CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-145

MEDICAL REVIEW(S)

Medical Officer's Review – NDA 21-145
Labeling Review

JUL 11 2000

NDA 21-145
Addendum #1

Submission date: 5/23/00
CDER Stamp date: 6/05/00
Review began: 6/15/00
Review completed: 6/19/00

Note: The following label was supplied by the sponsor on June 5, 2000 and is their last submitted draft labeling and patient package insert. Clinical recommendations for deletions are noted by strikeout and additions are in red.

DRAFT PACKAGE INSERT
May 23, 2000

WITHHOLD 10 PAGE (S)

Draft

Labeling

2.0 Recommendation

The changes made to the draft label and the patient package insert submitted above by the sponsor are those recommended for the final approval of NDA 21-145, Vaniqa (eflornithine hydrochloride cream), 15%.

/S/ MD 6/19/00

Denise Cook, M.D.
Medical Officer, Dermatology

Orig NDA 21-145

/S/ 6/26/00

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
Not in DFS

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

Labeling not to scale. My calculation is not 15% for the active.

/S/ 7/11/00

APPEARS THIS WAY
ON ORIGINAL

Medical Officer's Review of NDA 21-145

JUL 11 2000

NDA # 21-145

Submission date: 9/24/99
CDER Stamp date: 9/27/99
Assignment date: 10/13/99
Review began: 2/24/00
Review completed: 6/14/00

Sponsor:	Westwood-Squibb Colton Holdings Partnership 777 Scudders Mill Road Princeton, New Jersey 08536
Generic name:	Eflornithine Hydrochloride
Proposed trade name:	Vaniqa
Chemical name:	2-(difluoromethyl)-D, L-ornithine monohydrochloride monohydrate
Chemical structure:	(See labeling review)
Molecular formula:	$C_6H_{12}F_2N_2O_2$ HCL H_2O
Molecular weight:	[redacted]
Pharmacologic Category:	ornithine decarboxylase inhibitor
Proposed Indication(s):	Treatment of excessive facial hair in women
Dosage Form(s):	Cream
Route (s) of Administration:	Topical
NDA Drug Classification:	3S
Related Drugs:	Ornidyl®, formulation for intravenous use Indication: West African trypanosomiasis in patients age 15 and older
Related Reviews:	Statistical Review dated: pending Biopharm dated: pending

2 Table of Contents

3 Regulatory Background

3.1 Previous FDA Actions

IND —— This IND was originally placed on clinical hold in 1991 because there was insufficent animal data to support the proposed 6-month human use trial. Clinical hold was lifted on 2/3/94 and clinical studies commenced 3/7/94.

3.2 FDA/Applicant Meetings

End of phase 2 meeting (1/16/97) – At this meeting, the dosing interval of bid and a primary efficacy time evaluation of 24 weeks was agreed upon between the sponsor and the Agency. There should be a subject self-assessment scale. All other parameters were left open to discussion.

Teleconference (4/15/97) – During this teleconference the sponsor and the Agency agreed to the following parameters for the phase 3 studies:

The Physician's Global Assessment would be the primary efficacy variable with 4 categories (the wording of which was agreeable). Success would be based on the top two categories of on clear/almost clear and marked improvement.

A 20% difference between drug product and its vehicle would be an acceptable success rate. The denominator would be all those subjects entered into the study and the numerator would be those defined as a success above.

Photographs would remain a tool that the physician investigator uses in his/her global assessment at the site.

The video image analysis would be a secondary endpoint with a reduction of 50% hair growth viewed as a success.

An adequate representation of hair types from every ethnic population was to be included in the studies.

Advisory Committee Meeting (4/18/97) – This meeting was to present the drug product to the advisory committee because of its novel indication and to also present the efficacy variable, video image analysis.

4 Material Reviewed

Vol. 1.1, 1.2, 1.38-1.39, 1.51-1.58, 1.68-1.76, 1.86-1.90, 1.120-1.123, 1.136-1.137, 1.143-1.144
Amendments – BL, SU, BM, and AZ

5 Chemistry/Manufacturing Controls

BMS-203522 (eflornithine HCL, DMFO, 2-(difluoromethyl)-DL-ornithine monohydrochloride monohydrate) is a white crystalline powder which is soluble in water and slightly soluble in ether, chloroform and acetone.

The eflornithine hydrochloride 15% cream proposed for marketing is a ——— identical to that used in clinical trials. The cream contains 15% eflornithine hydrochloride monohydrate in a vehicle containing water, glyceryl sterate (and) —100 stearate, cetearyl alcohol (and) ceteareth-20, mineral oil, stearyl alcohol, dimethicone, propylparaben, methylparaben, and phenoxyethanol. See chemistry review for further details.

6 Animal Pharmacology/Toxicology

Topical dermal studies in rabbits did demonstrate some irritancy such that one study was aborted. Minipigs were then used as a more adequate animal model and no dermal irritancy was demonstrated. Teratogenicity studies did not reveal any fetal abnormalities, including no increased incidence of spontaneous abortions. The 2-year dermal carcinogenicity and 1-year photocarcinogenicity studies in the mouse elicited a "no response". The standard battery of genotoxicity studies were also negative (see pharm/tox review for further details).

7 Human Pharmacology, Pharmacokinetics, Pharmacodynamics

Eflornithine hydrochloride is an irreversible inhibitor of the enzyme ornithine decarboxylase (ODC). ODC is responsible for the catalysis of ornithine to prutrescine, and is a critical enzyme in cell proliferation and function. Follicular cell proliferation and synthetic functions are important factors in hair growth. Since ODC is present in the hair follicle, and implicated in the hair growth process, eflornithine 15% cream has been developed as a topical product to reduce the growth of unwanted facial hair in women.

The percutaneous absorption of BMS-203522 is minimal; the extent of absorption is 0.2% to 0.3% after a single dose and increased to 0.8% following one week of twice-daily topical application of a 15% w/w cream formulation in women with facial hirsutism who shaved prior to application. The percutaneous absorption of BMS-203522 remains low (< 1% of the dose) after twice-daily multiple dosing under conditions of clinical use, that included shaving within 2 hours before radiolabeled dose application. BMS-203522 absorbed following topical administration is eliminated primarily as unchanged BMS-203522 in urine. The trough plasma concentrations of BMS-203522 remain constant after 4 days of twice-daily treatment. Therefore, the percutaneous absorption and disposition of BMS-203522 appear to have reached steady state and further increase in absorption is unlikely.

