceptives for at least 3 months, abstinence, IUD, foam, condom, diaphragm, implant or injection).

Exclusion Criteria

Previous participation in investigation studies of eflornithine hydrochloride
Use of electrolysis, laser or epilation (waxing, Epilady®, sugaring, etc.) to remove hair within 2 months before the study
Use of chemical depilatories to remove facial hair within 2 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
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 formulation
Participation in an investigational study currently or within 30 days before the study, with exposure to investigational drug, including placebo
Pregnant or nursing mothers

Study Procedures

Study medication was administered topically, twice daily to affected areas of the face and anterior neck for the 26-week treatment period, even if hair growth abnormalities appeared to be resolved. Study medication was not applied during the 4-week no treatment period (weeks 27-30). A thin film of study medication was to be applied to affected areas of clean, dry skin and rubbed in gently and completely. At the initial visit (Day 1), the study staff demonstrated the proper application of study medication and witnessed the initial dosing to ensure subjects understood the instruction. Subsequent twice daily applications were to be separated by at least 8 hours. Subjects were instructed not to cleanse the treatment area within 4 hours after application, and to wash their hands immediately after applying study medication. Subjects could apply makeup or other topical products to the treated areas after the study medication had dried for at least 5 minutes following application.

If excessive irritation or other local signs of study medication intolerance occurred at any time during the 26-week period, the investigator could direct subjects to reduce frequency of application to once daily or once every other day. If irritation continued or if the subject could not return to regularly scheduled applications within one week of reducing the dose frequency, the subject was to be withdrawn from the study.

11.4.1.3.1 Population

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

APPEARS THIS WAY
ON ORIGINAL

11.4.1.3.2 Endpoints

The Physician's Global Assessment was an evaluation of the subject's facial hirsutism and followed the same parameters as in the double-blind, placebo-controlled studies. They consisted of 4 categories: clear/almost clear, marked improvement, improved, and no improvement/worse. This assessment was made at weeks 8, 16, and 26 subsequent to the baseline evaluation. [redacted] photographs were taken at the initial visit, week 12 and week 26. They were to be used as a tool in the global assessment.

Safety assessments included the reporting of adverse events by the subject and/or the observation of adverse events by the clinical investigator. Patients were also queried by the investigator for adverse events that were known to occur with the intravenous formulation of eflornithine hydrochloride, as requested by the US FDA. These included the occurrence of hair loss, facial swelling, seizures, hearing impairment, stomach upset, loss of appetite, headache, weakness, and dizziness. The other safety parameter included results of clinical laboratory tests. These included blood chemistry, hematology, pregnancy, and urinalysis. Investigators were required to assess the severity of all adverse events and to determine if the event was likely to be drug related.

11.4.1.3.3 Statistical considerations

The goal was to enroll 700 subjects at several study centers. The sponsor's approach was that a sample size of n=700 was sufficiently large such that if the true adverse event rate is at least 0.43%, then the probability is 95% that one or more subjects would report an adverse event. The following equation, based on the binomial distribution, was solved for n:

$$P(\text{at least one AE}) = 1 - (1-p)^n,$$

Yielding n = 700 subjects.

APPEARS THIS WAY
ON ORIGINAL

11.4.1.4 Results

11.4.1.4.1 Populations enrolled/analyzed

A total of 754 subjects were enrolled at 31 study centers. Five hundred forty-nine (549) subjects were enrolled at 18 sites in the United States. Two hundred five (205) subjects were enrolled at 13 sites in other countries, including 60 in Mexico, 40 in South Africa, 57 in France, 23 in The Netherlands, 15 in England, 6 in Sweden, and 4 in Australia. Six hundred and twelve (612) subjects completed 26 weeks of treatment and 578 subjects completed the study.

Of the 754 subjects enrolled in the study, 511 (67.8%) were White, 97 (12.9%) were Black, 110 (14.6%) were Hispanic/Latino, 19 (2.5%) were Asian/Pacific Islander, 6 (0.8%) were American/Alaskan Native, and 11 (1.5%) were classified as "Other". The overall mean age, height and weight were 41.3 years, 64.4 inches, and 180.2 pounds (see table 46).

Table 46
Demographic Characteristics
Intent-to-Treat
Protocol DE140-011

AGE	
N	753*
Mean	41.3
S.E.	0.45
Range	18-80
HEIGHT (INCHES)	
N	750
Mean	64.4
S.E.	0.10
Range	49-72
WEIGHT (LBS.)	
N	750
Mean	180.2
S.E.	1.85
Range	90-407
RACE	
White	511 (67.8%)
Black	97 (12.9%)
Asian/Pacific Islanders	19 (2.5%)
Hispanic/Latino	110 (14.6%)
American/Alaskan Native	6 (0.8%)
Other	11 (1.5%)
SKIN TYPE	
I: Always burn, never tan	45 (6.0%)
II: Usually burn, tan less than average	152 (20.2%)
III: Sometimes mild burn, tan about average	263 (34.9%)
IV: Rarely burn, tan more than average	162 (21.5%)
V: Brown skin, rarely burns, tans profusely	73 (9.7%)
VI: Black skin, rarely burns, tans profusely	58 (7.7%)

*Age was not available for one subject

Table 47 shows a summary of patient disposition in the study. A total of 57 subjects discontinued from the study due to their request (patient request). Two of the 57 subjects were considered adverse event discontinuations by coding convention and were categorized as such. The category of 'Patient Request' includes the following reasons: moving (10); dissatisfaction with the study treatment or related reason (9); unable to keep visit schedule (10); work responsibilities (9); other general reasons (9); not specified (5); adverse events (4); and did not like blood draws (1). The adverse event reasons stated by the subjects were: subject no. 454, bumps on chin; subject no. 1173, boil on chin; subject no. 966, burning sensation at site of application; subject no 1149, unable to keep with BID dosing/wants to treat chin acne. Two of these subjects (1149 and 966) were considered AE discontinuations.

Six subjects discontinued due to the classification of 'Other Reasons' noted as follows: subject no. 319 was unable to take time off work for appointments; subject no. 398 did not have

transportation to the study center; subject nos. 501 and 503 discontinued application of study medication at week 20; subject no 504 discontinued application of study medication at week 20 due to Study Coordinator error; and subject no. 543 relocated.

Two subjects were discontinued because they were ineligible and two subjects discontinued by physician's decision. Twenty-seven subjects were documented as being discontinued from the study due to adverse events. Eight of these subjects were not identified by the investigator as having dropped to an adverse event on the End of Study Status Form but were recorded as such because of the manner in which the data were coded. The reasons for these discontinuations given by the investigators on the End of Study Status Form were as follows: completed study (2), patient request (2), lost to follow-up (1), pregnancy (1), non-compliance (1), and physician's request (1).

Table 47
Summary of Subject Disposition
Protocol DE140-011

	TREATMENT BMS 203522 15% CRM	
	N	%
Study Completion	578	77
Lost to Follow-up	74	10
Patient request	55	7
Pregnancy	11	1.5
Other	6	1
Non-compliance	3	0.4
Physician's decision	2	0.3
Ineligible	2	0.3
Never treated with study drug	1	0.1
Adverse Event	27	4
Total	754	100

Three hundred and seventy subjects (51.2%) used plucking as a means of hair removal. Other methods used were shaving/cutting (201, 27.8%), shaving and plucking (133, 18.4%), bleaching (8, 1.1%), chemical depilatories (2, 0.3%), and "other" (8, 1.1%). A total of 32 subjects had no method of hair removal recorded (see table 48).

