

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-112

MEDICAL REVIEW(S)

JAN 13 2000

Medical Officer Review for Original NDA* 21-112

DDDDP#992973

1 General Information

1.1 NDA submission number 21-112

1.2 Applicant identification

1.2.1 Name Hill Dermaceuticals, Inc.
1.2.2 Address and telephone number 2650 South Mellowville Ave
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1.2.3 Name of company contact official Rosario G. Ramirez
Medical/Regulatory Affairs

1.3 Submission/review dates

1.3.1 Date of submission 3/19/99
1.3.2 CDER stamp date 3/22/99
1.3.3 Date submission received by reviewer 4/3/99
1.3.4 Date review begun 4/4/99
1.3.5 Date review completed 1/10/00

1.4 Drug Identification

1.4.1 Generic Names fluocinolone acetonide (0.01%); hydroquinone (4%); tretinoin (0.05%)

1.4.2 Proposed Trade Name TRILUMA

1.4.3 Chemical Names

fluocinolone acetonide: pregna-1,4-diene-3,20-dione, 6,9-difluoro-11,21-dihydroxy-16,17-[(1-methylethylidene)bis(oxy)]-, (6 α ,11 β ,16 α)-
hydroquinone: 1,4-benzenediol
tretinoin: (all-E)-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid

1.4.4 Chemical Formulas

fluocinolone acetonide: C₂₄H₃₀F₂O₆
hydroquinone: C₆H₆O₂
tretinoin: C₂₀H₂₈O₂

1.4.5 Molecular Weights

fluocinolone acetonide: 452.20
hydroquinone: 110.11
tretinoin: 300.44

1.5 Pharmacologic Categories

fluocinolone acetonide: corticosteroid; also antiinflammatory
hydroquinone: depigmenting agent
tretinoin: retinoid; also keratolytic

1.6 Dosage Form cream

1.7 Route of Administration topical

* Abbreviations used in this review: IND=Investigational New Drug Application; ITT=intent-to-treat; LOCF=last observation carried forward; NDA=New Drug Application; THR=fluocinolone acetonide 0.01%, hydroquinone 4%, tretinoin 0.05% combination, FH=fluocinolone acetonide 0.01%, hydroquinone 4% combination, HR=hydroquinone 4%, tretinoin 0.05% combination, FR=fluocinolone acetonide 0.01%, tretinoin 0.05% combination.

1.8 Proposed Indication & Usage Section

"TRADE NAME Cream is indicated for the treatment of cutaneous melanosis, for skin types II and III"

1.9 Proposed Dosage & Administration Section

"TRADE NAME Cream should be applied to the face and/or neck, once a day before bedtime. Gently wash the face and neck with tap water and mild non-ionic soap. Pat the skin dry and avoid using a harsh washcloth. Apply a thin film of the cream onto the hyperpigmented spot including about 1/2 inch of normal appearing skin surrounding the lesion. Rub lightly and uniformly into the skin. Do not use occlusive dressing. Apply medication at least 1 hour before bedtime.

During the day, the patient is directed to use sunblock or sunscreen, and protective clothing. Avoidance of sun exposure would be the ideal. Patients may also use moisturizers during the day."

1.10 Related Drugs

The following approved NDAs for two active ingredients are listed in the Orange Book (19th edition). These ingredients are also available as generic products under ANDAs.

<u>Fluocinolone acetonide</u>	<u>Tretinoin*</u>
12787 Medicis (cream)	20438 Roche (oral)
13960 Medicis (ointment)	19049, 17522, 17340 Johnson & Johnson (cream)
15296 Medicis (solution)	17955, 17579 Johnson & Johnson (gel)
16161 Medicis (cream)	16921 Johnson & Johnson (solution)
19452 Hill (Oil)	20475 Johnson & Johnson (microsphere gel)
20001 Hill (shampoo)	19963 Johnson & Johnson (emollient cream)
	20886 Ligand (gel)
	20400 Bertek (gel)
	20404 Bertek (cream)

Although not listed in the Orange Book, hydroquinone is available at concentrations of 1.5% to 2% under the Tentative Final Monograph for Skin Bleaching Drug Products. At higher concentrations (3 or 4%), hydroquinone is an ingredient of prescription topical creams (ICN, Medicis), gel (ICN) and solution (Neutrogena).

1.11 Material Reviewed

1.11.1 NDA volumes reviewed 1.1, 1.6

1.11.2 Amendments reviewed Submissions dated -

- 5/7/99 Response to request for details of safety data
- 5/11/99 Response to request for details of safety data
- 5/19/99 Response to request for details of safety data
- 8/27/99 Response to request for samples of test drugs
- 9/9/99 120-day Safety Update
- 9/27/99 Submission of requested photos and CRFs
- 10/12/99 Submission of requested photos
- 10/25/99 Submission of requested CRFs
- 10/28/99 Response to request for dates of studies and unblinding
- 11/4/99 Submission of CRF missing in 10/25/99 submission
- 11/8/99 Submission of proposed tradenames

1.12 Regulatory Background

Studies in support of this NDA were conducted under _____ This IND was submitted on 9/15/95 under the product name _____

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**APPEARS THIS WAY
ON ORIGINAL**

3 Chemistry/Manufacturing Controls See review by Chemistry Reviewer, who has recommended not-approvable action. The drug product has the following formulation:

	<u>%w/w</u>
Fluocinolone acetonide	0.01
Hydroquinone	4.00
Tretinoin	0.05
Magnesium aluminum silicate	
Butylated hydroxytoluene	
Cetyl alcohol	
Stearic acid	
Stearyl alcohol	
Methylparaben	
Propylparaben	
<hr/>	
Methyl gluceth-10	
Glycerin	
Citric acid	
Sodium metabisulfite	
Purified water	

4 Animal Pharmacology/Toxicology See review by Pharm/Tox Reviewer. Her conclusion is:

"From a pharmacology/toxicology standpoint, it is recommended that the application be not approvable. There is insufficient evidence of safety of the combination drug product or of novel degradants found in the combination."

5 Microbiology There is no Microbiology section in this NDA.

6 Human Pharmacokinetics/Pharmacodynamics See review by Biopharm Reviewer. Her conclusion is:

"There are no in vivo studies to determine the systemic absorption or HPA axis suppression for the proposed formulation. From the Clinical Pharmacology and Biopharmaceutics standpoint, the application is not acceptable."

7 Human Clinical Experience

7.1 Foreign experience Although individual components are available, the combination product with fluocinolone acetonide 0.01%, hydroquinone 4% and tretinoin 0.05% (THR) has not been marketed anywhere.

7.2 Post-Marketing Experience None

8 Clinical Studies

8.1 Introduction

The clinical studies in support of this NDA are listed in the following Table.

Study No.	Site(s)	Sample Size (M:F)	Dose	Treatment Duration	Control	Design
Controlled Studies						
24 East	3	202 (9:193)	THR* qd to face	8 wks double-blind, 12 wks open (THR)	TH, HR or TH qd to face	randmized, multi-center, comparative, parallel-gp same as above
24 West	2	175 (12:163)	same as above	same as above	same as above	same as above

Uncontrolled Studies

There are no uncontrolled studies to support efficacy and safety.

Dermal Safety Studies on Healthy Adult Volunteers

56 (Irritancy/sensitization)	1	49** (18:31)	THR 0.2 gm/app	<u>Induction</u> 9 app 48-hr patches over 3 weeks <u>Challenge</u> 2 app 48-hr patches	Vehicle 0.2 gm/app	randomized, double-blind intra-individual
57 (Photoallergenicity)	1	26** (13:13)	THR 10 µL/cm ² induction 5 µL/cm ² challenge	<u>Induction</u> 6 app 24-hr patches over 3 weeks (2 sites each time) <u>Challenge</u> 24-hr patches (2 sites)	---	open study
58 (Phototoxicity)	1	10 (4:6)	THR 5 µL/cm ²	6-hr patch	Vehicle 5 µL/cm ²	single-blind
59 (Irritancy/sensitization)	1	56** (17:39)	Fluo* acetamide hydroquinone tretinoin 0.2 gm/app	same as Study 56	Vehicle 0.2 gm/app	same as Study 56

*THR=fluocinolone acetamide 0.01%, hydroquinone 4%, tretinoin 0.05% combination, FH=fluocinolone acetamide 0.01%, hydroquinone 4% combination, HR=hydroquinone 4%, tretinoin 0.05% combination, FR=fluocinolone acetamide 0.01%, tretinoin 0.05% combination, app=application, Fluo=fluocinolone; **Excluding dropouts.

8.2 Indication #1 Cutaneous melanos

Cutaneous melanos refers to conditions where melanin hyperpigmentation occurs as a result of various causes. Etiologies may differ for epidermal and dermal melanos. The term is too broad to be an appropriate indication, as it is almost impossible to support this indication covering all varieties of melanos. Rather, the indication should be directed towards specific diagnoses, where studies can be conducted to determine the product's safety and efficacy in those conditions. For instance, the labels of currently available prescription products are more specific in terms of the conditions amenable to treatment with those products:

"Melanex® is indicated in the temporary depigmentation of hyperpigmented skin conditions such as chloasma, melasma, freckles, senile lentiginos, and other forms of melanin hyperpigmentation." (Melanex)

"For the gradual bleaching of hyperpigmented skin conditions such as chloasma, melasma, freckles, senile lentiginos and other unwanted areas of melanin hyperpigmentation." (Solaquin, Eldopaque, Eldoquin)

"LUSTRA is indicated for the gradual treatment of ultraviolet induced dyschromia and discoloration resulting from the use of oral contraceptives, pregnancy, hormone replacement therapy, or skin trauma." (Lustra)

In the current submission, the Sponsor has conducted two purportedly adequate and well controlled studies on melasma/chloasma in patients with (Fitzpatrick's) skin types II and III. This review will be focus on the treatment effect in these conditions.

Comment The Applicant has been advised previously that proper justification would be needed for an indication with restriction to patients of certain skin types. Such

justification has not been offered in this NDA. However, the Applicant does mention its intention to pursue future studies on patients of skin types IV, V and VI.

8.2.1 Trial #1. Sponsor's Study 024 East. "Double-Blind Comparative Study Of A New Formulation For The Treatment Of Patients With Cutaneous Melanosis" [Started 1/31/98, completed 2/25/99]

8.2.1.1 Objectives: To compare the efficacy and safety of the triad combination, THR (fluocinolone acetonide 0.01%, hydroquinone 4%, tretinoin 0.05%) for the treatment of patients with "cutaneous melanosis" (see below for selection criteria), with those of the dyad combinations: FH (fluocinolone acetonide 0.01%, hydroquinone 4%), HR (hydroquinone 4%, tretinoin 0.05%), and FR (fluocinolone acetonide 0.01%, tretinoin 0.05%).

