Although 569 patients entered into Study 29, only 550 had used TRI-LUMA Cream by the data cutoff date of 10/31/01. The remainder has not needed treatment or has no treatment information prior to being lost to follow-up. Among the 550 patients, 315 had more than one course of treatment, and the average duration of the total treatment in these patients exceeds 180 days. For patients with one course of treatment (N=235), the average time falls short of 180 days (167.6 days). The following Table shows cumulative treatment times and the number of patients who had treatment exceeding 3 or 6 months:

	Patient Numbers					
Total number of treatment courses→	1 (N=235)	2 (N=228)	3 (N=72)	4 (N=12)	5 (N=3)	Total
Cumulative Treatment Duration ↓						
≥12 weeks	164	216	71	12	3	466
≥24 weeks	102	154	49	9	3	317
≥28 weeks	90	130	38	6	3	267

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. The planned usage was intermittent, but some patients have had continuous use for up to 12 months.

The exposure data in this study has not been submitted. With 300-600 patients having had TRI-LUMA Cream application under proposed clinical use conditions, the database may be considered adequate for safety evaluation.

C. Methods and Specific Findings of Safety Review

In this section of the review, safety findings will be addressed in relation to the studies conducted by the Applicant:

- Dermal safety studies: Study 36 and 37
- Clinical pharmacology studies: Studies 104479-70 and 33
- Adequate and well-controlled phase 3 trials: Studies 28A and 28B
-

In addition, certain adverse events of special interest that are anticipated from the use of the active ingredients in TRI-LUMA Cream are discussed in this section.

1. Dermal Safety Studies

Reference is made to the Medical Officer Review of the original NDA for a review of the phototoxicity and photoallergenicity studies (Studies 58 and 57, respectively) on TRI-LUMA Cream. In the current response to NA Letter, two studies (Studies 36 and 37) are presented that address irritancy and sensitization potential of TRI-LUMA Cream.

a. Study 36. 21-day Cumulative Irritancy Study [conducted 4/2/01-4/23/01]

This study was conducted by Howard I. Maibach, M.D. of San Francisco, CA 94143.

Objective: to determine the relative irritancy potential (if any) of TRI-LUMA Cream, compared with (a) RA+HQ in cream vehicle, and (b) cream vehicle in healthy humans.

Design: randomized, third-party (evaluator) blind, intra-individual comparison study conducted in healthy adult volunteers. Test materials were placed onto patches (occlusive plastic chambers) and secured using paper tape to upper arms or backs of healthy volunteers, to the same site 5 days weekly (excluding weekends and holidays). Each day the patch was removed, the degree of irritation was evaluated on a scale of 0-4 (0=negative; 0.5=equivocal; 1=erythema; 2=erythema and induration; 3=erythema, induration, and vesicles; and 4=bullae), for a total of 15 readings over 21 days (patches left on during weekends).

Results:
Twenty-five healthy volunteers were enrolled. These included 12 white females and 13 white males aged 33 to 82 (mean 55). However, all but 4 of the subjects were aged 50 or above. There were no dropouts for this study. Cumulative irritancy scores are shown below:

	Cumulative Irritancy Scores
TRI-LUMA	247
RA+HQ	575.5
Cream vehicle	9

No allergic reactions were observed in this testing.

Comments

1. The Applicant concludes that TRI-LUMA was less irritating than the dyad of RA+HQ. This is an expected finding because the incorporation of corticosteroid in the preparation is supposed to reduce irritancy, and is an advantage of the triad combination over the RA+HQ dyad. Nevertheless, the triad combination still has substantial irritancy potential which is illustrated by its score of 247, as compared to the vehicle's score of 9.
2. This study was conducted with Caucasians, and almost no females in the reproductive age group. As melasma often occurs in females of reproductive age, caution should be exercised in the extrapolation of data from this study.

b. Study 37. Modified Draize Skin Sensitization Study [conducted 4/16/01-5/25/01]
This study was conducted by Howard I. Maibach, M.D. of San Francisco, CA 94143.

