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**APPEARS THIS WAY
ON ORIGINAL**

Executive Summary

I. Recommendations

A. Recommendations on Approvability

- Pending agreement by the Applicant to labeling revision and phase 4 commitment, it is recommended that TRI-LUMA Cream be approvable for the short-term treatment of moderate to severe facial melasma.
- The Applicant should revise the draft label as recommended in Appendix A.

B. Recommendations on Phase 4 Studies and/or Risk Management Steps

- The Applicant should provide the complete study reports for Studies 29 and 30 as soon as each study is completed, and provide Safety Updates in those submissions.
- The Applicant should commit to the collection of pregnancy outcome data arising from the use of TRI-LUMA Cream in pregnancy. The methodology should be discussed with the Agency. The Applicant should also monitor the unintended usage in pregnancy and provide measures on how this can be reduced.
- A waiver for pediatric study requirements may be granted.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

The current submission is a response to a Not-Approvable Letter dated 1/20/00.

In 1975, Willis and Kligman published on the topical treatment of cutaneous hyperpigmentation with combination of approved formulations containing corticosteroid, hydroquinone, and tretinoin. The Applicant submitted _____ to develop TRI-LUMA Cream containing _____

The Agency issued a Not-Approvable Letter to the Applicant on 1/20/00, which, among other deficiencies, cited four "Clinical/Statistical" items to be addressed:

- Long-term safety studies to comply with ICH E1A Guidance;
- A modified Draize test with sufficient patients to assess sensitization potential;
- An HPA axis suppression study with cosyntropin stimulation to assess adrenal suppression potential;
- Adequate and well-controlled trials comparing TRI-LUMA Cream to dyad components to determine the safety and efficacy of TRI-LUMA Cream.

Since the NA action in 2000, the Applicant has conducted a new Clinical Program and did the following new studies:

Study	Nature of Study	Utility
<u>Adequate and Well-Controlled</u> 28A 28B	Phase 3 dyad-controlled safety and efficacy study to establish contribution of ingredients of TRI-LUMA Cream. Phase 3 dyad-controlled safety and efficacy study to establish contribution of ingredients of TRI-LUMA Cream.	Substantial evidence of safety/efficacy. Substantial evidence of safety/efficacy.
<u>Long-Term (both ongoing)</u> 29	Open-label extension of 28A/28B with use of TRI-LUMA Cream for 12 months	E1A Guidance of ICH.
<u>PK/PD</u> 104479-70 33	Systemic availability of active ingredients of TRI-LUMA Cream. HPA axis suppression study.	Systemic safety. Corticosteroid effect.
<u>Dermal Safety</u> 36 37	Irritancy potential. Contact sensitization potential.	Local safety. Local safety.

Reports of the completed studies have been submitted in July, 2001, and partial report for the ongoing Study 29 in November, 2001. Partial safety data of the ongoing safety study, —, were submitted in a revised Integrated Summary of Safety on 12/20/01.

B. Efficacy

In two identical randomized, multi-center, investigator-masked studies, the Applicant evaluated patients of skin types I-IV and aged 21 to 75 with moderate or severe facial melasma, who applied TRI-LUMA Cream or a dyad combination of the active ingredients to the lesions before bedtime, after washing the face with a mild cleanser. Measures for sun avoidance, including the use of sunscreens, were taken. The study drug was administered daily for 8 weeks. The primary variable was defined as clearing of melasma lesions as judged by Investigator assessment of melasma severity. At the end of 8 weeks of treatment, the effectiveness of TRI-LUMA Cream in the treatment of facial melasma was demonstrated by its superiority over each of the dyads in clearing melasma lesions as shown in the following Table:

Proportion of Subjects with Melasma Severity Score of 0 at Day 56

	Proportion of Subjects with Melasma Severity Score of 0			
	TRI-LUMA	FA+HQ	FA+RA	HQ+RA
STUDY 28A	32/85 (37.6%)	3/85 (3.5%)	0/85	12/83 (14.5%)
STUDY 28B	10/76 (13.2%)	1/76 (1.3%)	3/76 (3.9%)	3/75 (4.0%)

A small number of patients using TRI-LUMA Cream also had clearing of melasma after 4 weeks of treatment, but not all of them maintained the treatment success by the end of 8 weeks.

In the open-label extension study in which all patients received intermittent courses of TRI-LUMA Cream in the treatment of melasma, TRI-LUMA Cream appeared to improve the severity of melasma. In patients who had repeated courses, both the remission time

and the treatment courses appeared to be shorter in subsequent courses. Clearing of lesions was generally not maintained.

C. Safety

Previous studies in the original NDA submission suggest that TRI-LUMA Cream has low potential for phototoxicity and photoallergenicity. In the new dermal safety studies, significant irritancy potential of TRI-LUMA Cream was demonstrated, but this was less than that of the dyad combination with hydroquinone and tretinoin. The sensitization study also suggests that TRI-LUMA Cream has sensitization potential.

In a pharmacokinetic study in which healthy volunteers applied TRI-LUMA Cream to their forearms in doses in excess of that expected in the treatment of facial melasma, minimal systemic absorption was found with each of its active ingredients. The plasma tretinoin levels achieved were within the normal range of endogenous levels. In a cosyntropin stimulation study to evaluate adrenal function, where patients used TRI-LUMA Cream for 8 weeks in the treatment of melasma, no significant changes were observed at the end of 8 weeks of treatment.

Studies on TRI-LUMA Cream in the treatment of facial melasma have included an adequate database in the phase 3 trials, and in the long-term safety studies for exposure to the drug product.

For the short-term clinical trials, patients were treated for a period of 56 days with daily application of TRI-LUMA Cream. The patient exposure information is as follows:

	Treatment Group			
	TRI-LUMA (N=161)	FA+HQ (N=161)	FA+RA (N=161)	RA+HQ (N=158)
	Number (%) of Patients			
Patients completing study	152 (94.4)	151 (93.8)	151 (93.8)	148 (93.7)
Total discontinued early	9 (5.6)	10 (6.2)	10 (6.2)	10 (6.3)
Discontinuation due to adverse event	0	1 (0.6)	4 (2.5)	1 (0.6)

FA=flucocinolone acetonide 0.01%, HQ=hydroquinone 4%, RA=tretinoin 0.05%.

For the open-label extension study, Study 29, in which patients were to be treated intermittently with TRI-LUMA Cream for melasma, the exposure data are shown below:

Total number of treatment courses→ Course ↓	Mean Number of Days in Treatment Courses				
	1 (N=235)	2 (N=228)	3 (N=72)	4 (N=12)	5 (N=3)
1 st	167.6	110.8	68.2	59.2	59.3
2 nd	-	96.0	64.5	46.3	39.3
3 rd	-	-	63.8	44.3	41.3
4 th	-	-	-	46.6	47.7
5 th	-	-	-	-	49.3
Total	167.6	206.8	196.5	196.3	237.0

Among the 550 patients who used TRI-LUMA Cream, 315 patients had more than one course of treatment, and the average duration of the total treatment in these patients exceeded 180 days. Without including prior TRI-LUMA treatment time (an additional 8 weeks) from Study 28, there are approximately 300 patients who have had cumulative

use of TRI-LUMA Cream for over 6 months and over 400 who used it for at least 3 months. Some patients have had continuous use for up to 12 months.

The clinical studies solicited anticipated adverse events with direct queries. The adverse event profile of TRI-LUMA Cream in the phase 3 trials can be shown in the following Table. In the long-term safety studies, this profile appears to be maintained.

Incidence and Frequency of Treatment-related Adverse Events with TRI-LUMA Cream in at least 1% or more of Patients (N = 161)	
Adverse Event	Number (%) of Patients
Erythema	66 (41%)
Desquamation	61 (38%)
Burning	29 (18%)
Dryness	23 (14%)
Pruritus	18 (11%)
Acne	8 (5%)
Paresthesia	5 (3%)
Telangiectasia	5 (3%)
Hyperesthesia	3 (2%)
Pigmentary changes	3 (2%)
Irritation	3 (2%)
Papules	2 (1%)
Acne-like rash	1 (1%)
Rosacea	1 (1%)
Dry mouth	1 (1%)
Rash	1 (1%)
Vesicles	1 (1%)

Anticipated adverse events looked for in the trials included erythema, skin peeling (desquamation), burning, irritation, telangiectasia, rosacea, dermatitis, atrophy and grayish discoloration of skin or black dots. Findings were consistent with expected application site reactions due to the active ingredients and no unwanted systemic effects have been observed.

In the long-term safety studies, 13 pregnancies exposed to TRI-LUMA Cream have been reported to-date. Most of the pregnancy outcomes have not been known. Three women gave birth to apparently healthy babies. One pregnancy was terminated prematurely, and another ended in miscarriage.

D. Dosing

The recommended dose/regimen of TRI-LUMA Cream is that used in the phase 3 and long-term clinical trials. The following is appropriate for labeling:

"TRI-LUMA Cream should be applied once daily at night. It should be applied at least 30 minutes before bedtime.

"Gently wash the face and neck with a mild cleanser. Rinse and pat the skin dry. Apply a thin film of the cream to the hyperpigmented areas of melasma including about ½ inch of normal appearing skin surrounding each lesion. Rub lightly and uniformly into the skin. Do not use occlusive dressing.

"During the day, use a sunscreen of SPF 30, and wear protective clothing. Avoid excessive sunlight exposure. Patients may use moisturizers and/or cosmetics during the day."

E. Special Populations

The clinical studies for TRI-LUMA Cream included primarily patients younger than 65, females, and Caucasians. It is therefore difficult to have meaningful subset analysis on the basis of demographic characteristics. Because of low systemic bioavailability for the active ingredients of TRI-LUMA Cream in the treatment of facial melasma, effects in patients with organ function impairment (liver or kidney) have not been explored.

Safety

- Analyses for safety by age (with cutoff at 40), race and skin types have been done. In age analysis, similar proportions of adverse events were observed in the ≤ 40 and > 40 age groups. The small sample sizes by race and skin type analysis do not allow for definitive conclusions. Analysis by gender has not been performed.

Efficacy

- Analyses for efficacy by race and by baseline severity was performed. In both Caucasians and non-Caucasians, TRI-LUMA Cream was better than dyads in achieving clearing of melasma lesions. TRI-LUMA Cream also appears to provide benefit to patients with moderate or severe melasma, but the benefit was less pronounced in those with severe melasma.
- Analysis by skin type has revealed that TRI-LUMA Cream gave numerically better results than each of the dyads in clearing melasma in skin types II, III and IV. There were too few patients in type I for any conclusions to be drawn.
- Analysis by hormonal methods of contraception has shown that TRI-LUMA Cream appears to be superior to each dyad in clearing melasma for both users and non-users of hormonal methods of contraception in women.

Considerations on Pregnancy

- Melasma occurs in pregnant women. However, the clinical trials excluded pregnant women, and women of child-bearing potential were put on birth control. As the patients withdrew from the trials upon discovery of pregnancy, they might not have had optimal treatment for evaluation of efficacy or safety. Information on the effect of TRI-LUMA Cream in pregnancy can only be obtained through inadvertent exposure.
- The concern about use in pregnancy arises from the fact that tretinoin is a teratogen. Thirteen exposed pregnant women have been reported in the long-term safety studies. Most of the pregnancy outcomes have not been known. Three women gave birth to apparently healthy babies. One pregnancy was terminated prematurely, and another ended in miscarriage. The pregnancy outcomes need follow-up and should be reported in future updates. Because the risk/benefit information on TRI-LUMA Cream may affect patients' decision-making, this product should have a Medication Guide. Use of TRI-LUMA Cream in pregnancy, like that of any other drug, should be discouraged, but the individual risk/benefit analysis should be left to the prescriber in conjunction with the patient.

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

- Established Names: tretinoin, hydroquinone & fluocinolone acetonide
- Proposed Trade Name: TRI-LUMA™ Cream
- Drug Classes: retinoid, depigmenting agent and corticosteroid
- Sponsor's Proposed Indication: treatment of melasma
- Proposed Dose/Regimen: tretinoin 0.05%, hydroquinone 4% & fluocinolone acetonide 0.01% - topical application of a thin film of the cream to hyperpigmented areas once daily, before bedtime, at night
- Proposed Age Groups: patients aged 18 or above

B. State of Armamentarium for Indication

- The proposed indication "treatment of melasma" is an indication for bleaching effect on pigmented skin. The following are listed in the PDR as products for this indication:
 - Alustra Cream (Medicis)
 - Eldopaque Forte 4% Cream (ICN)
 - Eldoquin Forte 4% Cream (ICN)
 - Lustra Cream (Medicis)
 - Lustra-AF Cream (Medicis)
 - Melanex Topical Solution (Neutrogena)
 - Solaquin Forte 4% Cream (ICN)
 - Solaquin Forte 4% Gel (ICN)

The above drug products all contain hydroquinone as active ingredient at 3% or higher concentration. Hydroquinone at 1.5 to 2% is an OTC product under a Tentative Final Monograph.
- A recently approved (12/10/99) product, Solagé (Westwood-Squibb), containing 2% mequinol (4-hydroxyanisole, the monomethyl ether of hydroquinone) and 0.01% tretinoin, is indicated for the treatment of solar lentigines.
- In addition, topical retinoid is approved for use as an adjunct in the treatment of mottled hyperpigmentation, which is a manifestation of photodamage. The marketed products are: Renova 0.02% and 0.05% Creams (Ortho).
- Dermabrasion and lasers have been used in the treatment of superficial benign cutaneous pigmented lesions. Many of these modalities lack specificity of injury, which has meant that normally pigmented and even non-pigment containing structures such as collagen as well as the hyperpigmented lesion itself have been

indiscriminately destroyed, resulting variously in hypopigmentation, hyperpigmentation, and scar formation in some cases.