In conclusion, the absorption, metabolism and excretion results of BMS-203522 from the animal studies were predictive of the results obtained in the human studies, confirming the low systemic absorption of the dermal doses of BMS-203522, the absence of metabolism of BMS-203522 *in vivo*, and the primarily renal excretion of BMS-203522 (see Biopharmaceutics review for further details).

8 Clinical Background

8.1 Relevant human experience

Eflornithine hydrochloride was approved by the FDA 2/12/90 under NDA 19-879 as Ornidyl®. It is approved as an intravenous solution for the treatment of the meningoencephalitic stage of Trypanosma brucei gambiense sleeping sickness in patients greater than 15 years of age. It has also been approved for this same indication in multiple European countries in 1991. Eflornithine hydrochloride in this topical formulation has not been used in humans prior to use in these clinical trials.

8.2 Foreign Experience

Eflornithine 15% Cream has not been approved in any countries, nor have any marketing applications been filed outside the U.S. Applications to be submitted to ——— are in preparation.

9 Proposed Label

9.1 Proposed Indication and Usage Section

VANIQA is indicated for the ——— facial hair in women.

9.2 Proposed Dosage and Administration Section

Apply a thin layer of VANIQA Cream to affected areas of the face ——— rub in thoroughly. Do not wash treated area for at least 4 hours. Use twice daily at least 8 hours apart or as directed by a physician.

Cosmetics or sunscreens may be applied over treated areas after cream has dried.

9.3 Proposed Clinical Studies Section

Two randomized double-blind studies involving 596 patients — treated with VANIQA, 201 with vehicle) treated twice daily for up to 24 weeks evaluated the efficacy of VANIQA Cream in the ——— facial hair in women. Physicians assessed the improvement or worsening from the baseline condition (Physician's Global Assessment [PGA]), 48 hours after shaving, of all treated areas. Statistically significant improvement for VANIQA versus vehicle was seen in each of these studies for "marked improvement" or greater response (24-week time point ——— $p \leq 0.001$).

Approximately — of patients showed marked improvement or greater (protocol definition of clinical success) after 24 weeks of treatment with VANIQA, compared to — with the vehicle.

——— Combined results of these two trials through 24 weeks are presented below.

PGA Outcome	VANIQA	Vehicle
Clear/almost clear	—	—
Marked improvement	—	—
Improved	—	—
No improvement/worse	—	—

Subgroup analyses appeared to suggest greater benefit for whites than non-whites —— respectively; p=0.017).

About 12% of women in the clinical trials were postmenopausal. Significant improvement in PGA outcome versus vehicle was seen in postmenopausal women.

[

]

Clinical trials with VANIQA Cream involved over 1370 women with —— facial hair of skin types I-VI, of whom 68% were white, — black, 11% Hispanic-Latino and 2% Asian-Pacific Islander.

Reviewer's Comment: Since the initial submission of the NDA, the sponsor has submitted an amendment proposing to change the indication to "treatment of unwanted —— facial hair in women."

10 Description of Clinical Data Sources

Study #DE140-005 – This was a phase 1 open-label, single-center, within subject, vehicle and positive-controlled study designed to determine the cumulative irritation potential of BMS203522 (eflornithine hydrochloride) 15% cream, vehicle cream and 0.5% sodium lauryl sulfate (SLS). Thirty subjects were enrolled and a total of 28 subjects completed the study. The first subject enrolled September 15, 1997 and the last subject completed the study October 6, 1997.

Study #DE140-004 – This was a phase 1 open-label, single-center, within subject, vehicle controlled study designed to determine the contact allergy sensitization potential of BMS-203522 (eflornithine hydrochloride) 15% cream and vehicle cream. Two hundred thirty subjects were enrolled. A total of 208 subjects completed the 5-week study. The first subject was enrolled on September 12, 1997 and the last subject completed the study on October 30, 1997.

Study #DE140-007 – This was a phase 1 open-label, single-center, within subject, vehicle controlled study to determine the phototoxic potential of BMS-203522 (eflornithine hydrochloride) 15% cream and vehicle cream. Twenty-five subjects enrolled in and completed the study. The first subject enrolled October 28, 1997 and the last subject completed the study October 30, 1997.

Study #DE140-006 – This was a phase 1 open-label, within subject, vehicle controlled study designed to determine the photoallergic potential of BMS-203522 (eflornithine hydrochloride) 15% cream and vehicle cream. Thirty subjects were enrolled and a total of 28 subjects completed the study. The first subject was enrolled on October 6, 1997 and the last subject completed the study November 14, 1997.

Study #DE140-001 – This was a phase 3 double-blind, randomized, vehicle controlled study to evaluate the safety and efficacy of BMS-203522 (eflornithine hydrochloride) 15% cream in the treatment of women with excessive facial hair. There were 287 subjects enrolled at ten centers in the United States. Two hundred twelve subjects completed the 24-week treatment phase and 209 completed the full 32 weeks. The first subject was enrolled on July 10, 1997 and the last subject completed on March 11, 1999.

Study #DE140-002 – This was a phase 3 double-blind, randomized, vehicle controlled study to evaluate the safety and efficacy of BMS-203522 15% (eflornithine hydrochloride) cream in the treatment of women with excessive facial hair. Three hundred nine subjects were enrolled at nine investigational sites. There were 8 sites in the United States and 1 site in Spain. Another site in the United Kingdom was sent medication but did not enroll any subjects. Two hundred forty subjects completed the 24-week treatment phase and 228 completed the full 32-week study. The first subject was enrolled on July 28, 1997 and the last subject completed the study on March 17, 1999.

Study #DE140-011 – This was a non-randomized open-label study to evaluate the safety of BMS-203522 15% cream in the treatment of women with excessive facial hair. A total of 754 subjects were enrolled at 31 study sites. Eighteen centers were in the U.S., 2 centers in Australia, 3 in France, 1 in Sweden, 1 in the Netherlands, 3 in Mexico, 1 in England, and 2 centers were in South Africa. Five hundred seventy-eight subjects completed the 6-month study with 176 subjects discontinuing. The first subject was enrolled on February 5, 1998 and the last subject completed the study on January 18, 1999.