Table 48
Method of Hair Removal Used during the Two Weeks Prior to the Study
Protocol DE140-011

Method of Removal	N	%
Shaving/Cutting	201	27.8
Plucking	370	51.2
Shaving & Plucking	133	18.4
Bleaching	8	1.1
Chemical depilatories	2	0.3
Other	8	1.1

In the medical history evaluation, 30 subjects presented with a medical history of polycystic ovarian disease. Thirteen were recorded under the GYN category and 17 were recorded under the Endocrine category.

11.4.1.4.2 Efficacy endpoint outcomes

The physician's global assessment was performed after 8, 16, and 26 weeks of treatment. Table 49 depicts the distribution of results determined by dichotomizing the PGA into "success" (at least marked improvement) and "failure" (less than marked improvement). After 8 weeks of treatment, the success rate was 27.1%. After 16 weeks of treatment, the success rate was 40.2% and by the end of treatment (26 weeks), the success rate was 47.3%.

Table 49
Physician's Global Assessment
Protocol DE140-011

Visit	Clear/ Almost Clear N (%)	Marked Improvement N (%)	Improved N (%)	No Improvement/ Worse N (%)	Total
Week 8	15 (2.2%)	169 (24.9%)	373 (54.9%)	123 (18.1%)	680
Week 16	38 (6.2%)	209 (34.0%)	312 (50.7%)	56 (9.1%)	615
Week 26	69 (11.3%)	220 (36.0%)	263 (43.0%)	59 (9.75)	611

Reviewer's Comment: As this is an open-label study, true efficacy of eflornithine 15% cream cannot be ascertained from the study. However, even though the ITT population to be evaluated would be a total of 754 patients or 711 (if one excludes most of the 'patient request' discontinuations), the difference in the percentages obtain in the above categories would vary by only a few percent. This study does support the double-blind efficacy trials.

11.4.1.4.3 Safety outcomes

Five hundred fifty-one (73%) subjects reported a total incidence of 1866 AEs. Multiple occurrences of a specific coded event were tabulated by counting the most severe AE resulting in the following summaries. A total of 229 (30% subjects reported 280 adverse events which were considered to be related to treatment by the investigator and 494 (66%) subjects reported 1071 adverse events which were considered to be unrelated to treatment by the investigator. Fifty-eight (8%) subjects reported 71 adverse events with relationship to study treatment either unassessable or unknown. Thirty-four (5%) subjects had serious adverse events, all which were assessed as unrelated to study medication. There were not any deaths reported and 27 subjects (4%) discontinued because of an adverse event (see table 50).

Table 50
Summary of Subjects Reporting Adverse Events
Protocol DE140-011

N	Adverse Events (Treatment-related) N* (%)	Adverse Events (Treatment-unrelated) N (%)	Adverse Events (Treatment-Unassessable) N (%)	Serious Adverse Events N (%)	Deaths N (%)	Discontinued for Adverse Events N (%)
754	229 (30%)	494 (66%)	58 (8%)	34 (5%)	0	27 (4%)

*N=number of subjects

Table 51 reports the number of subjects reporting adverse events by body system. Skin and appendages had the highest incidence of adverse events (24%).

Table 51
Number of Subjects Reporting
Adverse Events by Body System
Protocol DE 140-011

	Related to Treatment					
	Yes		No		Unassessable	
Body System	N	%	N	%	N	%
Total All Systems	229	30.4	494	65.5	58	7.7
Body As A Whole	42	5.6	295	39.1	28	3.7
Skin/Appendages	181	24.0	95	12.6	10	1.3
Digestive System	15	2.0	127	16.8	9	1.2
Urogenital System	1	0.1	125	16.6	7	0.9
Respiratory System	3	0.4	118	15.6	1	0.1
Metabolic/nutritional System	15	2.0	80	10.6	3	0.4
Nervous System	11	1.5	77	10.2	5	0.7
Cardiovascular System	2	0.3	40	5.3	3	0.4
Musculoskeletal System	0	0.0	40	5.3	1	0.1
Hemic/lymphatic System	5	0.7	34	4.5	1	0.1
Special senses	4	0.5	33	4.4	3	0.4
Endocrine System	1	0.1	7	0.9	0	0.0

Table 52 presents the 181 subjects with reports of treatment-related skin and appendages AEs. Those occurring greater than or equal to 1% were: acne (50 subjects, 6.6%), alopecia (36 subjects, 4.8%), erythema (25 subjects, 3.3%), dry skin (22 subjects, 2.9%), burning skin (21 subjects, 2.8%), irritation skin (18 subjects, 2.4%), pruritus (16 subjects 2.1%), stinging skin (16 subjects, 2.1%), folliculitis (11, subjects, 1.5%), rash (10 subjects, 1.3%), and tingling skin (9 subjects, 1.2%).

Table 52
Number of Subjects Reporting Skin And Appendages Adverse Events
Protocol DE140-011

	Related to Treatment					
	Yes		No		Unassessable	
Body System	N	%	N	%	N	%
Skin/Appendages	181	24	95	12.6	10	1.3
Acne	50	6.6	3	0.4	2	0.3
Alopecia*	36	4.8	30	4.0	2	0.3
Erythema	25	3.3	0	0.0	1	0.1
Dry Skin	22	2.9	3	0.4	0	0.0
Burning Skin	21	2.8	0	0.0	0	0.0
Irritation Skin	18	2.4	2	0.3	0	0.0
Pruritus	16	2.1	5	0.7	2	0.3
Stinging Skin	16	2.1	0	0.0	0	0.0
Folliculitis	11	1.5	5	0.7	1	0.1
Rash	10	1.3	7	0.9	0	0.0
Tingling Skin	9	1.2	0	0.0	1	0.1

*possible drug-related incidence actually 10 [1.3% (see text)]

Of the 752 subjects enrolled in the study who actually received treatment, 248 (33%) reported at least one skin-related adverse event; 176 (23.4%) were mild, 68 (9%) were moderate and 4 (0.5%) were severe. By study completion only 35% of subjects had experienced a skin-related adverse event; thus, the median time (the time by which 50% of the subjects had experienced a skin-related adverse event) was never reached within the duration of the study.

The symptom of hair loss was directly queried at each visit. Sixty-eight subjects (9%) reported 74 hair loss adverse events categorized as alopecia. Fifty-four of these AEs did not have the body location of the hair loss specified on the AE form. Thirty-six (36) of the 66 subjects with hair loss AEs reported an incidence sometime during the study, but not at the baseline visit or final visits. For these subjects, the reporting of hair loss episodes that during the course of the study may have been a function of the repeated querying at each visit for this specific symptom. Of the remaining 32 subjects, 14 presented at baseline with a medical history of hair loss, 10 had AEs of hair loss deemed by the investigator to be related to study treatment and 8 had AEs of hair loss that were considered by the investigators to be unrelated to study treatment.

The ten subjects with treatment related AEs of hair loss had no medical history or baseline reports of hair loss but had the AE at their final visit. Eight of the ten patients completed the study and in only one of the eight was the study medication reduced. The AE for that subject resolved in 4 days. Two of the ten subjects discontinued due to hair loss, one (subject 582) for overall hair loss of moderate intensity from the axillae, lower legs, and face of moderate intensity and one (subject 1209) because of hair loss of mild intensity (unspecified body location). Both of these events occurred at week 12 of the study.

Reviewer's Comment: *It does appear that direct query of the patients may have inflated the response regarding hair loss in this population of females. If the hair loss for 36 of the subjects was indeed a drug effect, then it had resolved by the end of the study without discontinuing use of the drug. It seems that the criteria for relating the hair loss to drug effect was based on whether*

the patient had a history of hair loss or baseline reports of hair loss and then described hair loss at the end of the study. This would in effect lower the number of individuals to 10 out of 754 (1.3%) rather than 36 (4.8%) denoted in table 52. Subject 582, who reported hair loss at week 12, may have had another mechanism, such as the onset of alopecia universalis, as the cause of hair loss.