Objective: to evaluate the relative sensitization and irritation potential of TRI-LUMA, compared with (a) RA+HQ in cream vehicle, and (b) cream vehicle, in a repeat insult patch test on healthy humans.

Design: randomized, third-party (evaluator) blind, intra-individual comparison study conducted in healthy adult volunteers, according to a modification of the method of Draize. Test patches (occlusive plastic chambers) were moistened with approximately 0.2 Gm of the test material and secured using paper tape to the upper arms or backs of the volunteers. The study was conducted over a period of approximately 6 weeks as follows: during the first three weeks (induction period), patches were applied thrice weekly, to the same test site, for 48-72 hours. Volunteers were to leave the patches on

and keep them dry following each application. Two weeks after removal of the last patch, they were re-challenged by applying a new patch to a previously unpatched site. This patch was left in place for 48 hours. Upon removal, the degree of sensitization and/or irritation was evaluated on a scale of G-4:

> G=minimal glazing, such as in the "peau d'orange"; 0=negative; 0.5=equivocal; 1=erythema; 2=erythema and induration; 3=erythema, induration, and vesicles; and 4=erythema, induration, and bullae, at 96 hours following application.

Positive reactions at the final reading were discussed with the sponsor to determine, by re-testing, whether the reaction was irritant or allergic in nature.

Results:

Two hundred and twenty one healthy volunteers participated in this study and 190 completed. There were no dropouts due to adverse events. The subjects included 109 females and 109 males, with a mean age of 49 years (range 21-80). Race distribution is as follows: Caucasians 108, Blacks 97, Hispanic 9, Asians 4, and "unknown" 3.

In the induction phase, the TRI-LUMA application site total irritancy score of 702 was less than the dyad site score of 808 but greater than that at the vehicle site (98). After the challenge period, the total score for the TRI-LUMA application site was 65.5, the dyad application site score was 81.5, and vehicle site 9.5.

Three subjects had erythema and edema (score=2) at the 96-hour reading of the challenge phase:

- # 63 positive with HQ+RA dyad,
- # 159 positive with HQ+RA dyad and the vehicle, and
- # 218 positive with HQ+RA dyad and TRI-LUMA.

Upon re-testing, they demonstrated the same positive response as the 96-hour readings. The Applicant concludes that it is uncertain whether the subjects had irritation or sensitization to a component of the HQ+RA dyad, TRI-LUMA, or the vehicle.

Comments

1. In the study report, the Applicant discussed the potential of sensitization by one of the active ingredients. All three active ingredients have been implicated as potential contact allergens in previous reports, but confirmation is usually difficult. There have been no commercially available tests for fluocinolone acetonide or tretinoin, while a recent review of the literature has failed to confirm or deny the sensitization potential of hydroquinone. From a regulatory standpoint, the result of this study should be labeled, but further investigation with individual components appears to be not warranted.
2. This study has adequate methodology and subject numbers and is an appropriate response to the second "Clinical/Statistical" deficiency item in the NA Letter of 1/20/01.

2. Clinical Pharmacology Studies

Two clinical studies were conducted to determine the PK/PD for TRI-LUMA Cream. They have been reviewed by the Biopharm Reviewer, and reference is made to Dr. A. Adebowale's review for details on these studies. A summary on the safety data is presented here.

a. Study 104479-70. An Open-Label Safety Study to Determine Maximum Systemic Exposure of [redacted] Cream [conducted 1/17/00-3/20/00 for Group I and 9/10/00-11/[redacted]/00 for Group II]

Objective: To determine maximal systemic exposure to TRI-LUMA [redacted] Cream, under the conditions used to assess clinical safety.

Comment The PK data have been reviewed by Dr. Adebowale. See Section III for comments on these data. Application in the treatment of facial melasma with a thin film of drug product would take less than one gram of the product. The amounts used in this study can be considered excessive usage.

