9.3.1 Investigator's

1.	David Pariser, M.D.	002/Norfolk, VA
2.	Leonard Swinyer, M.D.	003/Salt lake City, UT
3.	Anne Lucky, M.D.	004/Cincinnati, OH
4.	Peter Winters, M.D.	005/Indianapolis, IN
5.	Paul Espy, M.D.	006/Marietta, GA
6.	David Rodriguez, M.D.	007/Miami, FL
7.	Daniel Piacquadio, M.D.	008/LaJolla, CA
8.	Manuel R. Morman, Ph.D., M.D.	009/Rutherford, NJ
9.	Alan B. Fleissher, Jr., M.D.	010/Winston-Salem, NC
10.	Ann G. Martin, M.D.	011/St. Louis, MO
11.	Sewon Kang, M.D.	012/Ann Arbor, IL
12.	Bruce H. Thiers, M.D.	013/Charleston, SC
13.	Ross D. Bright, M.D.	014/Palo Alto, CA
14.	Mark Weinstein, M.D.	015/San Antonio, TX
15.	Ernest Ast, M.D.	016/Great Neck, NY
16.	Thomas Nigra, M.D.	017/Washington, DC
17.	Steven R. Hong, M.D.	020/Boulder, CO
18.	Joseph F. Fowler, Jr., M.D.	021/Louisville, KY

9.3.1.1 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.

9.3.1.2 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 frequency 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. Treatments were applied to individual lentigines on the face and forearms/backs of hands twice daily for up to 24 weeks, followed by a 4 week no treatment follow-up phase. Investigators and subjects were blinded to treatments by method of manufacture, identical packaging, and labeling with use of standard three-panel double-blind labels. Clinical observations were performed at Weeks 0, 1, 4, 8, 12, 16, 20, 24, and 28.

9.3.1.3 Protocol

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 a 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 to 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.

9.3.1.3.1 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 with a clinical diagnosis of solar lentigines at least moderately darker than surrounding skin (Grade 6) involving the dorsal forearm/backs of hands and the forehead or cheek area on the face.

9.3.1.3.2 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.

Reviewer's Comment: *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.*

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

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 below.

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.

9.3.1.3.3 Statistical considerations

Efficacy analyses were performed on both the Intent-to-Treat and Evaluable subject groups. The primary response measures were the Physician's Global Assessment and the Subject Self-Assessment Questionnaire. The elevation of these two response measures to primary status was requested by the US FDA. The secondary measures of efficacy were the Physician's Assessment of Overall Cosmetic Effect derived from the Cosmetic Assessment scale by dichotomizing it into "success" (≥moderate improvement) and "failure" (<moderate improvement) and Target Lesion Pigmentation. The Physician's Global Assessment and Physician's Assessment of Overall Cosmetic Effect were evaluated separately on the face and forearm/back of hands at each post-baseline visit. Target Lesion Pigmentation ratings of the face and forearm/back of hands were performed at each visit. The Self-Assessment Questionnaire was completed at the end of treatment phase and again at the 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.

9.3.1.4 Results

9.3.1.4.1 Populations enrolled/analyzed

A total of 580 subjects were enrolled at 18 study sites: 212 subjects in the 4HA/tretinoin group, 210 in the tretinoin group, 105 in the 4HA group and 53 in the vehicle group. Five hundred seventy-nine (579) subjects were evaluable at baseline for at least one treatment area (arm or face). Four hundred-ninety seven (497) subjects completed the 24 week treatment phase of the study and 492 completed the full 28 weeks.

Table 16
Demographic Characteristics
(Evaluable Subjects)

Parameter	Treatment			
	4HA/Tretinoin	Tretinoin	4HA	Vehicle
No. Of Subjects	212	210	104	53
Sex (%M/F)*	15/85	22/78	13/87	9/91
Race (%W/B/O)**	91/0/9	90/0/10	88/0/12	87/2/12
Mean Age (range-years)	63.2 (33-88)	64.2 (40-90)	65.2 (36-82)	62.9 (46-80)
Skin Types				
I	13(6%)	18(9%)	7(7%)	2(4%)
II	68(32%)	46(22%)	27(26%)	14(26%)
III	81(38%)	85(40%)	44(42%)	15(28%)
IV	42(20%)	54(26%)	23(22%)	19(36%)
V	8(4%)	7(3%)	3(3%)	3(6%)

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

Eighty-eight subjects discontinued the study as listed in Table 17 below:

Table 17
DE132-010
Reasons for Subject Discontinuation

Reason	Treatment				
	4HA/Tretinoin n=212	Tretinoin n=210	4HA n=105	Vehicle n=53	Total n=580
Adverse Events	26 (12%)	6 (3%)	5 (5%)	1 (2%)	38 (7%)
Patient Request	11 (5%)	9 (4%)	3 (3%)	1 (2%)	24 (4%)
Lost to Follow-up	3 (1%)	4 (2%)	2 (2%)	2 (4%)	11 (2%)
Non-Compliance	2 (1%)	4 (2%)	2 (2%)	1 (2%)	9 (2%)
Physician's Decision	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	1 (<1%)
Other	2 (1%)	0 (0%)	2 (2%)	1 (2%)	5 (1%)
Total	44 (21%)	24 (11%)	14 (13%)	6 (11%)	88 (15%)

Table 18
Distribution of Target Lesion Pigmentation - Baseline Site - Forearm
Evaluable Subjects

	TREATMENT								Total	
	4HA/Tretinoin		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	147	69.3	138	65.7	70	67.3	33	62.3	388	67.0
Markedly darker	65	30.7	65	31.0	29	27.9	18	34.0	177	30.6
Extremely darker	0	0	7	3.3	5	4.8	2	3.8	14	2.4
Total	212	100.0	210	100.0	104	100.0	53	100.0	579	100.0

Table 19
Distribution of Target Lesion Pigmentation - Baseline Site - Face
Evaluable Subjects

	TREATMENT								Total	
	4HA/Tretinoin		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	181	85.4	178	84.8	78	75.0	44	83.0	481	83.1
Markedly darker	31	14.6	29	13.8	24	23.1	9	17.0	93	16.1
Extremely darker	0	0	3	1.4	2	1.9	0	0	5	0.9
Total	212	100.0	210	100.0	104	100.0	53	100.0	579	100.0

9.3.1.4.2 Efficacy endpoint outcomes

This study had two primary efficacy endpoints, Physician's Global Assessment and the Subject Self-Assessment Questionnaire. The primary endpoint of the Physician's Global Assessment for the arms and face for the evaluable data set demonstrated the 4HA/tretinoin demonstrated significant superiority over each of its active components and vehicle on the arm ($p \leq 0.004$ and $p<0.001$, respectively) at the end of treatment. On the arm, 54%, 39%, 25% and 11% of subjects treated with 4HA/tretinoin, tretinoin, 4HA, and the vehicle, respectively, had at least moderate improvement. On the face, 4HA/tretinoin was significantly superior to 4HA and vehicle ($p=0.0001$) at the end of treatment. The comparison between 4HA/tretinoin and tretinoin on the face was not statistically significant either in the all-category analysis ($p=0.211$) or the dichotomized outcome analysis ($p=0.097$). A higher percentage of subjects in the 4HA/tretinoin group had a moderate improvement or greater compared to the tretinoin group (57% vs 48%). For the face, 57%, 48%, 34%, and 11% of subjects treated with 4HA/tretinoin, tretinoin, 4HA, and the vehicle, respectively, showed moderate improvement or better.

Tables 20 and 21 show the distribution of the physician global assessment for the end of treatment for the arm and face. Table 22 will show the success rate in Physician's Global Assessment for the arm and face.