Study #DE140-010 – This was a non-randomized, open-label study designed to evaluate the safety of BMS-20522 15% cream in the treatment of excessive facial hair growth in women. Two hundred sixteen subjects enrolled at nine investigational sites located in the U.S. One hundred forty-two subjects completed the one-year study and 74 subjects discontinued. The first subject was enrolled on January 12, 1998 and the last subject completed the study on March 25, 1999.

Reviewer's Comment: BMS-203522 is the formulation used for all the phase 1 and phase 3 clinical trials. It is the to-be-marketed formulation.

11 Clinical Studies

11.1 Dermal Toxicity Studies

Protocol #: DE140-005 Title: 21-Day Cumulative Irritation Test

This study was conducted at a single test site, The Education and Research Foundation, Inc. located in Lynchburg, VA. Claire Whitmore, M.D. was the principal investigator for the study; subinvestigators were ———— M.D. and ———— M.D.

Thirty healthy adult volunteer subjects were enrolled in the study. There were 5 males and 25 females, 19 who were White and 11 who were Black. The ages ranged from 29-73 years with a mean age of 48 years.

Three substances were used for this study to reach its objective: BMS-203522 15% cream, its vehicle (as a negative control), and 0.5% sodium lauryl sulfate, a known moderate to severe irritant, (as a positive control). The subjects had each of these substances, at a dose of 0.2 gm, applied fresh daily under occlusion to the same site of the upper back for 21 consecutive days. Evaluations of response were based on the following 5-point scale:

0	=	no sign of irritation
1	=	slight irritation
2	=	noticeable erythema with slight infiltration
3	=	erythema with marked edema
4	=	erythema with edema and blistering

If at any time a subject received a score of 4, that particular substance was discontinued and a score of 4 was carried forward to completion of the study.

Twenty-eight of the thirty subjects enrolled completed the study. Twenty subjects completed all scheduled visits; eight subjects each missed one scheduled visit. One subject missed 2 visits and was dropped from the study. One patient was dropped from the study because of adverse events.

Irritation Scores

BMS-203522 15% cream

All subjects had at least one score of 1 or greater. The highest daily reading was 1 for 5 subjects, 2 for 7 subjects, 3 for 1 subject and 4 for 17 subjects.

Vehicle cream

All subjects had at least 1 score of 1 or greater. The highest daily reading was 1 for 15 subjects, 2 for 12 subjects, 3 for 2 subjects, and 4 for 1 subject.

0.5% SLS

All subjects had at least 1 score of 1 or greater. The highest daily reading was 1 for 1 subject, 2 for 2 subjects, and 4 for 27 subjects.

The total cumulative and mean scores by treatment are presented in table A.

Table A
Total Cumulative and Mean Scores By Treatment
(n=30) Friedman's Test, p<0.001
Protocol DE140-005

Treatment	Total Cumulative*	Mean Score**	Tukey's***
BMS-203522 15% cream	701	1.33	B
BMS-203522 vehicle cream	396	0.76	C
0.5% sodium lauryl sulfate in petrolatum	1625	3.09	A

*Total Cumulative Score is the sum of all readings for all subjects for a given product
**Mean Score is the average score for all subjects for all readings for a given product
***Means with different letters are significantly different

Reviewer's Comment: *This study demonstrates that under exaggerated conditions, BMS-203522 15% cream is an irritant. The active ingredient, eflornithine hydrochloride, does contribute to this irritation, as the score in table A is almost double that of vehicle cream. BMS-203522 15% cream could cause irritation reactions in clinical use in susceptible individuals or under conditions of exaggerated use.*

Protocol #DE140-004 **Title: Repeat Insult Patch Test (Modified Draize Skin Sensitization Test)**

This study was conducted at a single investigational center, The Education and Research Foundation, Inc. located in Lynchburg, VA. Claire, Whitmore, M.D. was the principal investigator for the study; subinvestigators were ——— M.D. and ——— M.D. It was an open-label, within subject, vehicle controlled study.

Two hundred and thirty healthy adult volunteers were enrolled into the study. There were 57 males and 173 females, of which 135 were White, 94 were Black and 1 was an Asian/Pacific Islander. The subjects' ages ranged from 18-87 years with a mean age of 44.9 years.

Subjects were to have patches placed to the upper back of both 0.2 gm BMS-203522 15% cream and vehicle three times weekly for a three-week induction period. Patches were left in continuous contact with the skin between applications. Following a 2-week rest period, a single patch application was made to previously untreated skin and evaluated 48 hours later.

There were 208 patients considered evaluable at the end of the study (37 days). The 197 subjects who fully completed the study and attended all visits, and subjects 39 and 112 who missed one evaluation visit each but received all scheduled patch applications were exposed to 0.2 gm BMS-203522 15% cream at 10 separate applications, which totaled 2 gm of formulation. Twenty other subjects missed one visit each and were exposed to 1.8 gm of formulation. Subject 185, who completed the study but missed two visits was exposed to 1.6 gm of formulation.

Twenty-two subjects failed to complete the study. Fourteen dropped of their own volition, 4 were lost to follow-up, 3 were dropped by the investigator because of lack of compliance and one subject was dropped because of an adverse event considered to be unrelated to study procedures.

At each evaluation time point subjects were evaluated on the following five-point scale:

0	=	no sign of irritation
1	=	slight irritation
2	=	noticeable erythema with slight infiltration
3	=	erythema with marked edema
4	=	erythema with edema and blistering

Skin Responses

BMS-203522 15% cream

During induction, of the 208 subjects who completed the study, only 5 subjects had no evidence of a reaction at skin test sites. All other subjects had one or more scores of 1 or greater. Many subjects had scores of 2 or 3 during induction. There were also, in some subjects, scores of 4. When necessary, subsequent patches were applied to an alternate site.

At the initial challenge evaluation only 4 subjects had scores of greater than 1. Subject 63, 140, and 206 had initial challenge readings of 2, which fell to 1 or 0, 24 hours later. Subject 94 had an initial challenge score of 4, which fell to 2, 24 hours later.

Vehicle cream

During induction most subjects had scores of one or greater on at least one instance. A few subjects who had scores of 3 or 4 during induction had subsequent patching done at alternate sites.

At the initial challenge reading only subject 140 had an evaluation of greater than 1. This subject's initial score of 2 fell to 1, 24 hours later. All other challenge evaluations for vehicle cream were either 0 or 1.

Adverse Events

There were two subjects, subject 33 and subject 162 who complained of pruritus at the application site on one occasion during the induction phase of the study. These events were considered possibly related to study medication.