C. Important Milestones in Product Development

- Article by Willis and Kligman attesting to efficacy of a combination of corticosteroid, hydroquinone and tretinoin in the treatment of hyperpigmentation 1975
- Phase 3 studies, #24 East and West initiated 1995
- NDA 21-112 submission by Hill 1998
- Not-Approvable (NA) Letter issued for NDA 21-112 1999
- Teleconference between FDA and Hill on NA issues 1/20/00
- Phase 3 studies, #28A and #28B initiated 3/7/00
- Special Protocol Assessment issued 9/6/00
- Teleconference between FDA and Hill on issues related to submission of Response to NA Letter 6/18/01
- Submission of Response to NA Letter 7/20/01

D. Other Relevant Information

- TRI-LUMA has not been approved for marketing in any country.
- The NA Letter of 1/20/00 lists the following as the Clinical/Statistical basis of the non-approval:

There is insufficient information to support the safety, efficacy, and contribution of each of the three drug components of TRADENAME cream.

 1. Because melasma is often a chronic condition, and because melasma may regress upon discontinuation of therapy with TRADENAME cream, the safety for long-term use should be assessed (refer to the ICH E1A Guidance Document for additional information).
 2. A study with adequate sample size should be performed to determine the contact sensitization potential of the TRADENAME cream.
 3. Studies on systemic absorption and HPA axis function (adrenal suppression) should be provided to support the systemic safety of the TRADENAME cream.
 4. The contribution of each of the three drug components was assessed by comparing the TRADENAME cream with each of three creams that each omitted a different active drug (the three dyads). Superiority of TRADENAME cream over each of the three dyads has not been established. Also, the TRADENAME cream appears to offer no compelling advantage over the three dyads in local adverse events.

In addition, under Biopharmaceutics:
Data should be provided from *in vivo* studies to determine the systemic absorption and HPA axis (adrenal) suppression for the proposed formulation.

E. Important Issues with Pharmacologically Related Agents

Each of the three active ingredients has been approved for marketing for considerable time as topical agent for the treatment of appropriate conditions. They appear to be safe when used under current labeled conditions. There is also literature on combining the use of approved formulations that contain these ingredients in the treatment of cutaneous hyperpigmentation. The published literature supports combinations of these approved formulations when used in the treatment of cutaneous hyperpigmentation. Potentially, important safety issues relating to the use of the active ingredients include

the following list. However, the majority of these concerns may be more relevant to systemic administration, unless absorption from cutaneous source is significant.

- Cutaneous atrophy, adrenal suppression and other systemic adverse effects of glucocorticoids (e.g., diabetes, hypertension, and osteoporosis) (corticosteroid)
- Cutaneous irritation, teratogenesis, and neuropsychiatric effects (retinoid)
- Exogenous ochronosis, ocular pigmentation with potential corneal damage, and, in animal models, renal toxicity (hydroquinone)

II. Clinically Relevant Findings from Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

A. Chemistry

The CMC Review notes that the Applicant has satisfactorily addressed the deficiencies in the NA Letter of 1/20/00, and recommends approval of this NDA.

B. Animal Pharmacology and Toxicology

The Pharm/Tox Reviewer recommends this application be approvable, and has provided labeling suggestions. One of the suggestions is on conferring Pregnancy Category X to this product, the rationale being: "The consistent findings of embryo-fetal death and/or malformations warrant assignment of a Pregnancy Category X for this combination drug product for this indication." The issue on Pregnancy Category will be addressed in Section IX.D of this review.

C. Biopharmaceutics

The Biopharm Reviewer recommends that the application is "acceptable from a clinical pharmacology and biopharmaceutics perspective" and has made suggestions on labeling. For relevant clinical findings in her review, see Section III.

D. Statistics

The Biometrics Reviewer has not made recommendations regarding approvability. She deems that the phase 3 trials presented in the current response have shown TRI-LUMA Cream to be "superior to each of the three dyads in the primary efficacy endpoint". However, she has raised concerns on the randomization process and on the use of concomitant medications that may affect the outcome of the studies.

- It is this Reviewer's opinion, after reviewing the randomization code in detail, and upon submission of documentation by the Applicant attesting to randomizing study sites to Studies 28A and 28B prior to any patient enrollment (12/28/01), that the randomization of patients in these two phase 3 trials is valid.
- The Biometrics Reviewer's concern with prohibited medications is over the per-protocol analysis. Upon excluding patients who had concomitant medication violations, Study 28B would be unsuccessful with the primary efficacy parameter by per-protocol analysis. It is noted that two of the three primary comparisons (triad vs

each dyad) results in p-values near 0.05 with the ITT analysis. By excluding the concomitant medication violations for the per-protocol analysis, the power would be reduced and unable to reject the null hypothesis. Many of the violations are due to the use of nasal or inhaled corticosteroids, and are not expected to affect the outcome. Since the preplanned primary analysis is the ITT analysis, this Medical Officer believes that the superiority of TRI-LUMA Cream has been established.

- An additional issue raised by the Biometrics Reviewer is the difference between the patient static global assessment and the assessment by physician, as patient's assessment did not show superiority of TRI-LUMA Cream in some instances. In fact, there is a subtle difference between the descriptions in the scoring systems which could affect the assignment of scores in patient assessment vs physician assessments. This issue cannot be resolved at this point, but since the pre-planned primary endpoint is based on physician assessment, it is this Medical Officer's opinion that superiority of TRI-LUMA Cream has been established.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

- See Biopharm Review for details of the PK study. The following is a summary account of the PK study presented.
- In the current submission, a PK study report on Study 104479-70 has been provided. This study consists of two sequential groups, following the same protocol except for the dose of TRI-LUMA Cream applied. Group II was studied upon FDA recommendation to have maximal exposure to TRI-LUMA Cream in the study subjects.

Group I	1 Gm qd to one forearm for 8 weeks
Group II	6 Gm qd to both forearms (3 Gm per forearm) for 8 weeks

Application in the treatment of facial melasma with a thin film of drug product would take less than one gram of the product. The amount used in this study can be considered excessive usage.

- This study shows that systemic exposure as determined by intense blood sampling on Days 1, 7, and 14 is minimal for each of the active ingredients: tretinoin, fluocinolone acetonide and hydroquinone. The great majority of subjects had no quantifiable plasma levels of fluocinolone acetonide or hydroquinone. For tretinoin, about 57% of subjects in each Group (I or II) had detectable plasma levels, but they fell within the range of normal endogenous blood concentrations (2-5 ng/mL).

B. Pharmacodynamics

- The submission includes dermal safety studies on irritancy and sensitization potential (to be discussed in Section VII.C.1 of this Review), and a specific pharmacodynamic study to address adrenal suppression.
- An open-label study, Study 33, was conducted to evaluate secondary adrenal insufficiency using Cortrosyn® (cosyntropin) stimulation, with sampling for plasma cortisol pre-injection and 60 minutes post-injection. See Biopharm Review for details of the PD study. The following is a summary account of the PD study presented.
- Patients were treated for 8 weeks with TRI-LUMA Cream applied once daily to melasma lesions. The data are shown in the following Table:

Plasma Cortisol Levels with 60-Minute Cortrosyn ® Test

	Day1		Day28		Day56	
	Prestimulation	Poststimulation	Prestimulation	Poststimulation	Prestimulation	Poststimulation
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
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31						

The label for Cortrosyn® injection requires, for a 60-minute stimulation test, an approximate doubling of basal level to be considered normal adrenal function. In this study, most patients fell short of this **even before starting treatment with TRI-LUMA Cream**. Testing at Days 28 and 56 showed some minor deviation from pre-treatment response, but since the difference between beginning and end of treatment testing was not significant, it would not be prudent to draw a conclusion of adrenal suppression based on such data.

- By conducting and presenting this study, the Applicant has responded adequately to the third Clinical/Statistical item, and the sole Biopharm item of the NA Letter of 1/20/00.

IV. Description of Clinical Data and Sources

A. Overall Data

- This review is based primarily upon data in the current response to the NA Letter of 1/21/00, which contains the following clinical study reports:
 1. Studies 28A and 28B. These are identical phase 3 studies comparing the safety and efficacy of the triad product vs the three dyad combinations in the short-term treatment of melasma.
 2. Study 33. This is a safety study using stimulation with cosyntropin (Cortrosyn®) to evaluate the potential for adrenal suppression by the triad product upon application of a thin film to the face to treat melasma.
 3. Study 36. This is a phase 1 dermal safety study on irritancy potential.
 4. Study 37. This is a phase 1 dermal safety study on contact sensitization.
 5. Study 104479-70. This PK study provides data on systemic exposure to the active ingredients in the triad product (fluocinolone acetonide, tretinoin, and hydroquinone), when the triad is applied to the forearms of healthy volunteers daily for 8 weeks.
- On 11/22/01, the Applicant submitted a report for Study 29, which is the continuation of Studies 28A and 28B to obtain long-term safety data upon recurrent use of the drug product. Case report forms and case report tabulations for Study 29 were submitted on 12/10/01. A revised Study 29 Report and Integrated Summary of Safety (ISS) was submitted on 12/20/01. This ISS includes also data from a second long-term safety study, Study 30.
- The design of these studies is shown in the Table in Section IV.B.

B. Table Listing the Clinical Trials

- The following Table lists the clinical trials used to support this application. In addition to the studies described in Section IV.A., the Applicant includes three additional studies (pp. 7-0002 to 7-0004 of this submission) in their Table of clinical studies: Studies 24, 29 and 30. Report for Study 24 has been previously submitted and reviewed with the original NDA. Studies 29 and 30 are long-term safety studies which have been ongoing at the time of the current submission, and reports pending.

<u>Study No.</u>	<u>Title</u>	<u>Ph/ Inv</u>	<u>Design</u>	<u>Subjects randomized /completed</u>	<u>Drug</u>	<u>dose, frequency, duration</u>
28A	Efficacy and safety of TRI-LUMA in the treatment of patients with melasma of the face	3/7	Multi-center, randomized, investigator-masked, 4-arm, parallel group	melasma patients 338/317	TRI-LUMA FA+HQ FA+RA RA+HQ	Thin film qd 8 wks
28B	Efficacy and safety of TRI-	3/6	Multi-center,	melasma	TRI-LUMA	Thin film qd 8 wks

	LUMA in the treatment of patients with melasma of the face		randomized, investigator-masked, 4-arm, parallel group	patients 303/285	FA+HQ FA+RA RA+HQ	
24*	Double-blind, comparative study of new new formulation, for the treatment of patients with cutaneous melanosis (melasma)	3/5	Multi-center, randomized, "double-blind", 4-arm, parallel group	melasma patients 377/301	TRI-LUMA FA+HQ FA+RA RA+HQ	Thin film qd 8 wks followed by tapering TRI-LUMA up to 20 additional weeks
36	21-day cumulative irritancy study	1/1	Single center, randomized, investigator-blind	healthy volunteers 25/25	TRI-LUMA RA, HQ & vehicle	Occlusive patch qd 5d/wk for 3 wks
37	Modified Draize skin sensitization study	1/1	Single center, randomized, investigator-blind	healthy volunteers 221/190	TRI-LUMA RA, HQ & vehicle	Occlusive patch 3x/wk for 3 wks; 2 wks rest; one 48-hr patch for challenge
29	Long-term (12 month) safety and efficacy of TRI-LUMA in the treatment of melasma of the face	3/13	Open-label, multi-center	melasma patients 583/? (ongoing)	TRI-LUMA	Thin film qd as needed 12 months
30	Long-term (12 month) safety and efficacy of TRI-LUMA in the treatment of melasma of the face	3/5	Open-label, multi-center	melasma patients 228/? (ongoing)	TRI-LUMA	Thin film qd as needed 12 months
104479-70 Gp I	Open-label safety study to determine maximum systemic exposure of eam eam	1/1	Open-label, single center	healthy volunteers 45/43	TRI-LUMA	1 g on one forearm qd 8 wks
104479-70 GpII		1/1	Open-label, single center	healthy volunteers 14/13	TRI-LUMA	6 g on both forearms qd 8 wks
33	An Adrenal Suppression Study of TRILUMA Cream (0.01% Fluocinolone Acetonide + 4% Hydroquinone + 0.05% Tretinoin) in Patients with Melasma of the Face	2/2	Open-label, multi-center	melasma patients 29/29	TRI-LUMA	Thin film qd 8 wks

*Study 24 has previously been submitted to the original NDA in 1999, and consisted of two individual studies, 24 East and 24 West; TRI-LUMA= 0.01% fluocinolone acetonide + 4% hydroquinone + 0.05% tretinoin; RI-LUMA; FA=0.01% fluocinolone acetonide; HQ=4% hydroquinone; RA=0.05% tretinoin; Ph=phase; Inv=Investigator(s);

C. Postmarketing Experience Not Applicable

D. Literature Review

- Use of a combination of hydroquinone, tretinoin and a corticosteroid topically to treat hyperpigmentation has been reported in the literature. The following lists some of the most important publications relating to this application. In general, the literature suggests that such a triad appears to be effective, and is tolerated by most patients. However, safety when used long-term has not been documented.
 - Kligman AM, Willis I. A new formula for depigmenting human skin. *Arch Dermatol.* 1975;111(1):40-8.
 - Gano SE, Garcia RL. Topical tretinoin, hydroquinone, and betamethasone valerate in the therapy of melasma. *Cutis.* 1979;23(2):239-41.
 - Gilchrist BA, Goldwyn RM. Topical chemotherapy of pigment abnormalities in surgical patients. *Plast Reconstr Surg.* 1981;67(4):435-9.
 - Kang WH, Chun SC, Lee S. Intermittent therapy for melasma in Asian patients with combined topical agents (retinoic acid, hydroquinone and hydrocortisone): clinical and histological studies. *J Dermatol.* 1998;25(9):587-96.
 - Guevara IL, Pandya AG. Melasma treated with hydroquinone, tretinoin, and a fluorinated steroid. *Int J Dermatol.* 2001;40(3):212-5.