Table 20
Distribution of Physician Global Assessment
End of Treatment - Site - Arm
Evaluable Subjects

	Treatment								Total	
	4HA/Tretinoin		Tretinoin		4HA		Vehicle			
	N	PCTN	N	PCT	N	PCTN	N	PCTN	N	PCTN
Physician's Global Assessment										
Completely Clear	2	1.0	1	0.5	0	0	0	0	3	0.5
Almost Clear	15	7.2	8	3.9	1	1.0	0	0	24	4.2
Marked Improvement	25	12.0	28	13.5	3	2.9	1	1.9	57	10.0
Moderate	69	33.2	44	21.3	22	21.4	5	9.4	140	24.5
Slight Improvement	61	29.3	85	41.1	48	46.6	19	35.8	213	37.3
No Change	35	16.8	41	19.8	29	282.	28	52.8	133	23.3
Worse	1	0.5	0	0	0	0	0	0	1	0.2
Total	208	100.0	207	100.0	103	100.0	53	100.0	571	100.0
			p=0.0269		p=0.0001		p=0.0001			

Table 21
Distribution of Physician's Global Assessment
End of Treatment - Site - Face
Evaluable Subjects

	Treatment								Total	
	4HA/Tretinoin		Tretinoin		4HA		Vehicle			
	N	PCTN	N	PCTN	N	PCT	N	PCT	N	PCTN
Physician Global Assessment										
Completely Clear	8	3.8	7	3.4	0	0	0	0	15	2.6
Almost Clear	20	9.6	19	9.2	1	1.0	0	0	40	7.0
Marked	32	15.3	26	12.6	8	7.8	2	3.8	68	11.9
Moderate	58	27.8	48	23.2	26	25.2	4	7.5	136	23.8
Slight Improvement	59	28.2	74	35.7	35	34.0	24	45.3	192	33.6
No Change	32	15.3	32	15.5	33	32.0	22	41.5	119	20.8
Worse	0	0	1	0.5	0	0	1	1.9	2	0.3
Total	209	100.0	207	100.0	103	100.0	53	100.0	572	100.0
			p=0.211		p=0.001		p=0.001			

Table 22
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=208 111 (53%)	n=207 81 (39%) p=0.004	n=103 26 (25%) p<0.001	n=53 6 (11%) p<0.001
Face	n=209 118 (57%)	n=207 100 (48%) p=0.097	n=103 35 (34%) p<0.001	n=53 6 (11%) 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 23.

Table 23
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=208 112 (53.8%)	n=208 83 (39.9) p=0.004	n=104 26 (25%) p=0.001	n=53 6 (11.3%) p=0.001
Face	n=209 119 (56.9%)	n=209 103 (49.3) p=0.1	n=104 35 (33.7%) p=0.001	n=53 6 (11.3%) p=0.001

Patients were followed for 4 weeks in this study after cessation of treatment. It was felt by the sponsor that safety had been established in the first pivotal trial (DE132-005) by following the patients for 24 weeks and therefore, a shorter time period for follow-up was all that was necessary in this trial. Continuing with the primary efficacy variable of Physician's Global Assessment, 4HA/tretinoin continued to demonstrate statistical significance over its active components, tretinoin and 4HA, and vehicle for the arm in the evaluable dataset (p=0.02, p=0.0001, and p=0.0001, respectively). However, for the face in the evaluable dataset, statistical significance continued against 4HA and vehicle (p=0.0001 for both) but 4HA/tretinoin did not demonstrate statistical significance versus its active component, tretinoin (p=0.0613).

The ITT population at end of follow-up showed the same trend, with 4HA/tretinoin demonstrating statistical significance over its active components and vehicle for the arm (p=0.0159, p=0.0027, and p=0.0001, respectively) but not demonstrating the same for the face. In the ITT population for the face 4HA/tretinoin was statistically significantly better than 4HA and vehicle (p=0.0027 and p=0.0001, respectively) but not for tretinoin alone (p=0.0159).

It is important to note that for the dichotomized analysis at the end of treatment, 4HA/tretinoin only approached statistical significance for the arm (p=0.067). This suggests expected loss of drug effect over time. Table 24 summarizes the success rate at the end of follow-up for the evaluable patient population.

Table 24
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=164 79 (48%)	n=180 69 (38%) p=0.067	n=93 25 (27%) p<0.001	n=46 6 (13%) p<0.001
Face	n=166 99 (60%)	n=182 93 (51%) p=0.109	n=93 30 (32%) p<0.001	n=47 7 (15%) p<0.001

* 4 weeks after cessation of medication

The Subject Self-Assessment Questionnaire was the other primary efficacy variable and was completed by each subject at the end of the treatment period and again at the end of follow-up. This questionnaire consisted of 6 questions: overall appearance of face, overall appearance of forearms, overall appearance of hands, brown spots on the face, brown spots on the forearms, and brown spots on the hands. Success was based on the top two responses for Overall Appearance (completely or mostly improved) and for Brown Spots (completely or much lighter) at the end of treatment. In the evaluable population, 4HA/tretinoin was statistically significantly superior over 4HA and vehicle for all questions. 4HA/tretinoin was statistically superior to tretinoin on all questions related to the forearm and the hands but it was not statistically significantly better than tretinoin for the overall appearance of the face (p=0.120) or for brown spots on the face (p=0.355). These results are shown in table 25.

Table 25
Subject Self-Assessment Questionnaire at End of Treatment
Evaluable Subjects

Parameter	Treatment			
	4HA/Tretinoin	Tretinoin	4HA	Vehicle
Overall Appearance Face	n=193	n=192 p=0.120	n=94 p<0.001	n=49 p<0.001
	92 (48%)*	76 (40%)	24 (26%)	8 (16%)
Overall Appearance Forearms	n=193	n=195 p=0.001	n=94 p=0.046	n=49 p<0.001
	70 (36%)	40 (21%)	23 (24%)	6 (12%)
Overall Appearance Hands	n=193	n=190 p=0.001	n=94 p=0.018	n=49 p<0.001
	70 (36%)	39 (21%)	21 (22%)	5 (10%)
Brown Spots on Face	n=193	n=192 p=0.355	n=94 p=0.002	n=49 p=0.001
	88 (46%)	78 (41%)	25 (27%)	9 (18%)
Brown Spots on Forearms	n=193	n=195 p=0.020	n=94 p=0.049	n=49 p=0.017
	70(36%)	49 (25%)	23 (24%)	9 (18%)
Brown Spots on Hands	n=194	n=190 p<0.001	n=94 p=0.021	n=49 p=0.001
	72 (37%)	39 (21%)	22 (23%)	6 (12%)

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

The results in the ITT population of the Subject Self-Assessment Questionnaire were very similar to that of the evaluable population. 4HA/tretinoin was rated as significantly superior to 4HA and vehicle across all questions at the end of treatment. However, 4HA/tretinoin was not statistically significantly superior to tretinoin on the face, both for overall appearance and brown spots ($0.14<p<0.5$).

The results in the all-category analysis, as shown in tables 26-31, support the dichotomized outcome analysis above and the other primary efficacy variable, the Physician Global Assessment. Notably, there were not statistically significant differences between 4HA/tretinoin and tretinoin in appearance of the face ($p=.161$) and brown spots on the face ($p=0.453$).

Table 26
Distribution of Forearm Appearance
Evaluable Subjects

	Treatment								ALL	
	4HA/Tretinoin		Tretinoin		4HA		Vehicle			
	N	PCTN	N	PCTN	N	PCTN	N	PCTN	N	PCTN
Appearance Completely	2	1.0	3	1.5	0	0	0	0	5	0.9
Mostly Improved	68	35.2	37	19.0	23	24.5	6	12.2	134	25.2
Slightly Improved	94	48.7	116	59.5	42	44.7	19	38.8	271	51.0
No Improvement	19	9.8	36	18.5	29	30.9	23	46.9	107	20.2
Worse	10	5.2	3	1.5	0	0	1	2.0	14	2.6
All	193	100.0	195	100.0	94	100.0	49	100.0	531	100.0
			p=0.0060		p=0.0030		p=0.0001			

Table 27
Distribution of Facial Appearance
Evaluable Subjects

	Treatment								All	
	4HA/Tretinion		Tretinoin		4HA		Vehicle			
	N	PCTN	N	PCTN	N	PCTN	N	PCTN	N	PCTN
Appearance Completely Improved	6	3.1	3	1.6	2	2.1	0	0	11	2.1
Mostly Improved	86	44.6	73	38.0	22	23.4	8	16.3	189	35.8
Slightly Improved	76	39.4	8;8	45.8	41	43.6	22	44.9	227	43.0
No Improvement	21	10.9	27	14.1	29	30.9	17	34.7	94	17.8
Worse	4	2.1	1	0.5	0	0	2	4.1	7	1.3
All	193	100.0	192	100.0	94	100.0	49	100.0	528	100.0
			p=0.1606		p=0.0001		p=0.0001			

Table 28
Distribution of Hand Appearance
Evaluable Subjects

	Treatment								All	
	4HA/Tretinoin		Tretinoin		4HA		Vehicle			
	N	PCTN	N	PCTN	N	PCTN	N	PCTN	N	PCTN
Appearance										
Completely Improved	3	1.6	0	0	1	1.1	1	2.0	5	1.0
Mostly Improved	67	34.7	39	20.5	20	21.3	4	8.2	130	24.7
Slightly Improved	74	38.3	106	55.8	45	47.9	21	42.9	246	46.8
No Improvement	42	21.8	44	23.2	27	28.7	22	44.9	135	25.7
Worse	7	3.6	1	0.5	1	1.1	1	2.0	10	1.9
All	193	100.0	190	100.0	94	100.0	49	100.0	526	100.0
			p=0.0874		p=0.0631		p=0.0001			