Reviewer's Comment: *These results do reflect the potential for eflornithine 15% cream to cause contact irritation in clinical situations as noted in study DE140-005 but does not support that it is a sensitizer. The pruritus that occurred in two patients reflects the irritation potential of the drug product and does not suggest allergy as on challenge, patient 162 scored 0 and patient 162 had a score of 1 that 24 hours later was scored as 0.*

This study was conducted at a single investigational center, The Education and Research Foundation, Inc. located in Lynchburg, VA. Claire Whitmore, M.D. was the principal investigator for the study; subinvestigators were [redacted], M.D. and [redacted] M.D. It was an open-label, within subject, vehicle controlled study.

Twenty-five healthy adults enrolled in the study. Twenty were female, 3 were male and all were White. Their mean age was 39.5 years with a range from 22 to 76 years. Three sites on the back were prepared by stripping the skin with cellophane tape. The skin was stripped to the glistening layer, or maximum of 15 repetitions of the stripping process. Test products were applied to two of the sites. Subjects were treated with 0.2 gm applied to 2.54 square centimeters of tape-stripped skin.

Reviewer's Comment: *The protocol actually stated the dose was to be 2 milligrams of test product per square centimeter of tape-stripped skin. Inadvertedly, the subjects received more drug. This increased dosage should not affect the results or conclusions of this study.*

A portion of each site treated with test product was covered with an opaque material. The uncovered portions of the treated sites and untreated, tape-stripped site were exposed to irradiation (UVA and UVB) from a xenon lamp solar simulator. Irradiated test sites were exposed to 0.5 MEDs of UVB and to UVA for a duration of 10 times the MED equivalent.

Immediately, 20 minutes, 3 hours, 24 hours, and 48 hours after irradiation, all sites were examined for signs of reaction (see table B).

Table B
Daily Activities – Phototoxicity Test
Protocol DE140-007

Obtain informed consent Determine MED			
Time Day –7 to 0	**Treatment Site**		
	Treated Irradiated	**Treated Non-Irradiated**	**Untreated Irradiated**
Day 1 **Enrollment –Eligibility criteria**			
Tape Strip	X	X	X
Apply test product	X	X	X
UVA irradiation (10 x MED time)	X		X
UVB irradiation (0.5 x MED dose)	X		X
Evaluate and record skin reactions: **5 minutes post-irradiation** **20 minutes post-irradiation** **3 hours post-irradiation**	 X X X	 X X X	 X X X
Day 2 **Evaluate and record skin reactions** **(24 hours post-irradiation)**	X	X	X
Day 3 **Evaluate and record skin reactions** **(48 hours post-irradiation)**	X	X	X

The reactions observed were evaluated on the following five-point scale:

0	=	no sign of irritation
1	=	slight irritation
2	=	noticeable erythema with slight infiltration
3	=	erythema with marked edema
4	=	erythema with edema and blistering

Skin Responses

BMS 15% cream – Irradiated Sites

Fifteen of the 25 subjects had maximum skin responses scored as 1 at one or more observation times. Scores for the other 10 subjects were all 0. By the 48-hour observations, scores for all subjects except subject 20 were 0. At the 48-hour observations, scores for all subjects except subject 20 were o. At the 48 hour time subject 20 had a score of 1.

BMS-203522 15% cream – Non-irradiated Sites

All scores for all subjects at all times were 0.

Vehicle cream – Irradiated Sites

Fifteen of the 25 subjects had maximum scores of 1 at one or more observation times. Scores for the other 10 subjects were all 0. By the 48-hour observation, scores for all subjects except subject 20 were 0. At the 48 hour time subject 20 had a score of 1.

Vehicle cream – Non-irradiated Sites

All scores for all subjects at all times were 0.

Untreated Control – Irradiated Sites

Fifteen of the 25 subjects had maximum scores of 1 at one or more observation times. Scores for the other 10 subjects were all 0. By the 48-hour observation, readings for all subjects except subject 20 were 0. At the 48 hour time subject 20 had a score of 1.

Adverse Events

There were not any adverse events reported in this study.

Reviewer's Comment: One can conclude from the results of this study that BMS-203522 15% cream in clinical use would not be expected to cause phototoxic reactions.

Protocol #DE140-006 **Title: Photocontact Allergy Test – BMS-203522**

This study was conducted at a single investigational center, The Education and Research Foundation, Inc. located in Lynchburg, VA. Claire Whitmore, M.D. was the principal investigator for the study; subinvestigators were ——— M.D. and ——— M.D. It was an open-label, within subject, vehicle controlled study.

Thirty healthy volunteer subjects were enrolled in the study and 28 completed the study. Subjects 5 and 21 dropped from the study of their own volition. There were 5 males and 25 females, 29 were White and 1 was Black. The mean age was 41.4 years and ranged from 20-73 years.

Subjects had patches placed on the upper back. A dose of 0.2 gm of test material was used. Patches were left in place for 24 hours. After removal during induction, one of the duplicate sites and an unpatched, untreated site were irradiated with ultraviolet light (UVA and UVB). Following removal of the challenge patches, one of the duplicate sites and an unpatched, untreated site were irradiated with ultraviolet light (UVA). Challenge sites were evaluated for skin responses 5 and 20 minutes after light exposure, and again 24, 48, and 72 hours past exposure. See table C for daily procedures.

Table C
Daily Procedures for Photocontact Allergy Test
Protocol DE140-006

Pre-Study: Day –7 to 0, Obtain informed consent, Determine MED					
INDUCTION	Monday	Tuesday	Wednesday	Thursday	Friday
Week 1	Day 1	Day 2	Day 3	Day 4	Day 5
	Enroll subject, Patch	Remove patch irradiate Read sites	(Read sites) Patch	Remove patch Irradiate Read sites	
Week 2	Day 8	Day 9	Day 10	Day 11	Day 12
	(Read sites) Patch	Remove patch Irradiate Read sites	(Read sites) Patch	Remove patch Irradiate Read sites	
Week 3	Day 15	Day 16	Day 17	Day 18	Day 19
	(Read sites) Patch	Remove patch Irradiate Read Sites	(Read sites) Patch	Remove patch Irradiate Read sites	Rest period
REST PERIOD	Day 22	Day 23	Day 24	Day 25	Day 26
Week 4	——Rest Period——				
	Day 29	Day 30	Day 31	Day 32	Day 33
Week 5	——Rest Period——				
CHALLENGE	Day 36	Day 37	Day 38	Day 39	Day 40
Week 5	Patch new sites	Remove patch Irradiate Read sites at 5 minutes at 20 minutes	Read sites	Read sites	Read sites
0 Bracketed readings are for delayed reactions					

The reactions observed were evaluated on the following five-point scale:

0	=	no sign of irritation
1	=	slight irritation
2	=	noticeable erythema with slight infiltration
3	=	erythema with marked edema
4	=	erythema with edema and blistering

Skin Responses

BMS-203522 15% cream – Irradiated Sites

During induction all subjects had one or more skin responses scored as 1. There were no skin responses scored greater than 1. At challenge 10 of the 28 subjects had responses of 1 at the 5-minute or 20 minute evaluation. Responses for these subjects were 0 for remaining (24, 48, and 72 hour) challenge evaluations. All other subjects had scores of 0 for all challenge evaluations.