Design:
Group I: Male and female healthy human volunteers aged 18-55 years were treated with 1 Gm of TRI-LUMA once daily for 8 weeks, on one forearm. On Days 1, 4, 7, 14, 21, 35, and 56, blood plasma was collected to determine the concentration of each active ingredient of TRI-LUMA. Safety assessments included adverse events, clinical laboratory evaluations (hematology, chemistry, and urinalysis), and a physical examination.
Group II: Male and female healthy human volunteers aged 18-55 years were treated with TRI-LUMA once daily for 8 weeks, to entirely cover both forearms between the wrist and the elbow. The total dose of TRI-LUMA was approximately 6 Gm. Sampling was the same as in Group I. This group was studied because the Applicant was informed by FDA that the design in Group I with use of 1 Gm application was inadequate. Maximum exposure was needed to provide meaningful data, and it was determined that 6 Gm applied to both forearms would yield sufficient systemic exposure that would be in excess of that anticipated from treatment of facial melasma.

Results:
This study was conducted by [redacted]
45147. For comments on the PK data, see Section III.A.

A total of 59 volunteers were enrolled into Group I and Group II (45 and 14, respectively). One volunteer in Group I was African-American; all other volunteers in both studies were Caucasian. The volunteers in Group I had Fitzpatrick skin types ranging from II-IV; all volunteers in Group II had either Fitzpatrick skin type II or III. The majority (88%) of volunteers in both studies was female: 40 of 45 in Group I, and 12 of 14 in Group II. The age range across both studies was 21-55. A total of 55 volunteers completed the studies. Of the 4 patients who did not complete, 3 discontinued due to the adverse event of irritation at application site (5.1%).

A total of 55 subjects in Study 104479-70 had at least one adverse event during the study. Most events were of mild or moderate severity. Of the few severe adverse events observed, most were either application site pruritus or burning. The following Tables summarize the data.

Summary of Adverse Events in Clinical Pharmacology Study 104479-70

	Group I (N=45)	Group II (N=14)
Volunteers with at least one AE	42	13
Total adverse events	126	51
Treatment-related AE	53	31
Serious AE	0	0
Deaths	0	0
Non-lethal adverse events leading to discontinuation	2	1

Most Common Adverse Events (occurring in ≥10% patients) in Study 104479-70

	Group I (N=45)	Group II (N=14)
Volunteers with at least one adverse event	42	13
Total adverse events	126	51
Application site pruritis	43[a]	14
Headache	20	7

Application site burning	9	9
Cold or cold symptoms	7	1
Nausea	6	0
Metal taste in mouth	0	3
Sinus congestion	0	3
Hot flashes	0	2
Menstrual cramps	1	2

[a]Investigator terms; [b]number of adverse events

All adverse events resolved except in one volunteer (016 in Group I) who had ongoing exacerbation of nervousness. This event was judged by the investigator to be unlikely to be related to study medication.

Summary of Treatment-Related Adverse Events (TRAE) [a] in Study 104479-70

	Group I (N=45)	Group II (N=14)
Total AE	126	51
Total TRAE[b]	53	31
Application site pruritis	41	14
Application site burning	9	9
Generalized ecchymosis	0	2
Application site scratches on arm	1	0
Application site stinging	0	1
Non-application site erythema	1	0
Non-application site pruritis	1	0
Non-application site rash	0	1
Metal taste in mouth	0	3
Tingling, both arms	0	1

[a]TRAE=treatment-related adverse event, judged by investigator to be "possibly" or "probably" related to study medication; [b]Investigator terms

The majority of treatment-related adverse events were on the skin, at the application site. Several other skin events, at a location other than the application site, were also judged to be "possibly" or "probably" related to study medication. Metal taste in mouth and tingling in both arms were also judged to be "possibly" or "probably" related to study medication, respectively.

Special Adverse Event Data Collection (on irritancy). For Study 104479-70, investigators were to perform an evaluation of the test area at each study visit. Skin reaction scores were documented based on the following scale (***irritation scores***):

0=No irritation; 1=Minimal erythema, barely perceptible; 2=Moderate erythema, readily visible; or minimal edema; or minimal papular response; 3=Strong erythema; or erythema and papules; 4=Definite edema; 5=Erythema, edema, and papules; 6=Vesicular eruption; 7=Strong reaction spreading beyond test site.