V. Clinical Review Methods

A. How the Review was Conducted

- For this report, Studies 28A and 28B are reviewed for safety and efficacy for the short term treatment of melasma. Long-term safety and efficacy data from Study 29 are also reviewed to support chronic, intermittent use. In addition, reference is made to Study 24, which was provided in the original submission of NDA 21-112 and has been reviewed previously (see Medical Officer's Review dated 1/13/00).
- Safety data of another long-term study (Study 30) which have not been finalized, but partly presented in the ISS submitted on 12/20/01, are reviewed.
- Safety data from the cumulative irritancy and contact sensitization studies (36 and 37) are reviewed and presented.
- The studies on percutaneous absorption (104479) and adrenal suppression (33) have been reviewed in detail by Biopharm. The clinical relevance and pertinent safety data from these studies will be addressed in this review.

B. Overview of Materials Consulted in Review

- Material reviewed include:
NDA 21-112 Vol 14.1, 15-30 submitted on 7/20/01 in response to NA Letter
Submission of 11/22/01
Submission of 12/10/01
Submission of 12/20/01
FAXes of 12/27/01 and 12/28/01
Email submissions dated 1/3/02, 1/7/02, 1/11/02 and 1/14/02
Reviews of other Review Disciplines on the current Response to NA Letter (see Section II).

C. Overview of Methods Used to Evaluate Data Quality and Integrity

- DSI audits have been conducted on Sites 1 (Torok) and 12 (Menter) for Study 28A and 28B, respectively. Preliminary reports appear to indicate no major concerns with data integrity.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

- The trials presented in this submission were conducted under IRB approval and informed consent, in compliance with the principles of human subject protection and accepted ethical standards as required by 21 CFR 50 and 56.

E. Evaluation of Financial Disclosure

- Financial disclosure statement has been included in the submission of 7/20/01. Form 3454 has been presented in which the Applicant attests to not having entered into

financial arrangement with any of the clinical Investigators who performed the trials in support of this application. A list of the Investigators has been attached.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

1. In two adequate and well-controlled clinical trials with 8 weeks of daily application at bedtime, TRI-LUMA Cream has shown superiority over its components (dyad combinations) in the treatment of melasma of the face, in the presence of measures for sun avoidance, including the use of sunscreens. These studies can be considered adequate response to the fourth "Clinical/Statistical" deficiency item in the NA Letter of 1/20/00.

2. TRI-LUMA Cream also appears to improve melasma severity when used in intermittent courses to treat facial melasma; however, in the great majority of patients (90% or greater), recurrence of hyperpigmentation developed upon stopping TRI-LUMA treatment.

3. In the report for ongoing Study 29, the mean duration of treatment (128 to 49 days, 1st to 5th courses, respectively) and the mean remission time (74 to 39 days, between 1st and 2nd to between 4th and 5th courses, respectively) appear to decrease when multiple courses were taken. These apparent phenomena should be addressed in a true Final Report upon completion of the study.

4. Because of recurrence during or upon stopping treatment, the Applicant has studied chronic intermittent therapy with TRI-LUMA Cream. However, it may be more logical to have TRI-LUMA cream as initial therapy, followed by maintenance with an appropriate bleaching agent. This may incur less exposure to unneeded drugs than with chronic intermittent therapy. Labeling should clearly indicate that TRI-LUMA Cream is a combination product intended for short-term, and not for maintenance therapy of melasma.

5. The Applicant has studied skin types I-IV in the clinical trials. Although skin types V and VI have not been studied, melasma is not expected to be a significant issue in patients with very dark skin color. Moreover, excessive bleaching may result in hypopigmentation and undesirable cosmetic effect in these patients. Thus, additional studies in patients with skin types V and VI do not appear to be warranted.

B. General Approach to Review of the Efficacy of the Drug

- Phase 3 studies, 28A and 28B, are the adequate and well-controlled clinical trials used to support the safety and effectiveness of TRI-LUMA Cream in the treatment of melasma. The efficacy data of these two studies are reviewed in detail.
- Study 29, the continuation of Studies 28A and 28B, is used to support the long-term safety of TRI-LUMA Cream. The safety data of this study are reviewed in detail, and

its presented efficacy data are examined for any maintenance effect on depigmentation.

- Input from the Biometrics Reviewer is addressed.

C. Detailed Review of Trials by Indication

INDICATION SOUGHT: Treatment of Melasma

Two adequate and well-controlled clinical studies, 28A and 28B, were conducted and followed the same protocol. Therefore, their methodology is presented together, while the efficacy data are presented separately. These studies provide the substantial evidence supporting the safety and effectiveness of TRI-LUMA Cream in the treatment of melasma.

Two long-term studies, 29 and 30, are ongoing to collect safety data. These studies provide intermittent, open-label treatment to patients with TRI-LUMA Cream, when the Investigator deems that the patient has significant hyperpigmentation and starts the treatment. Study 29 is the open-label continuation of Study 28A and 28B. Limited efficacy data are also collected in Study 29.

1. Short-Term Efficacy

The effectiveness of TRI-LUMA Cream in the treatment of facial melasma was investigated in two studies, 28A and 28B, with patients using the triad combination in comparison to patients using combinations containing dyad ingredients of the to-be-marketed product. These two studies had identical protocols.

Studies 28A and 28B. Efficacy and Safety of TRI-LUMA (0.01% Fluocinolone Acetonide + 4% Hydroquinone +0.05% Tretinoin) in the Treatment of Patients with Melasma of the Face [Study 28A conducted 8/21/00 to 1/9/01; Study 28B conducted 8/22/00 to 10/31/00]

a. PROTOCOL

i. Objectives

To evaluate the efficacy and safety of TRI-LUMA [0.01% fluocinolone acetonide plus 4% hydroquinone plus 0.05% tretinoin (FA+HQ+RA)] Cream vs dyad combinations of its active ingredients (fluocinolone acetonide-hydroquinone, fluocinolone acetonide-tretinoin, and hydroquinone-tretinoin combinations) in the same vehicle in the treatment of melasma of the face.

ii. Design

Multi-center, randomized, investigator masked, 4-arm, parallel-group study with approximately 320 adults with melasma of the face, with treatment for a total of 8 weeks (56 days). The arms were:

- the triad combination of TRI-LUMA (FA+HQ+RA)
- the dyad combination of fluocinolone acetonide plus hydroquinone (FA+HQ),
- the dyad combination of fluocinolone acetonide plus tretinoin (FA+RA),
- the dyad combination of hydroquinone plus tretinoin (HQ+RA)

Comments

1. The design is compatible with requirements for testing combination products (21 CFR 300.50).
2. The studies are investigator-blind. Although this is not ideal, products containing tretinoin have a yellowish color, and this makes masking to patients impossible. However, if the Investigators had no access to information on the drug product being used, and not allowed to ask, this approach may be acceptable.

Patients were to apply a thin layer of study medication to the hyperpigmented lesion(s) once a day, approximately 30 minutes before bedtime, after having washed the facial area with a mild cleanser. They were evaluated for melasma severity (none, mild, moderate or severe) at Baseline and on Weeks 1, 2, 4, and 8.

The investigator assessed global improvement from Baseline using a 7-point scale (completely clear to worse) at each follow-up visit, using a Baseline photograph for comparison. The investigator and patient each made a static global assessment of all treated areas at Day 56 using a 3-point scale (completely cleared to significant hyperpigmentation present). Adverse events (subjective complaints) and concomitant medications were obtained at each visit. Anticipated adverse events, as described in the investigational drug brochure, including erythema, skin peeling, burning, stinging, telangiectasia, rosacea, dermatitis, atrophy and grayish discoloration of skin or black dots, were specifically solicited by the investigator at each visit. Clinical laboratory assessments were carried out at **selected** study centers.

After completing 8 weeks of treatment under Protocol 28, patients were to be subsequently enrolled into Protocol no. 29. Protocol 29 is a long-term, open-label study in which patients are treated with TRILUMA, as needed, for 12 months.

The study protocol and three protocol amendments, dated 6/28/00, 7/20/00, and 10/25/00, are provided.

Study Flow Chart

Procedures	DAY OF STUDY				
	0 (Screening)	7	14	28	56
Informed consent	X				
Demographics and history	X				
Inclusion/Exclusion	X				
Laboratory testing of blood and urine ^a	X				X
Enroll in study (issue patient number)	X				
UPT (females of child-bearing potential)	X				X
Identify melasma	X				
Photography	X				X
Investigator disease evaluation	X	X	X	X	X
Melasma severity grading	X	X	X	X	X
Physician global assessment		X	X	X	X
Patient global assessment		X	X	X	X
Adverse event identification		X	X	X	X
Dispense test product	X		X	X	
Weigh tube	X		X	X	X
Collect test product			X	X	X
Record missed doses		X	X	X	X
Concomitant/concurrent medications	X	X	X	X	X

^a At selected centers only

iii. Patient Selection

Inclusion Criteria-

1. Male and female patients 18 years of age and over with skin type I to IV and melasma of the face;
2. Patients in good general health confirmed by medical history;
3. Patients with moderate to severe melasma using the following guidelines:
 - a. stable (unchanged) melasma for at least three months;
 - b. macular lesions, neither depressed nor atrophic; and
 - c. melasma severity score of at least 2 (hyperpigmentation at least moderately darker than the surrounding normal skin);
4. Patients on oral contraceptives or estrogen replacement therapies who had not added and/or changed the therapy in the last six months, and had no intention of adjusting or changing the treatment.
5. Female patients of child-bearing potential with a negative urine pregnancy test who agreed to use effective methods of birth control or remain abstinent during treatment. Acceptable methods of birth control included ongoing hormonal contraceptives (oral, injectable or implantable), barrier methods, intrauterine devices and tubal ligation.
6. Patients who were willing and capable of cooperating to the extent and degree required by the protocol; and
7. Patients who read and signed an approved informed consent for this study.

Exclusion Criteria

1. Use of the following **topical** preparations on the face within the specified washout period(s):
 - topical corticosteroids 21 days
 - topical bleaching products 21 days
 - UV light therapy and sunbathing 21 days
 - topical retinoids 21 days
2. Use of the following **systemic** preparations within the specified washout period(s):
 - systemic corticosteroids 28 days
 - systemic cyclosporin, interferon 120 days
 - systemic acitretin, etretinate, isotretinoin 120 days
 - systemic methotrexate 120 days
 - systemic photoallergic, phototoxic and/or photosensitizing drugs 120 days
(chlorpromazine, benoxaprofen, piroxicam, tetracycline, thiazides, nalidixic acid, procainamide, phenytoin, ciprofloxacin, isotretinoin, antimalarial medications, and some cytostatic agents)
3. Required concurrent treatment that would interfere with study objectives and/or evaluations;
4. Presence of facial skin conditions that would have interfered with study objectives and/or evaluations (neurodermatitis, eczema, atrophy, telangiectasias, rosacea, etc.);
5. Immunocompromised or under immunosuppressive treatment;
6. Presence of a significant endocrine disorder that may have required contraindicated treatment with potent corticosteroids;
7. Known sensitivities to any of the ingredients in the test articles;
8. Exposure (through work or daily activities) to the sun on a regular basis and/or those who had consistent irritation of the exposed skin;
9. Sunbathed on a regular basis;
10. A history of alcohol or drug abuse;
11. Inability to communicate or cooperate with the investigator due to language problems, poor mental development, or impaired cerebral function;
12. Females who were pregnant or nursing; and
13. Participation in another investigational study within the last 30 days.

Withdrawal Criteria

Patients were free to withdraw at any time and for whatever reason. Prespecified reasons for discontinuing included, but were not limited to, the following:

- patient request - patient decided he/she did not want to continue (for any reason)
- adverse event - patient experienced a related OR unrelated event that would interfere with the study objectives/evaluations
- lost to follow-up - patient did not come in for a visit and could not be reached by phone
- treatment failure - in the investigator's judgment, the patient's condition required another form of treatment
- inclusion/exclusion discrepancy/violation - patient should not have been enrolled

- noncompliance - patient was not complying with protocol requirements (i.e. visit schedule, dosing regimen, etc.); a patient was to be discontinued if he/she missed two consecutive visits
- other - any other reason

iv. Administration Of Test Drugs

Each patient received both verbal and written instructions as to the proper dosing, and study medication application techniques were demonstrated. Patients were to apply, with clean fingers, a thin layer of study medication to the hyperpigmented lesion making sure to cover the whole lesion including the outside borders extending to the normal pigmented skin 30 minutes before bedtime after having washed the face with a mild cleanser. Patients could use mild moisturizers as needed. ***A mild cleanser and a mild moisturizer were provided by the sponsor. A sunscreen with a SPF 30 and both UVB and UVA protection was provided by the sponsor for the patient's daily use.*** The importance of using the sunscreen was explained to the patient. Protective clothing and avoidance of sun exposure to the face was recommended. Cosmetics were allowed. New tubes of study medication were dispensed by someone other than the investigator who was doing the evaluations.

