CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-922

MEDICAL REVIEW(S)

NOV 23 1998

Medical Officer's Review of NDA 20-922

NDA # 20-922
MO Review # 1

Submission: 12/30/97
Date assigned: 4/1/98
Draft Review: 10/19/98
Final Review: 11/12/98

Drug name:	4-Hydroxyanisole and All-Trans Retinoic Acid
Generic name:	2% 4-hydroxyanisole/0.01% tretinoin (4HA/tretinoin)
Proposed trade name:	(4-hydroxyanisole 2%, tretinoin 0.01% solution) Topical Solution
Chemical name:	1-hydroxy-4-methoxy benzene, (all-E)-3,7-Dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid
Sponsor:	Bristol-Myers Squibb Pharmaceutical Research Institute 100 Forest Avenue Buffalo, New York 1413-1091 (716) 887-7794
Pharmacologic Category:	Depigmenting agent/retinoid
Proposed Indication(s):	For the treatment of solar lentigines [redacted] resulting from chronic sun exposure
Dosage Form and Route of Administration:	Solution; topical
NDA Drug Classification:	1,4S
Related Drugs:	Tretinoin gel, 0.01% - NDA [redacted] Renova, tretinoin cream, 0.05% - NDA 19-963 approved on 7/19/89 [redacted] (hydroquinone)

Related Reviews:
Statistical Review dated: 9/8/1988
Biopharmacology Review dated: 6/2/98
Pharmacology/Toxicology Review dated: N/A
Microbiology Review dated: 7/15/98
Chemistry Review dated: N/A

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List of Tables

Study DE132-010

ADR Incidence

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ON ORIGINAL

3 Material Reviewed

IND [redacted] 4HA/tretinoin - July 6, 1992
NDA 20-922 - Volumes 1.1-1.2, 1.39-1.41, 1.47, 1.68-1.71, 1.85-1.86, 1.93, 1.96, 1.99-1.101, 1.107, 1.110-1.111, 1.114-1.119.
NDA 20-922 [redacted]
NDA 20-922 [redacted]

4 Chemistry/Manufacturing Controls

The chemistry review of the referenced DMF for 4-hydroxyanisole revealed a lack of identification and quantification of impurities in that drug substance. Chemistry has thus recommended a non-approval because the sponsor has failed to submit a DMF for the 4-hydroxyanisole portion of this drug substance.

The to be marketed formulation, W1133-M-08-A, has a [redacted] overage of tretinoin. This is different from the formulation used in the pivotal trials, W1133-08-B, which has a [redacted] overage of tretinoin. The formulations are otherwise identical. The USP does allow a 30% overage for tretinoin solutions. The formulations used in each arm of the pivotal trial DE132-005 and were identical to the formulations used in pivotal trial DE132-010.

5 Animal Pharmacology/Toxicology

A 3 month dermal dose-ranging study was conducted in CD-1 mice. Dermal irritation consisting primarily of erythema was seen in all treated groups, as well as some edema, eschar, desquamation, and pinpoint scabbing. In a 6 month dermal study in Sprague-Dawley rats, time and dose-related irritation was evident at the treatment site. The 2% 4-hydroxyanisole/0.01% tretinoin formulation was not phototoxic in hairless albino guinea pigs following UVA exposure. The formulation was also considered to be nonsensitizing in a modified [redacted] assay in hairless guinea pigs. A 2 year dermal carcinogenicity study in CD-1 mice was also negative. A 12 month dermal photocarcinogenicity study in albino hairless mice demonstrated a significant enhancement of UV-induced skin carcinogenesis and a significantly shorter time to tumor onset in all treated groups.

A segment II dermal teratology study was performed in rabbits with 4HA/tretinoin solution. A low incidence of marked hydrocephaly with visible doming of the head was observed in one mid-and two high-dose 4HA/tretinoin group fetuses and in two high-dose tretinoin-only fetuses. Accompaning malformations in these hydrocephalic fetuses consisted of cleft palate (2 of 5 fetuses) and appendicular skeletal defects (3 of 5 fetuses). These malformations appeared to be related to the retinoid component and similar effects have been reported previously with marketed tretinoin products. A no-observed-effect level for teratogenicity was established for this study at 4/0.02 mg/kg/day (0.2 ml/kg) for the 4HA/tretinoin formulation which is approximately equal to the maximum human dose. This safety factor is based on an estimated body surface area of 5%; in clinical studies patients were

treated on an average of 1.7% body surface area.

Reviewer's Comment: *Based on the above findings, the sponsor has decided that this drug product would be labeled pregnancy category X. The sponsor also recommends that this drug product be used as part of a sun prevention program in which patients use this product in conjunction with a sunscreen and/or protective clothing.*

6 Microbiology

According to the microbiologist, the drug product, 2% 4-hydroxyanisole/0.01% tretinoin has met all specifications related to microbiology.

7 Clinical Background

7.1 Relevant human experience

Tretinoin is marketed in the U.S. in concentrations ranging from 0.01% to 0.1% in topical preparations for the treatment of acne vulgaris and for use in the mitigation (palliation) of fine wrinkles, mottled hyperpigmentation, and tactile roughness resulting from chronic sun exposure.

4-hydroxyanisole is the monomethyl ether of hydroquinone. Hydroquinone is a known skin beaching agent, marketed in the US in OTC preparations at concentrations of 1.5% and 2% and in prescription products in 3% and 4%. The prescription products are indicated for the temporary depigmentation of hyperpigmented skin conditions such as chloasma, melasma, freckles, senile lentigines, and other forms of melanin hyperpigmentation.

4-hydroxyanisole has been marketed in Europe and other countries at concentrations of 5-20% and has also been used as an antioxidant in cosmetic products in the US at concentrations of 0.05%. Adverse effects reported for the topical 4HA product marketed in France include "the rare occurrence of irritation or sensitization reactions, slight risk of post-inflammatory hypermelanosis, reports of non-homogenious leucomelanodermia with confetti-type depigmentation and some reported cases of hypomelanosis occurring at a distance from the treated areas."

In two studies done by Morgan, BGD, et. al, (see under Literature, Section 8.2), 4-hydroxyanisole was intravascularly administered to humans in studies evaluating its safety and effectiveness in the treatment of advanced melanoma. In these studies the investigators reported a number of systemic adverse events including a "flushed" feeling, faintness, and nausea during the intra-arterial infusion of up to 4g twice a day for 14 days. Episodes of drowsiness and hypertension were also reported with the administration of intra-arterial doses of 4HA.

These studies also demonstrated that following the administration of 4HA, the drug is rapidly metabolized and eliminated from the body. Webster, DJT, et. al., (see under Materials Reviewed, Section 3), found the serum distribution half-life of 4-hydroxyanisole to be 6.3 minutes following the intra-arterial administration of 10g of 4HA twice a day in subjects with recurrent melanoma.

7.2 Important information from related INDs and NDAs

Known effects of tretinoin and hydroquinone have been elucidated in this review.

7.3 Foreign experience

This drug product (2% 4-hydroxyanisole/0.01% tretinoin) has not been approved in any countries, nor have any marketing applications been filed outside the U.S.

In Europe, 4-hydroxyanisole has been marketed in Austria, France, Greece, Spain, and Switzerland at concentrations ranging from 5 to 20% under the following trade names: Any, Any forte, Clairodermyl, Creme des 3 Fleurs d'Orient No 1 and No 2, Leucobasal, Leucodinine B, Novo-Dermoquinona and Trois Fleurs de'Orient. 4-hydroxyanisole also has antioxidant properties; it is listed under 21 CRF §177.1010 by the name p-methoxyphenol as an allowed antioxidant/stabilizer for use in certain plastics intended for use in contact with food. It has also been used in the U.S. as an antioxidant in cosmetics up to a concentration of 1%.

7.4 Human Pharmacology, pharmacokinetics, pharmacodynamics

According to the pharmacokineticist, based on the results of the pharmacokinetic study, #DE 132-008, in healthy human volunteers, an insignificant increase in the normal endogenous level of tretinoin occurs from the topically applied 2% 4-hydroxyanisole/0.01% all-trans retinoin acid solution. The total daily systemic exposure from 4-hydroxyanisole was 66.9 ng.hr/mL, which is about 35 times lower than that seen in a 6 month dermal toxicity study in the rat with the highest dose (40/0.2 mg/kg/day, i.e. 2 ml/kg/day). At a dose of 2 ml/kg/day only a very slight increase in neutrophil count and serum potassium was observed. Other effects were treatment site related irritation. The total application of 2% 4 hydroxyanisole/0.01% all-trans retinoic acid solution was about 3 times more than that used in the clinical studies for efficacy and safety. The reader is referred to the clinical pharmacology/biopharmaceutics review for further details.