Table 29
Distribution of Brown Spot Appearance on Forearms
Evaluable Subjects

	Treatment								All	
	4HA/Tretinoin		Tretinoin		4HA		Vehicle			
	N	PCTN	N	PCTN	N	PCTN	N	PCTN	N	PCTN
Brown Spots Completely Lightened	4	2.1	3	1.5	2	2.1	1	2.0	10	1.9
Much lighter	66	34.2	46	23.6	21	22.3	8	16.3	141	26.6
Slightly lighter	96	49.7	112	57.4	43	45.7	17	34.7	268	50.5
No change	25	13.0	32	16.4	28	29.8	23	46.9	108	20.3
Darker	2	1.0	2	1.0	0	0	0	0	4	0.8
All	193	100.0	195	100.0	94	100.0	49	100.0	531	100.0
			p=0.0390		p=0.0026		p=0.0001			

Table 30
Distribution of Brown Spot Appearance on Face
Evaluable Subjects

	Treatment								All	
	4HA/Tretinoin		Tretinoin		4HA		Vehicle			
	N	PCTN	N	PCTN	N	PCTN	N	PCTN	N	PCTN
Brown Spots Completely Lightened	14	7.3	10	5.2	4	4.3	1	2.0	29	5.5
Much Lighter	74	38.3	68	35.4	21	22.3	8	16.3	171	32.4
Slightly Lighter	79	40.9	88	45.8	39	41.5	23	46.9	229	43.4
No Change	24	12.4	26	13.5	30	31.9	17	34.7	97	18.4
Darker	2	1.0	0	0	0	0	0	0	2	0.4
All	193	100.0	192	100.0	94	100.0	49	100.0	528	100.0
			p=0.4526		p=0.0001		p=0.0001			

Table 31
Distribution of Brown Spot Appearance on Hands
Evaluable Subjects

	Treatment								All	
	4HA/Tretinoin		Tretinoin		4HA		Vehicle			
	N	PCTN	N	PCTN	N	PCTN	N	PCTN	N	PCTN
Brown Spots Completely Lightened	6	3.1	0	0	3	3.2	1	2.0	10	1.9
Much Lighter	66	34.0	39	20.5	19	20.2	5	10.2	129	24.5
Slightly Lighter	77	39.7	107	56.3	45	47.9	22	44.9	251	47.6
No Change	43	22.2	44	23.2	26	27.7	21	42.9	134	25.4
Darker	2	1.0	0	0	1	1.1	0	0	3	0.6
All	194	100.0	190	100.0	94	100.0	49	100.0	527	100.0
			p=0.0249		p=0.0388		p=0.0002			

For the secondary efficacy parameter of Target Lesion Pigmentation, 4HA/tretinoin showed significant superiority over both of its active components and vehicle on the arm ($p<0.0023$) at the end of treatment. For the face, 4HA/tretinoin was significantly superior to 4HA and vehicle (p=0.0001) at the end of treatment, but not statistically different from tretinoin (p=0.366). Tables 32 and 33 demonstrate the results for the forearm and face, respectively. Data was not available for the ITT population.

Table 32
Distribution of Target Lesion Pigmentation - End of Treatment - Site - Forearm
Evaluable Subjects

	Treatment								Total	
	4HA/Tretinoin		Tretinoin		4HA		Vehicle			
	N	PCTN	N	PCTN	N	PCTN	N	PCTN	N	PCTN
Target Lesion Pigmentation										
Equal Pigment	15	7.2	10	4.9	4	3.9	0	0	29	5.1
Slightly Darker	119	57.2	92	44.9	40	38.8	14	26.4	265	46.6
Moderately Darker	68	32.7	92	44.9	49	47.6	27	50.9	236	41.5
Markedly Darker	6	2.9	11	5.4	7	6.8	12	22.6	36	6.3
Extremely Darker	0	0	0	0	3	2.9	0	0	3	0.5
Total	208	100.0	205	100.0	103	100.0	53	100.0	569	100.0
			p=0.0023		p=0.0001		p=0.0001			

Table 33
Distribution of Target Lesion Pigmentation - End of Treatment - Face
Evaluable Subjects

	Treatment								Total	
	4HA/Tretinoin		Tretinoin		4HA		Vehicle			
	N	PCTN	N	PCTN	N	PCTN	N	PCTN	N	PCTN
Target Lesion Pigmentation										
Equal Pigment	31	14.8	26	12.6	2	1.9	0	0	59	10.3
Slightly Darker	118	56.5	115	55.8	46	44.7	15	28.3	294	51.5
Moderately Darker	58	27.8	60	29.1	49	47.6	32	60.4	199	34.9
Markedly Darker	2	1.0	5	2.4	4	3.9	6	11.3	17	3.0
Extremely Darker	0	0	0	0	2	1.9	0	0	2	0.4
Total	209	100.0	206	100.0	103	100.0	53	100.0	571	100.0
			p=0.3656		p=0.0001		p=0.0001			

For the secondary efficacy parameter of Physician's Assessment of Overall Cosmetic Effect in the evaluable population, 4HA/tretinoin was statistically significantly superior ($p \leq 0.0179$) to each of its active components and vehicle on the arm at the end of treatment.

4HA/tretinoin also demonstrated statistical significance to 4HA and vehicle on the face at the end of treatment. However, 4HA/tretinoin was not statistically significantly superior to tretinoin on the face at the end of treatment (p=0.0829). The ITT population supported this for the face (p=0.1).

Subgroup Analysis

The analysis for age differences (≥65 vs<65) in the end-of-treatment Physician's Global Assessment revealed no statistically significant age differences (p≥1.145), and no significant age-treatment interaction (p≥0.463) on either the arms or the face.

Analysis for differences in race (dichotomized into White and non-White) was performed, even thought only 10% of the subjects were non-White. No statistically significant race (p≥0.466) or race-treatment interactions (p≥0.452) were observed.

For the quantitative measures (skin type and baseline pigmentation), regression analyses were performed regressing the end-of-treatment Physician's Global Assessment on these quantitative measures. The results of the test for equality of slopes were not significant (p≥0.215), permitting a common slope model to be fit. Upon fitting the common slope model, the results indicate no statistically significant linear relationship between any of the quantitative measures and Physician's Global Assessment on either anatomical site (p≥0.349).

9.3.1.4.3 Safety outcomes

All subjects who received at least one dose of study medication were included in the safety analysis. Five hundred and eighty subjects (212 in the 4HA/tretinoin group, 210 in the tretinoin group, 105 in the 4HA group, and 53 in the vehicle group) received study medication and were part of the Intent-to-Treat population.

This protocol is the same as for Study DE132-005 and the reader is referred to section 8.2.1.4.3 for the details. The exception is that this study had only a four week follow-up period instead of 24 weeks.

Table 34 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 (28 weeks) and the age of the subject population. In this study, 4HA and vehicle were statistically significantly safer than either 4HA/tretinoin or tretinoin relative to drug related adverse events (p=0.001).

Table 34
DE132-010
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	212	171	80.7	150	70.8
Tretinoin	210	169	80.5	152	72.4
4HA	105	26	25	80	76.9
Vehicle	53	14	26	40	75.5

For the 4HA/tretinoin treatment group there were a total of 840 adverse events reported in 200 of 212 (94%) subjects. Four hundred twenty-five (51%) of these adverse events in 171 (81%) subjects were determined to be related to study medication treatment. The most frequently occurring treatment-related adverse events were: erythema, 137 (rate 64.6); burning/stinging/tingling, 87 (rate 41); desquamation, 60 (rate 28.3); pruritus, 42 (rate 20); skin irritation 17 (rate 8); and halo hypopigmentation (defined as hypopigmentation of skin surrounding the area of treated solar lentigines, 13 (rate 6.1)

The adverse event frequency for subjects in the tretinoin treatment group was similar to that of the 4HA/tretinoin treatment group with 781 adverse events reported by 194 of 210 (92%) subjects. Three hundred ninety-four (50%) of these adverse events in 169 (80%) subjects were considered to be related to treatment. The most frequently occurring treatment-related adverse events in this group were: erythema, 139 (rate 66.2); burning/stinging/tingling, 86 (rate 41); desquamation, 54 (rate 25.7), pruritus, 35 (rate 16.7), halo hypopigmentation, 11 (rate 5.2).

The incidence of adverse events reported for the 4HA treatment group was 239 in 84 of 105 (80%) subjects, with 42 (rate 40) of these events in 26 subjects reported as related to treatment. The most frequently occurring treatment-related adverse events were: burning/stinging/tingling, 10 (rate 9.5); erythema 9 (rate 8.6); and pruritus, 8 (rate 7.6).