8.2.1.2 Design: Multi-center, randomized, double-blind, comparative study in patients with "cutaneous melanosis". There are 4 treatment groups: (1) THR, (2) FH, (3) HR and (4) FR. Once daily treatment continued for 8 weeks in the double-blind phase of the study, and for selected patients (see below), there was an additional 12 weeks of treatment in the Long-Term Follow-up phase.

Treatment and Post-treatment periods The double-blinded treatment period consisted of 8 weeks. Follow-up visits were weekly in this phase, and every 2 or 4 weeks in the subsequent open phase (in selected patients), followed by the final visit after 8 more weeks of no treatment. The Schema is as follows: -

Double-Blind Phase Visits (Daily Treatment)	For Patients Given Triad In Double-Blind Phase Who Achieved Clearing	
	Open Phase Visits*	Post-Treatment Phase Visits
day 1 (Initial visit), test drug provided	End of 12 th week (after 4 weeks of 3x/wk treatment)	End of 28 th week (after 8 weeks of no treatment)
day 8 (week1),	End of 16 th week (after 4 weeks of 2x/wk treatment)	
day 15 (week2),	End of 20 th week (after 4 weeks of 1x/wk treatment)	
day 22 (week3), test drug provided		
day 29 (week4),	For Patients Given Triad In Double-Blind Phase Who Achieved Hyperpigmentation Score=1 at End of Double-Blind Phase	
day 36 (week5),	Open Phase Visits**	Post-Treatment Phase Visits
day 43 (week6), test drug provided	End of 10 th week End of 12 th week End of 14 th week End of 16 th week End of 20 th week (after 4 weeks of 3x/wk treatment) End of 24 th week (after 4 weeks of 2x/wk treatment) End of 28 th week (after 4 weeks of 1x/wk treatment)	End of 36 th week* (after 8 weeks of no treatment)
day 50 (week7),		
day 57 (week8), end 8 wks of treatment		

*If a patient achieved clearing during double-blind phase, unblinding would be done, and if given triad before, the patient was allowed to enter open phase; ** if a patient given daily triad treatment in the open phase achieved clearing, the dose-decreasing regimen would begin without going into the end of the 16th week.

Patients who had used the triad during the initial 8 weeks, and achieved hyperpigmentation score of 0 were allowed to enter the long-term phase, consisting of 12 weeks of dose-decreasing regimen followed by 8 weeks of no treatment.

8.2.1.3 Protocol Overview

8.2.1.3.1 Population and Procedures

8.2.1.3.1.1 Population

Inclusion criteria:

1. Facial and/or neck hyperpigmentation
2. Hyperpigmentation severity ≥ 2 on a 0-3 scale (see below); hyperpigmentation limited to chloasma/melasma, excluding lentigos, freckles and post-inflammatory hyperpigmentation
3. Clinical diagnosis of cutaneous melanosis unchanged, stable for a continuous period of 3 months prior to entry
4. Lesions were to be macular and neither depressed or atrophic
5. Skin types II or III (Fitzpatrick's)
6. ≥ 18 years of age and in good general health
7. Able to understand requirements of study and abide by protocol
8. Females of childbearing potential were to use adequate birth control; need negative urine pregnancy test before entry
9. Patients on oral contraceptives might be enrolled if hyperpigmentation score had remained unchanged or stable for at least 3 months before entry (during study, patients could not alter the use of the oral contraceptive)
10. Informed consent

Exclusion criteria:

1. Pregnancy, lactation or positive pregnancy test in female of childbearing potential
2. Known hypersensitivity to any component of test material
3. History of increased pigmentation and/or contact dermatitis with previous use of hydroquinone or tretinoin
4. Requirement for use of other drugs that might enhance pigmentation (hormonal treatments or gonadotrophic hormones not to be initiated during study)
5. Consistent skin irritation of exposed skin (e.g., by UV light)
6. Use of topical medications for hyperpigmented lesions or use of photosensitizing medication within 21 days of entry (including corticosteroids, hydroquinone or tretinoin preparations, alpha- and beta-hydroxy acid preparations and photosensitizers)
7. Any condition that would interfere with evaluation
8. Receipt of investigational drug within 4 weeks of entry
9. Use of or requirement for drug with known potential for toxicity to major organ within 3 months
10. History of poor cooperation, non-compliance or unreliability

Comments

1. The inclusion criterion for skin types is too restrictive.
2. The study of chloasma/melasma alone will limit the indication for ultimate labeling.

Early Termination of Therapy, Dropouts and Protocol Deviations

Drop-outs or patients terminated from the study were not replaced. The investigator would discontinue the participation of any individual (1) whose health or well-being might be threatened by continuation in the study, or (2) who experienced serious intercurrent illness.

The occurrence of an adverse experience believed to be due to an investigational drug might preclude its further use. If the occurrence warranted use of appropriate concomitant therapy, this information would be entered in the case report form, and the patient's progress followed for 1-2 weeks or until resolution. In the event that irritation due to study medication became severe or persisted unchanged for >7 days despite decreased dosing, the investigator would determine if it was necessary to discontinue. If there was a detection of black dots or grayish discoloration of the skin, such patient(s) would be withdrawn and not continue under a modified regimen. They would be observed for a period of 1 to 2 weeks to see if pigmentation persisted. Any patient might decide to discontinue the study at his/her own discretion at any time. Patients withdrawn for reasons unrelated to the study product were also considered "dropouts".

Protocol Deviations: Some protocol deviations could disqualify a patient. The patient would also be considered a "dropout" and not be replaced. A protocol deviation that would *not eliminate* the patient from efficacy and safety evaluation was early treatment success. Examples of patients with deviations to be considered "dropouts":

- the use of treatments or prescribed medicines that would affect outcome of the study;
- failure to follow the application schedule for the investigational drug product:
 - a) skipping >2 consecutive applications within a week, for >2 weeks (unless instructed by Investigator),
 - b) applying medication more than once a day, for 3 or more days;
- missing >3 consecutive visits;
- non-compliance to any part of the protocol especially application instructions and cleansing procedures.

8.2.1.3.1.2 Procedures

The baseline visit for the double-blind phase of the study was Day 1; patients were subsequently assessed weekly for efficacy and safety.

Application of Test Material:

The first application of the test material would be made under supervision of the investigator or his designee. Bathing or washing of the areas to be treated, using only Cetaphil soap or white Dove soap, would be done prior to administration. All used and unused tubes of medication were to be returned to the Investigator or his designee.

Application instructions were:

"With clean fingers, apply a thin film of the cream on the pigmented lesions, rub lightly and uniformly into the involved areas and to areas of normal appearing skin surrounding the lesions, to the extent of approximately a half inch. Do not cover or use any occlusive dressings. Apply the medication every day, at least 1 hour before bedtime.

In the morning, rinse the treated areas with tap water using only the hands. No washcloths, abrasive materials or soaps should be used to wash the treated areas, especially the face."

While on treatment, the patient was not to use harsh washcloths or soaps on treated areas. Areas being treated would be rinsed (washed) by hand, with tap water only. It would be emphasized to patients that the use of all other topical agents was not allowed. Only Cetaphil Cream, a moisturizer supplied by the sponsor, would be used. If cosmetic was used, the patient would wash the face (and other designated treated areas) with the supplied soap, following the procedures for non-traumatic washing, before the next application of medication.

Comment The procedure for application of study drug is part of the treatment regime that would ultimately be incorporated into label. The requirement for Cetaphil cream use to the exclusion of all others would also impact on labeling.

In the event that a patient developed irritation from the investigational drug, the frequency of application would be decreased from once a day to once every other day, for 7 days. If irritation became severe or persisted longer than 7 days despite decreased application, the investigator would consider discontinuing treatment or extending decreased dose for another 7 days.

After completing 8 weeks of treatment, the "blind" was broken and efficacy reviewed by Hill Dermaceuticals monitor, independent statistician, and the investigator(s). Having picked out the patients treated with the triad, THR, those who improved to a score of "1" and those that cleared (score of 0), were asked to return for long term follow-up:

Patients that cleared (grade of "0") at the end of 8 weeks would follow a dose decreasing regimen with the triad as follows:

First 4 weeks, apply every Mondays, Wednesdays, and Fridays; follow-up visit right after.

Next 4 weeks, apply every Mondays and Thursdays; follow-up visit.

Next 4 weeks, apply on Mondays only, then stop treatment; follow-up visit.

Next 8 weeks, without treatment, then go for last follow-up visit after the 8 weeks.

Patients whose grades went to a score of "1" after 8 weeks would continue using the triad daily, and evaluated every two weeks for up to 8 weeks or until the lesions cleared (grade of "0"), whichever came first. Then the patient would follow the dose decreasing regimen.

Patients that cleared during the 8-week double-blind phase were considered early treatment successes and removed from this phase. The treatment arm would be disclosed and those on the triad, THR, would be placed on the dose-decreasing regimen.

Supply and Accountability of Test Materials:

Hill Dermaceuticals, Inc., would supply all formulations in **identically appearing tubes**. Each investigator would be supplied with serially numbered treatment packets (numbers corresponding to patient numbers) each containing 2 tubes of formulation. Each patient would be dispensed a treatment at: Visit 1, Visit 4 (week 3), Visit 7 (week 6), Visit 9 (week 8), and the long-term follow-up visits LTFv-1 and LTFv -2. A Master Key, containing the concealed identity of the contents of each tube, was available to each investigator, to be opened only for urgent medical reasons. **The serially numbered treatment units were assigned to patients in order of their enrollment and the unit number would be designated as the "patient identification number".**

Dispensing and collection of test materials were recorded in the Test Materials Accountability record and checked by the Study Monitor at periodic visits. At the end of the study, all unused study materials as well as empty or partially used tubes had to be accounted for and returned to Hill Dermaceuticals with a copy of the Investigator's Drug Accountability Log and Return Shipment Inventory form. The investigator was to account for all supplies issued by Hill Dermaceuticals, Inc. for this study.

Use of Concomitant Medications, Cosmetics and Cleansing Agents:

The investigator would instruct the patient not to use other medication that could interfere with the test results (e.g., corticosteroid, alpha- or beta-hydroxy creams, skin "lightening" over-the-counter agents, or any photosensitizing agents) during the entire treatment period. **Patients were to use sun protection, and sunblock cream with SPF 15 and higher (e.g., sunblock with SPF 17 for sensitive skin containing a combination of zinc oxide and titanium dioxide micronized crystals, or sunscreen lotion SPF 15 with UVA/UVB protection free of fragrance or PABA) was provided.** Occasional use of make-up (cosmetics) was permitted, provided the patient observed cleansing procedures dictated in this protocol, i.e., non-traumatic washing of face with Cetaphil or white Dove soap, prior to test drug applications. Cetaphil soap or white (unscented) Dove soap for cleansing purposes, and Cetaphil cream or lotion for skin softening were provided. **No other skin cleanser or moisturizer would be used.**

Comment The ancillary measures including use of the sunblock cream provided by the Applicant and the exclusive use of Cetaphil cream or lotion for skin softening will impact on labeling.