Comment The names of the ancillary medications have been provided by the Applicant in December, 2001. The mild cleanser was Cetaphil Gentle Skin Cleanser. The sunscreens were Pre-Sun SPF 30 or Vanicream SPF 35. The non-mandatory moisturizer was Cetaphil Moisturizing Lotion.

Interfering and/or Concomitant Therapy

- Interfering therapies included all systemic and/or topical medications for treating melasma or those medications that exacerbate the condition. Interfering medications included bleaching agents, corticosteroids, retinoids, chlorpromazine, benoxaprofen, piroxicam, tetracyclines, thiazides, nalidixic acid, procainamide, phenytoin, ciprofloxacin, antimalarial medications, and some cytostatic agents.
- Every attempt was made to keep concomitant therapy dosing constant during the study. Any medication started or changed after the patient had been enrolled was entered on the Concomitant Medication form. A corresponding adverse event form was completed for therapies added after enrollment. If a patient was placed on a different medication for an ongoing condition present at Baseline, an adverse event form was not completed. However, documentation of this condition was to be clearly presented in the patient's chart.

v. Evaluations

The Applicant had extensive previous discussion with FDA on evaluation of melasma. The primary efficacy variable and the methodology for evaluation have been agreed to between the Applicant and the Agency.

(1) Efficacy

- Investigator's Static Assessment of Melasma Severity (primary efficacy variable)

It is a static rating scale:

- 0 = Melasma lesions approximately equivalent to surrounding normal skin or with minimal residual hyperpigmentation
- 1 = Mild (slightly darker than the surrounding normal skin)
- 2 = Moderate (moderately darker than the surrounding normal skin)
- 3 = Severe (markedly darker than the surrounding normal skin)

- Investigator assessment of global improvement from Baseline by comparing the extent of melasma at each follow-up visit to a full-face photograph obtained in a standardized manner at Baseline. It is a dynamic scale:

- 0 = Completely clear; 100% improvement/clearance from Baseline; no evidence of hyperpigmentation
- 1 = Almost clear; about 90% improvement/clearance from Baseline; minimal traces of hyperpigmentation
- 2 = Significant or marked improvement; about 75% improvement/clearance from Baseline; evidence of hyperpigmentation still remains
- 3 = Moderate improvement; about 50% improvement/clearance from Baseline; substantial decrease in hyperpigmentation but still prominent

- 4 = Slight improvement; about 25% improvement/clearance from Baseline; minimal but noticeable decrease of hyperpigmentation
 - 5 = No change from baseline
 - 6 = Worse; hyperpigmentation appears darker from Baseline presentation
- Investigator's static global assessment of melasma severity included an assessment of all treated areas using the following scale:
 - 0 = Completely clear; no evidence of hyperpigmentation
 - 1 = Nearly clear; only minor visual evidence of hyperpigmentation
 - 2 = Significant evidence of hyperpigmentation
 - Patient's static global assessment of melasma severity included an assessment of all treated areas by each patient at Day 56 using the following scale:
 - 1 = Completely cleared
 - 2 = Nearly cleared
 - 3 = Significant hyperpigmentation present

(2) Safety

Safety was measured by the occurrence of adverse events and laboratory testing of blood and urine at selected sites (nos. 3, 7, 9, and 11 for Study 28A; lab tests not done for 28B) and consisted of complete blood count (CBC), serum chemistries, and urinalysis. Anticipated adverse events, as described in the investigational drug brochure, including erythema, skin peeling, burning, stinging, telangiectasia, rosacea, dermatitis, atrophy and grayish discoloration of skin or black dots, were specifically solicited by the investigator at each visit and listed and detailed.

(3) Data Entry and Verification

_____ had data management responsibilities. After the CRFs were received from the study sites, each page was uniquely identified and tracked with a computer-generated barcode. A Windows NT® software package, customized for data entry, was used and an electronic audit trail was maintained. Concomitant medications were coded using the World Health Organization (WHO) Dictionary and adverse events were coded using the MedDRA Dictionary. Edit checks were performed based on data entry and quality assurance audits.

(4) Quality Assurance and Database Locking

_____ Data Management Department audited 100% of the critical efficacy and safety variables, and _____ Quality Assurance Department audited the full CRF data for 10% of the patients who were randomly chosen. The blinded code was maintained until all data clarifications had been resolved and decision on patient evaluability completed. Once all questions were resolved, the database was locked. The study conduct was monitored by _____ following GCP guidelines.

vi. Statistical Considerations

The primary efficacy analysis was to be performed according to the intent-to-treat principle. In addition, analysis on an evaluable subset was to be performed. Statistical tests were to be 2-sided overall and the results were to be considered statistically significant if the P -value was <0.05 . The ITT principle and the primary analysis are consistent with EDA recommendations.

(1) Population for Analysis

- Intent-to treat (ITT) population. The protocol originally defined the ITT population as all patients who received at least one application of the study material and had at least one post-baseline evaluation. At the recommendation of the FDA received June 26, 2000, this population was redefined as all patients who were randomized to therapy and dispensed the study material.
- Per-protocol (PP) population. The PP population was to comprise all patients who did not violate the protocol and who completed 8 weeks (56 days) of treatment. Before the study was unblinded, the PP population was redefined to include all patients who had at least one study evaluation and at least 4 weeks of treatment.

(2) Analysis Plan

The following variables were planned to be statistically analyzed:

- demographics and baseline characteristics: age, gender, race, and skin type
- primary efficacy: investigator's static assessment of melasma severity (success defined as a score of zero on the severity scale at Day 56)
- secondary efficacy: investigator's static assessment of melasma severity (secondary success defined as a score of 0 or 1 on the severity scale at Day 56), investigator's global improvement score, investigator's static global assessment, patient's static global assessment
- safety: frequency of adverse events

Primary Efficacy Variable

- Proportion of patients achieving score of zero on Investigator's static assessment of melasma severity at Day 56, analyzed with CMH test, stratified by center.

Secondary Efficacy Variables

- Proportion of patients achieving a score of 0 or 1 on Investigator's static assessment of melasma severity at Day 56 was the first secondary efficacy variable, to be analyzed with CMH test, stratified by center.
- Physician's assessment of improvement from Baseline score at Day 56, physician's static global assessment at Day 56, and patient's static global assessment at Day 56 were additional secondary efficacy variables. Rank analysis of variance procedures were used to evaluate these variables in the study report, but dichotomized analysis was performed by FDA's Biometrics Reviewer, Dr. Shiojjen Lee.
- Subgroup analyses for the effects of age, sex, and race were performed when the data allowed for such analyses. Analyses by age subgroupings were not performed because only three patients (all 66 years old) were outside the 18-65 age group.

Safety Variables

- Adverse events were displayed in summary tables by severity and relatedness to study drug, seriousness and frequency by body system. Inter-group differences in the incidence of adverse events were tested by the chi-square test.

(3) Determination of Sample Size. A previous study (Study 24) demonstrated that for the primary and secondary parameters, the least difference between TRILUMA Cream treatment and any dyad treatment was 20%. Based on a difference in proportions of 15%, $\alpha = 0.05$ (test level) and power of 80% to detect a difference of 15% or more between TRILUMA and the dyad combination, 80 patients per treatment arm were required.

(4) Method of Treatment Assignment/Blinding. Before start of the study, a randomization list assigning patients to one of four treatment groups in a 1:1:1:1 ratio was generated. Assignment to a treatment group was in sequential order of enrollment at a center. Patients were randomized in blocks of 4. This was an investigator-masked study and test products were not disclosed to investigators. The products were dispensed by the study coordinator or pharmacist and similarly returned to those individuals.

vii. Changes in the Conduct of the Study or Planned Analyses

There were three amendments to the study protocol.

- June 28, 2000. Expanded definition for female patients of childbearing potential in inclusion criteria to include that effective contraception or abstinence be followed during the treatment period. The definition of ITT population was also changed from "all patients who receive at least one application of the study material and have at least one post-baseline evaluation" to "all patients who were randomized to therapy and dispensed the study material". This was due to recommendation from the FDA.

- July 20, 2000. Added the word melasma in parentheses after the term melanosis of the face throughout the protocol. This amendment also added the requirement that anticipated adverse events be specifically solicited by the investigator at each visit and recorded on the adverse event form of the CRF.
- October 25, 2000. Changed cutaneous melanosis of the face (melasma) to just melasma of the face throughout the protocol. It also added global static assessment of melasma at Day 56, as evaluated by investigator and by patient, as secondary efficacy criteria. Such global assessments of all treated areas of the whole face at each follow-up visit were added. Laboratory testing (CBC, urinalysis, and serum chemistries) at selected study centers was added. The anticipated adverse events to be collected were specified: erythema, skin peeling, stinging, telangiectasia, rosacea, dermatitis, atrophy and grayish discoloration of the skin and black spots.

The following changes were also made to the study analysis:

- Before the study blind was broken, the per protocol population was redefined from that stated in the protocol (i.e., all patients who do not violate the protocol and complete 8 weeks of treatment). The change excluded a patient only if he/she had no evaluations or if he/she had less than 4 weeks of therapy. All other patients were included in the PP analysis.
- Hochberg multiple comparison adjustments were not used to test TRILUMA against each of the dyads as stated in the protocol. This change was made based on a recommendation from the FDA in a 9/6/00 letter.
- An additional exploratory efficacy analysis was to be done, with success defined as cleared at any time during the study (i.e., primary success) and also with success defined as either cleared or mild melasma (i.e., secondary success) at any time during the study.

b. RESULTS

Data quality is addressed by DSI. Two of the Investigational sites (Site 1 of Study 28A, Dr. H. Torok, and Site 12 of Study 28B, Dr. A. Menter) have been audited, and no major concerns on data integrity have been discovered.

i. Disposition of Patients

Study Sites

STUDY/CENTER	INVESTIGATOR	LOCATION	PATIENTS ENROLLED
28A/01	Helen M. Torok, MD	Medina, OH	60
28A/03	Leslie Baumann, MD	Miami, FL	74
28A/05	Joshua Wieder, MD	Los Angeles, CA	25
28A/07	Michael Jarratt, MD	Austin, TX	58
28A/09	David Pariser, MD	Norfolk, VA	33
28A/11	Dale Martin, MD	San Diego, CA	56
28A/13	Jonathan Weiss, MD/Joel Shavin, MD	Snellville, GA	32
28B/02	Susan Taylor, MD	New York, NY	59
28B/04	Terry Jones, MD	Bryan, TX	44
28B/06	Nicholas Lowe, MD	Santa Monica, CA	40
28B/08	Phoebe Rich, MD	Portland, OR	60
28B/10	Eduardo Tschén, MD	Albuquerque, NM	60
28B/12	Alan Menter, MD	Dallas, TX	40

Patient Disposition

	TRI-LUMA	FA+HQ	FA+RA	HQ+RA	TOTAL
STUDY 28A					
Entered	85	85	85	83	338
Completed study	81 (95.3%)	81 (95.3%)	79 (92.9%)	76 (91.6%)	317 (93.8%)
Discontinued	4 (4.7%)	4 (4.7%)	6 (7.1%)	7 (8.4%)	21 (6.2%)
Patient request	1 (1.2%)	1 (1.2%)	0	2 (2.4%)	4 (1.2%)
Adverse event	0	0	3 (3.5%)	1 (1.2%)	4 (1.2%)
Lost to follow-up	0	3 (3.5%)	3 (3.5%)	1 (1.2%)	7 (2.1%)
Non-compliance	1 (1.2%)	0	0	1 (1.2%)	2 (0.6%)
Other	2 (2.4%)	0	0	2 (2.4%)	4 (1.2%)
Per-Protocol population	81 (95.3%)	82 (96.5%)	80 (94.1%)	79 (95.2%)	322 (95.3%)
STUDY 28B					
Entered	76	76	76	75	303
Completed study	71 (93.4%)	70 (92.1%)	72 (94.7%)	72 (96.0%)	285 (94.1%)

Discontinued	5 (6.6%)	6 (7.9%)	4 (5.3%)	3 (4.0%)	18 (5.9%)
Patient request	2 (2.6%)	0	1 (1.3%)	1 (1.3%)	4 (1.3%)
Adverse event	0	1 (1.3%)	1 (1.3%)	0	2 (0.7%)
Lost to follow-up	2 (2.6%)	2 (2.6%)	1 (1.3%)	1 (1.3%)	6 (2.0%)
Patient ineligibility	1 (1.3%)	0	0	0	1 (0.3%)
Non-compliance	0	3 (3.9%)	1 (1.3%)	1 (1.3%)	5 (1.7%)
Per-Protocol population	73 (96.1%)	71 (93.4%)	72 (94.7%)	74 (98.7%)	290 (95.7%)

FA=flucinolone acetonide 0.01%, HQ=hydroquinone 4%, RA=tretinoin 0.05%.