The vehicle treatment group reported a total of 122 adverse events in 42 of 53 (79%) subjects, with 22 (18%) reported in 14 subjects determined to be related to treatment. The most frequent adverse events reported in this group were burning/stinging/tingling, 8 (rate 15.1) and erythema, 5 (rate 9.4).

Table 35
DE132-010
Adverse Events Occurring in At Least 1% of the Patient Population
(Treatment Related)

	4HA/Tretinoin		Tretinoin	
	Frequency	Rate^	Frequency	Rate
Special Senses*	6	2.8	4	1.9
Lab - Blood Urea Nitrogen^^	3	1.7	0	0
Skin & Appendages	413	194.8	386	183.8
Erythema	137	64.6	139	66.2
Burning/Stinging/Tingling	87	41	86	41
Desquamation	60	28.3	54	25.7
Pruritus	42	19.8	35	16.7
Irritation Skin	17	8.0	9	4.3
Rash	9	4.2	8	3.8
Skin Dry	9	4.2	7	3.3
Halo Hypopigmentation	13	6.1	11	5.2
Crusting	7	3.3	10	4.8
Hypopigmentation	10	4.7	5	2.4
Rash, vesicular, bullae	10	4.7	3	1.4
Melanosis	2	0.9	9	4.3
Application Site Reaction**	2	0.9	6	2.9

*Eye pain, lacrimation disorder, conjunctivitis, hemorrhage of the eye, and taste perversion which occurred at a rate of 1.9 in the 4HA and vehicle groups, also. ^ rate equals number of adverse events per 100 subjects
** Considered a contact allergic reaction
^^Values for the 4HA and Vehicle arms were 3 (3.4%) and 0 (0%), respectively

The number of adverse events related to study treatment which required a dose reduction were: 62 (rate 29) in the 4HA/tretinoin and 52 (rate 24) in the tretinoin treatment group. 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, burning/stinging/tingling, desquamation, pruritus, rash, and halo hypopigmentation.

The number of adverse events related to study treatment requiring a dose interruption were as follows: 254 (rate 120) in the 4HA/tretinoin group, 263 (rate 115) in the tretinoin group, and three (rate 2.9) in the 4HA group and five (rate 9.4) in the vehicle group. The most common event requiring a dose interruption for all four treatment groups was erythema. For the 4HA/tretinoin and tretinoin groups the next most common adverse events requiring a dose interruption were burning/stinging/tingling (rate 12.7 and 16.7 respectively), desquamation (rate 114.1 and 11.4 respectively), and pruritus (rate 13.2 and 7.1 respectively). Skin irritation (rate 5.7) followed as the next most frequent adverse event that required a dose interruption for the 4HA/tretinoin group and crusting (rate 4.3) was the next most frequent adverse event for the

tretinoin group.

Twenty-eight subjects (5%) prematurely discontinued the study due to adverse events that were considered related to treatment: 20 (9%) from the 4HA/tretinoin group, 5 (2%) from the tretinoin group, 2 (2%) from the 4HA group, and 1 (2%) from the vehicle group. The actual number of adverse events related to treatment that required study treatment to be discontinued were 68 (rate 32) for the 4HA/tretinoin group and 12 (rate 5.7) for the tretinoin group, 17 (rate 16) for the 4HA group and 4 (rate 7.5) for the vehicle group. For the 4HA/tretinoin group the most common adverse events that required discontinuation of study medication were erythema, pruritus, burning/stinging/tingling and desquamation. For the tretinoin group, the most common adverse events that required discontinuation of study medication were burning/stinging/tingling, and application site reaction. For the 4HA group, the most frequent adverse events that required discontinuation were dry skin and erythema. Statistically, there was a greater percentage of subjects in the 4HA/tretinoin group vs the tretinoin group who discontinued due to drug related adverse events (9% vs 2%, p=0.002).

Halo hypopigmentation occurred more frequently on the arms than on the face. Five of the 27 subjects also had a facial treatment site affected. In the 4HA/tretinoin group, 19 halo hypopigmentation adverse events occurred on average about 90 days after the start of treatment (range: [redacted] days) and the duration averaged about 82 days (range: [redacted] days). In the tretinoin treatment group, 17 halo hypopigmentation adverse events occurred on average about 71 days after the start of treatment (range: [redacted] days) and the duration averaged about 47 days (range: [redacted] days) following treatment discontinuation. In the 4HA treatment group, halo hypopigmentation occurred in one subject on day 33 after the start of treatment and the duration of this one reported adverse event was 25 days. In the vehicle treatment group 2 halo hypopigmentation adverse events occurred on average about 35 days after the start of the study and the duration averaged 51 days ([redacted] days).

In the laboratory parameters, all 4 treatment arms had at least 1% of the population with an elevated BUN (see table 35). Although tretinoin by itself showed some elevation of SGPT and SGOT, this did not happen in greater than 1% of the population in the 4HA/tretinoin arm.

9.3.1.5 Conclusions Regarding Efficacy Data

Study #DE132-010 supports the claim that on the arm 4HA/tretinoin is statistically significantly superior to each of its active components, 4HA and tretinoin, and vehicle for all efficacy variables, Physician's Global Assessment, Subject's Self-Assessment Questionnaire, Target Lesion Pigmentation and the Physician's Assessment of Overall Cosmetic Effect.

On the face in Study #DE132-010, at the end of treatment, the difference between 4HA/tretinoin and tretinoin was not statistically significant relative to the primary efficacy variable for the success rate in Physician's Global Assessment (p=0.097) or success rate in Subject Self-Assessment of overall appearance (p=0.12) and brown spots (p=0.355).

The results in the dichotomized outcome analysis are supported by the results in the all-category analyses. On the face, at the end of treatment, 4HA/tretinoin was not significantly better than tretinoin relative to the Physician's Global Assessment (p=0.211), the Patient's Assessment of overall appearance of the face (p=0.16), or the Patient's Assessment of the brown

spots on the face (p=0.453).

Results for the primary efficacy variables are supported by the results for the secondary efficacy variables. The difference between 4HA/tretinoin and tretinoin on the face at the end of treatment was not statistically significant relative to both Target Lesion Pigmentation (p=0.37) and Physician's Assessment of Cosmetic Effect (p=0.083).

The results in the Per Protocol population are supported by the results in the ITT population. On the face, at the end of treatment, in the ITT population, the difference between 4HA/tretinoin and tretinoin was not statistically significant relative to Physician's Global Assessment (p=0.14), Subject's Self-Assessment Questionnaire of overall appearance (p=0.15) and brown spots (p=0.50), or Physician's Assessment of Cosmetic Effect (p=0.1).

10 Overview of Efficacy

These two pivotal trials, DE132-005 and DE132-010, were able to demonstrate that 4HA/tretinoin was efficacious in treating solar lentigines on the forearms. Statistical significance was observed relative to both active components (tretinoin and 4HA) and vehicle in the one primary efficacy variable used in study -005, Physician Global Assessment ($p<0.001$). In both primary efficacy variables used in study 010, Physician Global Assessment ($p\leq 0.001$) and Patient Self-Assessment Questionnaire ($p\leq 0.046$), statistically significant superiority was observed in the forearm for 4HA/tretinoin versus its active components and vehicle.

Although not assessed separately in the Physician Global Assessment, the hands were assessed separately through the Patient Self-Assessment Questionnaire in study -010 as requested by the Agency. 4HA/tretinoin demonstrated statistical superiority relative to its active components and vehicle ($p\leq 0.021$) in this parameter.

4HA/tretinoin demonstrated statistical superiority over 4HA and vehicle for the treatment of solar lentigines of the face in both pivotal trials, DE132-005 and DE132-010, for the Physician Global Assessment ($p<0.001$). In the -010 trial, this statistical significance was also demonstrated in the Subject Self-Assessment Questionnaire relative to 4HA and vehicle ($p\leq 0.002$).

Although, 4HA/tretinoin was statistically significantly superior to tretinoin in pivotal trial -005 for Physician Global Assessment (($p=0.006$), this was not reproducible in pivotal trial -010 for Physician Global Assessment ($p=0.097$). The inability to replicate the result of the first trial on the face was further corroborated in the second trial, -010, by the other primary efficacy variable, the Subject Self-Assessment Questionnaire, where 4HA/tretinoin also did not demonstrate statistical significance relative to tretinoin for either overall appearance of the face ($p=0.120$) or brown spots on the face ($p=0.355$).

The secondary efficacy variables, Target Lesion Pigmentation and Physician's Assessment of Overall Cosmetic Effect, were supportive of the findings of the primary efficacy variables in each study.