7.5 Other relevant background information

Bristol-Meyers Squibb (BMS) and the FDA held an End-of-Phase II meeting on April 14, 1994 and multiple teleconferences were held between June 29, 1994 and July 2, 1996 to reach an agreement concerning the trial design and outcome variables. The following is a summary of the agreements reached during the clinical-related communications between BMS and the FDA concerning this NDA:

- ✦The primary efficacy measures for the pivotal studies would be:
  - ☆Physician Global Assessment with moderate improvement being the breakpoint for success

☆Subject's Self-Assessment

✦A subject evaluation assessing improvement was added to the pivotal studies.
✦Overall Cosmetic Effect would be a secondary efficacy measure
✦The key primary efficacy measure for the first pivotal study, DE132-005, would be the Physician's Global Assessment, since the Subject's Self-Assessment measure had an incomplete data set, being added after initiation of the study.

The following is a summary of other points that according to BMS were reached between BMS and the FDA in the same teleconferences held above:

✦The pivotal studies would have an unequal number of subjects in the four treatment arms (combination, tretinoin, 4-hydroxyanisole, and vehicle).
✦The back of the hands would be assessed separately from the forearms by the subjects.
✦Evidence of both a clinical and histological effect would need to be presented to support an indication for "treatment".

7.6 Proposed Label

7.6.1 Indication & Usage Section

TRADENAME (4-hydroxyanisole 2%, tretinoin 0.01%) Topical Solution is indicated for the treatment of solar lentigines

7.6.2 Clinical Studies Section

Clinical Results: Two adequate and well-controlled trials evaluated changes in treated hyperpigmented lesions on the face, forearms/back of hands in 421 patients treated with TRADENAME Topical Solution, 420 patients treated with tretinoin topical solution, 208 patients treated with 4-hydroxyanisole topical solution and 106 patients treated with vehicle for up to 24 weeks. In these studies, patients were to avoid sun exposure and use protective clothing, and use of sunscreens was prohibited. Physicians assessed the extent of improvement or worsening of all the treated lesions from the baseline condition on a 7 point scale. The results of these evaluations are shown below.

	Face		Forearms/Back of Hands	
	Tradename	Vehicle	Tradename	Vehicle
Moderate Improvement or greater[1]		15%		14%
Slight Improvement	28%			
No change[2]				

1Includes the following grades: Moderate Improvement, Marked Improvement, Almost Clear, Completely Clear.

Moderate Improvement or greater was considered clinically meaningful.
2Includes the following grades: No Change, Worse (less than 1% of patients treated with TRADENAME were rated as worse)

After 24 weeks of treatment, for the forearm/back of hands treatment site, the percentage of patients treated with tretinoin topical solution with moderate improvement or greater, slight improvement, or no change, were 37%, and 26%, respectively, and for 4-hydroxyanisole topical solution were 40% and 36%, respectively. For the face treatment site, the percentage of patients treated with tretinoin topical solution with moderate improvement or greater, slight improvement, or no change, were 46% and 21%, respectively, and for 4-hydroxyanisole topical solution were 33%, 30% and respectively.

In the clinical studies, some patients experienced temporary hypopigmentation of treated lesions (5%) or of the skin surrounding treated lesions (7%). Hypopigmentation of the skin surrounding treated lesions These resolved upon discontinuation of treatment to the lesion, and/or upon re-instruction on proper application to the lesion only.

7.6.3 Dosage and Administration Section

Reviewer's Comment: *The above comments in Section 7.6 are as submitted by the sponsor.*

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8 Description of Clinical Data Sources

8.1 Clinical Studies

Study #DE118-019-001 - This is a study to determine dermal irritation potential of two formulations of depigmentation solution BMS-181158/BMS-181159, its active components (4-hydroxyanisole solution and tretinoin solution), and its vehicle solution. This was an open-label, single-center, within subject, vehicle-and-positive-controlled study which included 31 healthy adults. The first subject enrolled August 7, 1992 and the last subject completed the study on August 29, 1992.

Study #DE118-018-001 - This is a study to determine the contact allergic potential of two formulations of depigmentation solution, BMS-181158/BMS-181159, its active components (4-hydroxyanisole solution and tretinoin solution), and its vehicle solution. Melenex topical solution was a fifth arm in the study. It was an open-label, single-center, within subject, vehicle controlled study which initially treated 225 subjects but in which 200 subjects completed the study. The first patient enrolled in the study on October 5, 1992 and the last patient completed the study on October 23, 1997.

Study #DE118-020-001 - This is a study to determine the photocontact allergy potential of two formulations of depigmentation solution, BMS-181158/BMS-181159, its active components (4-hydroxyanisole solution and tretinoin solution), and its vehicle solution. Melenex topical solution was a fifth arm in the study. This was an open-label, single-center, within subject, vehicle controlled study in which 28 patients initially enrolled and 27 patients completed. The first patient enrolled on November 2, 1992 and the last subject completed the study on October 23, 1992.

Study #DE118-021-001 - This is a study to determine the phototoxic potential of two formulations of depigmentation solution, BMS-181158/BMS-181159, its active components (4-hydroxyanisole solution and tretinoin solution), and its vehicle solution. Melenex topical solution was a fifth arm in the study. This was an open-label, single-center, within subject, vehicle controlled study in which 10 subjects enrolled and completed the study. The first subject enrolled on October 28, 1992 and the last subject completed the study on October 29, 1992.

Study #DE132-005 - This was a double-blind, vehicle controlled, multicentered study comparing the study drug, 4HA/tretinoin, to its individual active ingredients, 4HA and tretinoin, and vehicle in the treatment of solar lentigines. There were 595 patients that enrolled in the study and 476 patients completed it. There were fourteen centers, thirteen in the United States and one in Canada. The first subject enrolled on February 24, 1994 and the last subject completed the study on January 11, 1996.

Study #DE132-010 - This was a multi-center, randomized, parallel-group, double-blind study comparing the study drug, 4HA/tretinoin, to its individual active ingredients, 4HA and tretinoin, and vehicle in the treatment of solar lentigines. There was a total of 580 subjects enrolled at 18 study sites. All of the study centers were in the United States. The first subject enrolled on April 11, 1996 and the last subject completed the study on August 8, 1997.

The following studies were reviewed in this NDA for safety:

Study #DE132-004 - This was a randomized, pilot, double-blind, parallel group study of 4HA/tretinoin versus vehicle for the treatment of facial melasma. The trial took place with 5 centers. There was a total of 48 subjects who entered the trial of which 38 subjects completed. Patients were treated for up to 16 weeks, followed by a 24 week no treatment follow-up phase. The first subject enrolled on June 15, 1993 and the last subject completed the study on July 14, 1994.

Study #DE132-002 - This was a phase 2 multi-centered, randomized, parallel-group, double-blind study of 4HA/tretinoin versus its active components, vehicle, and Melanex topical solution in the treatment of solar lentigines. There were 221 subjects enrolled at 5 study sites in the United States and 194 subjects completed the study. Treatments were applied twice daily for up to 16 weeks followed by a 24 week no treatment follow-up phase. The first subject was enrolled on January 6, 1993 and the last subject completed the study on February 23, 1994.

Study #DE132-009 - This was a phase 3 open-label, non-controlled, multicentered study to evaluate 4HA/tretinoin for long term safety in the treatment of solar lentigines. A total of 259 subjects enrolled at 8 study sites in the United States and used the study drug for up to 52 weeks followed by a 4 week follow-up phase. A total of 196 patients completed the study. The first subject enrolled February 28, 1996 and the last subject completed the study August 7, 1997.

Study #DE132-011 - This was a prospective, open-label, multicenter study to evaluate 4HA/tretinoin with concomitant use of sunscreen in the treatment of solar lentigines. Treatment was applied daily for up to 24 weeks followed by a 4 week no treatment follow-up phase. A total of 96 subjects were enrolled at 4 study sites in the United States of which 77 completed the study. The first subject enrolled in the study June 14, 1996 and the last subject completed the study on May 2, 1997.

8.2 Literature

MorganBGD, O'Neill T, Dewey DL, Galpine AF, Riley PA. Treatment of Malignant Melanoma by Intravascular 4-Hydroxyanisole. Clin Oncol 1981; 7:227-34.
MorganBGD. Recent Results of a Clinical Pilot Study of Intra-arterial 4HA Chemotherapy in Malignant Melanoma. In: Riley PA, Editor. Hydroxyanisole: Recent Advances in Anti-Melanoma Therapy. Oxford: IRL Press, 1984:233-241.
Webster DJT, Whitehead RH, Tarr MJ, Hughes LE. A Phase I Study of 4-hydroxyanisole (4HOA) in Patients with Advanced Malignant Melanoma. In: Riley PA, Editor. Hydroxyanisole: Recent Advances in Anti-Melanoma Therapy. Oxford: IRL Press, 1984: 227-232.
Add other literature sources from V01 100.113

9 Clinical Studies

9.1 Dermal Toxicity Studies

9.1.1 Study DE118-019-001 - 21-Day Cumulative Irritation Test

The objective of this study was to determine the cumulative irritation potential of two formulations of depigmentation solution BMS-181158/BMS-181159 (W1133-M-01-A, W1133-M-07-A), 4-hydroxyanisole solution, tretinoin solution, vehicle solution, Melanex topical solution, which is a marketed product with an indication for the treatment of hyperpigmentation, and 0.5% sodium lauryl sulfate (SLS), a positive control for irritation.