BMS-203522 15% cream – Non-Irradiated Sites

During induction three subjects had single skin responses of 1. One subject had a single score of 2. Scores of all other subjects during induction were 0. At challenge 4 subjects had one or two scores of 1 at the 5-minute and 20-minute evaluations. All other challenge scores were 0.

Vehicle Cream – Irradiated Sites

During induction all subjects had one or more skin responses of 1. There were no scores greater than 1. At challenge 12 of the 28 subjects had responses of 1 at the 5-minute or 20-minute evaluation. Responses for these subjects were 0 for remaining (24, 48, and 72) challenge evaluations. All other subjects had scores of 0 for all challenge evaluations.

Vehicle Cream – Non-Irradiated Sites

During induction 16 subjects had one or two skin responses of 1. All other scores druing induction were 0. At challenge 4 subjects had one or two scores of 1 at the 5-minute and 20-minute evaluations. All other challenge scores were 0.

Untreated Control – Irradiated Sites

During induction all subjects had one or more skin responses of 1. There were no scores greater than 1. At challenge 10 subjects had one or two scores of 1 at the 5-minute and 20-minute evaluations. All other challenge scores were 0.

***Reviewer's Comment:** BMS-203522 15% cream does not demonstrate photoallergic properties under exaggerated conditions. It is not likely to exhibit potential to cause photocontact dermatitis under conditions of clinical use.*

11.2 **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 #DE140-001 **Title:** "BMS-203522 Cream 15% Versus Its Vehicle in the Treatment of Women with Excessive Facial Hair Growth – A Randomized, Double-Blind Evaluation"

11.2.1 Investigators

1.	David Rodriguez, M.D.	005/Miami, Fl
2.	David C. Wilson, M.D.	006/Lynchburg, VA
3.	David M. Pariser, M.D.	007/Norfolk, VA
4.	Amy J. McMichael, M.D.	008/Winston-Salem, NC
5.	Vera Price, M.D.	009/San Francisco, CA
6.	Adrian S. Dobs, M.D.	010/Baltimore, MD
7.	Frank Dunlap, M.D.	011/Tuscon, AZ
8.	Wilma Bergfeld, M.D.	012/Cleveland, OH
9.	Jonathan S. Weiss, M.D.	013/Snellville, GA
10.	H. Irving Katz, M.D.	014/Fridley, MN

11.2.1.1 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 an eight-week evaluation after treatment cessation.

11.2.1.2 Design

This was a double blind, randomized, vehicle-controlled, parallel group 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 1).

Table 1
Study Design and Procedures
DE140-001

	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									
Pelvic 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.

11.2.1.3 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 1 for flow chart).

11.2.1.3.1 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.

11.2.1.3.2 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**
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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.

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Figure 2 **Video Imaging - Upper Lip Middle Technique**
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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**
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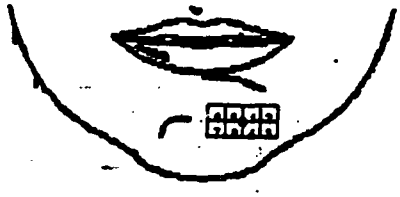

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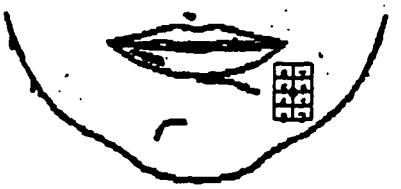
5. Video Imaging - Chin technique 2 – Center Tall

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 DE140-001



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?

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: Again, 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.

11.2.1.3.3 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 [redacted] and dirt, cleaning residue, or water on the lens of the [redacted]. 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 [redacted] in conjunction with [redacted] 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, a BMS staffer, 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 71% of the subjects. This included 128 of 190 subjects (67%) in the eflornithine 15% cream group and 77 of 97 subjects (79%) 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 date on almost ¾ of the enrolled population fairly evenly distributed between the drug and vehicle arms will probably be adequate.

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11.2.1.4 Results

11.2.1.4.1 Populations enrolled/analyzed

A total of 287 subjects were enrolled at the ten U.S. investigational sites. One hundred ninety subjects were randomized to receive eflornithine 15% cream. Ninety-seven subjects were randomized to vehicle cream. Table 2 describes the demographics of all subjects randomized (ASR) in the trial.

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Table 2
Demographic Characteristics
ITT Population
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	BMS203522 15%CRM	BMS203522 VEHCRM	OVERALL	P-VALUE
AGE				0.519
n+	187	97	284	
MEAN	43.0	43.9	43.4	
MEDIAN	42.0	43.0	42.0	
S.E.	0.76	1.27	0.66	
RANGE	19 - 73	21 - 74	19 - 74	
HEIGHT (INCHES)				0.987
n	185	96	281	
MEAN	64.4	64.4	64.4	
MEDIAN	64.5	65.0	64.5	
S.E.	0.21	0.30	0.17	
RANGE	53.5 - 71.0	52.0 - 70.5	52.0 - 71.0	
WEIGHT (LBS.)				0.682
n	185	96	281	
MEAN	196.7	194.0	195.8	
MEDIAN	192.0	193.6	192.0	
S.E.	4.1	4.6	3.2	
RANGE	93.0 - 423.9	115.1 - 390.0	93.0 - 423.9	
RACE*				0.096
WHITE	117 (62%)	51(53%)	168 (59%)	
BLACK	50 (27%)	33(34%)	83 (29%)	
HISPANIC/LATINO	19 (10%)	8(8%)	27 (9%)	
AMERICAN/ALASKAN NATIVE	1 (0.5%)	1(1%)	2 (0.7%)	
OTHER	1 (0.5%)	4(4%)	5 (2%)	
SKIN TYPE				0.158
I	9 (5%)	7(7%)	16 (6%)	
II	31 (16%)	13(13%)	44 (15%)	
III	56 (30%)	18(19%)	74 (26%)	
IV	36 (19%)	22(23%)	58 (20%)	
V	30 (16%)	20(21%)	50 (18%)	
VI	26 (14%)	17(18%)	43 (15%)	

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

Two subjects randomized to eflornithine 15% cream never applied the study medication: subject number 108 was never treated and subject number 342 was found to be ineligible prior to the first study medication application. There were no statistically significant differences between treatment groups in any demographic characteristic ($p \geq 0.096$).