One can argue that the degree of systemic absorption of eflornithine hydrochloride, according to pharmacokinetic data, makes this systemic effect unlikely. The C_{max} and AUC are 100-fold and 30-fold lower than that of the approved oral dose in which this systemic adverse event has been observed. Even given accumulation over time, there is a 1-log difference (lower) in the accumulation of the drug via the dermal route vs. the oral route (see biopharmaceutical review). The double-blind controlled studies support this theory also, as there was not a statistically significant difference seen between eflornithine15% cream and its vehicle (2% and 3%, respectively in –001 and 2% each in –002).

The majority of treatment-related adverse events were judged to be of mild intensity (192 reports, 84%). Most of the adverse events unrelated to study treatment were also of mild intensity (351 reports, 71%). There were no treatment related AEs of very severe intensity. Five subjects (<1%) had severe AEs that were considered to be related to treatment. There were 2 incidences of headache, both of which resolved but one subject discontinued. One subject had a severe burning sensation at the site of application of 3 days duration. Event resolved with discontinuation of medication, and subject withdrew. One subject had ingrown hair follicles and withdrew from the study. Another had furuncles times 2 that were treated and the subject completed the study. The last subject complained of a headache and deafness on study day 1. Study medication was reduced and both AEs resolved without treatment in 4 days and the subject completed the study.

There were a total of 45 serious adverse events reported in 34 subjects. All of these SAEs were judged not to be related to study medication. There were no deaths reported during the trial or in the follow-up period.

***Reviewer's Comment:** Upon review of the case summaries, it is agreed that the serious adverse events were unrelated to study medication.*

Of 27 subjects discontinuing from the study due to AEs, 16 (2.1%) had adverse events considered to be related to study therapy. Thirteen (1.7%) of these 16 subjects experienced AEs which were skin reactions. The treatment related skin adverse events included: acne (3), irritation skin (2), alopecia (2), dry skin (2), hair ingrown, rash, folliculitis, erythema, disorder skin (change in skin texture), and burning skin. These AEs were of mild or moderate intensity except for two of the skin AEs that were of severe intensity.

There were 19 AEs related to treatment reported by 15 subjects (2%) that required a dose reduction. The most common adverse events related to treatment requiring a dose reduction were acne and rash, erythema, irritation skin, burning skin, cheilitis, and folliculitis. The number of AEs related to treatment requiring a dose interruption was 15 reported by 13 subjects (2%). The most frequent AEs related to treatment that required dose interruption were rash, irritation skin, and acne.

Laboratory test results 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 26 showed

that most subjects had laboratory values within normal range at baseline and at the end of treatment. There were 21 laboratory abnormalities in 16 subjects that were considered treatment related adverse events. Twenty were mild and one was of moderate intensity (eosinophilia). The other AEs were leukopenia, anemia, increased LDH, SGOT, SGPT, glycosuria, bilirubinemia, hyperperglycemia, and hyperuricemia. No subjects required dose interruption, reduction, or discontinuation of study treatment. All of the AEs resolved during the study.

Reviewer's Comment: *The laboratory abnormalities were of mild intensity and did not require alteration in study medication. Given that they all resolved during the study, it is unlikely that the laboratory abnormalities can be attributed to the study drug with certainty.*

There were 11 pregnancies during the study. Three subjects had completed the treatment phase of the study (week 26) when the pregnancies were confirmed. There were 7 normal healthy babies, 1 spontaneous abortion, and 3 induced/elective abortions. The patient with the spontaneous abortion at 10 weeks gestation was on an oral contraceptive at the time of pregnancy and reported that she had not discontinued it. The patient stopped study medication and withdrew from the study on day 63.

Reviewer's Comment: *This one spontaneous abortion out of 11 pregnancies does not suggest an added risk because of use of eflornithine 15% cream, as this rate of 9%, is not higher than expected in the general population (see overview of safety for further discussion). This patient also may have had a complicating factor in that she was still taking an oral contraceptive at the time of conception.*

11.4.1.5 Conclusions Regarding Safety

One can conclude from this open-label safety study of 754 patients that eflornithine 15% cream is well tolerated for the treatment of excessive facial hair in women. The incidence of adverse events occurred by week 8 of the study, was primarily limited to the skin, and the majority were of mild severity and limited duration. The number of subjects (13, 1.7%) that discontinued from the study due to skin adverse events was low. The incidence and relationship of the specific systemic AEs may have been influenced, in part, by the study design. Laboratory abnormalities were mild, which could also be expected over a 6-month course of treatment. Further, these abnormalities resolved during treatment and patients' treatment course was not altered as a result of these variations. As discussed elsewhere in this review, the double-blind studies do not reveal any difference in the incidence of these adverse events between eflornithine 15% cream and its vehicle.

11.4.1.6 Conclusions Regarding Efficacy

Although this was an open-label trial, and therefore, cannot in the strictest terms be used to demonstrate efficacy, the results of the physician's global assessment for this population studied over 6 months, supports the efficacy results in the vehicle-controlled studies.

11.5 Sponsor's protocol #DE140-010 Title: "One Year Safety Evaluation-Open-Label Treatment of Women with Excessive Facial Hair with BMS-203522

11.5.1 Investigators

1. Ken Washenik, M.D., Ph.D.	003/New York, NY
2. Manuel R. Morman, M.D.	004/Rutherford, NJ
3. Stephen J. Kraus, M.D.	005/Atlanta, GA
4. Ernest Ast, M.D.	006/Great Neck, NY
5. Peter D. Hino, M.D.	007/Dallas, TX
6. Kathryn A. Kroeger, M.D.	008/Indianapolis, IN
7. Jeffrey Moore, M.D.	009/Evansville, IN
8. Leonard J. Swinyer, M.D.	010/Salt Lake City, UT
9. Karis McCarroll, M.D.	011/San Antonio, TX
10. Virginia C. Fieldler, M.D.	012/Chicago, IL

11.5.1.1 Objective/Rationale

The objective of this study was to evaluate the safety of BMS-203522 (eflornithine hydrochloride) 15% cream in the treatment of women with excessive hair growth by applying the cream twice daily for a period of one year.

11.5.1.2 Design

This was a non-randomized, open-label study. Study medication was applied twice daily for 52 weeks, followed by a four-week non-treatment phase. Clinical evaluations were performed at weeks 0, 2, 4, 8, 12, 16, 20, 28, 36, 44, 52, and 56. Physical examinations were performed at baseline and end of treatment. Blood and urine specimens were collected for analysis at each study visit. Photographs of the treatment area were taken at the initial visit to aid the investigator in evaluating the Physician's Global Assessment at subsequent visits. Adverse events were collected throughout the study.

11.5.1.3 Protocol

Inclusion Criteria

Adult women of legal age and capacity for consent.
Subjects may be of any skin type or race
Willing and able to apply study medication as directed, comply with study instructions and commit to all follow-up visits for the duration of the study
Signed a written informed consent.
Clinical diagnosis of facial hirsutism.
A customary frequency of removal of facial hair of two or more times per week.

The presence of a total of at least 20 terminal hairs on the upper lip and chin as determined by clinical observation.
Good general health and free of any disease state or physical condition which might have impaired evaluations or increased health risk to the subject by study participation.
Fertile subjects who agreed to use an effective form of birth control for the duration of the study (stabilized on oral contraceptives for at least 3 months, abstinence, IUD, foam, condom, diaphragm, implant or injection).