This was an open-label, single-center, within subject, vehicle-and-positive-controlled study in which all 31 healthy adult volunteers who enrolled in the study, completed the study. Test materials were applied under occlusive patches to sites on the subjects' backs. Fresh test materials were then applied to the same test sites daily, Monday through Saturday for 21 days. The results were are listed in table 1:

Table 1
Total Cumulative and Mean Scores by Treatment
(n=31)
Friedman's Test, $p \leq 0.001$

Treatment	Total Cumulative*	Mean Score**	Tukey's***
[redacted] Solution	1913	3.43	A
0.5% Sodium lauryl sulfate	1532	2.75	B
Depigmentation Solution - W1133-M-07-A	1468	2.63	B
Depigmentation Solution - W1133-M-01-A	1421	2.55	BC
Tretinoin Solution 0.01%	1317	2.36	C
4-Hydroxyanisole	900	1.61	D
Vehicle Solution	351	0.63	E

* 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.

Tukey's Studentized Range Test for multiple comparisons indicated the mean irritation score for Melanex topical solution was statistically significantly higher than all the other test products. SLS, the two depigmentation solutions and tretinoin solution had statistically significantly higher scores than 4-hydroxyanisole and vehicle solution. SLS and the two depigmentation solutions did not differ significantly from one another, however, 0.5% SLS and one of the depigmentation solutions (W1133-M-07-A) had statistically significantly higher

scores than tretinoin solution. There was no statistically difference between the scores for depigmentation solution (W1133-M-01-A) and tretinoin solution. 4-Hydroxyanisole solution had a statistically significantly higher score than vehicle solution.

In conclusion, while the two formulations of depigmentation solution were relatively irritating under study conditions, they were both significantly less irritating than Melanex topical solution, a marketed product with an indication similar to the proposed indication for this depigmentation solution. The two depigmentation solutions were slightly more irritating than their tretinoin solution component and significantly more irritating than their 4-hydroxyanisole solution and vehicle solution components. In terms of irritation potential, however, treatment of subjects with either depigmentation solution is acceptable.

9.1.2 Study DE118-018-001 - Repeated Insult Patch Test

The objective of this study was to determine the contact allergic potential of two formulations of depigmentation solution BMS-181158/BMS-181159 (W1133-M-01-A, W1133-M-07-A), 4-hydroxyanisole solution (W1133-M-02-A), tretinoin solution (W1133-M-04-A), vehicle solution (W1133-M-03-A), and Melanex Topical Solution (3% hydroquinone).

This was an open-label, single-center, within subject, vehicle controlled study in which 225 subjects were initially treated and 200 subjects completed the study. Test materials were applied under patches to sites on the subjects' backs three times per week for a three week induction period. Patches were left in place between readings. Following a two-week rest period, a challenge application was made to sites not previously treated with test products. Occlusive patches were used for all test products except Melanex. Because of excessive irritation associated with the application of Melanex under occlusive patches in another study, semi-occlusive patches were used in this study.

Six subjects discontinued study participation because of adverse events or because the medications used to treat adverse events were restricted by the protocol. Twelve subjects dropped for personal reasons, five dripped because they missed two visits and two subjects were dropped because they were taking medications restricted by the protocol.

Primary responses were evaluated using a 5-point scale about 5 minutes after patch removal as follows:

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

The clinical appearance of skin responses was graded using the above listed criteria for both the induction and challenge patches. Primarily, the challenge patches were considered in making a clinical judgement concerning whether or not a given test product produced allergenic responses. This clinical judgement is based on the intensity of the response and the pattern of change in intensity from the reading at 48 hours after application to the reading at 72 hours after

application. In general, this clinical judgement is based on the following criteria:

✦Readings of 0 or 1 at both 48 and 72 hours indicate no allergic reaction and/or mild irritation
✦Readings which increase in intensity from 48 to 72 hours such as:

48 hours	72 hours
0	1, 2, 3, or 4
1	2, 3, or 4
2	3 or 4
3	4

or reactions in which the signs spread beyond the border of the patch are indications of allergic sensitivity reactions.
✦Readings of 2 or higher, which do not decrease at 72 hours, are also indicators of allergic sensitivity reactions.
✦All other possibilities are responses considered related to irritation.

The results of this study were as follows:

Subject 159 had a 48 hour challenge reading of 1 and a 72 hour reading of 2 using depigmentation solution W1133-M-01-A. Approximately 5 months after challenge, the subject was rechallenged with patches containing W1133-M-01-A and vehicle solution. Subject 159 experienced reactions associated with allergic sensitization to the depigmentation solution.

Subjects 2 and 159, using depigmentation solution W1133-M-07-A, had 48 hour challenge readings of 1 and 72 hour readings of 2. Approximately 5 months after challenge, these 2 subjects were rechallenged with patches containing W1133-M-07-A and vehicle solution. Both subjects experienced reactions associated with allergic sensitization to the depigmentation solution.

No subjects experienced allergic sensitization to the individual components, 4-hydroxyanisole and tretinoin, of the depigmentation solution. Vehicle solution was considered to be irritating and not a sensitizer based on the initial phase of the study and either a strong irritant or a possible sensitizer based on the responses of subjects 2 and 159 on the 5 month rechallenge of a grade 2 and a grade 1 reaction, respectively.

In conclusion, both depigmentation solutions, W1133-M-01-A and W1133-M-07-A, produce allergic sensitization at a relatively low level, 0.5% - 1%.

9.1.3 Study DE118-020-001 - Photocontact Allergy Test

The objective of this study was to determine the photocontact allergy potential of two formulations of depigmentation solution BMS-181158/BMS-181159 (W1133-M-01-A, W1133-M-07-A), 4-hydroxyanisole solution, tretinoin solution, vehicle solution, and Melanex topical

solution.

This was an open-label, single-center, vehicle-controlled study in which 28 patients enrolled and 27 patients completed. Treatments were applied under 2 patches to all subjects twice a week during the three week induction period. After a one-week rest period, treatments were again applied under patches to 2 sites for each test product for the challenge period. Twenty-four hours after each application, patches were removed and one test site for each test product and an untreated control site were irradiated with ultraviolet light. For this study, an [redacted] was used with a [redacted] Unfiltered UVA output was 45.5 mw/cm^2, unfiltered UVB was 6.01mw/cm^2. With a [redacted] filter [redacted] in place (to provide UVA only) output was UVA-17.5 mw/cm^2; UVB-0.01 mw/cm^2.

Primary responses were the same as for the repeat insult patch test (see page 12). None of the patients who participated in this study exhibited any photocontact allergy for any of the test products.

9.1.4 Study DE118-021-001 - Phototoxicity Test

The objective of this study was to determine the phototoxic potential of two formulations of depigmentation solution, BMS-181158/BMS-181159 (W1133-M-01-A, W1133-M-07-A), 4-hydroxyanisole solution, tretinoin solution, vehicle solution, and Melanex topical solution.

This was an open-label, single-center, within subject vehicle controlled study in which ten adult subjects enrolled and completed the study. Single applications of all test products were made to tape-stripped skin sites on all subjects. A portion of each site was covered and the other portion irradiated with ultraviolet A-range and B-range light from a [redacted] Evaluations of skin responses were made immediately, 3 hours, and 24 hours after irradiation at both irradiated and non-irradiated sites. Also included in the evaluations was an untreated, tape-stripped, irradiated control site.

None of the patients experienced a phototoxic reaction to any of the test products. Therefore, both depigmentation solution formulations are unlikely to cause a phototoxic reaction in clinical use.

Reviewer's Comment: *Usually topical dermal studies are done with the to be marketed formulation, which according to the sponsor is W1122-M-08-A, which is not either of the formulations used in these topical dermal studies. It is duly noted, however, that the formulations used in the topical safety studies have a [redacted] overage of 4HA, while M-08-A only has a [redacted] overage. M-07-A, one of the formulations used in the dermal safety studies, is the same in every other respect to the to be marketed formulation. The other formulation used in the dermal safety studies, M-01-A, does not have citric acid and ascorbyl palmitate in its formulation (See table 3.1-2, Vol1.2.221). However, the outcomes in the dermal safety studies were the same for both formulations. Also, these studies are usually blinded and not done as open-label trials.*

9.2 Sponsor's protocol #DE132-005 Title: "A Double-Blind, Parallel Group Comparison of BMS-181158/BMS-181159 Solution (2% 4-Hydroxyanisole/0.01% Tretinoin) Versus Individual Active Agents and Vehicle in the Treatment of Solar Lentigines[redacted]

9.2.1 Investigators

1.	H. Irving Katz, M.D.	001/Fridley, MN
2.	Jonathan Weiss, M.D.	002/Snellville, GA
3.	Ronald Savin, M.D.	003/New Haven CT
4.	Suzanne Bruce, M.D.	004/Houston, TX
5.	Janet Hickman, M.D.	005/Lynchburg, VA
6.	Stanley Cullen, M.D.	006/Gainesville, Fl
7.	J. Michael Maloney, M.D.	007/Denver, CO
8.	Christopher G. Nelson, M.D.	008/St. Petersburg, FL
9.	Jerold Powers, M.D.	009/Scottsdale, AZ
10.	Toni Funicella, M.D.	010/Austin, TX
11.	Terry M. Jones, M.D.	011/Bryan, TX
12.	Jeffrey K. Moore, M.D.	012/Evansville, IN
13.	Virginia Fiedler, M.D.	013/Chicago, IL 60612
14.	Neil Shear, M.D.	017/Toronto, Ont./Canada

9.2.1.1 Objective/Rationale

The objective of this study was to evaluate the efficacy and safety of BMS-181158/BMS-181159 - W1133-M-08-B (2% 4-hydroxyanisole/0.01% tretinoin) solution as a depigmenting agent in the treatment of solar lentigines when administered topically twice daily for up to 24 weeks.