A total of 212 subjects (74%) completed the 24-week treatment phase of the study and 209 (73%) completed the full 32 weeks, which included the 8-week follow-up phase. A total of 78 patients were discontinued from the study. Only a small portion discontinued because of an adverse event, 6 (3%) in the eflornithine arm and 5 (5%) in the vehicle arm. A total of 31 subjects discontinued the study due to a "Patient request". Nineteen (10%) of these subjects were in the eflornithine 15% cream group and 12 (12%) were in the vehicle cream group. Reasons noted for discontinuing included: scheduling difficulty (16); moving (5); lack of efficacy [two subjects; one (<1%) in the eflornithine 15% cream group and one (1%) in the vehicle cream group]; various miscellaneous (8). Table 3 provides a summary of subject disposition for those who were enrolled in the study.

Table 3
Subject Disposition
ITT Population
DE140-001

		TREATMENT					
		BMS203522 15%CRM		BMS203522 VEHCRM		TOTAL	
		n	%	n	%	n	%
REASON	Off Trt Reason BMS Use						
Discontinued-Other	Patient request	19	10	12	12	31	11
	Non-compliance	6	3	1	1	7	2
	Lost to Follow-up	14	7	8	8	22	8
	Other	2	1	0	0	2	1
	Pregnancy	2	1	1	1	3	1
	Ineligible	1	1	0	0	1	.3
	Never treated with study drug	1	1	0	0	1	.3
Discontinued-AE	Pregnancy	1	1	0	0	1	.3
	Adverse Event	5	3	5	5	10	3
Completed	Completed treatment	139	73	70	72	209	73
TOTAL		190	100	97	100	287	100

Reviewer's Comment: *The study had only a small percentage of subjects who discontinued from treatment, with 73% in the eflornithine 15% cream arm and 72% in the vehicle arm completing the study. It is noted that the percentage of patients who requested to leave the study or were lost to follow up was small and only differed by 1-2 percentage points between the active and vehicle arm in each of those categories. It should be noted that no patient was discontinued or not allowed to participate in the study because of abnormal pelvic examinations or pap smears.*

Hair removal methods used two weeks prior to the study were comparable (p=0.764) for eflornithine 15% cream and its vehicle. The percentages using the methods of "shaving/cutting", "plucking", "shaving and plucking", and "plucking and other" were 49.5%, 20.7%, 29.5% and 0.4%, respectively (see table 4).

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Table 4
Method of Hair Removal Used during the Two Weeks Prior to the Study
ITT Population (N=285*)
Protocol DE140-001

METHOD OF HAIR REMOVAL	TREATMENT					
	BMS203522 15%CRM		BMS203522 VEHCRM		STUDY TOTAL	
	N	%	N	%	N	%
SHAVING/CUTTING	90	47.9	51	52.6	141	49.5
PLUCKING	41	21.8	18	18.6	59	20.7
SHAVING & PLUCKING	56	29.8	28	28.9	84	29.5
PLUCKING & OTHER	1	0.5	0	0	1	0.4
TOTAL	188	100.0	97	100.0	285	100.0

COCHRAN MANTEL-HAENSZEL TEST: P-VALUE = 0.764

*this is the ITT data set that does not include subjects 108 and 342 who never applied study medication

There was a statistically significant difference between the treatment group vectors of means on the baseline subject Self-Assessment questionnaire (multivariate p=0.015). Examination of the univariate results from the individual questions constituting the questionnaire revealed significant baseline differences in "Uncomfortable at work or class?" (p=0.006) and "Uncomfortable at social gatherings?" (p=0.036) revealing less discomfort in the eflornithine 15% cream assigned group compared to the vehicle-assigned group. The mean differences were small, approximately 6.5 and 5 units (on a 0-100 unit scale), respectively. To adjust for this initial bias which might extend on treatment, a multivariate analysis of covariance using these two significant baseline questions as covariates was performed on the assessment at all post-baseline periods (see table 5).

Table 5
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	20.2	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	82.67	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)

No differences were seen between the two treatment groups with respect to the prior medical history or presenting conditions. A total of 8 [seven (4%) in the eflornithine 15% cream

and one (1%) in the vehicle cream group] subjects presented with a medical history of polycycstic ovarian disease, all recorded under the genitourinary category.

Most subjects were exposed to study medications for 20-28 weeks, 141 subjects (74%) in the eflornithine 15% cream group and 71 subjects (73%) 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 21.85 weeks for the eflornithine 15% cream group compared to 20.99 weeks for the vehicle group.

There was complete product usage data at week 24 for the study medications dispensed and retrieved from 170 of 287 subjects (59%). These data are for subjects who completed 24 weeks of treatment and had complete tube weights at dispensing and return. The average weight of study medication used during the treatment phase for these subjects was 78.0 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 approximately 0.5 gram/day/subject for subjects in both treatment groups.

11.2.1.4.2 Efficacy endpoint outcomes

All efficacy analyses were performed on the ITT data set (n=287). 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 6 describes the protocol deviations that excluded some subjects from the evaluable data set.