8.2.1.3.2 Evaluability Criteria

Some protocol deviations disqualified subjects from the study. In such a case, the patient was considered a dropout. Dropouts were not replaced. The following protocol deviations disqualified patients from efficacy evaluations for all subsequent visits:

1. Use of prescribed medication or treatments (other than the test product) during the course of the study, if such medication could alter the results of the investigational product.
2. Failure to return.
3. Failure to use the test product for more than 2 consecutive applications within a week, for more than 2 weeks.
4. Missing more than 3 consecutive visits.
5. Non-compliance with the protocol, especially application instructions and cleansing procedures.

Comment Since the primary analysis will be based on the intent-to-treat population (ITT), all patients randomized and dispensed test drug will be considered evaluable.

8.2.1.3.3 Endpoints

A dermogram showing the area to be treated was included with the case report form. The clinical evaluations of each patient were performed by the same investigator whenever possible. Duration, status and location of the disease were recorded at Day 1. Target area was confined to the face and neck. The target area was graded based on the most severe lesion. If there were multiple treatment areas, then the scores of the most severe area, at baseline, was used in the efficacy analysis. The area to be used for the efficacy analysis was to be marked on the dermogram by the investigator at the baseline assessment.

1. Hyperpigmentation Scale:

0 = None : no abnormal hyperpigmentation or hypopigmentation

- 1 = Mild : minimal residual hyperpigmentation
- 2 = Moderate : partial or mild persistent hyperpigmentation
- 3 = Severe : marked hyperpigmentation

Comment The hyperpigmentation scoring system is confusing. The score of 1 (mild) means "minimal" while a score of 2 (moderate) means "mild". The only clear-cut score is 0 (none). The hyperpigmentation score=0 at week 8 has been chosen as the primary endpoint (see below).

2. Physician and Subject Global Improvement:

Physician Global Improvement

- 0 = Cleared 100% improved. No hyperpigmentation or hypopigmentation
- 1 = Excellent Improvement 75% and greater, but less than 100% improvement
- 2 = Good Improvement 50% to less than 75% improvement
- 3 = Slight Improvement Less than 50% improvement
- 4 = No Change No detectable improvement from initial evaluation
- 5 = Exacerbation Flare or rebound of condition

Subject Global Improvement

- 1 = Cleared
- 2 = Much better
- 3 = Slightly better
- 4 = Same, no improvement
- 5 = Worse

Patient Evaluation of the Product. Each patient would evaluate cosmetic acceptability of a) the formulation, and b) the results, at week 8 visit, using the following scale: 1=Excellent, 2=Good, 3=Fair, 4=Poor (=did not like).

3. Safety: At each return visit, patients would be questioned regarding the occurrence of adverse experiences (check list of adverse experiences not used). Adverse events would be reported with information on relatedness to the use of the test materials, severity and treatment instituted (if any). For the assessment of signs of local adverse effects:

Irritation and appearance of grayish discoloration or black spots were to be noted in the case report form. The appearance of grayish discoloration or black spots would result in immediate withdrawal from the study. Topical corticosteroid adverse effects such as atrophy, striae, telangiectasia, rosacea, perioral dermatitis and manifestations of systemic toxicity would be assessed and recorded. Local adverse effects were assessed using the following scale: 0=Absent, 1=Mild, 2=Moderate, 3=Severe.

4. Photography Color photographs of the treated areas were taken at all visits (or every other visit) until end result was achieved.

8.2.1.3.4 Statistical Considerations:

Sample size calculation: For a binomial analysis of the primary endpoint hyperpigmentation score=0 at Week 8, and assuming a difference in proportion between the triad, THR, and any of the dyad arms of 0.30, a sample size of 42 per group would detect a difference between groups at an alpha of 0.05, with a power of 80%. Based on a drop-out rate of 10%, each of the 3 Investigator sites would be expected to enroll approximately 18 patients per arm.

Randomization: Treatment numbers would be allocated sequentially (i.e., first patient enrolled would be assigned #01, subsequent patients to follow serial numbering 02, 03,

04, etc.). Hill Dermaceuticals, Inc. would randomly assign numbers to the 4 treatment arms according to a schedule known only to its monitors: **the number assignment would be chosen by lottery**. A master key disclosing the identity of test materials would be kept sealed. It would accompany all test materials given to the investigators, but could only be opened in emergency situations.

Comments

1. The stated randomization procedure of random assignment by lottery does not seem to have been observed (see below).
2. As the sealed master key with identity of test materials accompanying all test materials might be opened in emergency situations, when a patient's hyperpigmentation cleared or when the first patient at the site completed the double-blind period, this could lead to unblinding of all patients before the end of the trial. The master key should not have been provided.

Populations for Analysis:

- Primary Efficacy Population: Intent-to-Treat Population = all patients who had at least one application of the study drug. The ITT population would use the LOCF technique for missing data.
- Secondary Efficacy Population: Evaluable Population = all patients who did not violate protocol and either a) completed 8 weeks of treatment, or b) completely cleared (Score = 0) before the 8th week of treatment.

Primary Efficacy Parameter: proportion of ITT patients in each treatment group with hyperpigmentation score = 0 at Week 8.

Secondary Efficacy Parameters:

- proportion of ITT patients in each treatment group with hyperpigmentation score = 0 at Week 4, or a hyperpigmentation score=0 or 1 at Week 4 and at Week 8.
- proportion of Evaluable Patients with a hyperpigmentation score=0 at Week 4 and Week 8, or a hyperpigmentation score=0 or 1 at Week 4 and at Week 8.
- Physician and Patient Global Evaluations

Statistical Methods: Comparability of demographic data for each treatment group was tested by comparing the 4 arms with respect to demographic variables. Sex and race were compared using the Chi Square test. Age was compared using analysis of variance. The primary efficacy analysis, a comparison of the proportion of ITT subjects with hyperpigmentation score=0 between each dyad arm with the triad arm (THR), was tested using the Cochran-Mantel Haenszel test, adjusting for center. Secondary efficacy parameters were similarly analyzed or by using the Chi-Square test. Subgroup analysis of the effects of age, sex, and race, would be performed if there were sufficient numbers of subjects.

Safety: If an appreciable number of patients reported adverse experiences, the incidence rates would be compared using Fisher's exact test.

8.2.1.4 Study Results

8.2.1.4.1 Demographics, Evaluability

Investigators: The Investigators were:

- Dr. H. Torok, Medina, OH.
- Dr. J. Willis, Atlanta, GA.
- Dr. N. Brody, Manhasset, NY

Comment The Investigators were qualified.

Enrollment is as follows:

	<u>THR</u>	<u>FH</u>	<u>FR</u>	<u>HR</u>
Torok	25	25	25	25
Willis	20	20	20	20
Brody	9	3	5	5
Total	54	48	50	50
Dropouts	6	5	8	10
Completed	48	43	42	40

The following gives the reasons for dropout at each site:

	<u>Torok</u>	<u>Willis</u>	<u>Brody</u>	<u>Total</u>
Lost to follow-up	6	0	11	17
Patient withdrawal	4	0	0	4
Adverse events	1	6	1	8
	11	6	12	29

Comment Dr. Brody had 22 patients enrolled and 12 dropped out (55%). This would make data interpretation difficult.

Demographics: Demographics of the study subjects is shown as follows:

		<u>THR</u>	<u>FH</u>	<u>FR</u>	<u>HR</u>
Age (Mean±SD)		46±10	46±11	45±10	42±10
Sex	Male	4	2	2	1
	Female	50	46	48	49
Race	Black	22	14	18	17
	Caucasian	23	30	27	28
	Hispanic	8	4	5	5
	Unknown	1	0	0	0
Skin Type	II	28	32	28	29
	III	17	11	17	16
	Unknown	9	5	5	5

Comment There were no significant differences between the treatment arms for demographic parameters.

Evaluability As the primary analysis is with the ITT population, every patient is supposed to be evaluable, with LOCF methodology. However, there are the following problems, which make the majority of patients unevaluable:

1. Randomization. The protocol stipulates randomization by lottery (vol 1.6, p. 7-0100). However, the randomization code was identical at all study sites. Moreover, the first 10 patients were all assigned to the THR arm, and the next 24 patients to one of the dyads. This sequence cannot be considered random. The trial cannot be considered a randomized study, especially in a small center like Dr. Brody's where there were only 22 patients with 12 dropouts.

2. Coding of test drugs. The tubes of the test drugs were color-coded. The protocol states all formulations would be supplied in identically appearing tubes (vol 1.6, p. 7-

0105). This might result in recognition of which tube was associated with what type of response and potential unblinding. In fact, Dr. Torok admitted that she could tell which treatment a patient was getting by the color on the crimp of the tube used. She even had the key of the color coding written on a case report form (See DSI report).

3. Unblinding from protocol. The protocol allowed opening of the master key envelope for unblinding when a patient achieved clearing of hyperpigmentation, so that he or she might go into the open phase for the dose-decreasing regimen. In a submission dated 10/28/99, the Applicant provides the dates of unblinding and gave the following information: "Unblinding of all patients occurred at the 8th week of treatment. Start: 5-14-98, Last: 9-4-98". Allowing the master key envelope to be opened before the end of the double-blind phase of the study would render total unblinding of the study site.

4. Enrollment criteria violation. Certain baseline criteria were not entered into some of the case report forms at Dr. Willis's and Dr. Brody's sites. For instance, patients were required to have stable hyperpigmentation for the 3 months prior to entry, and to have skin types II or III. Dr. Brody's site did not have skin type information. Some of Dr. Willis's patients (e.g., #s 24, 56, 59, 61) did not have the information on duration of hyperpigmentation. Furthermore, some of Dr. Willis's patients did not have any lesions on the dermogram at baseline (#s 7, 8, 33, 39, 44). For these patients, it would be unclear whether they fit the target population intended for labeling.

5. Dropouts. As discussed above, the majority of Dr. Brody's patients dropped out (55%; 11 of the 12 dropouts with no known reason, just labeled lost to follow-up). It may be unwise to extrapolate data from the remaining minority to the entire group enrolled. Such extrapolation is particularly difficult at this site, since the first 10 patients were all assigned to the THR arm.

6. Adverse event reporting. The Applicant excluded Dr. Willis's site in safety analysis, as safety data from his site was considered unreliable: Dr. Willis did not document anticipated adverse effects from the study medications as adverse events. This would render safety data from that site unevaluable.

7. Questionable data documentation. In the case report form for the baseline visit, none of Dr. Willis's 80 patients reported use of medication within 2 weeks of entry or were documented to be using any concomitant medications. Even if one disregards other medications, this scenario appears to be highly unlikely, given the fact that there were females of child-bearing potential enrolled at the site who might use oral contraceptives. Birth control measures were required for such women, and oral contraceptives were allowed only if the patient was previously using them. In addition, all but one patient reported past use of skin bleaches. The unreliability of baseline and safety data from Dr. Willis's site makes it difficult to accept the efficacy data from that site.