Reviewer's Comment: *This formulation, W1133-M-08-B, is not the to be marketed formulation, which is W1133-M-08-A. Formulation W1133-08-B has a [redacted] overage of tretinoin and W1133-M-08-A has a [redacted] overage of tretinoin. The USP allows up to 30% overages for topical tretinoin solutions. The solutions are otherwise identical in every respect.*

9.2.1.2 Design

This was a multi-center, randomized, parallel-group, double-blind study of BMS-181158/BMS-181159 (4HA/tretinoin) versus 0.01% tretinoin alone, 2% 4-hydroxyanisole (4HA) alone, and vehicle in the treatment of solar lentigines[redacted] Subjects were randomized according to a computer-generated code to an unequal distribution of treatments balanced within each investigational site. Study medications were assigned in a 4:4:2:1 ratio to the 4HA/tretinoin, tretinoin, 4HA, and vehicle groups, respectively.

9.2.1.3 Protocol

A total of 595 subjects were enrolled at 14 study sites: 217 subjects each in the 4HA/tretinoin and tretinoin treatment groups, 106 in the 4HA group and 55 in the vehicle group. Patients were instructed to apply the study medication twice a day, for up to 24 weeks, followed by a 24 week no treatment observation phase. Clinical observations were performed at Weeks 0, 1,4, 8, 12, 16, 20, 24, 28, 36, and 48.

Inclusion and exclusion criteria were as follows:

Inclusion Criteria:

Completion of informed consent process
30 years of age or older
Were willing and able to apply study medication as directed, comply with study instructions, including use of ONLY Moisturel® Lotion as an emollient on the face and arms, and commit to all follow-up visits for the duration of the study.
Women of non-childbearing capacity were to be surgically sterile or post-menopausal by history. Post menopausal was defined as: at least 6 months since last menstrual period. All women were required to have a negative pregnancy test at entry and every visit.
Good general health and free of any disease state or physical condition (e.g. tan, skin conditions, hair, scars) which might have impaired evaluations of the test sites or increased the risk to the subject by study participation.
Clinical diagnosis of solar lentigines of at least Grade 6 (moderately darker than surrounding skin), involving the dorsal forearm and the forehead or cheek area on the face.
The lentigines present in each treatment area were defined as circumscribed macular lesions with even-brown pigmentation with regular margins, located in a sun-exposed area. The lentigines were not macroscopically hyperkeratotic, therefore, clinically not seborrheic keratoses or actinic keratoses.
The lentigines present in each treated area were surrounded by a sufficient amount of normally pigmented skin in order to adequately assess the change in pigment of the lesions.
Each forearm, including the dorsal hand, had a least 5 solar lentigines (6 if one was designated as a biopsy site). One of the forearm lesions, was at least 5 mm in length, and was designated the target lesion (biopsy lesion sites were at least 8 mm in length). The facial treatment area (EXCLUDING OCULAR AREA) had at least 3 solar lentigines, one of which was at least 5 mm in length, and was designated the target lesion.
Were willing to avoid sun-exposure, as much as possible, for the entire treatment and post-treatment periods. Treated areas were always to be covered with clothing or shielded from the sun (hat, scarf, long-sleeved clothing).

Skin Types I, II, III, IV, V

Exclusion Criteria:

History of sensitivity to any of the ingredients in the formulations.
Participation in an investigational study at enrollment or within the previous four weeks, or previous participation in DE132-002 or -004 investigation studies.
Pregnant or nursing mother, or woman of childbearing capacity.
Use of topical steroids or other topical medications (including retinoids) on the forearms and face within 4 weeks before enrollment or during study, or systemic steroids or retinoids within 8 weeks before enrollment or during the study.
History of skin cancer.
Use of other depigmenting products (e.g. hydroquinone) within 6 months before enrollment.
Recreational and/or occupational exposure to hydroquinone or hydroquinone-derivative containing products (e.g. photographic developer, industrial cleaning solutions).

Procedures and Observations

Subjects were not allowed to apply any topical steroids or other topical products on the designated treatment sites during the course of the study. Non-medicated soaps and shampoos were allowed. Non-excluded over-the-counter and prescribed medications were allowed as required, but the name of the medications and their purpose was recorded on the Previous and Concomitant Medications form. An Adverse Event form was completed for any condition requiring new medication started during the study. Sunscreens, sunscreen-containing cosmetics, tanning accelerators and moisturizers were not allowed on the designated treatment sites throughout the treatment or follow-up phases of the study. Moisturel® Lotion was the only emollient allowed on the treatment sites during the treatment and post-treatment phases of the study.

Subjects were entered into the study solely on the basis of a clinical examination and medical history taken at the Week 0 visit by a physician/investigator experienced in dermatology.

Subjects were instructed to apply the study medication twice daily to individual lesions within the treatment areas using the wand applicator provided. The medication was to be applied in the morning and evening at least 8 hours apart. The subjects were told not to shower or bathe the treatment areas for at least six hours after an application. The first application was made under the supervision of the investigator or the study staff. After use, the bottles were to be kept in the carton and protected from light. Moisturel Lotion was permitted to be applied 30 minutes after the study medication application.

During the treatment phase (visits 1-8), the investigator or designee completed the following procedures:

Obtained clinical evaluations, standardized photographs (if specified), pregnancy

test (all women subjects) and collected laboratory specimens as indicated.
At the Week 24 visit (or earlier if the pigmentation level equivalent to the normal untreated surrounding skin has been achieved for both ARM and FACE treatment areas), collected the study medication(s).
At the Week 24 visit (or earlier of the pigmentation level equivalent to the normal, untreated surrounding skin has been achieved for both ARM and FACE treatment areas), provided the Subject Self-Assessment Questionnaire to the subject to complete, date and sign the form, and return it to the study coordinator.
At the Week 24 visit (or earlier of the pigmentation level equivalent ot the normal, untreated surrounding skin has been achieved for both ARM and FACE treatment areas), obtained biopsy of treated lesion from selected subjects at designated study centers.

During the post-treatment phase (visits 9-11), the investigator or designee completed the following procedures:

Performed clinical evaluations, standardized photography (if specified), pregnancy test (all women subjects) and collected laboratory specimens. Post-treatment visits occurred at Weeks 28, 36, and 48, unless the treatment phase for a treatment area was discontinued prior to Week 24. In this case, the post-treatment visits was scheduled at 4, 12 and 24 weeks **AFTER** the treatment phase was discontinued for that area(s).
At the Week 48 visit, provided the Subject Self-Assessment Questionnaire to the subject. The subject was requested to complete the questionnaire, date and sign the form, and return it to the study coordinator.
At Week 48 visit, obtained biopsy specimen of treated lesion from selected subjects at designated study centers.

NOTE: The two treatment areas (forearm/hands and face) may have had separately scheduled post-treatment phase visits if one treatment area had reached adequate depigmentation before the other treatment area.

9.2.1.3.1 Population

The population was comprised of healthy adults, 30 years of age and older, both genders, (excluding women of childbearing potential) of Skin Types I, II, III, IV, and V.

9.2.1.3.2 Endpoints

Primary Efficacy Variables:

Physician's Global Assessment (performed at every visit except Visit 1)

Subject Self-Assessment Questionnaire (completed at end of treatment and end of follow-up)
The primary efficacy time point is the end of treatment.

Efficacy Measures

The Physician's Global Assessment, a primary response measure, was performed at each post-baseline visit using a 7-point scale for both face and arms (includes both dorsal forearms and backs of both hands). When performing the Physician's Global Assessment, investigators were to consider the subject's extent of improvement or worsening at each visit compared to the subject's condition at Week 0. Baseline photographs were used to assist the investigators in making this assessment. The following descriptors for each point were used:

Physician's Global Assessment Scale

Score	Characteristic	Description
0	Clear	No evidence of hyperpigmentation, 100% improvement.
1	Almost Clear	Very significant clearance (about 90%). Only minor evidence of hyperpigmentation remains.
2	Marked Improvement	Significant improvement (about 75%); some evidence of hyperpigmentation remains.
3	Moderate Improvement	Intermediate between slight and marked improvement; about 50% improvement in appearance of hyperpigmentation
4	Slight Improvement	Some improvement (about 25%); however, significant evidence of hyperpigmentation remains.
5	No Improvement	Hyperpigmentation condition has not changed.
6	Worse	Hyperpigmentation is worse than at week 0 (visit 1).