Patients in both studies were evaluated at the end of follow-up. In study -005, the variable assessed was the Physician Global Assessment and in study -010, both Physician Global

Assessment and Subject Self-Assessment Questionnaire were assessed. The first study, -005, followed patients for 24 weeks post treatment and at the end of that time, 4HA/tretinoin maintained its effect over tretinoin ($p=0.002$), 4HA ($p=0.008$) and vehicle ($p<0.001$) for the arm and also maintained its significance over tretinoin ($p=0.01$) and 4HA and vehicle ($p<0.001$) for the face. In the second study, -010, after only 4 weeks of followup post treatment, 4HA/tretinoin maintained its effect over 4HA and vehicle for the arm ($p<0.001$) and approached statistical significance against tretinoin for the arm ($p=0.067$) but was not statistically significant for the face ($p=0.109$) in the Physician Global Assessment. The Subject Self-Assessment Questionnaire confirmed these results as 4HA/tretinoin was only statistically significantly superior to tretinoin for brown spots on the hands ($p=0.042$). It did approach statistical significance for appearance of the forearm ($p=0.064$), appearance of the face ($p=0.059$), and brown spots on the forearms ($p=0.079$).

This data on the face in Study #DE132-010 is consistent with the findings of the data on the arms in both studies and that of the face in -005 in that 4-hydroxyanisole is a contributor, albeit a weak one, to the overall efficacy of 4HA/tretinoin in the treatment of solar lentigines. Tretinoin is the largest contributor to the efficacy of the drug product, but 4HA/tretinoin was much more statistically significant than vehicle and 4HA itself in the treatment of solar lentigines ($p \leq 0.001$) in both the Physician Global Assessment and the Subject Self-Assessment Questionnaire in all arms of the trials.

11 Overview of Safety

A total of 294 healthy volunteers were exposed to 4HA/tretinion (two formulations), tretinoin, 4HA, Melanex®,and vehicle, and an additional eight healthy volunteers who were only exposed to 4HA/tretinoin and 4HA/[^{3}H] tretinoin. Of the 302 subjects evaluated in the healthy volunteer studies (topical, dermal, and PK studies), 82.8% were female and 17.2% were male, and 99.3% were white and 0.7% were non-white. The mean age was 41.3 years (range 18-83 years). Twelve of 302 subjects (4.0%) who applied 4HA/tretinoin, tretinoin, 4HA, vehicle, and Melanex experienced 19 adverse events. Treatment related adverse events included erythema, desquamation, burning skin, and vesicular/bullous rash. There were six discontinuations in these studies but none were treatment related.

There were a total of 1794 subjects who were exposed to either 4HA/tretinoin, tretinoin, 4HA, vehicle, or Melanex during Studies DE132-002, -004, -005, -009, -010, or -011. For these studies, 853 subjects were exposed to 4HA/tretinoin; 471 subjects were exposed to tretinoin; 253 subjects were exposed to 4HA; 173 subjects were exposed to vehicle, and 44 subjects were exposed to Melanex. A total of 1050 subjects were exposed to study treatment for 24 weeks or longer [543 (63.7%) in the 4HA/tretinoin, 284 in the tretinoin, 150 in the 4HA, 73, in the vehicle, and 0 in the Melanex groups]. A total of 190 subjects (22.3%) were exposed to 4HA/tretinoin for 48 weeks or longer.

These 1794 subjects with hyperpigmented lesions who applied 4HA/tretinoin, tretinoin, 4HA, vehicle, or Melanex included 1499 (83.6%) who were female and 295 (16.4%) who were male, and 1696 (94.5%) who were White, 62 (3.5%) who were Hispanic/Latino, 22 (1.2%) who were Asian/Pacific Islander, and 14 (0.8%) who were Black or other. The mean age was 62.9

years (range 30-90 years). Of the 1175 subjects in the pivotal studies (-005 and -010), 968 (82.4%) were female and 207 (17.6%) were male, and 1102 (93.8%) were White, 43 (3.7%) were Hispanic/Latino, 21 (1.8%) were Asian/Pacific Islander, and 9 (0.8%) were Black or other. The mean age was 63.2 years (range, 33-90 years).

Table 36 presents the number of subjects reporting at least one related or unrelated adverse event. The proportion of subjects who had at least one adverse event was slightly higher in the 4HA/tretinoin and tretinoin groups (90% and 89%, respectively). The proportion of subjects who had an adverse event considered related to treatment was also highest in the 4HA/tretinoin and tretinoin treatment groups (66% and 71%, respectively). The proportion of subjects who had an adverse event considered not related to treatment was similar among treatment groups (73% in each of the 4HA/tretinoin groups and 78%, 80%, and 75% of subjects in the 4HA, vehicle, and Melanex treatment groups, respectively).

Table 36
Overall Number of Subjects Reporting At Least One Occurrence
Of a Related or Unrelated Adverse Event
(Subjects With Hyperpigmented Lesions)
Studies DE132-002, -004, -005, -009, -010, -011

Relationship	4HA/Tretinoin N=853		Tretinoin N=472		4HA N=254		Vehicle N=175		Melanex N=45	
	N	%	N	%	N	%	N	%	N	%
Related	559	65.5	333	70.6	53	20.9	33	18.9	13	28.9
Not Related	626	73.4	345	73.1	199	78.4	139	79.4	33	73.3
Subjects with at least one AE	769	90.2	420	89.0	205	80.7	143	81.7	35	77.8

Table 37 presents the number of subjects reporting at least one related or unrelated adverse event for the pivotal studies DE132-005 and DE132-010. The proportions of subjects in each category (related, not related, and total subjects with at least one adverse event) are similar to those in the overall safety database. In the pivotal studies, the proportion of subjects who had at least one adverse event was slightly higher in the 4HA/tretinoin and tretinoin groups (91% and 89%, respectively) than in the 4HA and vehicle groups. In addition, subjects in the 4HA/tretinoin and tretinoin treatment groups had a higher incidence of related adverse events (70% for both groups) than subjects in the 4HA and vehicle groups. Again, the proportion of subjects who had an adverse event considered not related to treatment was similar among treatment groups.

Table 37
Overall Number of Subjects Reporting At Least One Occurrence of a Related or Unrelated Adverse Event
Subjects with Hyperpigmented Lesions
Pivotal Studies DE132-005, -010

Relationship	4HA/Tretinoin N=429		Tretinoin N=427		4HA N=211		Vehicle N=108	
	N	%	N	%	N	%	N	%
Related	301	70.2	300	70.3	47	22.3	23	21.3
Not Related	322	75.1	307	71.9	163	77.3	81	75.0
Subjects with at least one AE	391	91.1	378	88.5	167	79.2	85	78.7

The overall rate of treatment-related adverse events by body system in all the studies evaluating subjects with hyperpigmented lesions (DE132-002, -004, -005, -009, -010, -011) was highest in the tretinoin group followed by the 4HA/tretinoin group. In the 4HA/tretinoin group, 2834 adverse events were reported in 769 subjects; of these events, 1187 were treatment-related (rate 139). In the tretinoin group, 1634 adverse events were reported in 420 subjects; of these events 758 were treatment-related (rate 161). In the 4HA treatment group, 584 adverse events were reported in 205 subjects; of these events 77 were treatment-related (rate 30). In the vehicle group, 411 adverse events were reported in 143 subjects; of these events 44 were treatment related (rate 25). In the Melanex® treatment group, 105 adverse events were reported in 35 subjects, of these events, 21 were treatment-related (rate 47).

Most adverse events considered related to treatment occurred in the "Skin and Appendages" body system. (See **ADR Incidence Table**, Section **10.2.1**) The three most frequently reported adverse events considered related to treatment were erythema (4HA/tretinoin - 49.4% vs. tretinoin - 55.3%), burning/stinging/tingling (4HA/tretinoin - 26.1% vs. tretinoin - 36.7%) , and desquamation (4HA/tretinoin - 14.1% vs. tretinoin - 19.7%). The next three most frequent events for the study drug, 4HA/tretinoin, were pruritus (12.3% vs tretinoin - 14.0%), halo hypopigmentation (7.0% vs. tretinoin - 3.4%), and hypopigmentation (5.4% vs. tretinoin - 1.7%). Of the skin-related adverse events reported, 767 (66.2%) were considered mild, 351 (30.3%) were moderate, 39 (3.4%) were severe, and 3 (0.3%) were very severe. These three very severe adverse events occurred in the 4HA/tretinoin group and included one event each of erythema, rash vesicular bullae, and hemorrhage eye. The drug-related adverse events that necessitated treatment responded to topical steroids, mostly mild to moderate strength.

The four most frequently reported adverse events in the two pivotal studies considered related to treatment were erythema, burning/stinging/tingling, desquamation, and pruritus. The other events considered related to treatment that occurred at a rate ≥5.0 were irritation skin, and halo hypopigmentation.