8. Ambiguity of hyperpigmentation score system. The scoring system (0-3) has overlapping descriptors that make interpretation difficult. Thus, score of 1 equals "*mild*" equals "*minimal* residual hyperpigmentation"; while 2 equals "*moderate*" equals "partial

or *mild persistent* hyperpigmentation". This confusing terminology does not allow easy interpretation of data other than a score of 0 (none, no abnormal hyperpigmentation or hypopigmentation). Since inclusion criteria required baseline hyperpigmentation score of ≥ 2 ("moderate", "partial or mild persistent hyperpigmentation"), it is not clear how efficacy data collected may be extrapolated to the population for which the drug is actually intended for.

Comment None of the three sites in this study may be considered to provide data with satisfactory quality for evaluation. Audits by DSI on Dr. Torok's and Dr. Willis's sites confirm this conclusion on those sites.

8.2.1.4.2 Efficacy

As none of the three sites in this study may be considered to provide data with satisfactory quality for evaluation, it is not possible to consider the study as adequate and well controlled. Although the Applicant presented primary efficacy analysis showing high statistical significance when comparing the triad, THR, vs each dyad at the end of the "double-blind" period, substantial evidence of superiority of the THR triad over the dyads remains to be obtained using data of proper quality. Therefore, efficacy data will not be presented here. Details are available in the Biometrics review by Dr. V. Freidlin.

It is noted that of the 43 patients who went into the long-term open phase of the study (Torok 23, Willis 20), 28 completed (Torok 20, Willis 8) and all patients repigmented.

Comment Efficacy obtained during the daily treatment phase was not sustained when THR dosing was tapered.

8.2.1.4.3 Safety

There were no serious adverse events or deaths reported. The Applicant presents the combined safety data of East and West studies but not an analysis of the adverse event incidences in each study. It is noted that the Applicant has excluded Dr. Willis's safety data because of incomplete reporting of adverse events. The study report does not specify adverse events other than local ones (erythema, peeling, burning, stinging, telangiectasia, rosacea, dermatitis, "others"; see Section 10 for the combined data).

Comment In this study, a total of 54 patients were enrolled into the THR arm and 48 completed 8 weeks of treatment. By excluding Dr. Willis's data, there were only 34 patients treated with THR (and 30 completed). These numbers fall short of those recommended for the assessment of safety in the ICH E1A guideline for products used in the long-term treatment of non-life-threatening conditions (300-600).

Adverse events leading to discontinuation were all in the double-blind phase:

Patient No.	Age/gender	Treatment	Adverse Event
HT22	49/F	HR	atrophy, irritation
NB3	32/F	THR	stinging and burning
IW14	48/F	HR	erythema, burning, peeling, stinging, contact dermatitis
IW43	50/F	FR	erythema, burning, peeling, stinging, contact dermatitis
IW49	59/F	FH	erythema, burning, stinging, contact dermatitis
IW50	22/F	HR	erythema, burning, peeling, stinging, contact dermatitis
IW59	66/M	HR	erythema, burning, peeling, stinging, contact dermatitis
IW78	50/M	THR	erythema, burning, peeling, stinging, contact dermatitis

There were no clinical laboratory data collected in this study.

8.2.1.5 Reviewer's Comments/Conclusions

1. This study is ~~not~~ considered adequate and well controlled because of problems in randomization, color coding of the drugs, unblinding from protocol, enrollment criteria violation, dropouts, adverse event reporting, questionable data documentation and ambiguity of hyperpigmentation grading system.
2. Because of data quality, substantial evidence of efficacy has not been established.
3. Repigmentation occurred when THR dosing was tapered.
4. Safety data are inadequate because of incomplete reporting from one Investigator and the small number of patients treated with THR. Although an analysis of adverse events reported in this study has not been provided by the Applicant, they appear to be primarily local at the application site.

8.2.2 Trial #2. Sponsor's Study 024 West. "Double-Blind Comparative Study Of A New Formulation For The Treatment Of Patients With Cutaneous [Started 3/17/98, completed 2/23/99]

8.2.2.1 Objectives: Identical to those in Study 024 East

8.2.2.2 Design: Identical to that in Study 024 East

8.2.2.3 Protocol Overview: Identical to that in Study 024 East, except for the planning on sample size. With 2 Investigator sites, each site would be expected to enroll approximately 25 per treatment arm to give 80% power at an alpha of 0.05.

8.2.2.4 Study Results

8.2.2.4.1 Demographics, Evaluability

Investigators: The Investigators were:
 Dr. P. Kelly, Los Angeles, CA.
 Dr. J. Wieder, Los Angeles, CA..

Comment The Investigators were qualified.

Enrollment is as follows:

	<u>THR</u>	<u>FH</u>	<u>FR</u>	<u>HR</u>
Kelly	30	30	30	30
Wieder	15	13	14	13
Total	45	43	44	43
Dropouts	9	8	13	17
Completed	36	35	31	26

The following gives the reasons for dropout at each site:

	<u>Kelly</u>	<u>Wieder</u>	<u>Total</u>
Lost to follow-up	28	2	30
Protocol deviation	2	2	4
"Other"	9	0	9
Adverse events	1	3	4
	40	7	47

Comment Dr. Kelly's site had substantial dropout (120 enrolled and 40 dropped out; 33%).

Demographics: Demographics of the study subjects is shown as follows:

		<u>THR</u>	<u>FH</u>	<u>FR</u>	<u>HR</u>
Age (Mean±SD)		40±8	40±7	39±7	39±7
Sex	Male	3	3	4	2
	Female	42	40	40	41
Race	Black	1	1	2	1
	Caucasian	13	6	7	10
	Hispanic	29	35	34	31
	Unknown	2	1	1	1
Skin Type	II	19	21	19	19
	III	26	22	24	22
	Unknown	0	0	1	2

Comment There were no significant differences between the treatment arms for demographic parameters.

Evaluability As the primary analysis is with the ITT population, every patient is supposed to be evaluable, with LOCF methodology. However, there are problems similar to those in the East study which make the majority of patients unevaluable:

1. Randomization. See Section 8.2.1.4.1.
2. Coding of test drugs. See Section 8.2.1.4.1.
3. Unblinding from protocol. See Section 8.2.1.4.1.
4. Enrollment criteria violation. Certain baseline criteria were not entered into some of the case report forms at Dr. Kelly's site:
 - Sixty-two patients did not have information on duration of hyperpigmentation at baseline (52%). Three patients lacked information on whether disease had been stable on entry.
 - One patient had no lesion shown on dermogram.
5. Dropouts. There were very significant dropouts at Dr. Kelly's site: 16/30 (53%) for the HR arm and 11/30 (37%) for the FR arm.
6. Questionable data documentation at Dr. Kelly's site:
 - The baseline hyperpigmentation scores of 38 of Dr. Kelly's patients were originally not meeting entry criterion on the case report form (score of 2 or greater). Of these, 29 had the score altered to 2 or 3 (changes dated at least 2-3 weeks after visit, up to 2-4 months later), and 9 records were not changed. The Applicant treated these 9 patients as dropouts.
 - The case report forms from Dr. Kelly's site show that at baseline, all but two patients answered "NO" to the questions on (1) use of OTC or prescriptions in past 2 weeks, and (2) use of concomitant medication. Like the data in Dr. Willis in the East study, this would seem highly unlikely.
 - Start and end date of adverse events were lacking in six patients (reported by DSI).
7. Ambiguity of hyperpigmentation score system. See Section 8.2.1.4.1.

Comment At least Dr. Kelly's site in this study may be considered to provide data with questionable quality for evaluation. Audit by DSI on Dr. Kelly's site confirms this conclusion.

8.2.2.4.2 Efficacy

The questionable data quality at Dr. Kelly's site does not allow data from that site to be considered as adequate and well controlled. Therefore, only Dr. Wieder's data are presented here (from Dr. V. Freidlin's analysis):

Primary Endpoint:

Proportion of Patients with Hyperpigmentation Score=0 at Week 8				
	THR	FH	FR	HR
Proportion	3/15 (20%)	2/13 (15%)	1/14 (7%)	2/13 (15%)
p-value (triad vs dyad)		1.0	0.6	1.0

Secondary Endpoints:

Only the physician global is presented here. The protocol also had other secondary endpoints which depended on hyperpigmentation scores=0 or 1. As discussed above, hyperpigmentation scores of 1 and 2 are ambiguous and not interpretable. These will not be further elaborated upon.

Proportion of Patients with "Cleared" by Physician Global Assessment at Week 8				
	THR	FH	FR	HR
Proportion	3/15 (20%)	2/13 (15%)	1/14 (7%)	2/13 (15%)
p-value (triad vs dyad)		1.0	0.6	1.0

Comment The data are inadequate to support superiority of THR vs the dyads.

It is noted that of the 38 patients who went into the long-term open phase of the study (Kelly 25, Wieder 13), 6 completed (Kelly 4, Wieder 2) and all patients repigmented.

8.2.2.4.3 Safety

There were no serious adverse events or deaths reported. The Applicant presents the combined safety data of East and West studies but not an analysis of the adverse event incidences in each study. The application does not specify any adverse events other than local ones (erythema, peeling, burning, stinging, telangiectasia, rosacea, dermatitis, "others"; see Section 10 for the combined data).

Comment In this study, a total of 45 patients were enrolled into the THR arm and 36 completed 8 weeks of treatment. Even when combined with the East study (99 enrolled; 84 completed) these numbers fall short of those recommended for the assessment of safety in the ICH E1A guideline for products used in the long-term treatment of non-life-threatening conditions (300-600).

Adverse events leading to discontinuation were as follows:

Patient No.	Age/gender	Treatment	Adverse Event
PK18	44/F	HR	erythema, peeling, milia
JW10	51/F	THR	breast cancer recurrence (long-term follow-up phase)
JW24	36/F	FH	red dry eyes, sore throat and headache
JW41	41/F	THR	increased "photosensitivity" (given Cipro); erythema
JW46	45/F	THR	erythema
JW52	29/F	THR	intense heat, erythema, peeling

Comment The patient disposition data showed 4 dropouts due to adverse events. Even by excluding — who dropped out at the long-term follow-up phase, there is one patient discrepancy between the two sets of data.

There were no clinical laboratory data collected in this study.

8.2.2.5 Reviewer's Comments/Conclusions

1. Part of this study (from Dr. Kelly's site) is not considered adequate and well controlled because of data quality.
2. Substantial evidence of efficacy has not been established with demonstration of superiority of triad over dyads in achieving hyperpigmentation score=0 at week 8.
3. Repigmentation occurred when THR dosing was tapered.
4. Safety data are inadequate because of the small number of patients treated with THR. Although an analysis of adverse events reported in this study has not been provided by the Applicant, they appear to be primarily local at the application site.

9 Overview of Efficacy

The Applicant developed the current triad formulation (fluocinolone acetonide 0.01%, hydroquinone 4%, tretinoin 0.05%) for the treatment of hyperpigmentation because there has been evidence in the literature that combined use of a topical corticosteroid, hydroquinone and tretinoin provided efficacy. However, the literature studies did not actually use the current combination. Two articles are presented to support this NDA:

A New Formula For Depigmenting Human Skin, By A. Kligman And I. Willis. Arch Dermatol 1975; 111:40-48.