The subject Self-Assessment Questionnaire, also a primary response measure, was completed at the end of treatment and the end of post-treatment (visit 8, week 24 and visit 11, week 48).

Each subject evaluated the improvement/worsening of the treated sites at end of treatment and end of follow-up. These assessments were done separately for the face, forearms, and backs of hands. The subjects were instructed to think back to how the areas they treated with the medication (face, forearms, back of hands) looked before they began treatment. The subjects were to respond to two questions.

1) How would you rate the overall appearance of your face, both forearms, and backs of your hands compared to when you started treatment?

0-completely improved
1-mostly improved
2-slightly improved
3-no improvement
4-worse

2) How do you compare the color of the brown spots that you were treating on your face, both of your forearms and the backs of your hands, to when you started treatment?

0-completely lightened
1-much lighter
2-slightly lighter
3-no change
4-darker

The Subject Self-Assessment Questionnaire was added as a response measure at the request of the U.S. Food and Drug Administration (FDA) after initiation of the study and its use could not be implemented until IRB approvals (Amendment and Informed Consent) were obtained. The delay in receiving IRB approvals allowed only 256 (43%) subjects in the evaluable population to complete the questionnaire at the end of treatment. Therefore, the data reflect an incomplete dataset for the end of treatment responses.

Reviewer's Comment: In this study, the primary efficacy endpoint will be the physician's global assessment, as less than 50% of patients completed the self- assessment questionnaire for the reasons discussed above. ~~The primary efficacy time point was not delineated in the submission, however, the statistician and this reviewer determined that "end of treatment"~~ would be the time point in which to evaluate success as this time point (24 weeks) was not variable across pivotal studies.

Secondary Efficacy Variables:

Physician's Assessment of Overall Cosmetic Effect (performed at every visit ~~except Visit 1)~~
Target Lesion Pigmentation rating (performed at every visit)

Efficacy Measures:

The characteristic of target lesion pigmentation was assessed using the 9-point bipolar ordinal scales listed in the following table.

Score	Description
0	Extremely lighter than pigment of surrounding skin (completely depigmented)
1	Markedly lighter than pigment of surrounding skin
2	Moderately lighter than pigment of surrounding skin
3	Slightly lighter than pigment of surrounding skin
4	Equal with pigment of surrounding skin
5	Slightly darker than pigment of surrounding skin
6	Moderately darker than pigment of surrounding skin
7	Markedly darker than pigment of surrounding skin
8	Extremely darker than pigment of surrounding skin

The target lesion pigmentation characteristic was evaluated by the investigator's examination of the target lesion in each treatment area and graded using an integer from 0-8. Evaluations were conducted at each of 11 visits. Each investigator was instructed to consider the condition at all treated sites at the time of the evaluation in relation to his knowledge of the disease, not in relation to evaluation of the subject at a previous visit.

The Physician's Assessment of Overall Cosmetic Effect was performed at each post-baseline visit using a 7-point scale.

When performing the Physician's Assessment of Overall Cosmetic Effect, the investigators were to compare the treatment site to the cosmetic appearance at Visit 1 (week 0). Baseline photographs were used to assist the investigators in making the evaluations. These ratings were to take into account the mix of pigmentation of the treated lesions and the surrounding, untreated skin.

The following descriptors for each point were used:

Score	Description
0	Completely clear of undesired pigment; no evidence of cosmetic deficit remaining; 100% improvement.
1	Very significant clearance of undesired pigment; minimal evidence of cosmetic deficit remaining; about 90% improvement.
2	Significant clearance of undesired pigment; slight evidence of cosmetic deficit remaining; about 75% improvement
3	Moderate clearance of undesired pigment; moderate evidence of cosmetic deficit remaining; about 50% improvement.
4	Slight clearance of undesired pigment; marked evidence of cosmetic deficit remaining; about 25% improvement.
5	No change in cosmetic appearance from Week 0 (visit 1).
6	Cosmetic appearance worse than at Week 0 (visit 1).

Safety Measures

Clinical Measures

Adverse events were sought at any time from the first application at the Week 0 visit through the completion of the study. These were volunteered by the subject or observed or elicited by the investigator or study staff. Darkening of the hyperpigmented condition (global grade=worse) was recorded as an adverse event. Worsening of the Physician's Assessment of Overall Cosmetic Effect was also recorded as an adverse event.

Lists of potential adverse clinical events reported to be associated with topical tretinoin (Retin-A®), and topical 4-hydroxyanisole use were provided to the investigator in the body of the protocol and in the Investigators' Brochure for 4HA/tretinoin. They were also provided in summary to the subjects in the consent forms they signed, copies of which they were given.

Laboratory Safety Measures

All study sites collected laboratory safety data on blood and urine specimens from all subjects at Weeks 0, 1, 4, 16, 24 (or end of treatment) and 48 (or 24 weeks after end of treatment). These included serum chemistries, hematology, and urinalysis. Pregnancy testing was done every four weeks until the end of the study.

Electron Microscopic Analysis

Biopsy specimens were taken from selected subjects at designated centers at baseline, end

of treatment, and end of follow-up. Two millimeter punch biopsy specimens were taken from a chosen forearm lesion of at least 8mm in length. Melanocyte morphology was assessed by the description of the shape of the outer membrane of melanocytes, presence or absence of non-pigmented melanosomes, size (in microns) of the melanosomes and a description of the shape of the organelles in the melanocytes. The assessment also included a description on the clustering of the melanosomes' presence and size (in microns) of the melanocyte dendritic processes, and the clustering of melanin in the keratinocytes.

9.2.1.3.3 Statistical considerations

Efficacy analyses were performed on both the Intent-to-Treat and Evaluable subject groups. The primary response measure initially was the Physician's Assessment of Overall Cosmetic Effect dichotomized into "success": (≥moderate improvement) and "failure" (< moderate improvement). However, after the inception of the study as requested by the U.S. FDA, the Physician's Global Assessment and Subjects' Self-Assessment Questionnaire replaced the Physician's Assessment of Overall Cosmetic Effect as the primary response measures. The Physician's Global Assessment and Physician's Assessment of Overall Cosmetic Effect were evaluated separately on the face and forearms/back of hands at each post-baseline visit. The Self-Assessment Questionnaire was completed at the end of the treatment phase and again at the last follow-up visit for evaluation of the overall appearance of the face, forearms, and back of the hands, separately.

Differences among treatment groups in the dichotomized "Physician's Assessment of Overall Cosmetic Effect" were analyzed by a weighted least squares categorical analysis (SAS-PROC CATMOD) using the Wald statistic. Within this analysis, contrasts were undertaken comparing 4HA/tretinoin separately against each of its components i.e., tretinoin, 4HA and vehicle.

The ordinally scaled measures (i.e., Physicians' Global Assessment, Target Lesion Pigmentation and the Subject Self Assessment Questionnaire) underwent rank transformation and were analyzed by an analysis of variance and contrasts undertaken between 4HA/tretinoin and its components.

Statistical analyses for efficacy parameters were performed at baseline, end of treatment, and at scheduled post-treatment periods.

Time to the pigmentation level becoming equivalent to normal, untreated surrounding skin was evaluated by a non-parametric survival analysis using the Gehan-Wilcoxon Statistic.

Safety analyses were performed on the Intent-to-Treat population. Nonparametric survival analysis using the modified Wilcoxon test was performed to test for differences among treatments in elapsed time of onset and frequency of skin-related adverse events.

9.2.1.4 Results

9.2.1.4.1 Populations enrolled/analyzed

Five hundred and ninety-five (595) subjects were enrolled at 14 investigational sites. Five hundred ninety-four (594) subjects were evaluable at baseline for at least one treatment area

(arm or face). Four hundred eighty-seven (82%) subjects completed the 24 week treatment phase of the study and four hundred and seventy-six (80%) subjects completed the full 48 weeks of the study with demographics as follows in Table 2:

Table 2
Demographic Characteristics
(Evaluable Subjects)

Parameter	Treatment			
	4HA/Tretinoin	Tretinoin	4HA	Vehicle
No. of Subjects	217	217	106	54
Sex (%M/F)*	20/80	20/80	12/88	13/87
Race (%W/B/O)**	98/0/2	98/0/2	98/0/2	96/0/4
Mean Age (range - years)	62.2 (37-85)	63.5 (34-84)	61.8 (39-85)	61.8 (38-76)
Skin Type				
I	21(10%)	15 (7%)	9 (8%)	3 (8%)
II	50 (23%)	62 (29%)	40 (38%)	12 (22%)
III	96 (44%)	87 (40%)	42 (40%)	29 (54%)
IV	46 (21%)	48 (22%)	14 (13%)	9 (17%)
V	4 (2%)	5 (2%)	1 (1%)	1 (2%)

*M/F: Male/Female
**W/B/O: White/Black/Other

One hundred nineteen (119) subjects discontinued for the following reasons listed in Table 3:

Table 3
Reason for Subject Withdrawals

Reason	4HA/Tretinoin n = 217	Tretinoin n = 217	4HA n = 106	Vehicle n = 55	Total n = 595
Voluntary Withdrawal+	14 (6%)	15 (7%)	12 (11%)	4 (7%)	45 (8%)
Non-Compliance	5 (2%)	5 (2%)	4 (4%)	2 (4%)	16 (3%)
Adverse Event*	17 (8%)	18 (8%)	4 (4%)	3 (5%)	42 (7%)
Lost to Follow-up	5 (2%)	7 (3%)	4 (4%)	0 (0%)	16 (3%)
Total	41(19%)	45 (21%)	24 (23%)	9 (16%)	119 (20%)

+Includes three subjects (#150 from the 4HA/tretinoin treatment group, #306 from the tretinoin treatment group, #128 from the 4HA treatment group) who withdrew from the study claiming lack of efficacy.
*Includes 12 subjects with adverse events that required steroid treatment (an additional 9 subjects received steroid treatment, but are recorded as non-compliance).