In Study 28A, 3 patients were randomized but discontinued from the study before using any of the study medications. These patients were excluded from the PP analysis. As well, 13 other patients were excluded because they had less than 4 weeks of treatment. In Study 28B, 6 patients were excluded from the PP analysis because they had no post-baseline evaluations and 7 patients were excluded for noncompliance because they had less than 4 weeks of treatment.

ii. Baseline Comparability

Study 28A	TREATMENT GROUP				P-value ^a
	TRILUMA (N=85)	FA+HQ (N=85)	FA+RA (N=85)	HQ+RA (N=83)	
Age (years)					
Mean (SD)	41.4 (8.6)	42.7 (8.1)	41.3 (8.7)	40.7 (8.0)	0.464
Range (min - max)	23.0-60.0	26.0-66.0	25.0-66.0	26.0-66.0	
Sex [n (%) of patients]					
Male	3 (3.5)	1 (1.2%)	1 (1.2%)	1 (1.2%)	0.606
Female	82 (96.5)	84 (98.8%)	84 (98.8%)	82 (98.8%)	
Race [n (%) of patients]					
White	56 (65.9)	57 (67.1)	64 (75.3)	58 (69.9)	0.175
Black	0 (0.0)	3 (3.5)	2 (2.4)	0 (0.0)	
Asian	4 (4.7)	3 (3.5)	2 (2.4)	0 (0.0)	
Other	25 (29.4)	22 (25.9)	17 (20.0)	25 (30.1)	
Skin Phototype [n (%) pts]					
Type I	8 (9.4)	8 (9.4)	8 (9.4)	8 (9.6)	0.946
Type II	27 (31.8)	24 (28.2)	31 (36.5)	31 (37.3)	
Type III	35 (41.2)	40 (47.1)	32 (37.6)	33 (39.8)	
Type IV	15 (17.6)	13 (15.3)	14 (16.5)	11 (13.3)	
	Treatment Group				
Study 28B	TRILUMA (N=76)	FA+HQ (N=76)	FA+RA (N=76)	HQ+RA (N=75)	P-value ^a
Age (years)					
Mean (SD)	43.2 (9.4)	44.1 (10.6)	42.6 (9.4)	45.4 (8.8)	0.287
Range (min - max)	22.0-66.0	21.0-75.0	22.0-74.0	30.0-71.0	
Sex [n (%) of pts]					
Male	1 (1.3)	4 (5.3%)	1 (1.3%)	2 (2.7%)	0.378
Female	75 (98.7)	72 (94.7%)	75 (98.7%)	73 (97.3%)	
Race [n (%) of pts]					
White	47 (61.8)	51 (67.1)	46 (60.5)	43 (57.3)	0.904
Black	4 (5.3)	3 (3.9)	5 (6.6)	4 (5.3)	
Asian	5 (6.6)	5 (6.6)	4 (5.3)	8 (10.7)	
Other	20 (26.3)	17 (22.4)	21 (27.6)	20 (26.7)	
Skin Phototype [n (%) pts]					
Type I	6 (7.9)	6 (7.9)	7 (9.2)	7 (9.3)	0.649
Type II	21 (27.6)	26 (34.2)	19 (25.0)	18 (24.0)	
Type III	32 (42.1)	22 (28.9)	24 (31.6)	24 (32.0)	
Type IV	17 (22.4)	22 (28.9)	26 (34.2)	26 (34.7)	

^a P-value for comparisons of the distributions of sex, race, and skin phototype among treatment groups was based on the Cochran-Mantel-Haenszel test. P-value for comparison of the distributions of age among treatment groups was based on an ANOVA model with treatment and center as factors.

Baseline severity comparison

The patients in Study 28A and 28B were enrolled with minimum melasma severity of "moderate" at baseline. The severity among the treatment groups is shown in the following Table:

	NUMBER (%) OF PATIENTS: BASELINE MODERATE/BASELINE SEVERE			
	Treatment Group			
	TRI-LUMA	FA+HQ	FA+RA	RA+HQ
Study 28A	69 (81)/16 (19)	56 (66)/29 (34)	63 (74)/22 (26)	51 (61)/32 (39)
Study 28B	55 (72)/21 (28)	52 (68)/24 (32)	48 (63)/28 (37)	45 (60)/30 (40)

iii. Primary Efficacy Endpoint

Proportion of Subjects with Melasma Severity Score of 0 at Day 56

STUDY 28A	TRI-LUMA	FA+HQ	FA+RA	HQ+RA	COMPARISON	
ITT analysis	32/85 (37.6%)	3/85 (3.5%)	0/85	12/83 (14.5%)	TRI-LUMA vs. FH	p<0.001
					TRI-LUMA vs. FR	p<0.001
					TRI-LUMA vs. HR	p<0.001
PP analysis	32/81 (39.5%)	3/82 (3.7%)	0/80 (0%)	12/79 (15.2%)	TRI-LUMA vs. FH	p<0.001
					TRI-LUMA vs. FR	p<0.001
					TRI-LUMA vs. HR	p<0.001
STUDY 28B	TRI-LUMA	FA+HQ	FA+RA	HQ+RA	COMPARISON	
ITT analysis	10/76 (13.2%)	1/76 (1.3%)	3/76 (3.9%)	3/75 (4.0%)	TRI-LUMA vs. FH	p=0.005
					TRI-LUMA vs. FR	p=0.042
					TRI-LUMA vs. HR	p=0.045
PP analysis	10/73 (13.7%)	1/71 (1.4%)	3/72 (4.2%)	3/74 (4.1%)	TRI-LUMA vs. FH	p=0.006
					TRI-LUMA vs. FR	p=0.039
					TRI-LUMA vs. HR	p=0.040

- TRI-LUMA Cream has demonstrated superiority over each of the dyad creams in clearing melasma at Day 56 in both Studies 28A and 28B.
- Multiplicity adjustment is not applied, as TRI-LUMA Cream has to show superiority over each of the dyad creams in order to acquire a claim of effectiveness in the treatment of melasma.

iv. Secondary Efficacy Endpoints

Four secondary efficacy endpoints in the protocol were:

- Proportion of subjects with investigator's assessment of severity score of 0 or 1
- Physician's assessment of global improvement from baseline
- Physician's static global assessment
- Patient's static global assessment

Proportion of Subjects with Melasma Severity Score of 0 or 1 at Day 56: ITT Analysis

STUDY 28A	TRI-LUMA	FA+HQ	FA+RA	HQ+RA	COMPARISON	
	73/85 (85.9%)	42/85 (49.4%)	23/85 (27.1%)	51/83 (61.4%)	TRI-LUMA vs FH	p<0.001
					TRI-LUMA vs FR	p<0.001
					TRI-LUMA vs HR	p<0.001
STUDY 28B	TRI-LUMA	FA+HQ	FA+RA	HQ+RA	COMPARISON	
	51/76 (67.1%)	26/76 (34.2%)	21/76 (27.6%)	23/75 (30.7%)	TRI-LUMA vs FH	p<0.001
					TRI-LUMA vs FR	p<0.001
					TRI-LUMA vs HR	p<0.001

Physician's Assessment for Global Improvement at Day 56: ITT Analysis

STUDY 28A	TRILUMA (N=85)	FA+HQ (N=85)	FA+RA (N=85)	HQ+RA (N=83)	COMPARISON
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100%	22 (25.9%)	2 (2.4%)	0	11 (13.3%)	TRI-LUMA vs FH TRI-LUMA vs FR TRI-LUMA vs HR	p<0.001 p<0.001 p=0.020
90%	22 (25.9%)	11 (12.9%)	2 (2.4%)	20 (24.1%)		
75%	17 (20.0%)	12 (14.1%)	6 (7.1%)	13 (15.7%)		
50%	15 (18.4%)	25 (29.4%)	16 (18.8%)	21 (25.3%)		
25%	4 (4.7%)	19 (22.4%)	36 (42.4%)	9 (10.8%)		
No change	1 (1.2%)	11 (12.9%)	17 (20.0%)	5 (6.0%)		
Worse	0	2 (2.4%)	3 (3.5%)	1 (1.2%)		
Missing	4 (4.7%)	3 (3.5%)	5 (5.9%)	3 (3.6%)		
STUDY 28B	TRILUMA (N=76)	FA+HQ (N=76)	FA+RA (N=76)	HQ+RA (N=75)		
100%	10 (13.2%)	1 (1.3%)	3 (3.9%)	3 (4.0%)	TRI-LUMA vs FH TRI-LUMA vs FR TRI-LUMA vs HR	p=0.005 p=0.042 p=0.045
90%	23 (30.3%)	6 (7.9%)	5 (6.6%)	9 (12.0%)		
75%	14 (18.4%)	15 (19.7%)	10 (13.2%)	9 (12.0%)		
50%	11 (14.5%)	12 (15.8%)	13 (17.1%)	17 (22.7%)		
25%	14 (18.4%)	29 (38.2%)	24 (31.6%)	25 (33.3%)		
No change	0	7 (9.2%)	16 (21.1%)	9 (12.0%)		
Worse	0	0	2 (2.6%)	0		
Missing	4 (5.3%)	6 (7.9%)	3 (3.9%)	3 (4.0%)		

¹ Dichotomization by Biometrics Reviewer and based on CMH test adjusting for study site. With success defined as 100% improvement.

Physician's Static Global Assessment at Day 56: ITT Analysis

STUDY 28A	TRILUMA (N=85)	FA+HQ (N=85)	FA+RA (N=85)	HQ+RA (N=83)	¹ COMPARISON	
Completely cleared	22 (25.9%)	2 (2.4%)	0	10 (12.0%)	TRI-LUMA vs FH	p<0.001
Nearly cleared	46 (54.1%)	30 (35.3%)	17 (20.0%)	37 (44.6%)	TRI-LUMA vs FR	p<0.001
Significant hyperpigmentation	13 (15.3%)	49 (57.6%)	63 (74.1%)	31 (37.3%)	TRI-LUMA vs HR	p=0.009
Missing	4 (4.7%)	4 (4.7%)	5 (5.9%)	5 (6.0%)		
	TRILUMA (N=76)	FA+HQ (N=76)	FA+RA (N=76)	HQ+RA (N=75)		
Completely cleared	11 (14.5%)	1 (1.3%)	3 (3.9%)	3 (4.0%)	TRI-LUMA vs FH	p=0.003
Nearly cleared	39 (51.3%)	22 (28.9%)	16 (21.1%)	19 (25.3%)	TRI-LUMA vs FR	p=0.025
Significant hyperpigmentation	22 (28.9%)	47 (61.8%)	54 (71.1%)	50 (66.7%)	TRI-LUMA vs HR	p=0.027
Missing	4 (5.3%)	6 (7.9%)	3 (3.9%)	3 (4.0%)		

¹ Dichotomization analysis is reviewer's analysis and is based on CMH test adjusting for study site, with success defined as "completely cleared".

Patient's Static Global Assessment at Day 56: ITT Analysis

STUDY 28A	TRILUMA (N=85)	FA+HQ (N=85)	FA+RA (N=85)	HQ+RA (N=83)	¹ COMPARISON	
Completely cleared	12 (14.1%)	2 (2.4%)	1 (1.2%)	6 (7.2%)	TRI-LUMA vs FH	p=0.002
Nearly cleared	51 (60.0%)	30 (35.3%)	16 (18.8%)	46 (55.4%)	TRI-LUMA vs FR	p<0.001
Significant hyperpigmentation	18 (21.2%)	49 (57.6%)	62 (72.9%)	26 (31.3%)	TRI-LUMA vs HR	p=0.071
Data missing	4 (4.7%)	4 (4.7%)	6 (7.1%)	5 (6.0%)		
	TRILUMA (N=76)	FA+HQ (N=76)	FA+RA (N=76)	HQ+RA (N=75)		
Completely cleared	6 (7.9%)	1 (1.3%)	1 (1.3%)	3 (4.0%)	TRI-LUMA vs FH	p=0.053
Nearly cleared	49 (64.5%)	28 (36.8%)	19 (25.0%)	25 (33.3%)	TRI-LUMA vs FR	p=0.053
Significant hyperpigmentation	17 (22.4%)	41 (53.9%)	52 (68.4%)	44 (58.7%)	TRI-LUMA vs HR	p=0.301
Data missing	4 (5.3%)	6 (7.9%)	4 (5.3%)	3 (4.0%)		

¹ Dichotomization by Biometrics Reviewer and based on CMH test adjusting for study site, with success defined as "completely cleared".

- The Biometrics Reviewer also used the last observation carried forward (LOCF) method to handle missing data. Results of the analyses were consistent with the above.
- For each of the secondary endpoints, TRI-LUMA Cream demonstrated superiority over dyad creams in both studies, except for "patient's static global assessment", when success is defined as "completely cleared". Even with this definition, TRI-LUMA Cream was superior to the dyads FH and FR in Study 28A. It is noted that in contrast to Investigators, patients were less likely to give an evaluation of "completely cleared" at Day 56. The reason for this is unclear, but the definitions in

the scoring systems are slightly different, and it is possible that this might lead to subtle differences between how patients vs Investigators scored their static globals.

- The Applicant intends to make a claim in the label that patients treated with TRI-LUMA Cream demonstrated gradual improvement in melasma severity throughout the 8-week study period, but the greatest improvement was noted after at least 4 weeks of treatment. The clearing of melasma as evaluated by the Investigator assessment of melasma severity over the course of treatment can be shown in the following Table.