Table 6
Protocol Deviations of Subjects Excluded from The Evaluable Dataset
Protocol DE140-001

REASON FOR EXCLUSION	BMS203522 15%CRM		BMS203522 VEHCRM		TOTAL	
	n	PCTN	n	PCTN	n	PCTN
SUBJECTS WITH GLOBAL ASSESSMENTS NOT PERFORMED 48 HOURS AFTER SHAVING	14	7.4	6	6.2	20	7.0
SUBJECTS USING PROHIBITED MEDICATION CONCURRENTLY[1]	6	3.2	6	6.2	12	4.2
SUBJECTS THAT WERE NON-COMPLIANT*	9	4.7	2	2.1	11	3.8

*All subjects were in the category "dose change/improper application"
[1] these subjects were using systemic hormonal therapy

Primary Efficacy Measure

The Physician's Global Assessment at 24 weeks was the primary response measure. The results indicate a statistical significance of eflornithine 15% cream over its vehicle (p=0.001). Forty-three subjects (23%) out of 188 treated with eflornithine 15% cream were classified successes compared with only 4 (4%) of 97 subjects treated with its vehicle. Results of the

evaluable dataset show a similar statistical superiority of eflornithine 15% cream over vehicle (p=0.001). Table 7 and 8 present these results.

Table 7
Distribution of Physician's Global Assessment At Week 24
End of Treatment – ITT Population
Protocol DE140-001

		TREATMENT		
	ASSESSMENT	BMS203522 15%CRM	BMS203522 VEHCRM	TOTAL
SUCCESS	CLEAR/ALMOST CLEAR	11 (5.9%)	0 (0.0%)	11
	MARKED IMPROVEMENT	32 (17.0%)	4 (4.1%)	36
	SUBTOTAL	43 (22.9%)	4 (4.1%)	47
FAILURE	IMPROVED	56 (29.8%)	24 (24.7%)	80
	NO IMPROVEMENT/WORSE	88 (48.4%)	69 (71.1%)	160
	SUBTOTAL	145 (77.1%)	93 (95.9%)	240
TOTAL		188	97	287

COMPARISON BETWEEN TREATMENTS

COCHRAN MANTEL-HAENSZEL TEST: P-VALUE = 0.001

Reviewer's Comment: *The ITT population for the eflornithine arm is 188 because two patients never received medication. 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's total was 176 for the eflornithine arm, and 92 for the vehicle arm instead of 188 and 97, respectively. Therefore, in constructing table 7, 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 8
Distribution of Physician's Global Assessment at Week 24
End of Treatment – Evaluable Subjects
Protocol DE140-001

		TREATMENT		
	ASSESSMENT	BMS203522 15%CRM	BMS203522 VEHCRM	TOTAL
SUCCESS	CLEAR/ALMOST CLEAR	11 (6.6%)	0 (0.0%)	11
	MARKED IMPROVEMENT	30 (18.1%)	3 (3.5%)	33
	SUBTOTAL	41 (24.7%)	3 (3.5%)	44
FAILURE	IMPROVED	71 (42.8%)	32 (37.7%)	103
	NO IMPROVEMENT/WORSE	54 (32.5%)	50 (58.8%)	104
	SUBTOTAL	125 (75.3%)	82 (96.5%)	207
TOTAL		166	85	251

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 4, 8, and 16. At week 4, 5.3% (10/188) of subjects treated with eflornithine 15% cream were deemed successes compared with 0% (0/97) treated with the vehicle (p=0.017). At week 8, 12.8% (24/188) of subjects treated with eflornithine 15% cream were categorized as successes versus 3.1% (3/97) treated with the vehicle (p=0.007). By week 16, 19.1% (36/188) of subjects treated with eflornithine 15% cream were judged successes compared with 0% (0/97) treated with vehicle (p=0.001). Figure 1 demonstrates the Physician's Global Assessment over time.

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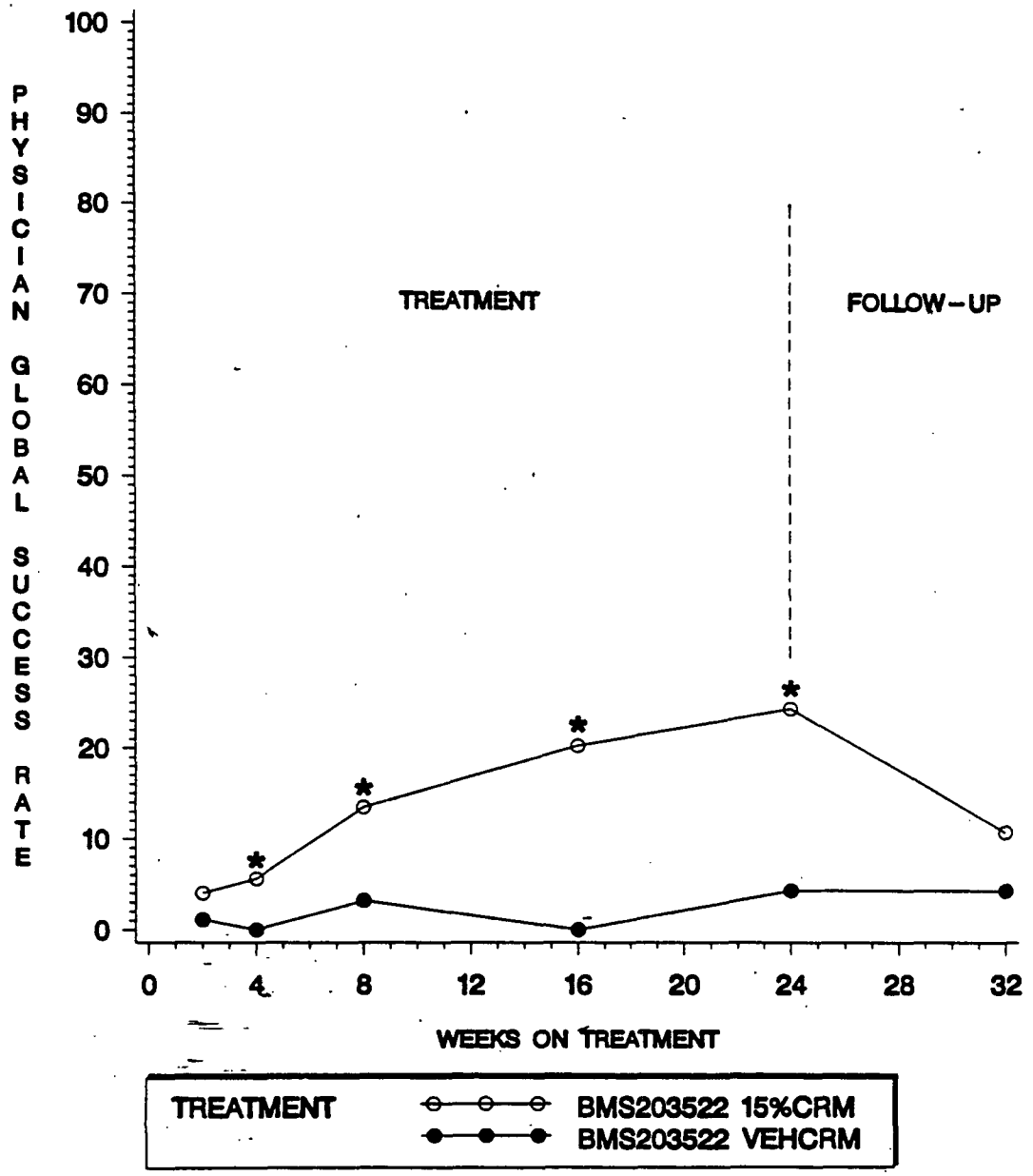
Figure 1
Physician's Global Assessment – ITT Population
Protocol DE140-001