Table 4
Distribution of Target Lesion Pigmentation - Baseline Site - Arm
Evaluable Subjects

	Treatment								TOTAL	
	4HA/TRET		TRETINOIN		4HA		VEHICLE			
	N	PCTN	N	PCTN	N	PCTN	N	PCTN	N	PCTN
Target Lesional Pigmentation										
Extremely lighter	0	0	0	0	0	0	0	0	0	0
Markedly lighter	0	0	0	0	0	0	0	0	0	0
Moderately lighter	0	0	0	0	0	0	0	0	0	0
Slightly lighter	0	0	0	0	0	0	0	0	0	
Equal pigment	0	0	0	0	0	0	0	0	0	0
Slightly darker	0	0	0	0	0	0	0	0	0	0
Moderately darker	109	50.2	99	45.6	62	58.5	30	55.6	300	50.5
Markedly darker	90	41.5	101	46.5	34	32.1	17	31.5	242	40.7
Extremely darker	18	8.3	17	7.8	10	9.4	7	13.0	52	8.8
Total	217	100.0	217	100.0	106	100.0	54	100.0	594	100.0

Table 5
Distribution of Target Lesion Pigmentation - Baseline Site - Face
Evaluable Subjects

	Treatment								TOTAL	
	4HA/TRET		TRETINOIN		4HA		VEHICLE			
	N	PCTN	N	PCTN	N	PCTN	N	PCTN	N	PCTN
Target Lesional Pigmentation										
Extremely lighter	0	0	0	0	0	0	0	0	0	0
Markedly lighter	0	0	0	0	0	0	0	0	0	0
Moderately lighter	0	0	0	0	0	0	0	0	0	0
Slightly lighter	0	0	0	0	0	0	0	0	0	0
Equal pigment	0	0	0	0	0	0	0	0	0	0
Slightly darker	0	0	0	0	0	0	0	0	0	0
Moderately darker	172	79.6	159	73.6	82	78.1	38	70.4	451	76.3
Markedly darker	37	17.1	48	22.2	19	18.1	14	25.9	118	20.0
emely darker	7	3.2	9	4.2	4	3.8	2	3.7	22	3.7
l	216	100.0	216	100.0	105	100.0	54	100.0	591	100.

9.2.1.4.2 Efficacy endpoint outcomes

The primary endpoint of the Physician's Global Assessment for the arms and the face at treatment cessation for the evaluable data set demonstrated that 4HA/tretinoin was statistically superior over each of its active components and vehicle. On the arm, 52%, 35%, 24%, and 17% of subjects treated with 4HA/tretinoin, tretinoin, 4HA, and the vehicle, respectively, had at least moderate improvement ($p<0.001$ for the component arms). For the face, 56%, 43%, 33%, and 19% of subjects treated with 4HA/tretinoin, tretinoin, 4HA, and the vehicle, respectively, showed moderate improvement or better ($p=0.006$ for the tretinoin arm, and $p<0.001$ for the 4HA and vehicle arms).

Tables 6 and 7 show the distribution of the physician global assessment for the end of treatment for the arm and face. Table 8 will show the success rate in Physician's Global Assessment for the arm and face.

Table 6
Distribution of Physician Global Assessment
End of Treatment - Site - Arm
Evaluable Subjects

	Treatment								Total	
	4HA/Tret		Tretinoin		4HA		Vehicle			
	N	PCTN	N	PCTN	N	PCTN	N	PCTN	N	PCTN
Physician Global Assessment										
Completely clear	4	1.9	2	0.9	0	0	0	0	6	1.0
Almost clear	8	3.8	3	1.4	0	0	0	0	11	1.9
Marked improvement	26	12.3	16	7.5	6	5.7	0	0	48	8.2
Moderate	72	34.0	54	25.4	19	18.1	9	17.0	154	26.4
Slight improvement	51	24.1	71	33.3	35	33.3	14	26.4	171	29.3
No change	50	23.6	67	31.5	45	42.9	30	56.6	192	32.9
Worse	1	0.5	0	0	0	0	0	0	1	0.2
Total	212	100.0	213	100.0	105	100.0	53	100.0	583	100.0
			p=0.0008		p=0.0001		p=0.0001			

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Table 7
Distribution of Physician Global Assessment
End of Treatment - Site - Face
Evaluable Subjects

	Treatment								Total	
	4HA/Tretinoin		Tretinoin		4HA		Vehicle			
	N	PCTN	N	PCTN	N	PCTN	N	PCTN	N	PCTN
Physician Global Assessment										
Completely clear	5	2.4	2	0.9	3	2.9	0	0	10	1.7
Almost clear	18	8.5	11	5.2	1	1.0	0	0	30	5.2
Marked improvement	36	17.0	27	12.7	8	7.7	1	1.9	72	12.4
Moderate improvement	60	28.3	51	24.1	22	21.2	9	17.0	142	24.4
Slight improvement	58	27.4	68	32.1	28	26.9	13	24.5	167	28.7
No change	35	16.5	53	25.0	42	40.4	30	56.6	160	27.5
Worse	0	0	0	0	0	0	0	0	0	0
Total	212	100.0	212	100.0	104	100.0	53	100.0	581	100.0
			p=0.0017		p=0.0001		p=0.0001			

Table 8
Success Rate in Physician's Global Assessment
(Percent of Subjects with Moderate or Greater Improvement at End of Treatment)
Evaluable Subjects

Treatment Site	Treatment			
	4HA/Tretinoin	Tretinoin	4HA	Vehicle
Arm	n=212 110(52%)	n=213 75 (35%) p<0.001	n=105 25 (24%) p<0.001	n=53 9 (17%) p<0.001
Face	n=212 119 (56%)	n=212 91 (43%) p=0.006	n=104 34 (33%) p<0.001	n=53 10 (19%) p<0.001

The intent-to-treat (ITT) population results were very similar for the success rate in the physician's global assessment as demonstrated in Table 9.

Table 9
Success Rate in Physician's Global Assessment
(Percent of Subjects with Moderate or Greater Improvement at End of Treatment)
ITT Population

Treatment Site	Treatment			
	4HA/Tretinoin	Tretinoin	4HA	Vehicle
Arm	n=213 115 (54%)	n=214 76 (36%) p=0.001	n=105 25 (24%) p=0.001	n=54 9 (17%) p=0.001
Face	n=213 122 (57%)	n=214 92 (43%) p=0.003	n=105 35 (33%) p=0.001	n=54 10 (19%) p=0.001

Patients were followed after treatment for 24 weeks and during this post-treatment phase, 4HA/tretinoin continued to demonstrate statistically significant superiority to each of its active components and vehicle for the Physician's Global Assessment ($p \leq 0.0033$ in the all-category analysis and $p \leq 0.01$ in the dichotomized outcome analysis). Table 10 presents the success rate at the end of follow-up.

Table 10
Success Rate in Physician's Global Assessment
(Percent of Subjects with Moderate or Greater Improvement at End of Follow-up)
Evaluable Subjects

Treatment Site	Treatment			
	4HA/Tretinoin	Tretinoin	4HA	Vehicle
Arm	n=167 64(38%)	n=164 39 (24%) p=0.002	n=78 18 (23%) p=0.008	n=45 4 (9%) 9<0.001
Face	n=170 87 (51%)	n=165 64 (39%) p=0.01	n=78 22 (28%) p<0.001	n=45 8 (18%) p<0.001

The secondary efficacy endpoint, target lesion pigmentation, supports the claim that 4HA/tretinoin is significantly superior ($p \leq 0.0197$) over both its active components and vehicle on both the arm and face at the end of treatment. Fifty-three percent, 46%, 33%, and 21% of subjects treated on the arm with 4HA/tretinoin, tretinoin, 4HA, and the vehicle, respectively, demonstrated slightly darker to equal pigmentation relative to surrounding skin. For the face, 66%, 58%, 54%, and 36% of subjects treated with 4HA/tretinoin, tretinoin, 4HA, and the

vehicle, respectively, had slightly darker to equal pigmentation compared to surrounding skin. Tables 11 and 12 present the data which can be compared to the baseline data in tables 4 and 5.