The formulation studied in this article was a fixed combination of 0.1% dexamethasone, 5% hydroquinone and 0.01% tretinoin. Dosing was twice daily for 5-7 weeks. Since (1) the strengths of hydroquinone and tretinoin differ from those of the current formulation, and dexamethasone has been replaced by fluocinolone acetonide, and (2) the dosing regimen is different, the data in this article would not support safety and efficacy of the current triad.

Topical Tretinoin, Hydroquinone, And Betamethasone Valerate In The Therapy Of Melasma, By S. Gano And R. Garcia. Cutis 1979; 23:239-241.

The medications studied in this article were not in a fixed combination. Patients applied tretinoin 0.05% cream in the morning, betamethasone valerate 0.1% cream in the afternoon and hydroquinone 2% cream before bedtime. Since (1) the strength of hydroquinone differs from that in the current formulation, and betamethasone valerate has been replaced by fluocinolone acetonide, and (2)

the dosing regimen is different, the data in this article also would not support safety and efficacy of the current fixed triad combination.

Dose-ranging. Dose-ranging studies have not been conducted in the development of the current triad fixed combination.

Trials for Safety/Efficacy. Two clinical studies were performed to examine safety and efficacy in "cutaneous melanosus" with an identical protocol (024): East study and West study. They were done to compare the THR triad combination with each of the 3 possible dyads in order to satisfy the combination policy. The Applicant considers the studies adequate and well controlled phase 3 trials.

Study No.	Site(s)	Sample Size (M:F)	Dose	Treatment Duration	Control	Design
Controlled						
24 East	3	202 (9:193)	THR* qd to face	8 wks double-blind, 12 wks open (THR)	TH, HR or TH qd to face	randmized, multi-center, comparative, parallel-gp
24 West	2	175 (12:163)	same as above	same as above	same as above	same as above

*THR=fluocinolone acetonide 0.01%, hydroquinone 4%, tretinoin 0.05% combination, FH=fluocinolone acetonide 0.01%, hydroquinone 4% combination, HR=hydroquinone 4%, tretinoin 0.05% combination, FR=fluocinolone acetonide 0.01%, tretinoin 0.05% combination.

The hyperpigmentation studied in these trials was restricted to chloasma/melasma in patients with Fitzpatrick skin types II and III. However, these studies cannot be considered adequate and well controlled because of problems in randomization, color coding of the drugs, unblinding from protocol, enrollment criteria violation, dropouts, adverse event reporting, questionable data documentation and ambiguity of hyperpigmentation grading system. Such problems affecting the data from 4 out of the 5 study sites (Torok, Willis, Brody, Kelly) make it impossible to yield substantial evidence to establish efficacy in the treatment of "cutaneous melanosus" or even chloasma/melasma. The remaining center (Wieder) had only up to 15 patients per study arm, and superiority of the triad over the dyads was not demonstrated at week 8 of daily treatment. The problems with these studies can be summarized as follows:

Problems associated with design that made the studies not adequate and well controlled:

1. Randomization of the first 34 patients not random (first 10 with THR and 11-34 with dyads).
2. Study medication tubes not identical (color-coded), rendering recognition of test drug and unblinding.
3. Master key envelope to be opened in emergency or when a patient reached hyperpigmentation score=0 or when the first patient completed the first 8 week "double-blind" period, thus breaking the blind.
4. Hyperpigmentation scoring ambiguous: score of 1=mild=minimal, score of 2=moderate=mild

Problems concerning conduct of the studies:

- Willis – (1) None apparently had (a) use of any medication within 2 weeks of entry, or (b) concomitant medications; or (2) past use of bleaching agents (except #55, who answered yes). This is highly unlikely.
- Brody – (1) None had skin type documented (the study restricted to skin types 2 and 3); (2) Lacking signature or questionable signatures on CRFs.
- Kelly – (1) None apparently had (a) use of any medication within 2 weeks of entry, or (b) concomitant medications [except for 2 patients]; (2) duration of hyperpigmentation for Patients #13 to #72, #74 and #80 = blank; (3) changes in hyperpigmentation scores on the admission form (see below) dated at least 2-3 weeks after the visit, could be 2-4 months later, except for #58 (same as admission visit).

The following are additional enrollment criteria violations (from baseline CRF; patient numbers provided in Table) that render study population undefinable (see Section 8.1.2.3.1.1 for Inclusion and Exclusion criteria):

East Study

THR	TH	FT	HF
IS-7 No lesion* IS-8 No lesion	IS-33 No lesion IS-56 [stab] IS-59 [stab]		IS-24 [stab] IS-39 No lesion IS-44 No lesion IS-61 [stab]
NB-3 [prev 2wk med=yes/no?] NB-6 [prev 2wk med=yes/no?] NB-8 [stab]	NB-11 [stab] NB-18 [stab]	NB-17 [stab] NB-19 [stab]	
HT-69 Will start on BCP HT-84 used hydrquinone, retin-A & Azelex up to entry			HT-72 Will start BCP

*No lesion=no lesion documented in baseline dermogram; [stab]=question on stability of disease not answered (inclusion criterion 3); BCP=birth control pill; IS=Willis, NB=Brody, HT=Torok.

West Study

THR	TH	FT	HF
JW-9 Azelex cream	JW-14 Azelex cream JW-37 Karon lotion	JW-12 Cutivate cream to day1 JW-30 [stab]	
PK-3 [score 1→2] PK-4 [score 1→2] PK-5 [score 1→2] PK-6 [score 1→2] PK-7 [score 1→3] PK-10 No lesions* PK-52 [score 1→2] PK-62 [score 1→2] PK-69 [stab] PK-83 [score <2]	PK-11 [score 1→2] PK-18 [score 1→2] PK-20 [score 1→2] PK-22 [score 1→2] PK-32 [BL<2] PK-45 [score 1→2] PK-50 [score 1→2] PK-54 [score 1→2] PK-56 [score 1→2] PK-63 [BL<2] PK-106 [stab]	PK-12 [BL<2] PK-19 [score 1→2] PK-25 [score 1→2] PK-38 [score 1→2] PK-48 [BL<2] PK-55 [score 1→2] PK-66 [score 1→2] PK-77 [BL<2] PK-85 [score 1→2]	PK-15 [score 1→2] PK-24 [score 1→3] PK-26 [score 1→2] PK-28 [score 1→2] PK-31 [BL<2] PK-39 [score 1→2] PK-44 [BL<2] PK-49 [score 1→2] PK-60 [score 1→2] PK-65 [BL<2] PK-72 [score 1→2] PK-73[stab]

*No lesion=no lesion documented in baseline dermogram; [stab]=question on stability of disease not answered (inclusion criterion 3); [score 1→2] or [score 1→2] refers to late corrections for baseline hyperpigmentation scores; [score <2] refers to baseline hyperpigmentation score violation (inclusion criterion 2 required score of ≥2); JW=Wieder, PK=Kelly

Repigmentation occurred when THR dosing was tapered in all patients whose hyperpigmentation initially cleared and had long-term follow-up.

Subset analyses with stratification by age, sex and race would not be appropriate with the current data, as the patient numbers are too small in the remaining reliable center (Wieder; up to 15 per arm) to yield meaningful analysis.

Conclusions on Efficacy

1. The clinical trials were not designed to support “cutaneous melanosis” *per se* but chloasma/melasma.
2. Because of data quality, substantial evidence for efficacy of the fixed triad combination has not been established for the treatment of chloasma/melasma.
3. In patients who had clearing of hyperpigmentation, the pigmentation recurred upon tapering of the dosing of the triad product.

10 Overview of Safety

Dataset. The following studies have been conducted in support of the safety of the triad combination:

Study No.	Site(s)	Sample Size (M:F)	Dose	Treatment Duration	Control	Design
Controlled Studies						
24 East	3	202 (9:193)	THR* qd to face	8 wks double-blind, 12 wks open (THR)	TH, HR or TH qd to face	randomized, multi-center, comparative, parallel-gp
24 West	2	175 (12:163)	same as above	same as above	same as above	same as above
Dermal Safety Studies on Healthy Adult Volunteers						
56 (Irritancy/sensitization)	1	49** (18:31)	THR 0.2 gm/app	<u>Induction</u> 9 app 48-hr patches over 3 weeks <u>Challenge</u> 2 app 48-hr patches	Vehicle 0.2 gm/app	randomized, double-blind intra-individual
57 (Photoallergenicity)	1	26** (13:13)	THR 10 µL/cm ² induction 5 µL/cm ² challenge over 3 weeks	<u>Induction</u> 6 app 24-hr patches (2 sites each time) <u>Challenge</u> 24-hr patches (2 sites)	Vehicle	open study
58 (Phototoxicity)	1	10 (4:6)	THR 5 µL/cm ²	6-hr patch	Vehicle 5 µL/cm ²	single-blind
59 (Irritancy/sensitization)	1	56** (17:39)	Fluo* acetamide hydroquinone tretinoin 0.2 gm/app	same as Study 56	Vehicle 0.2 gm/app	same as Study 56

*THR=fluocinolone acetamide 0.01%, hydroquinone 4%, tretinoin 0.05% combination, FH=fluocinolone acetamide 0.01%, hydroquinone 4% combination, HR=hydroquinone 4%, tretinoin 0.05% combination, FR=fluocinolone acetamide 0.01%, tretinoin 0.05% combination, app=application, Fluo=fluocinolone; **Excluding dropouts.

Demographics. The demographics parameters were similar in these two studies. The data are shown as follows:

	Study	THR	FH	FR	HR
Age (Mean±SD)	East	46±10	46±11	45±10	42±10
	West	40±8	40±7	39±7	39±7
Sex (M:F)	East	4:50	2:46	2:48	1:49
	West	3:42	3:40	4:40	2:41
Race (B:C:H:U)*	East	22:23:8:1	14:30:4:0	18:27:5:0	17:28:5:0
	West	1:13:29:2	1:6:35:1	2:7:34:1	1:10:31:1
Skin Type (I:II:III:Unknown)	East	28:17:9	32:11:5	28:17:5	29:16:5
	West	19:26:0	21:22:0	19:24:1	19:22:2

*B:C:H:U=Black:Caucasian:Hispanic:Unknown; THR=fluocinolone acetamide 0.01%, hydroquinone 4%, tretinoin 0.05% combination, FH=fluocinolone acetamide 0.01%, hydroquinone 4% combination, HR=hydroquinone 4%, tretinoin 0.05% combination, FR=fluocinolone acetamide 0.01%, tretinoin 0.05% combination, app=application, Fluo=fluocinolone; **Excluding dropouts.

Comment Both studies enrolled primarily females. The mean ages were slightly younger in the West study. The East study had mostly Caucasians and African Americans, while the West study had Hispanics as the majority racial group; this is reflected in the skin type distribution of the two studies.