***indicates statistically significant treatment difference (p≤0.05)**

As shown in Figure 1, 8 weeks post-treatment (week 32), the difference between the two groups was no longer statistically significant (p=0.123), demonstrating regression of the

treatment effect. Of those subjects treated with eflornithine 15% cream, 10.8% (15/139) were categorized as success while only 4.3% (3/70) of the vehicle group were so judged (also see table 9).

Table 9
Distribution of Physician's Global Assessment at Regression Week 32 (8 weeks post-treatment) - ITT Population
Protocol DE140-001

		TREATMENT		
	ASSESSMENT	BMS203522 15%CRM	BMS203522 VEHCRM	TOTAL
SUCCESS	CLEAR/ALMOST CLEAR	2 (1.4%)	0 (0.0%)	2
	MARKED IMPROVEMENT	13 (9.4%)	3 (4.3%)	16
	SUBTOTAL	15 (10.8%)	3 (4.3%)	18
FAILURE	IMPROVED	50 (36.0%)	24 (34.3%)	74
	NO IMPROVEMENT/WORSE	74 (53.2%)	43 (61.4%)	117
	SUBTOTAL	124 (89.2%)	67 (95.7%)	191
TOTAL		139	70	209

COMPARISON BETWEEN TREATMENTS

COCHRAN MANTEL-HAENSZEL TEST: P-VALUE = 0.123

Table 10 presents a summary of subjects who had any improvement in their condition as indicated by the Physician's Global Assessment evaluation.

Table 10
Number of Subjects with Improvement* in Physician's Global Assessment
Protocol DE140-001

Evaluation	BMS-203522 15% CRM	BMS-203522 VEHCRM
Week 2	56 (30%) N=188	16 (17%) N=97
Week 4	69 (37%) N=188	23 (24%) N=97
Week 8	105 (56%) N=188	32(33%) N=97
Week 16	103 (55%) N=188	25 (26%) N=97
Week 24	99 (53%) N=188	28 (29%) N=97
Week 32	65 (47%) N=139	25 (36%) N=70

*Includes categories of Improved, Marked Improvement and Clear/Almost Clear; last observation is 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 analysis of the difference between treatments in baseline mean hair growth (length) indicated no statistically significant baseline treatment group difference (p=0.323). 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=0.793).

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=0.158). Of the subjects treated with eflornithine 15% cream, 6.3% were deemed successes compared to 1.3% for those treated with the vehicle (see table 11).

Table 11
Video Image Analysis – Percent Success in Hair Growth at Week 24
End of Treatment
Protocol DE140-001

PERCENT CHANGE FROM BASELINE	TREATMENT: BMS203522 15%CRM N (%)	BMS203522 VEHCRM N (%)	TOTAL N
SUCCESS (>=50%)	8 (6.3%)	1 (1.3%)	9
FAILURE (< 50%)	120 (93.8%)	76 (98.7%)	196
TOTAL	128	77	205

FISHER'S EXACT TEST (2-TAIL). P-VALUE=0.158

The results of the analysis at the secondary intermediate evaluation periods for hair length reduction (weeks 2-16) revealed no statistically significant treatment differences ($p \geq 0.052$); however, significance was approached at week 8 (p=0.052) and week 16 (p=0.053). At week 16, success rates were 5.9% and 0% for eflornithine 15% cream and its vehicle, respectively. As expected from these results, at week 32 (eight weeks after treatment cessation)

the difference between treatments was not statistically significant (p=0.603). Success rates were 1.8% for eflornithine 15% cream and 3.6% for the vehicle.

The results for mean spatial mass at the primary evaluation (week 24) demonstrated a statistically significant treatment difference (p=0.0001), favoring eflornithine 15% cream over its vehicle. The mean spatial mass for the subjects treated with eflornithine 15% cream was 0.037mm^2, while for those treated with vehicle, mean spatial mass was 0.046 mm^2. Table 12 shows the results for mean spatial mass at 24 weeks and also for mean hair length. Table 13 gives the video image analysis for mean percent reduction in hair growth at the end of treatment (week 24).

Table 12
Video Image Analysis – End of Treatment
Week 24
Protocol DE140-001

	BMS203522 15%CRM	BMS203522 VEHCRM	OVERALL	P-VALUE
HAIR LENGTH				0.001
n	160	87	247	
MEAN	0.404	0.484	0.432	
S.E.	0.009	0.015	0.008	
RANGE				
SPATIAL MASS				0.0001
n	160	87	247	
MEAN	0.037	0.046	0.040	
S.E.	0.001	0.002	0.001	
RANGE				

Table 13
Video Image Analysis – End of Treatment
Mean Percent Reduction in Hair Growth
Protocol DE140-001

WEEK 24: END OF TREATMENT	BMS203522 15%CRM	BMS203522VEHCRM	OVERALL
n	128	77	205
MEAN	16.8	-1.3	10.0
S.E.	2.5	4.0	2.3

Reviewer's Comment: *Although the sponsor was unable to collect data for every subject (see section 11.2.1.3.3- Video Image Analysis), the video image analysis was supportive of the physician global assessment. The difference in spatial mass between eflornithine 15% cream and vehicle was statistically significant (p=0.0001) 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=0.158, table11), compared to vehicle there was statistical significance in reduction of hair length (p=0.001, table 12). There was also a trend favoring the eflornithine group over vehicle, 6.3% deemed success as compared to 1.3% for vehicle. The mean percent reduction in hair growth also favored the eflornithine group (16.8% reduction vs. –1.3%).*