In comparison to the pivotal studies, Study DE132-009 (a long-term, 56 week, open-

label study of the safety of 4HA/tretinoin) and Study DE132-011 (an open-label 28 week study of the safety of 4HA/tretinoin with concomitant sunscreen use) reported similar safety results. The most frequently reported adverse events were skin-related, and erythema occurred at similar rates across all four studies. Interestingly, in the long-term study (DE132-009), burning/stinging/tingling, desquamation, pruritus, and irritation skin occurred at lower rates than in the pivotal studies; however, halo hypopigmentation and hypopigmentation adverse events occurred at a slightly greater rate than in the pivotal studies. In the open-label, concomitant sunscreen study (DE132-011), rates of burning/stinging/tingling and hypopigmentation were similar to the pivotal studies. Rates of desquamation, pruritus, and halo hypopigmentation were slightly lower than those found in the pivotal studies. Based on these comparisons, the rates of adverse events are not remarkably different with long-term use of 4HA/tretinoin or with concomitant use of sunscreen.

In the pivotal studies, adverse events by treatment location (forearms/hands and face) were examined separately. A greater number of erythema, desquamation, pruritus, halo hypopigmentation, crusting, and hypopigmentation adverse events were reported on the forearms than on the face for subjects treated with 4HA/tretinoin and tretinoin. For example, erythema occurred on the forearm in the 4HA/tretinoin group 49.4% of the time compared to 39.2% of the time on the face in the same group. In contrast, a greater number of burning/stinging/tingling adverse events were reported on the face compared to the forearms for the 4HA/tretinoin group and tretinoin group (30.3% and 30.9%, respectively for the face compared to 18.9% and 19.4%, respectively for the forearm).

In study DE132-005, skin biopsies were collected from selected subjects at selected study sites for electron microscopic evaluation at baseline, at the end of the 24 week treatment period, and again at the end of the 24 week no treatment follow-up period. Treatment with 4HA/tretinoin appeared to produced the most potent depigmenting effect with activity on melanocytes and the surrounding keratinocytes. The biopsies obtained at the end of the 24 week no treatment follow-up period showed normalization of cytologic and ultrastructural alterations seen at the end of treatment. (See Electron Microscopic Analysis, page 34). Based on the electron microscopy analysis and the fact that many of the halo hypopigmentation and hypopigmentation adverse events resolved in the same time frame, the drug effects seen at the end of treatment were concluded to be temporary and reversible.

The 120 day safety update consisted of only 12 hypopigmentation events that had persisted beyond the end of the trials. The majority occurred in the 4HA/tretinoin group and all but three subjects had their hypopigmentation resolve by the end of the 120 days. The final three patients are still being followed as of April 1, 1998.

Although not analyzed in these studies, and even given that the numbers are small, subgroup safety analysis for race concerning the skin and appendageal adverse events would be important for labeling.

From the pivotal studies, subgroup analysis for gender and age group (dichotomized into <65 and ≥ 65) differences in time-to and frequency of a skin-related adverse event indicated no statistically significant age differences ($p=0.835$) or gender differences ($p=0.923$) in the 4HA/tretinoin group. Additionally, skin type was not significantly associated with time-to/frequency of a skin-related adverse event ($p=0.957$).

11.1 Significant/Potentially Significant Events

11.1.1 Deaths

Study 132-005(Site#009) - 63 year old male patient enrolled in study 3/30/94, diagnosed with pancreatic cancer[redacted] Patient discontinued from the study on[redacted] and died in [redacted] Patient had received 4HA/tretinoin

Study 132-009 (Site#005) - 63 year old female patient enrolled in study 4/1/96, history of lung cancer. Patient died during the study on[redacted]

Study 132-005, 47 year old female diagnosed with metastatic cancer during the follow-up phase, completed the study, and died three months later.

11.1.2 Other Significant/Potentially Significant Events

Allergic contact dermatitis occurred in the 4HA/tretinoin group and tretinoin group in 1 patient each at a rate of 0.5%.(Study 132-005). Also urticaria in the 4HA/tretinoin group at 0.5% for the same study.

11.1.3 Overdose Experience

Excessive use of 4HA/tretinoin on hyperpigmented lesions or normal skin may result in increased erythema, dry skin, hypopigmentation, or pruritus.

Oral ingestion of the drug (tretinoin) may lead to the same adverse effects as those associated with excessive oral intake of vitamin A (hypervitaminosis A). If oral ingestion occurs, the patient should be monitored, and appropriate supportive measures should be administered as necessary.

Oral ingestion of a single dose of 5.0 ml/kg 4HA/tretinoin in rats was only slightly toxic. The minimal acute oral lethal dose (LD) for the 2% BMS-181158/0.01% BMS-181159 formulation appears to be greater than 5.0 ml/kg, indicating slight toxicity to rats. Clinical signs observed were related to the high alcohol content (77%) of the formulation.

11.2 Other Safety Findings

11.2.1 ADR Incidence Tables

The following table lists drug related adverse events in patients with hyperpigmented lesions from all studies (DE132-002, -004, -009, -010, -011) who were treated with either 4HA/tretinoin, tretinoin, 4HA, or vehicle. Percentages are from a total of 1794 subjects including subjects treated with Melanex®.

Table 38
Adverse Events Occurring in >1% of the Population
All Studies

Body System	4HA/Tretinoin		Tretinoin		4HA		Vehicle	
	N	PCTN	N	PCTN	N	PCTN	N	PCTN*
Skin and Appendages Erythema	421	49.4	261	55.3	13	5.1	8	4.6
Burning/Stinging/Tingling	223	26.1	173	36.7	26	10.2	20	11.4
Desquamation	120	14.1	93	19.7	7	2.8	2	1.1
Pruritus	105	12.3	66	14.0	12	4.7	3	1.7
Rash	27	3.2	21	4.4	0	0.0	1	0.6
Irritation Skin	45	5.3	25	5.3	1	0.4	1	0.6
Halo Hypopigmentation	60	7.0	16	3.4	2	0.8	2	1.1
Skin Dry	27	3.2	18	3.8	3	1.2	1	0.6
Hypopigmentation	46	5.4	8	1.7	2	0.8	0	0.0
Crusting	21	2.5	18	3.8	0	0.0	1	0.6
Rash Vesicular Bullae	18	2.1	8	1.7	0	0.0	0	0.0
Application Site Reaction*	9	1.1	11	2.3	1	0.4	0	0.0
Laboratory Urine Abnormality	26	3.0	15	3.2	10	3.9	8	4.6
SGPT	12	1.7	12	2.9	2	0.9	2	1.3
SGOT	8	1.1	9	2.1	2	0.9	3	1.9
BUN	12	1.7	6	1.4	6	2.6	2	1.3

* Patients who were considered to have a contact allergic reaction

11.2.2 Laboratory Findings, Vital Signs, ECGs

There was no statistically significant difference in laboratory abnormalities for 4HA/tretinoin as compared to any of its components. Specifically, abnormalities in LFT's and BUN were comparable and low across all groups. Although urine abnormalities totaled 3.0% for 4HA/tretinoin, there was not one abnormality that reached the 1% level.

11.2.3 Special Studies

Skin biopsies were performed in study DE132-005 and discussed in "Overview of Safety".

11.2.4 Drug-Demographic Interactions

The preclinical teratogenicity study in rabbits demonstrated retinoid-induced malformations. The sponsor has therefore requested that the clinical use of 4HA/tretinoin on solar lentigines be restricted to women of non-childbearing potential. Further, because there was enhanced photocarcinogenicity in hairless mice, sun exposure should be limited when being treated with 4HA/tretinoin.

11.2.5 Drug-Disease Interactions

No drug/disease interactions were expected, and none was reported by an investigator.

11.2.6 Drug-Drug Interactions

The U.S. package inserts for Retin-A® and/or Renova® (tretinoin) indicate that concomitant use of topical medications, medicated or abrasive soaps, and cleansers, soaps and cosmetics that have a strong drying effect, and products with a high concentration of alcohol, astringents, spices or lime, permanent wave solutions, electrolysis, hair depilatories or waxes, or products that could irritate the skin should be used with caution because of possible interaction with tretinoin. Particular caution is recommended in using preparations containing sulfur, resorcinol, or salicylic acid with tretinoin. It is also suggested to "rest" a patient's skin until the effects of such preparations subside before use of tretinoin is begun. Furthermore, the U.S. package insert for Renova also warns that Renova should not be used if the patient is taking other drugs known to be photosensitizers (eg, thiazides, tetracyclines, fluoroquinolones, phenothizines, sulfonamides) because of the possiblility of augmented phototoxicity. These same precautions, pending approval, will also be recommended for the use of 4HA/tretinoin.