Table 11
Distribution of Target Lesion Pigmentation - End of Treatment - Arm
Evaluable Subjects

	Treatment								TOTAL	
	4HA/TRET		TRETINOIN		4HA		VEHICLE			
	N	PCTN	N	PCTN	N	PCTN	N	PCTN	N	PCTN
Target Lesional Pigmentation										
Extremely lighter	0	0	0	0	0	0	0	0	0	0
Markedly lighter	0	0	0	0	0	0	0	0	0	0
Moderately lighter	1	0.5	0	0	0	0	0	0	1	0.2
Slightly lighter	0	0	0	0	0	0	0	0	0	0
Equal pigment	17	8.0	8	3.8	3	2.9	0	0	28	4.8
Slightly darker	95	44.8	90	42.3	32	30.5	11	20.8	228	39.1
Moderately darker	73	32.4	72	33.8	51	48.6	25	47.2	221	37.9
Markedly darker	18	8.5	34	16.0	13	12.4	15	28.3	80	13.7
Extremely darker	8	3.8	9	4.2	6	5.7	2	3.8	25	4.3
Total	212	100.0	213	100.0	105	100.0	53	100.0	583	100.0
p-value			0.0197		0.0006		0.0001			

Table 12
Distribution of Target Lesion Pigmentation - End of Treatment - Face
Evaluable Subjects

	Treatment								TOTAL	
	4HA/TRET		TRETINOIN		4HA		VEHICLE			
	N	PCTN	N	PCTN	N	PCTN	N	PCTN	N	PCTN
Target Lesional Pigmentation										
Extremely lighter	0	0	0	0	0	0	0	0	0	0
Markedly lighter	0	0	0	0	0	0	0	0	0	0
Moderately lighter	0	0	0	0	0	0	0	0	0	0
Slightly lighter	0	0	0	0	0	0	0	0	0	0
Equal pigment	26	12.3	15	7.1	5	4.8	0	0	46	7.9
Slightly darker	113	53.3	107	50.5	51	49.0	19	35.8	290	49.9
Moderately darker	61	28.8	66	31.1	35	33.7	23	43.4	185	31.8
Markedly darker	10	4.7	22	10.4	9	8.7	9	17.0	50	8.6
Extremely darker	2	0.9	2	0.9	4	3.8	2	3.8	10	1.7
Total	212	100.0	212	100.0	104	100.0	53	100.0	581	100.0
ue			0.0173		0.0056		0.0001			

The Subject Self-Assessment Questionnaire will not be used as a primary efficacy endpoint in this study as it was incorporated after a substantial number of subjects had completed the treatment phase of the study. Of the subjects enrolled in the study 256 of 594 (43%) were able to complete the questionnaire at the end of the treatment phase. Although only 43% of the patient population were able to complete this phase, it is interesting to note that 4HA/tretinoin was not statistically significantly better than tretinoin for all 6 questions. Table 13 presents the results.

Table 13
Success Rates for Subject Self-Assessment at End of Treatment
P-values for 4HA/tretinoin over Individual Components
Evaluable Subjects

Parameter	Treatment			
	4HA/tretinoin	Tretinoin	4HA	Vehicle
Overall Appearance Face	n=97	n=94 p=0.946	n=39 p=0.017	n=26 p=0.024
	40 (41%)*	40 (43%)	8 (21%)	4 (15%)
Overall Appearance Forearms	n=92	n=90 p=0.319	n=39 p=0.876	n=25 p=0.712
	19 (21%)	25 (28%)	8 (21%)	4 (16%)
Overall Appearance Hands	n=96	n=92 p=0.908	n=39 p=0.1	n=26 0.026
	29 (30%)	28 (30%)	7 (18%)	2 (8%)
Brown Spots on Face	n=97	n=94 p=0.554	n=39 p=0.171	n=26 p=0.093
	38 (39%)	34 (36%)	11 (28%)	5 (19%)
Brown Spots on Forearms	n=92	n=90 p=0.955	n=39 p=0.426	n=25 p=0.265
	26 (28%)	26 (29%)	9 (23%)	4 (16%)
Brown Spots on Hands	n=96	n=92 p=0.847	n=39 p=0.027	n=26 p=0.17
	29 (30%)	30 (33%)	5 (13%)	4 (15%)

*The number and percent (%) of subjects who rated themselves completely or mostly improved (Overall Appearance) and completely or much lighter (Brown Spots)

For the secondary efficacy variable, Physician's Assessment of Overall Cosmetic Effect, 4HA/tretinoin was also statistically significantly better than each of its active components and vehicle for both the arm and face at end of treatment ($p \leq 0.0043$).

In the ITT population for the secondary efficacy parameter of Target Lesion Pigmentation, 4HA/tretinoin again showed significant superiority ($p \leq 0.008$) over both its active components and vehicle, on both the arm and face at the end of treatment.

A separate analysis was undertaken to explore pigmentation changes that occurred at treatment sites after discontinuation of therapy. The primary emphasis of the evaluation was to determine the degree of repigmentation that resulted when treatment was stopped.

There was evidence of repigmentation of the target sites at the end of regression (24 weeks) for the two treatments. For the 4HA/tretinoin and tretinoin groups, 37% and 35% of subjects, respectively , showed signs of repigmentation on the arm. Occurrence of repigmentation of target lesions on the face was not as high, with 16% and 23% of subjects showing signs of repigmentation in the 4HA/tretinoin and tretinoin groups, respectively. In contrast, only a small percentage of subjects in the two treatment groups continued to show signs of depigmentation at the end of regression (7% arms and 14% face for 4HA/tretinoin and 3% arms and 5% face for tretinoin). Although the numbers of subjects in the 4HA and vehicle groups are smaller, the pattern of target lesion pigmentary changes in the subset who improved while on treatment is consistent with that noted for the two most active treatment groups.

Electron Microscopic Analysis

Biopsy specimens were taken from selected subjects at designated study sites at baseline, end of treatment, and end of regression. A total of 67 subjects who had a forearm lesion of at least 8 mm in length elected to participate in this portion of the study. Twenty-six (12%) were from the tretinoin group alone, 22 (10%) were from the 4HA/tretinoin group, 11 (10%) were from the 4HA alone group and 8 (15%) were from the vehicle group. Two millimeter punch biopsy specimens were taken from the designated forearm lesion and processed for evaluation by electron microscopy. Melanocyte morphology was assessed by the description of the size (in microns) and shape of the melanocytes, a description of the shape of the outer membrane of melanocytes, presence or absence of nonpigmented melanosomes, size (in microns) of the melanosomes, and description of the shape of the organelles in the melanocytes. The assessment also included a description of the clustering of the melanocytes, presence and size (in microns) of the melanocyte dendritic processes, and the clustering of melanin in the keratinocytes.

Overall, the pathologist's findings showed that vehicle treatment did not show any signs of skin alteration, including changes in melanocytes or keratinocytes. Treatment with 4HA alone did cause some decreased melanin pigmentation which was manifested by alteration of both melanocytes and keratinocytes, including some inflammatory changes. This decrease in melanin pigmentation was manifested by decreased melanosome synthesis by melanocytes, and also decreased melanosome transfer to surrounding keratinocytes. The tretinoin alone treatment also caused decreased pigmentation. Importantly, however, the alteration of melanin pigmentation with tretinoin was considered related to inflammatory changes which also affected changes in surrounding keratinocytes resulting in increased thickening of the epidermis (i.e., acanthosis as well as hypergranulosis). Sometimes, specimens showed hyperkeratosis as well as incontinence of melanin pigmentation. The combination of 4HA/tretinoin appeared to have the most potent depigmentation changes, with effect not only on melanocytes, but also on the surrounding keratinocytes. It was hypothesized by the pathologist that the decrease in melanin pigmentation may result in the altered symbiotic relationship between melanocytes and keratinocytes. 4HA/tretinoin, therefore, will affect, to some extent, not only some melanocytes directly but also the surrounding keratinocytes. Whether this is related simply to irritation or some immunological reaction is not certain. However, there was a significant lymphocytic infiltration seen at the end of treatment.

An important finding was observed when the end of regression specimens were compared with end of treatment and pre-treatment specimens. Specimens obtained at the end of regression showed recovery from the depigmentation effect or cellular alteration. Cellular features were similar to the non-treated pre-treatment control specimens. It was concluded from these results that the drug effect seen at the end of treatment is temporary and is a reversible phenomenon.

Subgroup Analysis

The analysis for age differences (≥65 vs <65) in end-of-treatment Physician's Global Assessment revealed no statistically significant age differences ($p \geq 0.121$), and no significant age-treatment interaction ($p \geq 0.712$) on either the arms or the face. The analysis for gender differences at end of treatment in Physician's Global Assessment indicated not statistically significant gender differences ($p \geq 0.097$) or treatment-gender interactions ($p \geq 0.643$) on either the arms or the face. Analysis for race were not performed as only 2% of the subjects were non-Caucasian.