Exclusion Criteria

Previous participation in investigation studies of eflornithine hydrochloride
Use of electrolysis, laser or epilation (waxing, Epilady®, sugaring, etc.) to remove hair within 2 months before the study
Use of chemical depilatories to remove facial hair within 2 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
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 formulation
Participation in an investigational study currently or within 30 days before the study, with exposure to investigational drug, including placebo
Pregnant or nursing mothers

Study Procedures

Study medication was administered topically, twice daily to affected areas of the face and anterior neck for the 52-week treatment period, even if hair growth abnormalities appeared to be resolved. Study medication was not applied during the 4-week no treatment period (weeks 53-56). A thin film of study medication was to be applied to affected areas of clean, dry skin and rubbed in gently and completely. At the initial visit (Day 1), the study staff demonstrated the proper application of study medication and witnessed the initial dosing to ensure subjects understood the instruction. Subsequent twice daily applications were to be separated by at least 8 hours. Subjects were instructed not to cleanse the treatment area within 4 hours after application, and to wash their hands immediately after applying study medication. Subjects could apply makeup or other topical products to the treated areas after the study medication had dried for at least 5 minutes following application.

If excessive irritation or other local signs of study medication intolerance occurred at any time during the 52-week period, the investigator could direct subjects to reduce frequency of application to once daily or once every other day. If irritation continued or if the subject could not return to regularly scheduled applications within one week of reducing the dose frequency, the subject was to be withdrawn from the study.

11.5.1.3.1 Population

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

11.5.1.3.2 Endpoints

The Physician's Global Assessment was an evaluation of the subject's facial hirsutism and followed the same parameters as in the double-blind, placebo-controlled studies. They consisted of 4 categories: clear/almost clear, marked improvement, improved, and no improvement/worse. This assessment was made at weeks 8, 20, 36 and 52 subsequent to the baseline evaluation. ——— photographs were taken at the initial visit, and at week 20 and week 52 as a tool to aid in the global assessment.

Safety assessments included the reporting of adverse events by the subject and/or the observation of adverse events by the clinical investigator. Patients were also queried by the investigator for adverse events that were known to occur with the intravenous formulation of eflornithine hydrochloride, as requested by the US FDA. These included the occurrence of hair loss, facial swelling, seizures, hearing impairment, stomach upset, loss of appetite, headache, weakness, and dizziness. The other safety parameter included results of clinical laboratory tests. These included blood chemistry, hematology, pregnancy, and urinalysis. Investigators were required to assess the severity of all adverse events and to determine if the event was likely to be drug related.

11.5.1.3.3 Statistical considerations

The goal was to enroll 200 subjects at several study centers. The sponsor's approach was that a sample size of n=200 was sufficiently large such that if the true adverse event rate is at least 1.48%, then the probability is 95% that one or more subjects would report an adverse event. The following equation, based on the binomial distribution, was solved for n:

$$P(\text{at least one AE}) = 1 - (1-p)^n,$$

Yielding n = 200 subjects.

11.5.1.4 Results

11.5.1.4.1 Populations enrolled/analyzed

A total of 216 subjects enrolled at 9 study centers. One additional site did not enroll any subjects (Virginia Fiedler, M.D.). One hundred forty-four subjects completed 52 weeks of treatment and 142 subjects completed the 56-week study.

The study sample consisted of a mixture of racial groups: 165 subjects (76.4%) were White, 32 subjects (14.8%) were Black, 13 subjects (6.0%) were Hispanic/Latino, 3 subjects (1.4%) were Asian/Pacific Islander, 1 subject (0.5%) was American/Alaskan Native, and 2 subjects were classified as "Other". The overall mean age, height, and weight were 42.5 years, 64.6 inches, and 191.5 pounds, respectively (see table 53).

Table 53
Demographic Characteristics
Intent-to-Treat
Protocol DE140-010

AGE	
N	216
Mean	42.5
S.E.	0.87
Range	19-77
HEIGHT (INCHES)	
N	216
Mean	64.6
S.E.	0.18
Range	57-71
WEIGHT (LBS.)	
N	216
Mean	191.5
S.E.	3.54
Range	104-350
RACE	
White	165 (76.4%)
Black	32 (14.8%)
Asian/Pacific Islanders	3 (1.4%)
Hispanic/Latino	13 (6.0%)
American/Alaskan Native	1 (0.5%)
Other	2 (0.9%)
SKIN TYPE	
I: Always burn, never tan	27 (12.5%)
II: Usually burn, tan less than average	57 (26.4%)
III: Sometimes mild burn, tan about average	58 (26.9%)
IV: Rarely burn, tan more than average	32 (14.8%)
V: Brown skin, rarely burns, tans profusely	18 (8.3%)
VI: Black skin, rarely burns, tans profusely	24 (11.1%)

Table 54 shows a summary of patient disposition in the study. A total of 62 subjects (29%) discontinued from the study for reasons other than AEs. Of these, twenty subjects (9%) requested discontinuation from the study and were classified as 'Patient Request'. This category included the following responses: dissatisfied with study treatment or related reason (5); work related (4); personal reasons (3); moving (2); subject's concern with abnormal laboratory values

(2); unable to keep study visits (1); lost interest (1); time consuming (1); and did not want to continue (1).

Table 54
Summary of Subject Disposition
Protocol DE140-010

	TREATMENT BMS 203522 15% CRM	
	N	%
Study Completion	144	67
Lost to Follow-up	30	14
Patient request	20	9
Pregnancy	3	1
Other	4	2
Non-compliance	4	2
Physician's decision	1	0.5
Ineligible	1	0.5
Never treated with study drug	2	1
Adverse Event*	9	4
Total		

*Subject 210 was reported by the investigator as study completed but discontinued study medication at week 40. Due to BMS coding convention, this subject was classified as an AE drop.

Eighty-nine subjects (41.4%) used plucking as a means of hair removal. Other methods are delineated in table 55.

Table 55
Method of Hair Removal Used during the Two Weeks Prior to the Study
Protocol DE140-010

Method of Removal	N	%
Shaving/Cutting	78	36.3
Plucking	89	41.4
Shaving & Plucking	45	20.9
Other	3	1.4
Not Reported	1	0.5

11.5.1.4.2 Efficacy endpoint outcomes

The Physician's Global Assessment was performed after 8, 20, 36, and 52 weeks of treatment. Table 56 depicts the distribution of results determined by dichotomizing the Physician's Global Assessment into "success" (at least marked improvement) and "failure (less than marked improvement). After 20 weeks of treatment, 18.4% were a success, after 36 weeks of treatment, 21.4% were a success, and after 52 weeks of treatment, 23.9% were a success.

Table 56
Physician's Global Assessment
Protocol DE140-010

Visit	Clear/ Almost Clear N (%)	Marked Improvement N (%)	Improved N (%)	No Improvement/ Worse N (%)	Total
Week 8	1 (0.5%)	23 (11.9%)	118 (61.1%)	51 (26.4%)	193
Week 20	1 (0.6%)	31 (17.8%)	108 (62.1%)	34 (19.5%)	174
Week 36	6 (3.9%)	27 (17.5%)	99 (64.3%)	22 (14.3%)	154
Week 52	5 (3.4%)	30 (20.5%)	83 (56.8%)	28 (19.2%)	146

Reviewer's Comment: *As this is an open-label study, true efficacy of eflornithine 15% cream cannot be ascertained from the study. However, the trend demonstrated here supports the efficacy trials.*

11.5.1.4.3 Safety outcomes

One hundred ninety-three (89%) subjects reported a total incidence of 1015 AEs. A total of 91 (42%) subjects reported 173 adverse events which were considered to be related to treatment by the investigator and 182 (84%) subjects reported 815 adverse events which were considered to be unrelated to treatment by the investigator. Thirteen (6%) subjects reported 26 adverse events with relationship to study treatment either unassessable or unknown. There was 1 death reported and 12 (6%) subjects discontinued because of an adverse event (see table 57).