11.2.7 Withdrawal Phenomena/Abuse Potential

The potential for abuse of 4HA/tretinoin is limited by the product being dispensed in 30ml bottles.

11.2.8 Human Reproduction Data

The Renova® U.S. package insert states, "Thirty cases of temporally-associated congenital malformations have been reported during two decades of clinical use of another formulation of topical tretinoin (Retin-A®). Although no definite pattern of teratogenicity and no causal association has been established from these cases, five of the reports describe the rare birth defect category holoprosencephaly (defects associated with incomplete midline development of the forebrain). The significance of these spontaneous reports in terms of risk to the fetus is not known."

According to the sponsor, published data for 291 pregnancy outcomes show no difference in the rates of malformation between exposed and unexposed fetuses (see references listed under

section 7.2). A prospective, observational, controlled study to compare the rate of malformations among fetuses exposed and unexposed to topical tretinoin was performed in Toronto, Ontario, Canada by Shapiro, L., et.al. (See reference listed under section 7.2). Results of 94 topical tretinoin-exposed cases and their 133 controls showed no differences in the live births, miscarriages, or elective terminations of pregnancy. Among the live-born babies who were exposed to topical tretinoin during the first trimester, the incidence of major malformations did not differ from the controls. This study includes the largest sample size to date of women who used topical tretinoin in early pregnancy. The results failed to show an increased risk in congenital malformations for users of topical tretinoin.

12 Conclusions

The topical dermal studies which compared the drug product to each of its individual components and Melanex topical solution demonstrated that 4HA/tretinoin is a skin irritant, being less irritating than Melanex, slightly more irritating than tretinoin, and significantly more irritating than 4HA and vehicle. The drug product, 4HA/tretinoin demonstrated under study conditions a low potential, 0.5-1%, of causing contact sensitization. It was not found to either demonstrate photoxicity or photosensitization. Although these studies were not conducted in a blinded fashion that would have been preferred, the safety results obtained in the pivotal clinical trials do not deviate from these findings. Specifically, there was not a statistical difference between the drug product, 4HA/tretinoin and tretinoin alone in terms of contact irritation or contact sensitization.

The pivotal trials of this NDA, DE132-005 and DE132-010, are sufficient to demonstrate that 2% 4-hydroxyanisole/0.01% tretinoin is indicated for the treatment of solar lentigines. The sponsor demonstrated through two pivotal trials that the drug product could adequately improve solar lentigines in the target areas selected, the forearms and the face. Both studies were able to demonstrate clinical and statistical significance for use of the drug product on the forearms, and Study DE132-005 was able to demonstrate efficacy of 2% 4HA/0.01% tretinoin on solar lentigines of the face. This was using the Physician Global Assessment as the primary efficacy variable where $p<0.001$.

This data on the face in Study #DE132-010 is consistent with the findings of the data on the arms in both studies and that of the face in -005 in that 4-hydroxyanisole is a contributor, albeit a weak one, to the overall efficacy of 4HA/tretinoin in the treatment of solar lentigines. Tretinoin is the largest contributor to the efficacy of the drug product, but 4HA/tretinoin was much more statistically significant than vehicle and 4HA itself in the treatment of solar lentigines ($p \leq 0.001$) in both the Physician Global Assessment and the Subject Self-Assessment Questionnaire in all arms of the trials.

Safety of 2% 4-hydroxyanisole/0.01% tretinoin was similar in its profile to tretinoin 0.01% alone. The most frequently reported adverse events which were erythema, burning/stinging/tingling, and desquamation occurred at a slightly lower rate in the 4HA/tretinoin group as compared to the tretinoin group, but at at higher rate than in 4HA alone and vehicle. Hypopigmentation occurred more frequently in patients using 4HA/tretinoin as compared to tretinoin but in the majority of the cases, the hypopigmentation was reversible upon discontinuation of the drug product. This was supported by electron microscopic findings.

Application site reaction, which was considered by the investigators to be an allergic contact dermatitis occurred at a slightly lower rate for 4HA/tretinoin as compared to tretinoin (1.1% and 2.3% respectively). Elevation of liver function tests, namely SGOT and SGPT, also occurred at a lower rate in the 4HA/tretinoin group than in the tretinoin group. The percent of patients was not higher than 1.7% for the 4HA/tretinoin group. In this reviewer's opinion, especially given the widespread use of tretinoin on a long term basis, this would not require specific monitoring of patients. The elevation of the BUN was essentially the same for 4HA/tretinoin and tretinoin (1.7% and 1.4%, respectively) and the for the same reason would not require specific monitoring.

In summary, the trials thus far completed have demonstrated that 2% 4-hydroxyanisole/0.01% tretinoin is efficacious for the treatment of solar lentigines [redacted] It has further demonstrated a good safety profile for long term use in a selected population.

APPEARS THIS WAY
ON ORIGINAL

13 Recommendations

It is recommended that this drug product, 2% 4-hydroxyanisole/0.01% tretinoin receive an approvable for the treatment of solar lentigines. There are, however, two clinical deficiencies that the sponsor should address:

[redacted]

/S/

Denise Cook, M.D.
Medical Officer, Dermatology

11/20/98

cc: HFD-540
HFD-340
HFD-540/CSO/CrossF
HFD-540/CHEM/TimmerW
HFD-520/MICRO/
HFD-540/PHARM/NostrandtA
HFD-540/MO/CookD
HFD-540/TL/WalkerS

For Concurrence Only:
HFD-540/TL/WalkerS
HFD-540/DD/WilkinJ
HFD-105/OD/Delap

See TL Concurrence 11/22/98 SW.

/S/ 11/23/98

APPEARS THIS WAY
ON ORIGINAL

The applicant has demonstrated that 4-hydroxyanisole/tretinoin is safe and effective in the treatment of actinic lentigines. The applicant has not demonstrated that 4-hydroxyanisole/tretinoin is safe and effective in the treatment of [redacted] The protocol inclusion criteria limit study entry criteria to "actinic lentigines".

Clinical outcomes

Physicians Global

The physicians' global assessment outcomes (Table 1 below) provide the basis for the conclusion that the combination product has superior clinical efficacy to each of the individual components. The comparison on the face in trial DE132-010 of 4HA/tretinoin vs. tretinoin alone did not reach statistical significance, however, this is only statistical failure in four such comparisons. The target lesion pigmentation scores demonstrate clinical success in this comparison.

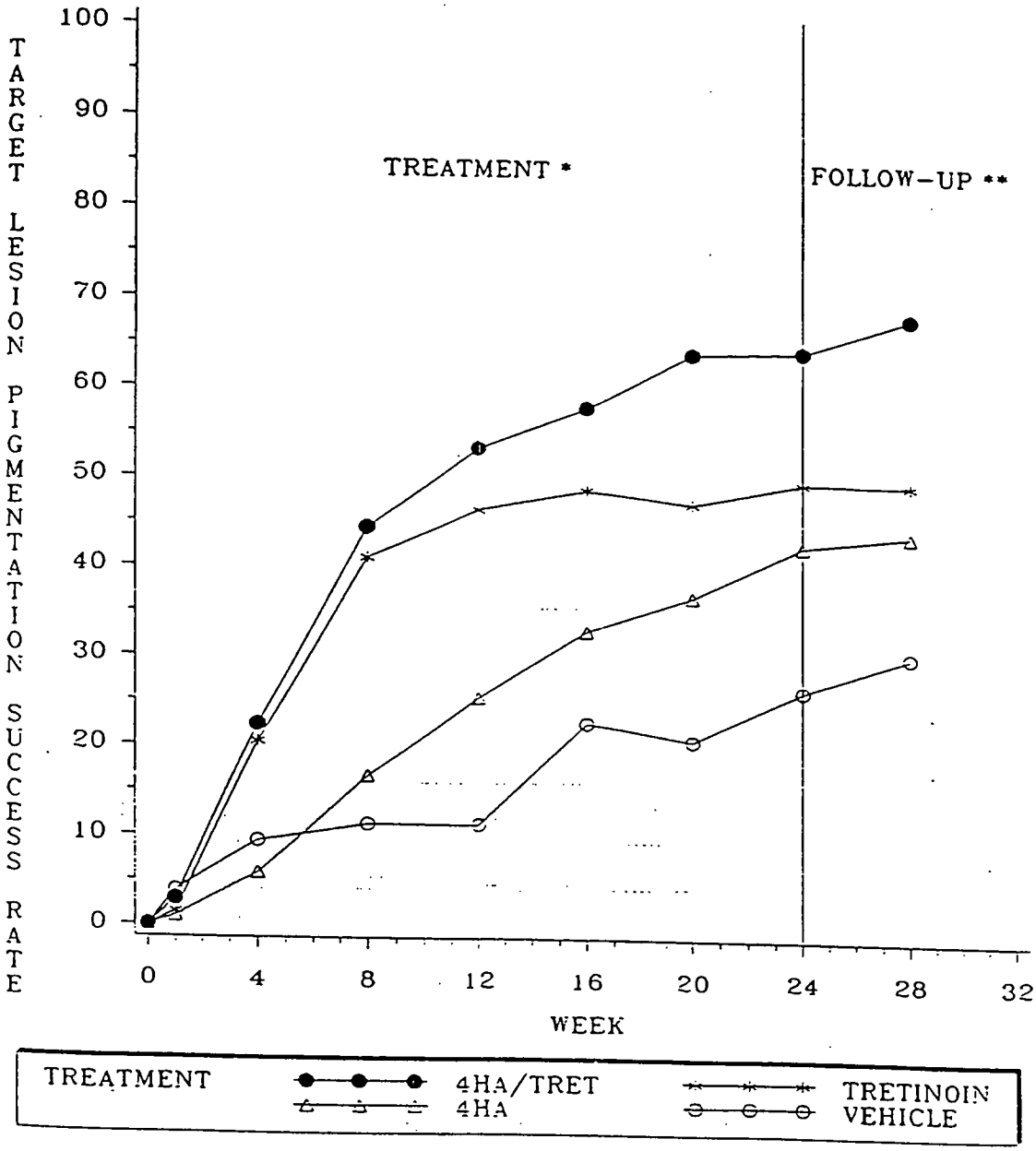
Treatment Site/Study	Treatment(Study DE132-005 and DE132-010) (TABLE 1) **Success Rate in Physician's Global Assessment (Percent of Subjects with Moderate or Greater Improvement at End of Treatment) ITT Population**			
	4HA/Tretinoin	Tretinoin	4HA	Vehicle
Arm 005	n=213 115 (54%)	n=214 76 (36%) p=0.001	n=105 25 (24%) p=0.001	n=54 9 (17%) p=0.001
Arm 010	n=208 112 (53.8%)	n=208 83 (39.9) p=0.004	n=104 26 (25%) p=0.001	n=53 6 (11.3%) p=0.001
Face - 005	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
Face 010	n=209 119 (56.9%)	n=209 103 (49.3) p=0.1	n=104 35 (33.7%) p=0.001	n=53 6 (11.3%) p=0.001