Drug Exposure. Although 377 patients were enrolled in the two studies, the number of patients exposed to 8 weeks of use of the triad combination with daily application to the face (as for proposed labeling) was 48 (only 30 if Dr. Willis's data are excluded) in the East study and 36 in the West study. This gives a total of 84 (66, if Dr. Willis's data are excluded). This falls far short of the recommendations in the ICH E1A guideline concerning patient numbers to be studied for products developed for the long-term treatment of non-life-threatening conditions (300-600).

Only 32 patients completed the long-term phase of the study (dose tapering of the triad down to 3x/wk for 4 weeks, 2x/wk for 4 weeks, weekly for 4 weeks, with or without an interim 8 weeks of additional triad daily dosing after the first 8 weeks of daily dosing). Since repigmentation occurs when dosing is tapered, it may be anticipated that the product will be intended for chronic use. The safety data on long-term daily use are inadequate from these two studies to support long-term usage.

10.1 Significant/Potentially Significant Events

10.1.1 Deaths No deaths were reported.

10.1.2 Other Significant/Potentially Significant Events

Serious adverse events. The Application does not list any "serious" adverse events. However, it is noted that among the patients discontinued due to adverse events, one patient withdrew because of breast cancer recurrence (in the long-term phase) (patient JW10).

Discontinuations from adverse events.

	Patient No.	Age/gender	Treatment	Adverse Event
East Study	HT22	49/F	HR	atrophy, irritation
	NB3	32/F	THR	stinging and burning
	IW14	48/F	HR	erythema, burning, peeling, stinging, contact dermatitis
	IW43	50/F	FR	erythema, burning, peeling, stinging, contact dermatitis
	IW49	59/F	FH	erythema, burning, stinging, contact dermatitis
	IW50	22/F	HR	erythema, burning, peeling, stinging, contact dermatitis
	IW59	66/M	HR	erythema, burning, peeling, stinging, contact dermatitis
	IW78	50/M	THR	erythema, burning, peeling, stinging, contact dermatitis
West Study	PK18	44/F	HR	erythema, peeling, milia
	JW10	51/F	THR	breast cancer recurrence (long-term follow-up phase)
	JW24	36/F	FH	red dry eyes, sore throat and headache
	JW41	41/F	THR	increased "photosensitivity" (given Cipro); erythema
	JW46	45/F	THR	erythema
	JW52	29/F	THR	intense heat, erythema, peeling

10.1.3 Overdosage exposure

No information is provided in the NDA. The following is derived from the labels of the drug products containing the active ingredients:

- Topical corticosteroid class labeling: Topically applied PRODUCT can be absorbed in sufficient amounts to produce systemic effects.
- Hydroquinone 4% cream (Lustra, Lustra-AF): There have been no systemic reactions reported from the use of topical hydroquinone. However, treatment should be limited to relatively small areas of the body at one time, since some patients experience a transient skin reddening and a mild burning sensation which does not preclude treatment.
- Tretinoin 0.05% emollient cream (Renova): Application of larger amounts of medication than recommended will not lead to more rapid or better results, and marked redness, peeling, or discomfort may occur. Oral ingestion of the drug may lead to the same side effects as those associated with excessive oral intake of Vitamin A.

10.2 Other Safety Findings

10.2.1 ADR Incidence Tables

ADR Tables. The NDA does not provide the ADR incidence Tables for the individual clinical trials: East study and West study. The combined data are presented in the Integrated Summary of Safety as follows. This analysis excluded the 80 patients at Dr. Willis's site (20 per arm):

Adverse event	THR (N=79)	FH (N=74)	FR (N=73)	HR (N=71)
Erythema	74.4% (59)*	35.2% (26)	41.9% (31)	61.6% (44)
Peeling	58.2% (46)	7.0% (5)	40.5% (30)	67.1% (48)
Burning	27.8% (22)	5.6% (4)	24.3% (18)	30.1% (21)
Stinging	21.5% (17)	7.0% (5)	17.6% (13)	24.7% (18)
Telangiectasia	15.2% (12)	4.2% (3)	4.1% (3)	2.7% (2)
Rosacea	11.4% (9)	5.6% (4)	6.8% (5)	9.6% (7)
Dermatitis	3.8% (3)	1.4% (1)	2.7% (2)	5.5% (4)
"Other"	20.3% (16)	18.3% (14)	16.2% (12)	23.3% (17)

*The application only gives percent incidence. The absolute numbers have been back calculated from the percentages.

Comment The dyad FH combination appears to give the least application reactions and the triad THR and the dyad HR combinations gave higher incidences of local reactions than the two dyads FH and FR. This appears to be especially so for the THR triad in terms of telangiectasia and rosacea. Although statistical analysis of these data has not been provided, the triad THR does not appear to be superior in terms of safety when compared to the dyads.

Severity of adverse events. The application has not separated the analysis of severity in terms of the treatment arms. These have been pooled as in the following Table. Nevertheless, it can be observed that most of the local adverse events were of mild severity, with less frequent incidence of "moderate" events, and rare occurrence of "severe" reactions.

Adverse event	Mild	Moderate	Severe
Erythema	138 (50%)	20 (7%)	2 (1%)
Peeling	115 (41%)	12 (4%)	3 (1%)
Burning	51 (18%)	12 (4%)	3 (1%)
Stinging	40 (14%)	9 (3%)	2 (1%)
Telangiectasia	19 (10%)	1 (<1%)	-
Rosacea	18 (7%)	7 (2%)	-
Dermatitis	7 (3%)	3 (1%)	-

"Other" adverse events. There was approximately 20% incidence of "other" adverse events in each treatment arm. The Applicant did not provide a breakdown of these "other" events and simply made this statement:

"Aside from the commonly observed adverse events, expected or otherwise, other reactions that were observed in the study with some frequency are itching, acne breakout, dryness of the skin, and papules. Other adverse reactions observed with minimal incidence (one or two) are herpes zoster, cheilitis, pulled muscle, tooth ache, stye, swelling of the face, scratch, migraine, strep throat, sore throat, urinary tract infection, heat rash, angioma, poison ivy, impetigo, herpes simplex. Nervous stasis, anxiety depression, excessive bleeding, and breast cancer, all of which are not related to the study drugs."

Comment It is not possible to interpret the data without knowledge of the events in relation to the treatment groups.

Adverse events in the long-term phase. The report notes that some "mild erythema, peeling" occurred when dose tapered to every other day. No adverse events were reported with 2x/week or 1x/week applications.

10.2.2 Laboratory Findings, Vital Signs, ECGs

No clinical laboratory data were collected in the trials in support of this NDA.

10.2.3 Special Studies

Four dermal safety studies were conducted on healthy volunteers in the facility of

<u>Study No.</u>	<u>Site(s)</u>	<u>Sample Size (M:F)</u>	<u>Dose</u>	<u>Treatment Duration</u>	<u>Control</u>	<u>Design</u>
56 (Irritancy/sensitization)	1	49** (18:31)	THR* 0.2 gm/app	<u>Induction</u> 9 app 48-hr patches over 3 weeks <u>Challenge</u> 2 app 48-hr patches	Vehicle 0.2 gm/app	randomized, double-blind intra-individual
57 (Photoallergenicity)	1	26** (13:13)	THR 10 µL/cm ² induction 5 µL/cm ² challenge	6 app 24-hr patches over 3 weeks (2 sites each time) <u>Challenge</u> 24-hr patches (2 sites)	---	open study
58 (Phototoxicity)	1	10 (4:6)	THR 5 µL/cm ²	6-hr patch	Vehicle 5 µL/cm ²	single-blind
59 (Irritancy/sensitization)	1	56** (17:39)	Fluo* acetamide hydroquinone tretinoin 0.2 gm/app	same as Study 56	Vehicle 0.2 gm/app	same as Study 56

*THR=fluocinolone acetamide 0.01%, hydroquinone 4%, tretinoin 0.05% combination, Fluo=fluocinolone, app=application.
**Excluding dropouts.

Study 56. Repeat Insult Patch Test [Started 8/25/97, completed 10/24/97; unblinded 11/4/97 (double-blind)]

This was a standard irritancy/sensitization study conducted by Dr. I. Willis. It consisted of 3 phases:

Induction: THR (site 1) and vehicle (site 2) patches were placed on the scapular region for 48 hours (72 hours over weekend) for each application. Nine consecutive patches were placed over 3 weeks.

Rest: 2 weeks.

Challenge: 2 successive patches, each over 48 hours, were applied.

Scoring for irritation was: 0=negative, 1=slight erythema, 2=erythema/induration, 3=erythema/irritation/vesicles, 4=erythema/induration/bullae.

There were 56 subjects with 7 dropouts so that 49 completed the study (18 males and 31 females). During the induction phase, 45 subjects developed "irritation" (including hyperpigmentation) with the THR triad, typically starting at day 2 and continuing to the end of induction:

Irritation scores of 1 or 2 with hyperpigmentation at some point	10
Irritation score of 2	6
Irritation score of 1	18
Irritation scores of 1, 2 and 3	6
No irritation, slight hyperpigmentation	5
No irritation, no hyperpigmentation	4

No sensitization was documented.

Comment This study had only 49 completed patients and would not fulfil the regulatory requirement for a study on sensitization potential.

Study 57. Photocontact Allergenicity Study for Cream [Started 10/3/97, completed 12/8/97; open study]

This study was conducted by Dr. I. Willis and Dr. J. Menter. It was an open study testing only the THR triad without control. THR occlusive patches were applied at 2 sites, using 10 µL/cm² on the mid or lower back in the induction phase. They were applied for 24

hours, removed, site 1 irradiated, and site 2 held as control. This sequence of events was repeated 2x/week for 3 weeks. Light source was a _____ and the irradiation dose used was _____. Ten days after the last induction exposure, challenge was done with similar occlusive application, using _____ untreated areas (2 sites). After removal, site 1 was irradiated with UVA at _____. Readings of the sites were done 24 and 48 hours later.

There were 29 patients enrolled and 3 dropped out. Of the 26 who completed the study, there were 13 males and 13 females. The following results on irritation during induction were presented:

	No reaction	With Irritation		
	Both sites	Site 1 only	Site 2 only	Both sites
Subject numbers	3	6	2	15

*site 1=UVA irradiated site, site 2=control site

One subject had a positive challenge, showing reaction at 48 and 72 hours. The subject was rechallenged with the monads and vehicle. All sites had positive reactions 2+ (erythema with infiltration raised, spreading beyond the borders, with or without vesicles) to 3+ (large vesiculobullous, vividly red, infiltrated plaques) after 48 hours. Retesting was further done at 4 new sites: 3 sites with blank patches and then UVA and one site to a vial of hot water. The irradiated sites had no reaction. The site subjected to hot water showed a positive reaction (details not given), but no reactions were observed at 24 or 72 hours.