	NUMBER (%) OF PATIENTS WHO HAD MELASMA SEVERITY SCORE OF "CLEARED"			
	Treatment Group			
	TRI-LUMA	FA+HQ	FA+RA	RA+HQ
Study 28A	N=85	N=85	N=85	N=83
Day 0	0	0	0	0
Day 7	0	0	0	0
Day 14	0	0	0	0
Day 28	5	1	0	6
Day 56	32	3	0	2
Study 28B	N=76	N=76	N=76	N=75
Day 0	0	0	0	0
Day 7	0	0	0	0
Day 14	0	0	0	0
Day 28	2	0	0	0
Day 56	10	1	3	3
Study 28A+28B	N=161	N=161	N=161	N=158
Day 0	0	0	0	0
Day 7	0	0	0	0
Day 14	0	0	0	0
Day 28	7	1	0	6
Day 56	42	4	3	5

- As shown in the above Table, in Study 28A, TRI-LUMA Cream was not superior to the RA+HQ combination at week 4, and in Study 28B, there were two successes in the TRI-LUMA group and none in the dyad groups. It is also important to note that early clearing is not necessarily maintained. Among the 7 patients who had clearing at Week 4 of TRI-LUMA therapy, 2 in Study 28A (Patient 1-52, 9-461) and 2 in Study 28B (2-74 and 4-208) reverted to have mild melasma at Week 8. Thus, although there may be a trend showing patients generally improve with further treatment beyond 4 weeks, this is not invariably the case.

v. Subset Analysis

The Applicant has performed demographic subset analysis of the efficacy data in the Integrated Summary of Efficacy. The pooled data from Studies 28A and 28B on the primary efficacy variable, melasma severity score=0 at Day 56, are presented here.

(1) Analysis by Sex

Primary treatment success (melasma severity score = 0) at Day 56 was analyzed for males and females. The analysis for **females** paralleled that for the total population since the majority of the population was female. TRI-LUMA was statistically significantly ($P<0.001$) superior to each individual dyad. Two of the four **males** in the TRI-LUMA group achieved success. None of the 10 men in each of the three dyad groups achieved treatment success.

(2) Analysis by Age

Analyses by age subgroupings were not performed because of the small number of patients who were greater than **65 years** old.

(3) Analysis by Race

Primary treatment success (melasma severity score = 0) at Day 56 was analyzed by race. The analysis for **Caucasians** paralleled that for the total population since the majority of the population was white in both studies. There was statistically significant difference ($P < 0.001$) between TRI-LUMA and each of the other dyad treatments. Two of the 13 **Blacks/Asians** in the TRI-LUMA group achieved success. Among the 39 Blacks/Asians in the dyad groups, there were no successes. For patients of "**Other**" races, 11 of 45 (24.4%) in the TRI-LUMA group achieved success compared with 2 of 122 patients (1.6%) in the dyad groups. Both successes in a dyad group were from the RA+HQ group. The difference was statistically significant between the TRI-LUMA group and the other dyad groups separately ($P \leq 0.011$) for patients of "Other" races.

(4) Analysis by Skin Phototype

Analysis by skin phototype has not been performed in the original response. The Applicant presented this analysis through email on 1/3/02. TRI-LUMA Cream is numerically better than each dyad for all the skin types tested except Type I, but the patient numbers for Type I are too small to draw conclusions on.

Study 28A+28B SKIN TYPE ↓	NUMBER (%) OF PATIENTS AT DAY 56 WITH MELASMA SEVERITY SCORE OF "CLEARED"			
	Treatment Group			
	TRI-LUMA	FA+HQ	FA+RA	RA+HQ
I	3/14 (21%)	1/14 (7%)	0/15	4/15 (27%)
II	13/48 (27%)	1/50 (2%)	2/50 (4%)	7/49 (14%)
III	21/67 (31%)	2/62 (3%)	0/56	2/57 (4%)
IV	5/32 (16%)	0/35	1/40 (3%)	2/37 (5%)

(5) Analysis by Baseline Severity of Melasma

Primary treatment success (melasma severity score = 0) at Day 56 was analyzed by baseline melasma severity. TRI-LUMA Cream appears to provide benefit to patients with moderate or severe melasma, but the benefit is less pronounced in those with severe melasma.

DAY 56 SEVERITY ↓	NUMBER (%) OF PATIENTS AT DAY 56: BASELINE MODERATE/BASELINE SEVERE			
	Treatment Group			
	TRI-LUMA	FA+HQ	FA+RA	RA+HQ
Study 28A	[N=69 (81)/16 (19)]	[N=56 (66)/29 (34)]	[N=63 (74)/22 (26)]	[N=51 (61)/32 (39)]
Clear	27 (32)/5 (6)	3 (4)/0	0/0	10 (12)/2 (2)
Mild	33 (39)/8 (9)	31 (37)/8 (9)	21 (25)/2 (2)	25 (30)/14 (17)
Moderate	5 (6)/3 (4)	20 (24)/11 (13)	39 (46)/7 (8)	13 (16)/12 (15)
Severe	0/0	0/9 (11)	0/11 (13)	1 (1)/3 (4)
"Missing"	4 (5)/0	2 (2)/1 (1)	3 (4)/2 (2)	2 (2)/1 (1)
Study 28B	[N=55 (72)/21 (28)]	[N=52 (68)/24 (32)]	[N=48 (63)/28 (37)]	[N=45 (60)/30 (40)]
Clear	9 (12)/1 (1)	1 (1)/0	3 (4)/0	2 (3)/1 (1)
Mild	30 (40)/11 (15)	20 (26)/5 (7)	14 (18)/4 (5)	16 (21)/4 (5)
Moderate	13 (17)/6 (8)	28 (37)/8 (11)	28 (37)/9 (12)	24 (32)/10 (13)
Severe	0/2 (3)	0/8 (11)	0/15 (20)	0/15 (20)
"Missing"	3 (4)/1 (1)	3 (4)/3 (4)	3 (4)/0	3 (4)/0

Study 28A+28B	[N=124 (77)/37 (23)]	[N=108 (67)/53 (33)]	[N=111 (69)/50 (31)]	[N=96 (61)/62 (39)]
Clear	36 (22)/6 (4)	4 (2)/0	3 (2)/0	12 (8)/3 (2)
Mild	63 (39)/19 (12)	50 (31)/13 (8)	35 (22)/6 (4)	41 (26)/18 (11)
Moderate	18 (11)/9 (6)	48 (30)/19 (12)	67 (42)/16 (10)	37 (23)/22 (14)
Severe	0/2 (1)	0/17 (11)	0/26 (16)	1 (<1)/18 (11)
"Missing"	7 (4)/1 (<1)	5 (3)/4 (2)	6 (4)/2 (1)	5 (3)/1 (<1)

(6) Analysis by Use of Hormonal Methods of Contraception

Analysis by hormonal methods of contraception has not been performed in the original response. The Applicant presented this analysis through email on 1/14/02. TRI-LUMA Cream appears to be superior to each dyad in clearing melasma for both users and non-users of hormonal methods of contraception in women.

Study 28A+28B HORMONAL CONTRACEPTION	NUMBER (%) OF PATIENTS AT DAY 56 WITH MELASMA SEVERITY SCORE OF "CLEARED"			
	Treatment Group			
	TRI-LUMA	FA+HQ	FA+RA	RA+HQ
Users	10/39 (26%)	1/36 (3%)	2/34 (6%)	3/32 (9%)
Non-Users	16/67 (24%)	3/69 (4%)	2/68	6/74 (8%)

2. Long-Term Intermittent Use

The Applicant is conducting two long-term open-label studies, 29 and 30, to examine safety for intermittent use of TRI-LUMA Cream in the treatment of melasma of the face. Part of the evaluations in these studies includes collection of efficacy data. Although these are uncontrolled studies and cannot be considered adequate to determine effectiveness, they do yield some useful information regarding drug exposure and remission/relapse. In two previous clinical trials (Studies 24 East and 24 West), all patients who responded to TRI-LUMA Cream had relapse of hyperpigmentation when the drug was discontinued or tapered.

At the time of this review, only partial efficacy data from Study 29 are available. No efficacy data from Study 30 have been presented. Therefore, the review given below only pertains to the available data from Study 29.

Study 29. Long-term (12-month) Safety and Efficacy of TRILUMA [0.01% Fluocinolone Acetonide + 4% Hydroquinone +0.05% Tretinoin] in the Treatment of Patients with Melasma of the Face [Ongoing Study, Started 8/21/00]

Study 29 is the open-label extension of Studies 28A and 28B.

a. PROTOCOL

i. Objectives:

- To provide long-term local and systemic safety information of TRILUMA in the treatment of melasma of the face.
- Although efficacy is not the primary objective of this study, investigator evaluations will be performed. The protocol states: "(t)he product is indicated for temporary relief of melasma of the face and not for continuous use."

ii. Design:

This was a long-term (12-month), multi-center, open-label study of TRILUMA Cream in the treatment of melasma of the face. Approximately 585 patients previously treated under Protocol 28 were to be enrolled at up to 13 sites. This was to allow for at least 100 evaluable patients with 12-months of TRILUMA usage. All patients entering this study were to continue to meticulously use sunscreen on the face on at least a daily basis especially on those areas subject to melasma. A sunscreen of SPF 30 with UVB and UVA protection was provided by the study site for this purpose. Female patients of childbearing potential were required to have a negative pregnancy test result prior to and at the end of each treatment period.

Two groups of patients entered Protocol 29 from Protocol 28:

- patients who had satisfactory resolution of melasma, i.e., achieved a severity score rating of 0 or 1 during Protocol 28. Upon entry into Study 29, they were followed every 2 months and retreated as needed (PRN). When in the judgement of the investigator and patient they required further treatment, they could, at any time during the 12-month period, be retreated once daily (QD) with TRILUMA until satisfactory resolution (melasma severity score of 0 or 1) or lack of response (melasma >1). Patients were to treat the affected areas of the face as described in Protocol 28.
- patients in Studies 28 who did not achieve satisfactory melasma severity scores, were retreated under Protocol 29. Patients with severity scores of greater than 0 or 1 and/or requirement of further treatment were retreated QD with TRILUMA upon entry and followed-up monthly during retreatment until satisfactory resolution or lack of response, at which time treatment was stopped except for use of sunscreen. They, like the previous group of patients, continued to be followed-up every 2 months when off treatment.

Comment The fact that a course of treatment is terminated on the basis of satisfactory resolution with melasma severity score of 0 or 1, or lack of response (score >1) makes it impossible to know whether completion of a course is associated with what kind of severity status. The outcome could be "cleared", "mild", "moderate" or "severe".

Study Flowchart

Procedures	STUDY OVERALL		
	Study Day 0 ^a	Weeks 8, 16, 24, 32, 40, etc.	Week 52
Informed consent	X		
Demographics and history	X		
Inclusion/Exclusion	X		
Laboratory testing of blood and urine ^b	X		X
Enroll in study (issue patient number)	X		
UPT (females of child-bearing potential)	X		X
Identify melasma lesions	X		
disease evaluation investigator	X		X
Melasma severity grading	X	X	X
Initiate treatment	PRN	PRN	
Adverse event identification		X	X
Concomitant/concurrent medications	X	X	X
Procedures	DURING TREATMENT		
	DAY 0 ^a	WEEKS 4, 8, 12, 16, 24, ETC.	FINAL WEEK
UPT (females of child-bearing potential)	X	X ^c	X
Identification of melasma lesions	X		
Disease evaluations by investigator	X	X	X
Melasma severity grading	X	X	X
Physician global assessment		X	X
Patient global assessment		X	X
Adverse events		X	X
Laboratory tests of blood and urine ^b	X		X
Dispense test product	X	X	
Weigh tube	X	X	X
Collect test product		X	X

Record missed doses		X	X
Concomitant/concurrent medications	X	X	X
^a At selected centers only; ^b Protocol 29; ^c at the beginning and end of treatment			

iii. Patient Selection

Inclusion

1. Male and female patients 18 years of age and over with skin phototype I to IV and melasma of the face and previously enrolled in study Protocol 28;
2. Female patients of childbearing potential with a negative urine pregnancy test who agree to use effective methods of birth control or remain abstinent during treatment. Acceptable methods of birth control include ongoing hormonal contraceptives (oral, injectable, or implantable), barrier methods, intrauterine devices, and tubal ligation;
3. Patients willing and capable of cooperating to the extent and degree required by the protocol;
4. Patients that have read and signed an approved informed consent for this study. All patients must receive a copy of the signed consent.