Target Lesion Pigmentation Scores

Target lesions pigmentation scores are strongly supportive of efficacy. Patients enrollment criteria include a clinical diagnosis of solar lentigines of at least 6 (moderately darker than surrounding skin). The target lesion pigmentation scale had 9 levels (0-8, ranging from 0=completely depigmented, 4=equal with pigment of surrounding skin, 8= extremely darker than pigment of surrounding skin). The success rates for the target lesion pigmentation scores in Study DE 132-010 consistently demonstrate that 4-hydroxyanisole/tretinoin is clinically superior to the active components alone (Tables 2 and 3 below[1])

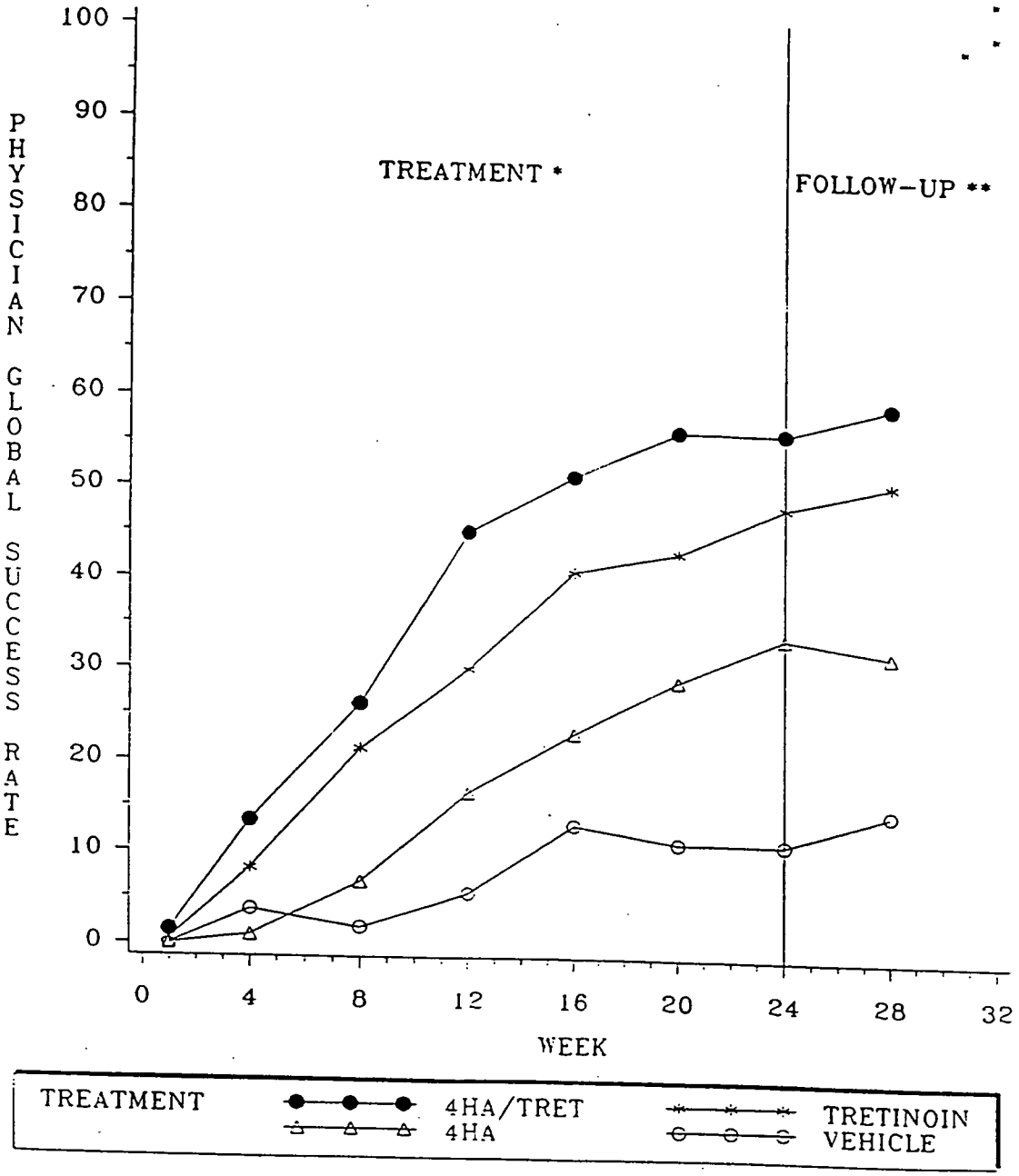
[1] Applicant's Tables 6.4.1-1 and 1-2 Study DE132-010

Success Rates for Target Lesion Pigmentation (Arm)



* Last treatment observation carried forward to 24 weeks (end of treatment)
** Time after end of treatment: 28 = 4 weeks after end of treatment

Success Rates for Physician's Global Assessment (Face)



* Last treatment observation carried forward to 24 weeks (end of treatment)
** Time after end of treatment: 28 = 4 weeks after end of treatment

Patient's Global Assessment

Outcomes from the patient's assessment provide evidence of the clinical utility of 4-hydroxyanisole/tretinoin vs. the individual active components. Six questions were addressed to the subjects in order to assess the patient's perception of the drug effect. 4-hydroxyanisole/tretinoin consistency provides an effect which is deemed to be useful by the subjects in the clinical trials.

Safety Analysis

The primary local adverse events of concern to patients and physicians are primarily irritation and depigmentation (halo hypopigmentation). The applicant should present data for these adverse events for a range of skin types, as this is necessary to adequately describe local adverse events in the final printed labeling. This could be provided via a Phase 4 commitment.

Labeling

The application is currently pending a Non-Approval from Chemistry for significant DMF discrepancies. An addendum to the clinical review addressing labeling will be provided when the applicant has successfully rectified the Chemistry Non-Approval issues.

CLINICAL RECOMMENDATION:

The application is APPROVABLE for the indication of solar lentigines. The sponsor has provided inadequate information to demonstrate safety and efficacy in the treatment of

The applicant should commit to providing a Phase 4 study to obtain relevant local safety data on skin type subsets, specifically addressing concerns about local hypopigmention in persons of color.

/S/ 11/23/98

Susan J. Walker, M.D.
Clinical Team Leader

As above. The TL review supports and extends the MO review by the additional graphical presentation of data from DE 132-010 that support the contribution of BOTH actives to the combination product.

/S/ 11/23/98

HFD-540
540/Wilkin
540/Walker
540/Cook
540/Cross