Comment

1. The Applicant did not provide the UV absorption spectrum of the drug product. Without this information, it is not clear whether the photo-testing or the wavelengths chosen is appropriate.
2. The sample size appears to be adequate for photoallergenicity testing, although a larger sample would yield better predictive information.
3. The positive challenge test in one patient suggests photoallergenicity to vehicle, as positive reactions were seen with all monads and vehicle as well. The additional testing with blank patches and hot water showed that the reaction was not due to irradiation. Although the study report concluded the reaction to hot water as consistent with heat irritation, this is not pertinent to the challenge finding with THR.

Study 58. Phototoxicity Study of _____ (Started 9/22/97, completed 9/26/97; unblinded 9/26/97 (single-blind))

This study was conducted by Dr. J. Menter. It consisted of 6-hour occlusive patches with _____ of THR or vehicle, each to two sites. One set of sites was irradiated with UVA and visible light _____ of UVA) after patch removal. Light source was a _____ Reactions were graded immediately, 24 and 48 hours after irradiation.

Ten subjects were enrolled and completed the study. No evidence of phototoxicity was observed.

Comment

1. The Applicant did not provide the UV absorption spectrum of the drug product. Without this information, it is not clear whether the photo-testing or the wavelengths chosen is appropriate.
2. The sample size appears to be adequate for phototoxicity testing.

Study 59. The Contact Irritation and Sensitization Potential of _____ Cream [Started 3/30/98, completed 5/15/98; unblinded 5/18/98 (double-blind)]

This study was conducted by Dr. I. Willis. It had a protocol identical to that of Study 56, only to differ in the materials to be tested. In this study, the 3 monad ingredients of THR and the vehicle cream were studied. Sixty healthy volunteers were enrolled and 56 completed (17 males and 39 females). Results are as follows:

Site	Test Drug	Induction	Challenge
1	tretinoin 0.05%	No irritation	No reaction
2	hydroquinone 4%	25 with slight erythema, 3 with erythema/induration	No reaction
3	fluocinolone acetonide 0.01%	3 with slight erythema	No reaction
4	vehicle	11 with slight erythema, 1 with erythema/induration	No reaction

Comment This study did not test the triad combination but only the monads and vehicle. It is not of regulatory utility. In addition, the tretinoin site showed no irritation while the vehicle site had 12 patients who showed reaction. These data are highly unusual.

10.2.4 Drug-Demographic Interactions

Insufficient reliable data are available to allow a meaningful analysis of drug-demographic interactions.

10.2.5 Drug-Disease Interactions

The Applicant notes interaction in patients that had telangiectasias and/or rosacea prior to entry, with slight exacerbation of these lesions by the use of the THR triad (see Section 10.2.1).

10.2.6 Drug-Drug Interactions No drug-drug interaction studies have been performed. The clinical trials excluded patients who needed use of photosensitizing drug products, PUVA treatments, other bleaching agents and/or hydroxy acid products. Hormonal treatment that had remained stable with dose and administration within 3 weeks of entry was allowed. The most common concomitant medications were non-steroidal anti-inflammatory agents, analgesics or cold medications. An analysis of the effect of these concomitant medications or hormonal treatment on the safety or efficacy of THR triad combination has not been provided.

10.2.7 Withdrawal Phenomena/Abuse Potential

The application did not address withdrawal phenomenon or abuse potential. It is well known that topical corticosteroid treatment may be associated with "rebound phenomenon". In the clinical trials for the treatment of chloasma/melasma in this NDA, tapering of THR was associated with repigmentation in all cases.

10.2.8 Human Reproduction Data

No information is available on the triad THR combination regarding effects on human reproduction. Products containing the active ingredients, fluocinolone acetonide, tretinoin, and hydroquinone are under pregnancy category C.

10.2.9 Specific Adverse Effects of the Ingredients

The following adverse effects are in the labels of the active ingredients:

Topical Corticosteroid Class labeling:

- These reactions are listed in an approximately decreasing order of occurrence: burning, itching, irritation, dryness, folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, skin atrophy, striae, and miliaria.
- Topically applied PRODUCT can be absorbed in sufficient amounts to produce systemic effects (HPA axis suppression).

Hydroquinone:

Lustra:

- Occasional cutaneous hypersensitivity (localized contact dermatitis)
- On rare occasions, a gradual blue-black darkening of the skin may occur (ochronosis).

Melanex:

- The following have been reported: dryness and fissuring of the paranasal and infraorbital areas, erythema, and stinging.
- Hydroquinone has been known to produce irritation and sensitization in susceptible individuals.

Solaquin:

- Hydroquinone is a skin bleaching agent which may produce unwanted cosmetic effects if not used as directed.
- Minor redness is not a contraindication, but where there is itching or vesicle formation or excessive inflammatory response, further treatment is not advised.
- Occasional hypersensitivity (localized contact dermatitis).

Tretinoin:

Retin-A:

- The skin of certain sensitive individuals may become excessively red, edematous, blistered, or crusted.
- True contact allergy to topical tretinoin is rarely encountered.
- Temporary hyper- or hypopigmentation has been reported with repeated application of tretinoin.
- Some individuals have been reported to have heightened susceptibility to sunlight while under treatment with tretinoin.

Renova:

- Local reactions such as peeling, dry skin, burning, stinging, erythema, and pruritus were reported by almost all subjects during therapy with RENOVA.

Comment The adverse effects of the THR triad combination are consistent with those of the active ingredients. However, it is noted that in the clinical trials of this NDA, hypopigmentation and ochronosis have not been reported.

One of the inactive ingredients is sodium metabisulfite. The warning is present in some hydroquinone drug products (e.g., Solaquin) concerning this ingredient: "Contains sodium metabisulfite, a sulfite that may cause serious allergic type reactions (e.g., hives, itching, wheezing, anaphylaxis, severe asthma attack) in certain susceptible persons."

10.3. Safety Conclusions

1. The safety database is inadequate, and the sample size, especially for anticipated long-term usage, is insufficient to support evaluation of rare events.
2. The adverse effects of the THR triad appear to be primarily local. The triad THR combination appears to be no better than the dyads in terms of local adverse reactions, and in fact its use may be more prone to be associated with telangiectasia and rosacea.

3. Systemic effects, especially systemic levels and HPA axis suppression, have not been determined.
4. The study on contact sensitization potential is inadequate because of small sample size.

11 Risk-Benefit Analysis

- This application has not demonstrated superiority of THR triad over the component dyads, and thus efficacy for the treatment of "cutaneous melanosis" or chloasma/melasma has not been established.
- The triad THR combination appears to be no better than the dyads in local adverse reaction incidences, and in fact its use may be more prone to be associated with telangiectasia and rosacea. Moreover, safety has not been adequately studied because of (1) lack of sufficient long-term data and (2) small number of patients completing one course of THR triad therapy in the clinical studies and having reliable data (66).
- There is insufficient information on systemic toxicity because of lack in vivo studies on systemic absorption and on HPA axis.
- The lack of demonstrated efficacy for "cutaneous melanosis" and the potential increase in local toxicity, together with inadequate information on systemic toxicity argues against approval of THR for its intended use according to the proposed labeling.

12 Labeling Recommendations

As this application is not recommended for approval, no recommendation on labeling will be made.

13 Recommendations

13.1 Approval, Approvable, Non-approval This NDA is not recommended for approval.

13.2 Phase 4 Studies Not applicable

13.3 Labeling changes Not applicable

13.4 Other

1. It is recommended that two adequate and well controlled studies be conducted to support a specific hyperpigmentation indication, under Good Clinical Practice conditions. There should be sufficient follow-up for determination of safety for long-term use and less restrictive enrollment criteria (e.g., skin types).
2. A study with adequate sample size should be performed to determine the contact sensitization potential of the THR triad cream.
3. Studies on systemic absorption and HPA axis function should be provided to support systemic safety of the THR combination product.

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1-12-00

Hon-Sum Ko, M.D.

cc: NDA 21-112

HFD-540

HFD-540/CSO/Lutwak

HFD-540/CHEM/Pappas

HFD-540/PHARM/Nostrandt

HFD-880/BIOPHARM/Lee

HFD-540/MO/Walker/Ko

HFD-725/BIOMETRICS/Freidlin

sw 1-12-00

QW 1/13/00

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Appendix I

Contents in Forms FDA 483 Issued to the Investigators Audited

Dr. Helen Torok:

1. At least 24 tubes of _____ were received and used on at least 12 patients prior to the start of this study. At least 40 sample tubes were used to treat patients after the study ended.
2. The tubes of study cream were color coded (not identical). The blind was broken after about 5 weeks when the first subject reached an efficacy score of 0 and the master key envelope was opened.
3. Treatment numbers were to be allocated sequentially but many subjects were not in chronological order. Five subjects who entered the study a second time were purposely allocated to the _____ group.
4. Drug accountability records
 - a. There were no receipt records for the initial tubes for subjects #22-100, for the third set of tubes for #4 and 35, or for replacement tubes for #20, 21, 32, 35, 40, 42, and 45.
 - b. The Weekly Progress Report sheets did not document the initial dispensing of tubes for 12 subjects.
 - c. There were many instances where the dispensing/return information on the Weekly Progress Report sheets did not agree with information in the Case Report Forms.
 - d. There was no record of returns to Hill of the second set of tubes for 44 subjects or used tubes for 46 subjects.
 - e. Records of returns to Hill did not indicate the number of tubes or if they were used or unused.
 - f. The Case Report Form for #41 indicates tubes were returned at week 8 but there was no documentation of dispensing additional tubes for Long Term Follow-up.
5. Inclusion/Exclusion Criteria
 - a. Six subjects either did not meet one of the inclusion criteria or lacked documentation that they did.
 - b. The Admission Criteria sheet for subject #17 was marked that she met item 1 and 2 of the exclusion criteria.
 - c. The Admission Criteria sheet for subject #44 was dated 5/15/98 which was the date of her week 1 visit.
6. Follow-up Treatment
 - a. Two of 12 subjects continued onto the eight week follow up treatment without having an efficacy score of 1 at the end of the initial eight weeks of treatment.
 - b. Subject #4 went onto long term follow-up with an efficacy score of 2. Subject #69 went onto long term follow-up without completing the eight week follow-up treatment because she would only continue if she could return once a month.

7. Six subjects did not have photos taken two visits in a row.
8. Scores and global evaluations
 - a. The week 8 slide for subject #6 showed she had slight residual pigmentation but the Case Report Form was marked as none and cleared.
 - b. The case Report Form for #7 was marked as none and cleared but there was a note the right cheek was very, very faint.
 - c. The Long Term Follow-up sheets for #9 were not marked as exacerbation even though the score had increased from 0 to 1.
9. There was no documentation of IRB approval for the recruitment ads or for the plan to provide monetary compensation to subjects.
10. Consent Form
 - a. indicated the subjects would be randomly assigned to the treatment groups but this was not the case for subjects 1-34
 - b. indicated the doctor would not know what treatment the subject was on but this was not the case after the Master Key envelope was opened
 - c. the described procedures did not include using non-traumatic techniques for washing the affected area; only using soap, moisturizer and sunscreen supplied by the sponsor; approved forms of birth control must be used to prevent pregnancy; or the need to avoid exposure to UV lights
 - d. risks did not include some of the possible adverse effects listed in the protocol and investigator's brochure such as gray discoloration, black dots, atrophy, telangiectasia, stinging, systemic toxicity, scaliness, vasoconstriction, folliculitis, and pituitary-adrenal suppression
 - e. did not mention monetary compensation or how discontinuing would affect the amount the subject would be paid
 - f. did not define cutaneous melanosis
 - g. did not mention the number of subjects or other sites
11. Dr. Torok did not review each of the Case Report Forms.