Exclusion

1. Female patients who are pregnant or nursing;
2. Required concurrent treatment that would interfere with study objectives and/or evaluations;
3. Presence of facial skin conditions that would have interfered with study objectives and/or evaluations (neurodermatitis, eczema, atrophy, telangiectasias, rosacea, etc.);
4. Immunocompromised or under immunosuppressive treatment;
5. Presence of a significant endocrine disorder that may have required contraindicated treatment with potent corticosteroids;
6. A known sensitivity to any of the ingredients in the test articles;
7. Exposure (through work or daily activities) to the sun on a regular basis and/or those who had consistent irritation of the exposed skin;
8. Sunbathing on a regular basis;
9. A history of alcohol or drug abuse;
10. Inability to communicate or cooperate with the investigator due to language problems, poor mental development, or impaired cerebral function.

iv. Administration Of Test Drug

Same as in Studies 28A and 28B

v. Evaluations

(1) Efficacy

- The efficacy parameters: (1) Investigator's Assessment of Melasma Severity, (2) Physician's Global Assessment and (3) Patient's Global Assessment, were equivalent to the (a) Investigator's *Static* Assessment of Melasma Severity, (b) Physician's *Static* Global Assessment and (c) Patient's *Static* Global Assessment of Study 28. The term "static" has been removed, but the assessments were static.
- The only difference between these variables for the two protocols was in one of the scores for Physician's Global Assessment (1 = "Almost" clear, only minor visual evidence of hyperpigmentation). For Physician's *Static* Global Assessment in Study 28, this was ~~1~~ = "Nearly" clear, only minor visual evidence of hyperpigmentation.
- One efficacy variable was dropped for Study 29: Investigator Assessment of Global Improvement from Baseline, which was evaluated in Study 28.
- The Physician and Global Assessments were only made in visits during and at the end of a treatment course, while the Investigator's Assessment of Melasma Severity scores were made at all visits.

(2) Safety

Local and systemic safety was the primary purpose of this study. Safety was measured by the occurrence of adverse events and laboratory tests. Laboratory testing of blood

and urine was performed at selected sites (nos. 3, 7, 9, and 11) at the start of the study, each time treatment was initiated and completed, and at the final study visit. They consisted of complete blood count (CBC), serum chemistries, and urinalysis. A urine pregnancy test (UPT) was conducted at the start of the study, each time treatment was initiated and completed, and at the final study visit. Laboratory tests were conducted at a central laboratory. Any clinically significant change in laboratory values was to be reported as an adverse event and followed accordingly.

(3) Data Entry and Verification

The investigator maintained detailed records on all study patients. Completed CRFs were reviewed within 1 week of each study visit for a given patient. Upon study completion or at any other specified time, the study monitor will collect the forms and leave a copy at the investigator's site. Results of any diagnostic tests conducted during the study were included in the source documentation. _____ had data management responsibilities for this study. After the CRFs were received from the study sites, each page of the CRF was uniquely identified and tracked with a computer-generated barcode. A Windows NT® software package, customized for data entry, was used and an electronic audit trail was maintained. All data were double entered by two independent data entry clerks. Concomitant medications were coded using the World Health Organization (WHO) Dictionary and adverse events were coded using the MedDRA Dictionary.

(4) Quality Assurance

The conduct of the study was monitored by representatives of _____ following GCP guidelines. The monitor reviewed the forms and evaluated the completeness and accuracy of the data by comparing the CRF to the patient's chart. The investigator allowed the Sponsor's representatives and any regulatory agency to examine all study records, CRFs, corresponding patient medical records, clinical drug dispensing records, drug storage areas, and any other documents considered source documentation.

vi. Statistical Considerations

(1) Analysis Plan

Efficacy. Since this is an open-label study without control, only descriptive summary statistics will be presented.

- The three efficacy variables examined were the Physician's Assessment of Melasma Severity Score, the Physician's Global Assessment, and the Patient's Global Assessment. For each variable, counts and percentages were provided. The investigator assessment of the melasma severity was summarized by using both the last observation carried forward and observed case approaches.
- Change from baseline to each subsequent visit in investigator assessment of melasma severity was presented by contingency tables for all patients, prior TRILUMA patients, and prior dyads patients.
- The number of patients with worsening, no change, or improvement in investigator assessment of melasma severity was summarized by counts and percentages at each visit.
- The number of patients with cleared melasma severity and the number of patients experiencing cleared melasma severity without reoccurrence was shown by counts and percentages as well.

Safety

- Adverse events were coded against MedDRA prior to analyses. Study medication "related" adverse events were tabulated. The events were presented by age, race, skin phototype, and duration of exposure to study medication. Total number of events for each level of relationship to study medication was also provided. For the above analyses, additional tables were presented for patients on TRILUMA greater than or equal to 180 days.
- The number of patients experiencing serious adverse events was summarized by body system, preferred term and severity. In addition, a listing of patients who discontinued from the study due to laboratory abnormalities and/or adverse events was to be provided.
- The number and percentage of patients who used concomitant medications was also provided by ATC (anatomical therapeutic chemical) class and preferred term.

(2) Determination of Sample Size

Patients previously treated under Protocol 28 were encouraged to enter Study 29 to allow for early discontinuations to yield sufficient patient numbers for analysis of 300 patients for the 6-month cumulative use period, and 100 patients for the 12-month analysis. Sample size was not determined on the basis of power.

vii. Changes in the Conduct of the Study or Planned Analyses

There were six amendments to the study protocol.

(1) The first amendment, dated June 28, 2000, expanded the definition for female patients of childbearing potential in inclusion criterion 5 to include that effective contraception or abstinence be followed during the treatment period. This change followed an IRB recommendation. The definition of the ITT population was also changed from "all patients who receive at least one application of the study material and have at least one post-baseline evaluation" to "all patients who were randomized to therapy and dispensed the study material". This change was made to comply with a recommendation from the FDA received June 26, 2000.

(2) The second amendment, dated July 20, 2000, added the word melasma in parentheses after the term melanosis of the face throughout the protocol. This amendment also added the requirement that anticipated adverse events, as described in the investigational drug brochure, be specifically solicited by the investigator at each visit and recorded on the adverse event form of the CRF.

(3) The third amendment dated October 26, 2000, changed cutaneous melanosis of the face (melasma) to just melasma of the face throughout the protocol. It also added:

- global assessment of melasma at Day 56 by investigator and by patient, as secondary efficacy criteria;
- physician and patient global assessments of all treated areas of the whole face at each follow-up visit;
- laboratory testing (CBC, urinalysis, and serum chemistries) at selected study centers;
- anticipated adverse events, as described in the Investigator's Brochure, were specified (erythema, skin peeling, stinging, telangiectasia, rosacea, dermatitis, atrophy and grayish discoloration of the skin and black spots) and to be queried.

(4) The fourth amendment dated June 13, 2001 clarified the definition of chronic use. In order to comply with E1A Guidelines of the ICH, chronic use was defined as applying the product three or more times within one year.

(5) The fifth amendment dated August 28, 2001 changed the length of time patients in Protocol 28 on TRI-LUMA used the study medication in Protocol 29 (the 12-month study) to include the 8 weeks of treatment they received in Protocol 28A or 28B. These patients will have completed the study at their 12-month anniversary date. The remainder of the patients were to continue in Protocol 29 until they reach 12 months of treatment. The final study report was to be prepared as soon as the first 100 patients complete Protocol 29. A supplemental report will be prepared when the rest of the patients complete the study.

(6) The sixth amendment dated September 13, 2001 further clarified the definition of chronic use. The phrase "repeated intermittent use of the drug greater than 6 months" is intended to mean the continuous or cumulative use time of TRILUMA, greater than or equal to 6 months. The data to be presented for the 12-month safety study will include patients that have continuous or cumulative use times of TRILUMA greater than 6 months. The patients were to have been followed for a 12-month time period. The Protocol was also amended to show extension of the studies for 6 months.

b. RESULTS

According to the fifth protocol amendment dated 8/28/01, patients with prior TRI-LUMA treatment in Study 28 actually entered Study 29 at the same time as they enrolled in Study 28. However, the study report provides disposition, baseline, and efficacy data based on "entry" into Study 29 after the 56 days of treatment in Study 28. Therefore, the information thus provided covers an up to one-year period of study with intermittent treatment for the prior dyad group, and an up to 44-week (i.e., 52-8) period for the prior TRI-LUMA group.

i. Disposition of Patients

<u>Study Sites</u>		
<u>Center</u>	<u>Investigator</u>	<u>Location</u>

01	Helen Torok, MD	Medina, OH
02	Susan Taylor, MD	New York, NY
03	Leslie Baumann, MD	Miami, FL
04	Terry Jones, MD	Bryan, TX
05	Joshua Wieder, MD	Los Angeles, CA
06	Nicholas Lowe, Gary Lask, Helene Rosenzweig, MDs	Santa Monica, CA
07	Michael Jarratt, MD	Austin, TX
08	Phoebe Rich, MD	Portland, OR
09	David Pariser, MD	Norfolk, VA
10	Eduardo Tschen, MD	Albuquerque, NM
11	Dale Martin, MD	San Diego, CA
12	Alan Menter, MD	Dallas, TX
13	Jonathan Weiss, MD	Snellville, GA

Patient disposition as given in the study report dated 12/20/01 (data cutoff date 10/31/01) is as follows:

	N (% OF PATIENTS)		
	Prior TRI-LUMA	Prior Dyad	TOTAL
Number of Patients Who Entered Study 28	161	480	641
Number of Patients Who Completed Study 28	152	450	602
Number of Patients Who "Entered" Study 29	148 ¹	437	585
Number of Patients Who Completed Study	5 (3.4)	0 (0.0)	5 (0.9)
Number of Patients Who Discontinued Study	43 (29.1)	148 (33.9)	191 (32.6)
Number of Patients Who Remained in the Study	100 (67.6)	289 (66.1)	389 (66.5)
Reason for Discontinuation from Study			
Patient Request	14 (32.6)	45 (30.4)	59 (30.9)
Adverse Event	6 (14.0)	22 (14.9)	28 (14.7)
Lost to Follow-up	11 (25.6)	40 (27.0)	51 (26.7)
Treatment Failure	1 (2.3)	4 (2.7)	5 (2.6)
Inclusion/Exclusion Discrepancy/Violation	2 (4.7)	2 (1.4)	4 (2.1)
Non-Compliance	2 (4.7)	20 (13.5)	22 (11.5)
Other	7 (16.3)	15 (10.1)	22 (11.5)
Number of Patients Included in the ITT Population ²	142 (95.9)	427 (97.7)	569 (97.3)

Percentages use patient numbers "entering" Study 29 as denominator. ¹Refers to patients from TRI-LUMA group of Study 28 who participated in continuation after initial 8 weeks (strictly speaking, these patients had entered Study 29 when enrolled in Study 28).
²ITT population includes all patients who "entered" Study 29 and received study drug.

- There were 16 patients not included in the ITT population because they were never dispensed study drug upon entry into Study 29, due to the presence of little or no melasma, and had not required re-treatment by the cut-off date (October 31, 2001). The number of patients who withdrew due to adverse events was 28 (14.7%) overall, 6 (14.0%) in the prior TRI-LUMA group and 22 (14.9%) in the prior dyad group.

ii. Baseline Characteristics

Demographics and Baseline Characteristics (Intent-to-Treat Population)

- The number of patients with **severe** melasma decreased after TRI-LUMA treatment from 62 (11%) at Day 0 to 12 (2%) at 6 months of the study, and 11 (3%) by 10 months of the study.

Physician's Assessment of Melasma Severity (LOCF Approach)

	N (%) OF PATIENTS		
	Prior TRI-LUMA	Prior Dyad	TOTAL
Day 0, N	142	427	569
Cleared	27 (19.01)	11 (2.58)	38 (6.68)
Mild	87 (61.27)	162 (37.94)	249 (43.76)
Moderate	26 (18.31)	194 (45.43)	220 (38.66)
Severe	2 (1.41)	60 (14.05)	62 (10.90)
Month 6 (Days 167-196), N	129	375	504
Cleared	39 (30.23)	76 (20.27)	115 (22.82)
Mild	71 (55.04)	210 (56.00)	281 (55.75)
Moderate	18 (13.95)	78 (20.80)	96 (19.05)
Severe	1 (0.78)	11 (2.93)	12 (2.38)
Month 10 (Days 287-316), N	114	307	421
Cleared	19 (16.67)	67 (21.82)	86 (20.43)
Mild	79 (69.30)	181 (58.96)	260 (61.76)
Moderate	15 (13.16)	49 (15.96)	64 (15.20)
Severe	1 (0.88)	10 (3.26)	11 (2.61)

Change in Investigator Assessment Of Melasma Severity By Baseline Severity

	Baseline Severity→	NUMBER (%) OF PATIENTS			
		Cleared	Mild	Moderate	Severe
Month 6 (Days 167-196), N	Cleared	6	38	17	1
	Mild	18	101	83	13
	Moderate	6	18	26	17
	Severe	0	0	0	6
Month 10 (Days 287-316), N	Cleared	4	27	22	0
	Mild	20	97	74	16
	Moderate	3	20	15	14
	Severe	0	0	0	3

- More of the **prior TRI-LUMA** patients started Study 29 with cleared or mild melasma compared to the prior Dyads groups. Patients with **prior dyads** began to have less severe melasma after they switched to TRILUMA treatment. (data not shown)
- Changes analyzed by prior treatment are shown in the following Tables:

Number of Patients with Cleared Melasma Severity at Any Time During Study 29

	N (%) OF PATIENTS		
	Prior TRI-LUMA	Prior Dyad	TOTAL
No. Patients Cleared of Melasma at Any Time, N	142	427	569
Yes	94 (66.20)	215 (50.35)	309 (54.31)
No	48 (33.80)	212 (49.65)	260 (45.69)
No. Patients Cleared of Melasma at Any Time and no Recurrence, N	87	199	286
Yes	4 (4.60)	20 (10.05)	24 (8.39)
No	83 (95.40)	179 (89.95)	262 (91.61)

Proportion of patients cleared of their melasma symptoms at any time was 309/569 (54%).