Table 57
Summary of Subjects Reporting Adverse Events
Protocol DE140-010

N	Adverse Events (Treatment-related) – N (%)	Adverse Events (Treatment-unrelated) N (%)	Adverse Events (Treatment-Unassessable) N (%)	Serious Adverse Events N (%)	Deaths N (%)	Discontinued for Adverse Events N (%)
216	193* (89%)	91 (42%)	182 (84%)	13 (6%)	1 (1%)	12 (6%)

*Subject 167 had an AE of dizziness of unreported relationship. This subject is not included in the total.

Table 58 reports the number of subjects reporting adverse events by body system. Skin and appendages had the highest incidence of adverse events (33.8%).

Table 58
Number of Subjects Reporting Adverse Events by Body System
Protocol DE 140-010

	Related to Treatment					
	Yes		No		Unassessable	
Body System	N+	%	N	%	N	%
Total All Systems	91	42.1	182	84.3	13	6.0
Body As A Whole	15	6.9	132	61.1	6	2.8
Skin/Appendages	73	33.8	44	20.4	1	0.5
Digestive System	18	8.3	54	25.0	3	1.4
Nervous System	5	2.3	40	18.5	2	0.9
Special Senses	5	2.3	14	6.5	2	0.9
Metabolic/nutritional System	2	0.9	38	17.6	1	0.5
Hemic/lymphatic System	1	0.5	15	6.9	1	0.5
Cardiovascular System	0	0.0	18	8.3	2	0.9
Endocrine	0	0.0	2	0.9	0	0.0
Musculoskeletal System	0	0.0	33	15.3	0	0.0
Respiratory System	0	0.0	67	31.0	3	1.4
Urogenital System	0	0.0	67	31.0	3	1.4

+Within any body system category a subject may be included in more than one relationship category.

The most frequent classification for AEs related to treatment was skin and appendages. A total of 101 subjects (47%) reported 181 skin and appendages AEs. Table 59 presents the 73 subjects (34%) with reports of treatment-related skin and appendages AEs. The most frequent treatment-related skin and appendages AEs were: dry skin (16 subjects, 7%), acne (15 subjects, 7%), alopecia (14 subjects, 7%), pruritus (11 subjects, 5%), burning skin (10 subjects, 5%), stinging skin (9 subjects, 4%), hair ingrown (8 subjects, 4%), rash (7 subjects, 3%), tingling skin (7 subjects, 3%), and erythema (5 subjects, 2%).

Table 59
Number of Subjects Reporting Skin And Appendages Adverse Events
Protocol DE140-010

	Related to Treatment					
	Yes		No		Unassessable	
Body System	N	%	N	%	N	%
Skin/Appendages	73	33.8	44	20.4	1	0.5
Dry Skin	16	7.4	1	0.5	0	0.0
Acne	15	6.9	4	1.9	0	0.0
Alopecia	14	6.5	9	4.2	0	0.0
Pruritus	11	5.1	8	3.7	0	0.0
Burning Skin	10	4.6	1	0.5	0	0.0
Stinging Skin	9	4.2	1	0.5	0	0.0
Hair ingrown	8	3.7	1	0.5	0	0.0
Rash	7	3.2	8	3.7	1	0.5
Tingling Skin	7	3.2	0	0.0	0	0.0
Erythema	5	2.3	0	0.0	0	0.0

Of the 216 subjects enrolled in the study, 101 subjects (47%) reported at least one skin-related adverse event; of these, 68 (67%) were mild, 31 (31%) were moderate and 2 (2%) were severe. Twenty-five percent of the subjects experienced a skin-related adverse event by the first 4 weeks of treatment. After 26 weeks of treatment, 46% of the subjects had experienced a skin-related AE. By 52 Weeks (nominal end of treatment), 50% of the subjects (the median) had experienced a skin-related adverse event. By study completion the percentage increased slightly to 52%.

As previously noted, the most frequently reported treatment-related AE was dry skin. All dry skin AEs were of mild intensity, except one, which was of moderate intensity. Two subjects with mild severity had their dose interrupted. One subject discontinued from the study due to four mild skin-related AEs including dry skin.

Most of the acne AEs were mild in severity (75%), with the remainder reported as moderate. Few acne AEs resulted in dose reduction (3) or dose interruption (3). One subject discontinued from the study due to an AE of mild acne.

A total of 35 subjects (16%) reported 88 systemic adverse events considered to be related to treatment by the investigator. Most of these AEs [76 AEs in 30 subjects (14%)] were a result of the specifically queried symptoms that occur with intravenous eflornithine (Ornidyl®).

One of the specifically queried symptoms was that of hair loss (alopecia) and was the third most frequently reported AE. Twenty-one subjects (13%) reported 28 hair loss adverse events categorized as alopecia regardless of relationship to treatment. Twelve of these AEs did not have the body location of the hair loss specified on the AE CRF.

Thirteen of the 21 subjects with hair loss AEs reported an incidence sometime during the study, but not at the baseline visit or final visits. Of the remaining 8 subjects (3.7%), 6 presented at baseline with a medical history of hair loss. Two subjects with treatment-related AEs of hair loss had no medical history or baseline reports of hair loss but had the AE at their final visit.

There were 27 serious adverse events reported in 18 subjects (8.3%). All SAEs were judged to be unrelated to study treatment.

There was one death reported in this study. Subject 112, a 73-year-old female, died in an automobile accident on study day 61 as the result of craniocerebral blunt force injury.

Twelve subjects (5.5%) discontinued the study as a result of adverse events. Of the 12 subjects, 3 (1%) had 9 adverse events considered to be related to study therapy. Eight of these were treatment-related skin adverse events and included: pruritus (2), acne, irritation skin, dry skin, rash, erythema, and edema face. These AEs were of mild intensity except for one of the pruritus AEs that was of unreported intensity.

Laboratory results for those subjects who had baseline and end of treatment tests 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 52 (end of treatment) show that most subjects had laboratory values within normal range at baseline and at the end of treatment.

The parameter of alanine aminotransferase (ALT) had 13 subjects (9.0%) change from normal to high and 2 subjects (1.4%) changed from high to normal. Most of these subjects had ALT values in the high end of the normal range at baseline and shifted to the low end of the high range at the end of treatment. The other liver enzymes [alkaline phosphatase (ALP) and aspartate aminotransferase (AST)] had fewer subjects with the normal to high shift: AST, 5 subjects (3.5%) and ALP, 2 subjects (1.4%).

Reviewer's Comment: *According to the summaries, only 2 patients (0.9%) had elevation of the ALT that was considered possibly related to study medication. One patient had her dose interrupted because she also had elevation of AST, LDH, and bilirubin. However, the events resolved and the patients completed the study. For the other liver enzyme elevations, only one additional patient [for a total of 2 (0.9%)] had an elevation of LDH which was considered possibly related to study medication. This percentage of patients with possible treatment related laboratory abnormalities presents an acceptable safety profile for use of eflornithine 15% cream.*

There were 3 pregnancies reported during the study. All subjects discontinued use of the study medication and subsequently withdrew from the study. One pregnancy was confirmed on study day 127. This subject electively terminated the pregnancy. Another patient with a history of a spontaneous abortion had a spontaneous abortion on day 282 prior to the patient's knowledge of the pregnancy. Her birth control method was an IUD. The final pregnancy was confirmed on study day 253 and the patient withdrew from the study on day 254. Amniocentesis approximately 6 weeks later revealed a normal karotype and no evidence of chromosome abnormality. The patient, a 44 year old, delivered a full term healthy female.