Dr. Isaac Willis:

1. The initial IRB approval was granted 12/5/97. However, the reviewing IRB was not notified of the protocol revisions dated 12/17/97, 2/18/98 and the final version dated 6/3/98. Also, the Final Report to the IRB dated 8/30/98, did not include the adverse event and discontinuation of subject #78 (which would have increased the total "dropped" to 6 rather than 5).
2. Test article accountability records do not include the amount and dates of all products received from the sponsor or returned to the sponsor for subjects 73-80 (only 16 tubes were documented as received, whereas 49 was used). Also, the records do not account for those tubes used during the extended follow-up phase of the study (documentation is limited to two letters that reference two shipments of test article to the study site).
3. There is no record of audits by a monitor throughout the study, other than one letter that referenced a monitoring visit 9/30/98.

4. There is no documentation showing the duration of hyperpigmentation for patients 6, 14 and 23 (the CRF is blank in these cases) and for the CRF for subjects #29 and 53 state only 2 months, although 3 months was the minimum entry criterion. No previous pertinent medical history could be found for these patients to support their eligibility based on this criterion. (Patients 6 and 39 did have history of the condition on file, but not within the year prior to their study entry – the criteria specifically states “persisted unchanged, stable for a continuous period of 3 months prior to entry into the study!”)
5. Source documents available do not allow for verification of such things as: degree of hyperpigmentation (score of 0-3), duration of condition (for many subjects), previous treatments/medications for condition, presence of macular lesions, skin type, and patient evaluation of the product.
6. Patients 1, 4, 38 and 6 qualified for long-term follow-up, but they were not scheduled for it as directed in the protocol. Also, patient 10 underwent the long-term follow-up regimen designed for a subject whose week 8 score was a “1”; however, #10 had a week 8 score of “0”, which required a different regimen. Also, subject #74, who had a score of “2”, was followed long-term, but did not qualify.
7. A disparity was noted in the accountability records for subjects (1-72) – the sponsor’s ledger shows the return of 396 tubes, but the investigator’s dispensing ledger shows the return of 406 tubes from the subjects.

Dr. Paul Kelly:

1. The protocol was not adhered to as follows:
 - a. The protocol for the inclusion criteria required a degree of hyperpigmentation from moderate to severe [a score of at least 2 on a 4-point scale (0=none to 3=severe)]. The following subjects were enrolled in the study with a score of 1 (mild degree of hyperpigmentation): Patient# 12, 31, 32, 44, 48, 63, 65, 77 and 83.
 - b. The source documents and case report forms regarding Adverse Events were not completed for the start date, duration, stop date, severity and treatment instituted. For example:

<u>Source document/CRF</u>	<u>Date of worksheet</u>	<u>Patient#</u>
“Week 4” worksheet	6/23/98	31
“Week 4” worksheet	6/23/98	31
“Week 1” worksheet	5/12/98	14
“Week 2” worksheet	5/19/98	14
“Week 8” worksheet	6/25/98	5
“Week 2” worksheet	7/15/98	83
“Week 4” worksheet	7/30/98	83
“Week 1” worksheet	6/03/98	32
“Week 2” worksheet	6/10/98	32
“Week 2” worksheet	8/20/98	114
“Week 3” worksheet	8/27/98	114

2. The source documents entitled, “Week 1”, “Week 2”, “week3”, “Week 4”, “Week 5”, “Week 6”, “Week 7”, and “Week 8” could not be found for Patient #32 enrolled in the study.

3. Source documents are incomplete in that hyperpigmentation scale was not documented during the patient's visit. For example:

<u>Source document/CRF</u>	<u>Date of worksheet</u>	<u>Patient#</u>
"Week 3" worksheet	6/19/98	31
"Week 4" worksheet	6/23/98	31
"Week 8" worksheet	7/30/98	31
"Week 1" worksheet	5/12/98	14
"Week 2" worksheet	5/19/98	14
"Week 4" worksheet	6/02/98	14
"Week 6" worksheet	6/17/98	14
"Week 7" worksheet	6/23/98	14
"Week 1" worksheet	5/05/98	5
"Week 2" worksheet	5/12/98	5
"Week 3" worksheet	5/15/98	5
"Week 6" worksheet	6/04/98	5
"Week 7" worksheet	6/17/98	5
"Week 8" worksheet	6/25/98	5
"Week 3" worksheet	6/26/98	44

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ON ORIGINAL**

Date: January 20, 2000

This addendum addresses the issues of Financial Disclosure (21 CFR 54) and Pediatric Use Information (21 CFR 314.55) requirements for this NDA.

Financial Disclosure

The Applicant certified (date of certification: 3/16/99) that the Applicant had not entered into any financial arrangements with the Clinical Investigators Neil Brody, M.D., A. Paul Kelly, MD, Helen Torok, MD, or Joshua Wieder, MD, whereby the value of compensation to the Investigator could be affected by the outcome of the study. Each of these listed Investigators was required to disclose to the Applicant whether the Investigator had a proprietary interest in this product or a significant equity in the Applicant, but did not disclose any such interests. Helen Torok, M.D. and Neil Brody, M.D. were two of the Investigators for the clinical study 024 East, entitled "Double-Blind Comparative Study of _____ a New Formulation for the Treatment of Patients with Cutaneous Melanosis". A. Paul Kelly, MD and Joshua Wieder, MD were the two Investigators for the clinical study 024 West, entitled "Double-Blind Comparative Study of _____, a New Formulation for the Treatment of Patients with Cutaneous Melanosis".

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-
- (1) The clinical study was a multi-center trial.
 - (2) Investigators, sub-investigators and patients were blinded throughout the course of the trial. The Investigators and sub-investigators were not aware of the investigational product that was dispensed to the patients. During the course of the study, at each patient visit, the investigators and sub-investigators remained blinded as they conducted the patient evaluation. The blind was broken only after the study was fully completed.
 - (3) Each patient was graded at the initiation of the study as to the severity of their disease.

Comments

Pediatric Use Information

The Applicant has requested a full waiver of pediatric use information requirements for this NDA, on the basis that -

- (1) The product does not represent a meaningful therapeutic benefit for pediatric patients and is not likely to be used in a substantial number of pediatric patients because Cutaneous Melanosis does not affect the pediatric population; and
- (2) Necessary studies are impossible or highly impracticable because the number of adolescent patients (ages 12-16) suffering from Cutaneous Melanosis is extremely small and geographically dispersed.

The Applicant has further attempted to justify the waiver by noting that -

- (1) the proposed drug product _____, was designed to treat hyperpigmentation of the chloasmic or melasmic types that occurs only in sexually mature females;
- (2) an available population of pediatric and adolescent individuals with this disorder would be almost impossible to find; and
- (3) there are no other known hyperpigmentary disorders that could be found in the pediatric and adolescent population for comparative study of the proposed drug product.

Comments

1. This Reviewer would not agree with the Applicant that "there are no other known hyperpigmentary disorders that can be found in the pediatric and adolescent population for comparative study of this proposed drug product _____ Pigmented lesions may be found in the pediatric population for study, including ephelides, café-au-lait spots, Albright's syndrome lesions, Becker's nevus, post-inflammatory hyperpigmentation, etc.
2. The requested indication for this NDA is "cutaneous melanosis". This indication would include pigmentary lesions other than melasma/chloasma. As such, it would not be subject to a full waiver. However, the Applicant has also indicated that the drug product, _____ was "designed to treat hyperpigmentation of the chloasmic or melasmic types that occurs only in sexually mature females", and the clinical studies were done with the exclusion of all other types of hyperpigmentation. Therefore, the indication "cutaneous melanosis" is inappropriate and only "melasma/chloasma" may be considered.
3. It is recognized that the condition melasma/chloasma is unlikely to occur in the pediatric population. Since the current submission is not approvable, the granting for a waiver is immaterial. A full waiver may be granted if melasma/chloasma is to be the indication sought by the Applicant in a resubmission.

SI
Hon-Sun Ko, M.D.

1-21-00

cc: NDA 21-112
HFD-540
HFD-540/CSO/Lutwak
HFD-540/CHEM/Pappas
HFD-540/PHARM/Nostrandt
HFD-880/BIOPHARM/Lee
HFD-540/MO/Walker/Ko
HFD-725/BIOMETRICS/Freidlin

SI 1/21/00

Clinical Review of NDA 21-112 Response to Not-Approvable Letter

APPLICATION NUMBER: 21-112/AZ
Major Amendment/Response to NA Letter
Division Tracking Number 018536

SUBMISSION/REVIEW DATES

SUBMISSION DATE: 7/20/01
CDER STAMP DATE: 7/25/01
ASSIGNED DATE: 8/2/01
FILING DATE: 9/18/01
REVIEW COMPLETION DATE: 1/18/02

APPLICANT NAME: Hill Dermaceuticals Inc.
ADDRESS: 2650 Mellonville Ave
Sanford, FL 32773

NOMENCLATURE

TRADE (GENERIC) NAME: TRI-LUMA® Cream

CHEMICAL NAMES OF ACTIVE INGREDIENTS:

fluocinolone acetonide: *pregna-1,4-diene-3,20-dione, 6,9-difluoro-11,21-dihydroxy-16,17-[(1-methylethylidene)bis(oxy)]-, (6 α ,11 β ,16 α)-* 0.01%
hydroquinone: 1,4-benzenediol 4%
tretinoin: (*all-E*)-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid 0.05%

MOLECULAR FORMULAS:

fluocinolone acetonide: $C_{24}H_{30}F_2O_6$
hydroquinone: $C_6H_6O_2$
tretinoin: $C_{20}H_{28}O_2$

MOLECULAR WEIGHTS:

fluocinolone acetonide: 452.20
hydroquinone: 110.11
tretinoin: 300.44

DOSAGE FORM: Cream
ADMINISTRATION ROUTE: Topical

REVIEWER NAME: Hon-Sum Ko
TITLE: Medical Officer
DIVISION: Dermatologic and Dental Drug Products

DOCUMENTS REVIEWED: NDA 21-112 AZ volumes 14.1, 14.15-14.30
NDA 21-112 BZ submitted 11/22/01
NDA 21-112 BM submitted 12/10/01
NDA 21-112 BM submitted 12/20/01
Email submissions dated 1/3/02, 1/7/02,
1/11/02 and 1/14/02

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