Number of Patients with Worsening, No Change, or Improvement in Melasma Severity

	N (%) OF PATIENTS		
	Prior TR-ILUMA	Prior Dyad	TOTAL
Month 6 (Days 187-196), N	88	262	350
Worsening	23 (26.14)	19 (7.25)	42 (12.00)
No Change	42 (47.73)	97 (37.02)	139 (39.71)
Improvement	23 (26.14)	146 (55.73)	169 (48.29)
Month 10 (Days 287-316), N	91	224	315
Worsening	29 (31.87)	14 (6.25)	43 (13.65)
No Change	41 (45.05)	78 (34.82)	119 (37.78)
Improvement	21 (23.08)	132 (58.93)	153 (48.57)

Proportion of patients with improvement at Month 6 was 169/350 (48.29%); by Month 10 it was 153/315 (48.57%).

- It is difficult to interpret these data, because the baselines were uneven for Study 29. Patients ranged from those who already had clearing of their melasma after TRI-LUMA treatment in Study 28 to ones who did not respond to dyads. Thus, changes are not really comparable between the prior treatment groups.

(2) Physician and Patient Global Assessments of Melasma

IMPROVEMENT	N (%) OF PATIENTS	
	Physician Global	Patient Global
	TOTAL N=569	TOTAL N=569
Month 1 (Days 15-45), N	468	467
Completely cleared	40 (8.55)	34 (7.28)
Nearly cleared	303 (64.74)	292 (62.53)
Significant hyperpigmentation	125 (26.71)	141 (30.19)
Month 10 (Days 287-316), N	240	241
Completely cleared	27 (11.25)	21 (8.71)
Nearly cleared	172 (71.67)	182 (75.52)
Significant hyperpigmentation	41 (17.08)	38 (15.77)

- With physician's global assessment, 125 (27%) had significant hyperpigmentation at Month 1 and only 41 (17%) still had significant hyperpigmentation at Month 10.
- According to patient's global assessment, 141 patients (30%) had significant hyperpigmentation at Month 1; in contrast, only 38 (16%) still had significant hyperpigmentation at Month 10.

(3) Number of Treatment Courses and Duration of Treatment Courses

The majority of patients in the entire ITT population, and in each of the Study 28 treatment groups, had no more than two treatment courses in Study 29.

	TOTAL NUMBER OF TREATMENT COURSES					Total Pt No.
	1	2	3	4	5	
Patient Numbers	235	228	72	12	3	550

The following Table shows the mean and range of the duration of each treatment course 1-5. Mean treatment course duration generally decreased with increasing number of treatment courses. The reason for this phenomenon is unclear. As the study is not yet completed at the time of reporting, it is possible that subsequent treatments were ongoing at the data cutoff date, and the perceived shorter length of the incomplete courses affects the mean duration. Obviously it is important to know whether the phenomenon is real, and whether, if real, it is due to better responsiveness or lack of

efficacy. This issue needs to be revisited in a true Final Report is presented after study completion.

TREATMENT DURATION PER COURSE - ITT POPULATION	
Treatment Courses Undertaken (N=patient-courses)	Mean (Min, Max) Treatment Duration in Days
1 (N=550)	128.1 (6, 378)
2 (N=315)	86.3 (10, 320)
3 (N=87)	60.4 (22, 194)
4 (N=15)	46.8 (22, 138)
5 (N=3)	49.3 (33, 80)

(4) Duration of Remission

The following Table provides the mean and range of the days between treatment courses. The mean duration of time between treatment courses appears to decrease with increasing number of treatment courses. The reason for this is also obscure, and needs to be addressed in the true Final Report upon completion of the study.

DAYS BETWEEN TREATMENT COURSES - ITT POPULATION	
Time Between	Mean (Min, Max)
Courses 1 and 2	73.5 (8, 254)
Courses 2 and 3	58.5 (8, 224)
Courses 3 and 4	44.9 (9, 112)
Courses 4 and 5	38.7 (30, 48)

On 12/28/01, the Applicant has provided data on the status of melasma severity in patients at the end of the **completed** treatment courses, and the minimum severity during the courses. The data are summarized as follows:

LAST INVESTIGATOR ASSESSMENT OF MELASMA SEVERITY IN A COMPLETED COURSE (N (%))					
Course	Cleared	Mild	Moderate	Severe	Total
1	2 (1%)	254 (81%)	55 (17%)	4 (1%)	315
2	0	67 (77%)	18 (21%)	2 (2%)	87
3	0	11 (73%)	3 (20%)	1 (7%)	15
4	0	1 (33%)	2 (67%)	0	3
Minimum Severity <i>During</i> Each Treatment Course (N (%))					
Course	Cleared	Mild	Moderate	Severe	Total
1	6 (2%)	261 (83%)	45 (14%)	3 (1%)	315
2	0	69 (79%)	16 (18%)	2 (2%)	87
3	0	11 (73%)	3 (20%)	1 (7%)	15
4	0	1 (33%)	2 (67%)	0	3

Consistent with the finding in the phase 3 studies, it is found that patients who had clearing of melasma during the treatment course do not necessarily maintain this treatment success. There are more patients with "cleared" during the treatment period than at the end of treatment. Similarly there are more patients with "mild" melasma during, but not at the end of, treatment.

D. Efficacy Conclusions

1. In two adequate and well-controlled clinical trials with 8 weeks of daily application at bedtime, TRI-LUMA Cream has shown superiority over its components (dyad combinations) in the treatment of melasma of the face, in the presence of measures for sun avoidance, including the use of sunscreens. Pending acceptable DSI audit results,

these studies can be considered adequate response to the fourth "Clinical/Statistical" deficiency item in the NA Letter of 1/20/00.

2. TRI-LUMA Cream also appears to improve melasma severity when used in intermittent courses to treat facial melasma; however, in the great majority of patients (90% or greater), recurrence of hyperpigmentation developed upon stopping TRI-LUMA treatment.

3. In the report for ongoing Study 29, the mean duration of treatment (128 to 49 days, 1st to 5th courses, respectively) and the mean remission time (74 to 39 days, between 1st and 2nd to between 4th and 5th courses, respectively) appear to decrease when multiple courses were taken. These apparent phenomena should be addressed in a true Final Report upon completion of the study.

4. Because of recurrence during or upon stopping treatment, the Applicant has studied chronic intermittent therapy with TRI-LUMA Cream. However, it may be more logical to have TRI-LUMA cream as initial therapy, followed by maintenance with an appropriate bleaching agent. This may incur less exposure to unneeded drugs than with chronic intermittent therapy. Labeling should clearly indicate that TRI-LUMA Cream is a combination product intended for short-term, and not for maintenance therapy of melasma.

5. The Applicant has studied skin types I-IV in the clinical trials. Although skin types V and VI have not been studied, melasma is not expected to be a significant issue in patients with very dark skin color. Moreover, excessive bleaching may result in hypopigmentation and undesirable cosmetic effect in these patients. Thus, additional studies in patients with skin types V and VI do not appear to be warranted.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

1. An adequate sample size has been exposed to TRI-LUMA Cream for at least 6 months to yield a satisfactory database in compliance with the recommendations of ICH Guidance E1A.
2. In the phase 3 trials, TRI-LUMA Cream demonstrated an acceptable safety profile during the 8 weeks of treatment. A lower proportion of patients in the TRI-LUMA treatment group (75.16%) experienced adverse events than in the FA+RA and RA+HQ treatment groups (81.37% and 87.34%, respectively). Only the FA+HQ treatment group experienced fewer adverse events (59.01%). Most of the adverse effects from the use of TRI-LUMA Cream have been found to be application site reactions, and no unexpected findings have surfaced to-date.
3. Patients in Study 29, the long-term extension of the phase 3 studies, had a similar profile of adverse events of special interest (erythema, skin peeling (desquamation), burning, irritation, telangiectasia, rosacea, dermatitis, atrophy and grayish discoloration of skin or black dots) as they did in the phase 3 studies. No meaningful percentage increase was reported in telangiectasia, atrophy, or other events often associated with long-term exposure to topical application of the ingredients in TRI-LUMA.

4. Clinical laboratory testing in phase 3 studies and in the long-term safety study, Study 29, has shown no consistent, clinically significant abnormalities.
5. The clinical studies also included pregnancy test in women of child-bearing potential. Eleven patients developed pregnancy in Study 29. Most of the pregnancy outcomes are not yet available at the time of this review, but for those with known information to-date, no birth defects have been reported.
6. Systemic availability of the active ingredients has been evaluated in a PK study, Study 104470-79, and minimal systemic absorption has been observed. In the case of tretinoin, the plasma levels, if detected, have been within the range seen with endogenous levels. A study to determine adrenal suppression using Cortrosyn stimulation (Study 33) was conducted, and no convincing evidence of suppression has been found.
7. Dermal safety studies with adequate subject numbers have been conducted, and presented either at the original NDA or in the current response to NA Letter. They have documented that TRI-LUMA Cream may be a contact sensitizer, but probably of low phototoxicity or photoallergenicity potential. The product is irritating, but its effect is less than that of the dyad containing tretinoin and hydroquinone, likely on account of the corticosteroid as an ingredient.

B. Description of Patient Exposure

- The safety database is derived primarily from clinical trials conducted by Hill Dermaceuticals, Inc., covering two identical adequate and well-controlled studies 28A and 28B, and their open-label extension with intermittent TRI-LUMA Cream therapy (Study 29).
- Two previous clinical trials (Studies 24 East and 24 West) also provided safety data on TRI-LUMA Cream. However, because of concerns on data quality (see Medical Officer Review of original NDA), these studies are not relied on in the current safety review.
- In addition, there are safety data from dermal safety studies in the current (irritancy and sensitization potential; Studies 36 and 37, respectively) and previous (phototoxicity and photoallergenicity; Studies 58 and 57, respectively) submissions.
- Safety information from two clinical pharmacology studies (PK and PD [adrenal suppression study], Studies 104479-70 and 33, respectively) have also been provided in response to the NA Letter of 1/20/00.

Patient numbers enrolled in the above studies are shown in the Table on clinical trials in Section IV.B.

TRI-LUMA Cream does not cure hyperpigmentation; it bleaches temporarily, and in previous studies (Study 24 East and 24 West), it has been shown that discontinuation or tapering led to re-pigmentation, and thus the potential for chronic use, even if not recommended. One of the deficiencies in the Not-Approvable Letter in 2000 was the

lack of long-term safety data, and the Applicant was advised to comply with ICH's E1A Guidance¹.

In the current response, adequate long-term use information has been presented.

For Studies 28A and 28B, the short-term clinical trials, patients were treated for a period of 56 days with daily application of TRI-LUMA Cream before bedtime. The two trials will be considered together in this safety review, because they are of identical design, and the combined data give greater power to detect events of less frequent occurrence. The patient exposure information is as follows:

	Treatment Group			
	TRI-LUMA (N=161)	FA+HQ (N=161)	FA+RA (N=161)	RA+HQ (N=158)
	Number (%) of Patients			
Patients completing study	152 (94.4)	151 (93.8)	151 (93.8)	148 (93.7)
Total discontinued early	9 (5.6)	10 (6.2)	10 (6.2)	10 (6.3)
Discontinuation due to adverse event	0	1 (0.6)	4 (2.5)	1 (0.6)

Of the 641 randomized patients, the majority, 602 (93.9%), completed 8 weeks of the study. Two patients were randomized to the TRI-LUMA group but discontinued from the study before using any of the study medication. Approximately the same percentage of patients in each treatment group (around 6%) discontinued early. No patients in the TRI-LUMA group discontinued due to an adverse event. From these two studies, 152 patients had exposure to TR-LUMA Cream for 8 weeks.

Two previous clinical trials (Studies 24 East and 24 West) also provided 8-week safety data on TRI-LUMA Cream in 99 patients (84 completers). As discussed above, because of concerns on data quality (see Medical Officer Review of original NDA), these studies are not relied on in the current safety review.

The open-label extension of Studies 28A and 28B is Study 29, in which all patients have been treated intermittently with TRI-LUMA Cream for melasma. The following gives exposure information in Study 29. The data given below include only treatment time within 29, and has not included treatment time from Study 28 for those patients with prior TRI-LUMA therapy.

Total number of treatment courses→	Mean Number of Days in Treatment Courses				
	1 (N=235)	2 (N=228)	3 (N=72)	4 (N=12)	5 (N=3)
Course ↓					
1 st	167.6	110.8	68.2	59.2	59.3
2 nd	-	96.0	64.5	46.3	39.3
3 rd	-	-	63.8	44.3	41.3
4 th	-	-	-	46.6	47.7
5 th	-	-	-	-	49.3
Total	167.6	206.8	196.5	196.3	237.0

¹ The E1A document gives a set of principles for the safety evaluation of drugs intended for the long-term treatment (chronic or repeated intermittent use for longer than 6 months) of non-life-threatening diseases. Available information suggests that most adverse events first occur, and are most frequent, within the first few months of drug treatment. The number of patients treated for 6 months at dosage levels intended for clinical use, should be adequate to characterize the pattern of adverse events over time. To achieve this objective the cohort of exposed subjects should be large enough to observe whether more frequently occurring events increase or decrease over time as well as to observe delayed events of reasonable frequency (e.g., in the general range of 0.5%-5%). Usually 300 to 600 patients should be adequate.