Reviewer's Comment: *Eflornithine 15% cream does not appear from these data to confer any added risk to pregnancy. However, given this drug will be used for cosmetic purposes, the benefit must outweigh any theoretical risk to the fetus for continuation once pregnancy is confirmed.*

11.5.1.5 Conclusions Regarding Safety

This one-year safety study of eflornithine 15% cream used twice daily in 216 healthy adult women with excessive facial hair demonstrates that the drug product is well tolerated. Skin related adverse events accounted for the majority of adverse events. Most of these adverse events occurred by the 5 weeks of study treatment. Most were well tolerated by the subjects, were mild in severity, and of limited duration. The number of patients that discontinued from the study due to skin related adverse events was low (3, 1%) and the adverse events were classified as mild in severity. There were also very few dose modifications secondary to adverse events.

The number of subjects reporting systemic adverse events, excluding alopecia, that are known to occur with the systemic formulation of eflornithine hydrochloride was 31 (14%). The majority were from the digestive system, 18 (8%). This incidence of reporting may have been secondary to the design of the study which queried patients for specific events each visit. None of these incidences required discontinuation from the study. This may also have been true for the report of alopecia in the study. Only 2 subjects (0.9%) did not have either a medical history of hair loss or a report of hair loss at baseline, but had hair loss at the end of the study. These two patients did complete the study without a change in medication but did not have resolution of the event at study end. Laboratory results did not reveal any consistent out of range values that could be attributed to the drug product. The variations were mild and most resolved during treatment. Only one patient discontinued and it was reported by the investigator to be unrelated to study medication.

In conclusion, this study supports the safety of using eflornithine 15% cream up to a year to treat excessive facial hair in women.

11.5.1.6 Conclusions Regarding Efficacy

Although this was an open-label trial, and therefore, cannot in the strictest terms be used to demonstrate efficacy, the results of the physician's global assessment for this population studied over 12 months [%success (21% at 36 weeks, 24% at 52 weeks] supports the efficacy results in the vehicle-controlled studies.

12 Overview of Efficacy

The primary data set for evaluating efficacy in this NDA for eflornithine 15% cream was derived from the two phase 3 multicenter double-blind, randomized vehicle controlled clinical trials that had an intent-to-treat (ITT) population of 594 women with excessive facial hair.

The trial design was adhered to well during the study except for the discovery that sometimes the protocol had been violated when the same investigator did the PGA and also queried the patient for adverse events (this will be discussed later). There was not a statistical significant difference found among the patients regarding demographics in either study. The median age was 41 years. The median height was 64.4 inches. The patients were all somewhat overweight with a median weight of 188.9 pounds. There was a fair representation of ethnic groups, with 68% White subjects, 17% Black subjects, 11% Hispanic/Latino subjects, 0.59% American/Alaskan Native subjects, 1.61% Asian, and 2% of subjects checking the "other" category. Although the Hispanic/Latino representation was somewhat lower in the pivotal trials, their numbers did increase in the long-term safety trials (15%). The mean treatment durations for the eflornithine groups in the DE140-001 and DE140-002 studies were 21.9 and 22.4 weeks, respectively. For the vehicle groups, the mean treatment durations were 21.0 weeks and 22.3 weeks, respectively.

The primary efficacy variable was the Physician's Global Assessment at week 24 of treatment. Both studies each demonstrated a statistical superiority for eflornithine 15% cream over its vehicle ($p \leq 0.001$). When both studies are combined, 126/393 patients (32%) treated with eflornithine 15% cream were success compared to 17/201 patients (9%) treated with vehicle (see table 60).

Table 60
Distribution of Physician's Global Assessment at Week 24
Protocols DE140-001, De140-002

	TREATMENT					
ASSESSMENT	BMS203522 15%CRM			BMS203522 VEHCRM		
	-001	-002	POOLED	-001	-002	POOLED
SUCCESS						
CLEAR/ALMOST CLEAR	11(6.3%)	10(5.1%)	21(5.3%)	0(0.0%)	0(0.0%)	0(0.0%)
MARKED IMPROVEMENT	32(18.2%)	73(35.6%)	105(26.7%)	4(4.1%)	13(12.5%)	17(8.5%)
SUBTOTAL	43(22.9%)	83(40.5%)	126(32.1%)	4(4.1%)	13(12.5%)	17(8.5%)
FAILURE						
IMPROVED	56(29.8%)	45(22.0%)	101(25.7%)	24(24.7%)	28(26.9%)	52(25.9%)
NO IMPROVEMENT/WORSE	88(48.4%)	77(37.6%)	165(42.0%)	69(71.1%)	60(60.6%)	129(64.2%)
SUBTOTAL	145(77.1%)	122(59.5%)	267(68.0%)	93(95.9%)	91(87.5%)	184(91.5%)
TOTAL	188	205	393	97	104	201

COMPARISON BETWEEN TREATMENTS: -001 p≤0.001
-002 p≤0.001

It is interesting that the subjects in study 2 had almost twice as much success with treatment when compared to study 1 (40.5% vs. 22.9%). A subgroup analysis for race (White, Black, Other) and skin type (I&II, III&IV, V&VI) to look for explanations for this variance between studies did not reveal a reason for the difference (see statistical review).

It is also noted that a statistically significant number of subjects consistently, across both studies, experienced success in treatment as compared to vehicle as early as week 8 of treatment (p=0.007 for study -001 and p=0.001 for study –002). Although not a criterion for success, when the trials are combined, 58% of subjects using eflornithine 15% cream showed improvement in their condition compared to 34% of subjects who used vehicle. Followup of patients after treatment ended consistently demonstrated a loss of effect of eflornithine 15% cream by eight weeks post treatment.

The secondary efficacy variables which were video image analysis and subject self-assessment questionnaire were supportive of the primary efficacy variable. The video image analysis is a new tool which measured both hair length and spatial mass. Due to the complexity of the technology and its implementation, only 75% of the data collected at week 24 from each study was considered analyzable. In each study and in the pooled data at week 24, the results demonstrated a statistically significant treatment difference (p≤0.0004), favoring eflornithine 15% cream over its vehicle (see table 61).

Table 61
Video Image Analysis – Spatial Mass Assessment At Week 24
Protocol DE140-001, DE140-002

	TREATMENT					
	BMS203522 15%CRM			BMS203522 VEHCRM		
	-001	-002	POOLED	-001	-002	POOLED
SPATIAL MASS (mm^2)						
n	160	178	338	87	92	179
MEAN	0.037	0.036	0.037	0.046	0.043	0.045
S.E.	0.001	0.001	0.001	0.002	0.002	0.001
RANGE						
P-VALUE*	0.0001	0.0004	0.0001			

* Comparison to respective vehicle

The other variable of the video image analysis, the measure of hair length, at week 24, did not demonstrate statistical significance for either study in terms of success (>50% reduction in hair length). However, the overall reduction in hair length of the eflornithine 15% cream arm as compared to vehicle was statistically significant (p=0.001). When the data is pooled from both studies looking at a 50% reduction in hair length as compared to vehicle, then statistical significance is achieved [(p=0.016), see table 62].

APPEARS THIS WAY
ON ORIGINAL

Table 62
Video Image Analysis – Hair Growth (Length) at Week 24
Protocol DE140-001, DE140-002

	TREATMENT					
	BMS203522 15%CRM			BMS203522 VEHCRM		
PERCENT CHANGE FROM BASELINE	-001 N (%)	-002 N (%)	POOLED N (%)	-001 N (%)	-002 N (%)	POOLED N (%)
SUCCESS (>=50%)	8(6.3%)	13(8.6%)	21(7.5%)	1(1.3%)	2(2.6%)	3(2.0%)
FAILURE (< 50%)	120(93.8%)	138(91.4%)	258(92.5%)	76(98.7%)	75(97.4%)	151(98.1%)
TOTAL	128	151	279	77	77	154
P-VALUE*	0.158	0.085	0.016			

* Comparison to respective vehicle

The final efficacy variable, the subject's self-assessment questionnaire measured the subjects' degree of discomfort regarding their excessive facial hair by asking six questions. In both studies, the majority of patients felt that improvement had occurred in their facial appearance over the course of the study. This rating was statistically significant for all 6 questions ($p \leq 0.005$).