9.2.1.4.3 Safety outcomes

All subjects who received at least one dose of study medication were included in the safety analysis. Five hundred and ninety-five subjects (217 in each of the 4HA/tretinoin and tretinoin groups, 106 in the 4HA group and 55 in the vehicle group) received study medication and were part of the Intent-to-treat population.

The protocol specified twice daily dosing to all solar lentigines, individually, on the forearms, backs of hands, and face for an estimated maximum total body surface area exposed of less than 5%. Subjects were instructed to treat areas until all of the solar lentigines were clear (equal pigment with the surrounding skin) or up to a maximum of 24 weeks. The maximum volume of study medication possible for exposure was 360 ml. Most subjects used one bottle (30ml) or less during each monthly interval.

Following the maximum 24 weeks treatment phase, a 24 week no treatment follow-up phase was specified in the protocol. Subjects were evaluated for duration of effect and adverse events (or resolution dates for previously reported adverse events) at 4, 12, and 24 weeks following the completion of treatment.

Table 14 shows the number of subjects with related and unrelated adverse events. Similar percentages of subjects receiving either 4HA/tretinoin or tretinoin experienced treatment-related adverse events. The percentages of subjects in each of the four treatment groups who experienced non-treatment related adverse events were similar. The percentages are high likely due to the length of the study (48 weeks) and the age of the subject population. 4HA and vehicle were significantly safer than 4HA/tretinoin or tretinoin relative to drug related adverse events ($p=0.001$).

Table 14
DE132-005
Number of Subjects with Related and Unrelated Adverse Events

Treatment	N	Subjects with Related Adverse Events		Subjects with Unrelated Adverse Events	
		n	%	n	%
4HA/Tretinoin	217	130	59.9	164	75.6
Tretinoin	217	131	60.4	155	71.4
4HA	106	21	19.8	83	78.3
Vehicle	55	9	16.4	41	74.5

For the 4HA/tretinoin treatment group there were a total of 797 adverse events reported in 191 of 217 (88%) subjects. Three hundred nine (rate 142) of these adverse events in 130 (60%) subjects were determined to be related to study medication treatment. The most frequently occurring treatment-related adverse events were: erythema, 106 (rate 49); burning/stinging/tingling, 61 (rate 28); desquamation, 43 (rate 20); pruritus, 28 (rate 13); skin irritation, 15 (rate 7); and "halo" hypopigmentation, 15 (rate 7). Rate refers to the number of adverse events per 100 subjects exposed to treatment.

The adverse event frequency for subjects in the tretinoin treatment group was similar to that of the 4HA/tretinoin treatment group with 697 adverse events reported by 184 of 217 (85%) subjects. Three hundred (rate 138) of these adverse events in 131 (60%) subjects were considered to be related to treatment. The most frequently occurring treatment-related adverse events in this group were: erythema, 99 (rate 46); burning/stinging/tingling, 70 (rate 32); desquamation, 38 (rate 18), pruritus, 26 (rate 12), and skin irritation, 15 (rate 7).

The incidence of adverse events reported for the 4HA treatment group was 252 in 83 of 106 (78%) subjects, with 29 (rate 27) of these events in 21 (20%) subjects reported as related to treatment. The most frequently occurring treatment-related adverse events were: burning/stinging/tingling, 11 (rate 10); erythema, 4 (rate 4); desquamation, (rate 4), and pruritus, 4 (rate 4).

The vehicle treatment group reported a total of 116 adverse events in 43 of 55 (78%) subjects, with 10 (rate 18) of these in 9 (16%) subjects determined to be related to treatment. The most frequent adverse event reported in this group was burning/stinging/tingling, 7 (rate 13).

Table 15 delineates the frequency and rate at which adverse events related to treatment occurred for 4HA/tretinoin vs tretinoin.

Table 15
DE132-005
Adverse Events Occurring in At Least 1% of the Patient Population
(Treatment Related)

	4HA/Tretinoin		Tretinoin	
	Frequency	Rate**	Frequency	Rate
Laboratory - Blood Urea Nitrogen*	3	1.4	6	2.9
Skin and Appendages				
Erythema	106	48.8	99	45.6
Burning/Stinging/Tingling	61	28.1	70	32.3
Desquamation	43	19.8	38	17.5
Pruritus	28	12.9	26	12
Irritation Skin	15	6.9	15	6.9
Rash	7	3.2	6	2.8
Halo hypopigmentation	15	6.9	5	2.3
Skin dry	7	3.2	8	3.7
Crusting	5	2.3	8	3.7
Melanosis	3	1.4	5	2.3
Rash/Vesicular/Bullae	5	2.3	5	2.3
Hypopigmentation	4	1.8	2	0.9
Erosion Skin	3	1.4	4	1.8

*Values for the 4HA and vehicle arms were 2 (2.0%) and (1.9%), respectively
**Rate refers to the number of adverse events per 100 subjects exposed to treatment

The number of adverse events related to study treatment which required a dose reduction was identical [69(rate 32)] for the 4HA/tretinoin and tretinoin treatment groups. The 4HA and vehicle treatment groups had no adverse events related to treatment that required a dose reduction. The most common events requiring a dose reduction were erythema, desquamation, burning/stinging/tingling, pruritus, skin irritation, and skin dryness.

The number of adverse events related to study treatment requiring a dose interruption were as follows: 80(rate 37) in the 4HA/tretinoin group, 96 (rate 44) in the tretinoin group, and six (rate 5) in the 4HA group. The vehicle treatment group had no treatment related adverse event that required dose interruption. The most common event requiring a dose interruption for all three treatment groups was erythema (rates of 15.2, 19.8, and 0.9, respectively) followed by burning/stinging/tingling (rates 5.1, 5.5, and 0.0, respectively). Skin irritation was more common in the 4HA/tretinoin group (rate 4.1) whereas desquamation was more common in the tretinoin and 4HA groups (rates 5.5 and 0.9 respectively). Dose interruption or reduction was required for vesicular bullous eruption in both the 4HA/tretinoin group (rate 3.2) and the tretinoin group (rate 1.8).

The number of adverse events related to treatment that required study treatment to be discontinued were 12 (rate 6) for the 4HA/tretinoin group and 12 (rate 6) for the tretinoin group. There were no adverse events related to treatment that required the study treatment to be

discontinued for the 4HA or vehicle groups. The most common adverse events related to treatment that required discontinuation of study medication were pruritus, erythema, and skin irritation. Neither the 4 HA/tretinoin nor the tretinoin group had the drug discontinued for an allergic reaction. Each arm had 1 incident of vesicular/bullous eruption where the drug had to be discontinued (rate 0.5). 4HA/tretinoin also had one event of contact dermatitis (rate 0.5%) where the drug had to be discontinued.

The number of adverse events related to study medication where treatment was required were 16 (rate 7) in the 4HA/tretinoin group and 12 (rate 6) in the tretinoin group. No subject in the 4HA or vehicle group had a treatment-related adverse event that required treatment intervention. The most common event requiring treatment for 4HA/tretinoin and tretinoin was erythema.

Halo hypopigmentation occurred more frequently on the arms than on the face. All 21 subjects who developed this phenomenon had an arm treated site affected. Five of the 21 subjects also had a facial treated site affected (no subject had only a facial treated site affected). In the 4HA/tretinoin treatment group halo hypopigmentation occurred on average about 127 days after the start of treatment (range: [redacted] days) and the duration averaged about 117 days (range: [redacted] days) following treatment discontinuation. In the tretinoin treatment group, halo hypopigmentation occurred at average about 159 days after the start of treatment (range: [redacted] days) and the duration averaged about 94 days (range: [redacted] days) following treatment discontinuation.

The results of the clinical laboratory test analyses did not reveal consistently out-of-range values or treatment-related abnormalities except in the area of blood urea nitrogen where 4 (1.9%) in the 4HA/tretinoin group had a high value. Although the tretinoin arm showed some elevation of the SGPT and SGOT, the 4HA/tretinoin-arm did not have elevations in greater than 1% of the population.

9.2.1.5 Conclusions Regarding Efficacy Data

Study DE132-005 supports the claim that 4HA/tretinoin is statistically significantly superior ($p \leq 0.006$) to both its active components (4HA and tretinoin) and vehicle in the treatment of lentigines on the arm and face in the Physician's Global Assessment at the end of treatment. This finding is supported by the secondary efficacy variables of target lesion pigmentation and physician's overall cosmetic effect. The electron microscopic changes observed in post-treated lesions support that the clinical effect of 4HA/tretinoin, results in reversible histologic changes in melanosome production and transfer.

9.3 Sponsor's protocol # DE132-010 **Title:** "A Double-blind, Parallel Group Comparison of the Efficacy and Safety of BMS-181158/BMS-181159 Solution (2% 4-hydroxyanisole/0.01% tretinoin) versus Individual Active Agents and Vehicle in the Treatment of Solar Lentigines[redacted]