Subset analysis was performed for method of hair removal, age, postmenopausal female and race. The analysis for the effect of prestudy hair removal techniques revealed no statistically significant effect of hair removal ($p=0.070$) nor of its interaction with treatment ($p=0.256$). When dichotomized for age (> or < 65 years), the majority of the patients were less than 65 years of age. Approximately 7% were 65 years or older and approximately 1% were 75 years old or older. No overall differences in safety were observed. Efficacy was evaluated in postmenopausal patients, as 12% of subjects across all phase 3 studies were in this category. In the pivotal trials, statistical significance was observed favoring eflornithine 15% cream over vehicle [($p \leq 0.001$) see table 63] in this subset of patients.

Table 63
Postmenopausal Status on Physician's Global Assessment
Protocols DE140-001, DE140-002

		TREATMENT					
		BMS203522 15%CRM		BMS203522 VEHCRM		STUDY TOTAL	
		N	PCTN	N	PCTN	N	PCTN
PHYSICIAN'S GLOBAL ASSESSMENT	SUCCESS	18	38.3	0	0	18	23.1
	FAILURE	29	61.7	31	100.0	60	76.9
	CATEGORY TOTAL	47	100.0	31	100.0	78	100.0

Fisher's Exact Test (2-Tail) P ≤ 0.001

The analysis for race revealed a statistically significant effect for race ($p=0.017$), which indicates uniform racial differences across treatments in the percentage of success. Across both

treatments, Whites had a significantly higher success rate (29%) on the Physician's Global Assessment than did non-Whites (16%). For those treated with eflornithine 15% cream, there was a success rate of 37% and 22% for Whites and non-Whites, respectively. The explanation for this is unclear. However, non-Whites, mostly Black subjects, did have significant treatment benefit. In the Black subjects, 22% (23/106) were graded a success who were treated with eflornithine 15% cream compared to 5% (3/63) who were treated with vehicle. It is possible that the different contrasts between skin and hair led to different grading ranges as the appearance of "darkening of skin" or "five o'clock shadow" was one of the grading parameters in the PGA.

Finally, as stated earlier, there was a protocol violation reported in both efficacy studies were the same investigator assessed the patient for efficacy and adverse events. Therefore, because this may have caused unintentional unblinding because some adverse events were certainly related to the drug product, a robust analysis was performed by the statistician where patients who experienced stinging, tingling, and rash in the eflornithine group were treated as failures. This analysis showed only small changes in both studies. The success rate was 20.2% in robustness analysis vs. 22.9% in Study –001 and 33.7% vs. 40.5% in study –002 (see statistical review).

13 Overview of Safety

13.1 Significant/Potentially Significant Events

The most significant adverse events that can be attributed to eflornithine 15% cream are related to the skin and appendages system. These events occurred in a higher percentage of subjects using eflornithine 15% cream compared to vehicle. These included stinging skin (4.1% vs. 2.5%), burning skin (3.5% vs. 2.0%), erythema (2.5% vs. 0%), tingling skin (2.2% vs. 1.5%), and folliculitis (1.0% vs. 0%).

13.1.1 Deaths

There was one death that was unrelated to study medication. In study DE140-010, the 1-year open-label safety study, subject 112, a 73-year-old female, died in an automobile accident on study day 61 as the result of craniocerebral blunt force injury.

13.1.2 Other Significant/Potentially Significant Events

13.1.3 Overdose Experience

Given the low percutaneous penetration of this drug, overdosage via the topical route is not expected.

13.2 Other Safety Findings

13.2.1 ADR Incidence Tables

This incidence table is for all phase 3 trials and the pharmacokinetic study. This includes the double blind trials (-001 and –002), the open-label safety trials (-010 and –011) and the pharmacokinetic study with 10 patients (-003).

Adverse Events Occurring in 1% or More of Subjects
Women with Excessive Facial Hair
On the To-Be-Marketed Formulation of Eflornithine 15% Cream

	Related to Treatment											
	BMS203522 15% Cream N=1373						BMS203522 Vehicle Cream N=201					
	Yes		No		Unassessable*		Yes		No		Unassessable*	
Body System	n+	%	n	%	n	%	n	%	n	%	n	%
Total All Systems	502	36.5	1000	72.7	139	10.1	80	39.8	155	77.1	37	18.4
Acne	149	10.8	80	5.8	18	1.3	43	21.4	31	15.4	11	5.5
Pseudofolliculitis Barbae	67	4.9	53	3.9	15	1.1	31	15.4	26	12.9	10	5.0
Alopecia	56+	4.1+	52	3.8	8	0.6	5	2.5	4	2.0	1	0.5
Stinging Skin	56	4.1	3	0.2	0	0.0	5	2.5	0	0.0	0	0.0
Headache	55	4.0	302	22.0	39	2.8	10	5.0	56	27.9	6	3.0
Burning Skin	48	3.5	3	0.2	1	0.1	4	2.0	0	0.0	0	0.0
Dry Skin	45	3.3	11	0.8	0	0.0	6	3.0	1	0.5	0	0.0
Pruritus	42	3.1	17	1.2	2	0.1	8	4.0	2	1.0	1	0.5
Erythema	35	2.5	3	0.2	1	0.1	0	0.0	0	0.0	0	0.0
Tingling Skin	30	2.2	0	0.0	1	0.1	3	1.5	0	0.0	0	0.0
Dyspepsia	26	1.9	135	9.8	11	0.8	4	2.0	21	10.4	1	0.5
Irritation Skin	25	1.8	4	0.3	0	0.0	2	1.0	0	0.0	0	0.0
Rash	21	1.5	22	1.6	2	0.1	0	0.0	3	1.5	1	0.5
Dizziness	18	1.3	88	6.4	8	0.6	3	1.5	20	10.0	2	1.0
Folliculitis	14	1.0	8	0.6	2	0.1	0	0.0	2	1.0	0	0.0
Hair ingrown	13	0.9	1	0.1	0	0.0	4	2.0	1	0.5	0	0.0
Edema face	10	0.7	27	2.0	1	0.1	6	3.0	4	2.0	1	0.5
Anorexia	9	0.7	70	5.1	3	0.2	4	2.0	14	7.0	2	1.0
Nausea	9	0.7	31	2.3	1	0.1	2	1.0	1	0.5	0	0.0
Asthenia	4	0.3	68	4.9	6	0.4	2	1.0	11	5.5	1	0.5
Vertigo	1	0.1	3	0.2	1	0.1	2	1.0	0	0.0	0	0.0

n = number of subjects
*relationship to study treatment is unknown
+the incidence has been assessed to be 18 (1.3%), see safety conclusions and safety reviews of each study.

If burning/stinging/tingling adverse events are combined as one, then 8.9% of subjects treated with eflornithine 15% cream had these events considered related to treatment compared to 5% of subjects treated with vehicle cream.

13.2.2 Laboratory Findings, Vital Signs, ECGs

There were not any consistently out-of-range laboratory findings that with certainty could be attributed to active drug.

13.2.3 Special Studies

The topical dermal studies revealed the potential of eflornithine 15% cream to have the potential to cause a contact dermatitis of the skin under conditions of clinical use in a susceptible individual or under the conditions of exaggerated use.

13.2.4 Drug-Demographic Interactions

Eflornithine 15% cream, although efficacious in both Whites and non-Whites, did appear to be more efficacious in Whites, with 37.4% a success in Whites as compared to a 22.3% success in non-Whites. The same can be said for Whites as compared to Blacks, with a success of 37.4% in Whites as compared to 21.7% in Blacks.

13.2.5 Drug-Disease Interactions

Eflornithine 15% cream, used as indicated for excessive facial hair in women, is not known to have a significant interaction on any disease state.

13.2.6 Drug-Drug Interactions

There are no known drug-drug interactions.

13.2.7 Withdrawal Phenomena/Abuse Potential

There is none known.

13.2.8 Human Reproduction Data

There were 22 pregnancies in the trials. Twenty of the pregnancies occurred in individuals using active drug and 2 were on vehicle. Of the twenty pregnancies there were 9 healthy infants, 5 spontaneous abortions, 5 induced/elective abortions, and 1 birth defect (Down's Syndrome to a 35-year-old). Of the 5 spontaneous abortions, 1 patient had completed the study and the date of the miscarriage coupled with the gestational age of the fetus, indicated that the patient had been off active drug for a month at the time of conception.

13.3 Safety Conclusions

Eflornithine 15% cream was studied in 1373 patients, the majority of whom used the drug product for at least 6 months. For comparison, 201 patients were treated with the vehicle cream. Of the 1373 subjects treated with eflornithine 15% cream, 80% (1100/1373) had at least one adverse event compared to 87% (175/201) treated with vehicle cream. The percentage of subjects who experienced an adverse event that was considered related to treatment was very similar between the two treatment groups, 37% for eflornithine 15% cream vs. 40% for vehicle cream.

Eflornithine 15% cream was well tolerated in this population. The number of patients that discontinued due to a treatment related adverse event was low with 2% of subjects using eflornithine 15% cream discontinuing compared to 1% that used the vehicle cream. This is consistent with the fact that the majority of the treatment related adverse events were mild (75%) with fewer being moderate (24%) and even fewer being severe (2%).

Adverse event reactions for most body systems occurred at a similar rate in both the eflornithine 15% cream group and the vehicle cream group, 36.5% and 39.8%, respectively. The majority of treatment related adverse events were skin related. The events that occurred more often in the eflornithine 15% cream group over vehicle were stinging skin, burning skin, erythema, tingling skin, irritation skin, rash, and folliculitis. These events were well tolerated and led to very few drug interruptions, reductions, or discontinuations.

A few adverse events deserve special mention and explanation. The incidence of acne and pseudofolliculitis barbae in the pivotal trials was very similar. Acne occurred in 21.3% of patients in the eflornithine 15% cream arm and in 21.4% of patients in the vehicle cream arm. Similarly, PFB occurred in 16.2% of patients in the eflornithine 15% cream arm and in 15.4% of patients in the vehicle arm. When the open label trials are added to the eflornithine arm of the pivotal trials, the incidence of acne and PFB fall to 10.8% and 4.9%, respectively. It is important to note that in the pivotal trials the investigators were instructed to look and evaluate these two adverse events and they were not asked to do the same in the open-label trials. Even with the instructions, and the fact that the incidence is greater in the pivotal trials, the results from it are more valid because it points out that the occurrence of these two events, because they occurred in the same percentage of patients, is not due to eflornithine 15% cream. The incidence of acne in the open-label trials was 6.7% and PFB did not occur greater than 1% in either trial. Therefore, one can conclude that if not so instructed by the protocol, the true incidence of acne and PFB would be lower than 10.8% and 4.9% respectively and furthermore, would be fairly similar between the two arms.

but could be due to the vehicle.
/S/

The incidence of alopecia was 4.1% overall for the eflornithine 15% cream arm and 2.5% for the vehicle arm when all four phase 3 studies are combined, if one were to only look at the numbers without deeper analysis. A higher number of reports of alopecia were attributed to drug product in the open-label trials. This could have been due to the fact that the drug is known to inhibit hair growth and there was not a control arm, which may have caused increased sensitization and over-reporting. Further, from the review of the onset and baseline histories (see text and reviewer's comment pages 91-92 and section 11.5.1.5, page 102), in study –011, this reviewer concluded that the drug product may have been responsible for the event in 10/754 subjects (1.3%) and in study –010 in 2/ 216 subjects (0.9%). It is important to note that in the double-blind trials the incidence of alopecia was 1.5% (6/393) for the eflornithine 15% cream

arm compared to 2.5% (5/201) in the vehicle arm. When all phase 3 trials are combined, given the new analysis, the incidence of alopecia in subjects using eflornithine 15% cream was 18/1363 (1.3%) as compared to the vehicle arm where 5/201 subjects reported alopecia (2.5%). Therefore, in this reviewer's opinion, the incidence of alopecia using this drug is not significant when compared to vehicle.

Systemic events that were known to occur with the intravenous form of eflornithine hydrochloride, Ornidyl®, were specifically queried of all subjects or obtained through laboratory specimens in the phase 3 trials, both double-blind and open-label. Given the pharmacokinetic profile of topical eflornithine 15% cream, it seems unlikely that enough drug product is absorbed sufficiently enough to account for any systemic events. This is supported by the fact that when all phase 3 trials are combined, the incidence of systemic events is similar. For adverse events that occurred in 1% of patients or greater, a slightly higher percentage of subjects in the vehicle cream arm as compared to the eflornithine 15% cream arm experienced the event (see ADR Incidence Table, Section 13.2.1). It can be concluded that this data did not reveal any systemic events that could be attributed to eflornithine 15% cream.

Finally, there were 5 patients out of 22 who became pregnant during the trials who experienced a spontaneous abortion. Of these 5 patients, it was determined that one patient had discontinued studied medication for 1 month at the time of conception (week 28 of the trial). Therefore, 4 of the 5 patients who experienced a spontaneous abortion had been on eflornithine 15% cream at conception. This is a spontaneous abortion rate of 18% (4/22). The patients' ages were 28, 31, 35, 39, and 41. It is clinically recognized that the rate of spontaneous abortion is 12% in females less than 20 years old and increases to 26% in females greater than 40 years of age (Williams Obstetrics, 20th Ed., 1997). Further, two of the 4 patients had a history of a prior spontaneous abortion and one of those two was also using an IUD, which may have affected the outcome of the pregnancy. Even without the complicating histories, the spontaneous abortion rate experienced in these trials is not higher than would be expected in the general population and therefore should not be attributed to eflornithine 15% cream.

The above discussed safety profile of eflornithine 15% cream provides adequate safety data that would also apply to the adolescent female. There are not any systemic or local intolerance factors unique to the adolescent female that would warrant further study in that age group for the topical use of this drug product as directed in the label.

14 Conclusions

Eflornithine 15% cream is both efficacious and safe for the treatment of unwanted excessive facial hair in females age 12 and older.

15 Recommendations

It is recommended that eflornithine 15% cream be approved for the indication of treatment of unwanted excessive facial hair in females age 12 years and older with labeling changes to be found in the addendum to this review.

/S/

Denise Cook, M.D.
Medical Officer, Dermatology

6/14/00

cc: HFD-540
HFD-340
HFD-540/CSO/WrightM
HFD-540/CHEM/Pappas
HFD-520/MICRO/
HFD-540/PHARM/HillB
HFD-540/MO/CookD
HFD-880/Biopharm/Ghosh
HFD-725/Stats/LiQ
Draft 6-1-00
~~Not~~ in DFS

NDA 21-145

For Concurrence Only:
HFD-540/Clinical TL/Walker
HFD-540/DivDir/WilkinJ

/S/
6/15/00

1) [redacted]

2) The results from the human dermal safety tests include pertinent negatives that could inform labeling along with the information on irritancy potential.

3) The pregnancy data from clinical trials should be added to labeling.

4) The indication should convey that this product may be used in settings where there is no pathology (i.e. some facial hair may occur normally and be unwanted. Not all "patients" presenting this product should believe they have a "medical problem".

/S/