Effects on superficial layers of the skin were recorded as follows (***superficial skin scores***):

A=Slight glazed appearance; B=Marked glazing; C=Glazing with peeling and cracking; F=Glazing with fissures; G=Film of dried serious exudate covering all or portion of the patch site; H=Small petechial erosions and/or scabs.

Additional comments were added as a footnote.

The majority of volunteers in **Group I** had no irritation (score=0). Of those who showed signs of irritation, most had ***irritation scores*** of 1 or 2 (minimal erythema, or moderate erythema or minimal edema and papular response), and most had ***superficial skin scores*** of A. Four volunteers had superficial skin scores of B on *any* study day. Many of the irritation scores and all of the superficial skin scores improved over time, and all had a superficial skin score=0 on Day 56. Subject 016 had a strong irritation response (irritation score=5 and 6 on Days 7 and 8, respectively) and a strong superficial skin response (superficial score=H on Day 7). The superficial skin response improved to 0 on Days 8 and 14, and the irritation score improved to 2 on Day 14 (irritation score=2). Nonetheless, the subject discontinued from study due to irritation on Day 21. Only one other subject (025) had a strong irritation response >3 (6 on Day 14); this score improved to 2 at Day 15.

In **Group II**, the majority had no irritation on most study days. The exception was on Day 35, when 12 of 14 study patients had some irritation. All ***irritation scores*** except one on Day 35 were 3 or less: patient (Patient 002) had a score=6. Many of the scores improved over time, so that at Day 56, half of the study

patients had irritation scores=0. The majority of patients also had ***superficial skin scores***=0. On days when patients had superficial skin scores>0, the majority of these scores were A. Superficial skin scores were worst on Day 56: one patient had a superficial skin score of B, one had F, and one had G. Subject 002 had a score of G on Day 35 and an irritation score of 6 on that day; this subject withdrew from the study due to irritation at application site.

Comment There are no unexpected adverse event data. The adverse reactions are basically local application site reactions.

b. Study 33. An Adrenal Suppression Study of TRI-LUMA Cream in Patients with Melasma of the Face [conducted 3/26/01-6/7/01]

Objective: to evaluate the potential of TRI-LUMA cream to suppress the HPA axis in patients with melasma.

Comment The study data on adrenal testing have been reviewed by Dr. Adebowale. See Section III for comments on the data.

Design: Males and females age ≥18 with moderate to severe melasma, and with normally functioning HPA axis (defined by serum cortisol level of ≥10 mcg/dL at 8 AM, and a 60-minute response to 0.25 mg of Cosyntropin stimulation with serum cortisol ≥18 mcg/dL) were studied. They were treated once daily for 8 weeks with TRI-LUMA to cover the entire facial area, for a total maximum exposure of approximately 360 mg daily. Blood samples for serum cortisol evaluations were taken before and after stimulation at Pretreatment, Week 4, and Week 8, between approximately 7:30 AM and 9:00 AM and prior to receiving the applied dose of study medication for that study day. Other safety assessments included adverse events and clinical laboratory evaluations (hematology, chemistry, and urinalysis).

Results:
This study was conducted by and For comments on the cosyntropin stimulation test results, see Section III.B.

A total of 29 patients with melasma, but with normal HPA axis function, and with Fitzpatrick skin types I-IV were enrolled. The majority (24; 82.7%) was of skin type II or III. The majority (23; 79.3%) was also Caucasian; 1 patient (3.4%) was Asian, and 5 (17.2%) were of "other" race. Two patients were male; the remaining patients (27 of 29 patients; 93.1%) of patients were female. Age range was 27-68, with the majority of patients (23 patients; 79.3%) between 40-59: mean = 49.2 years. All were treated with TRI-LUMA Cream to the ***entire*** facial area, for a total daily exposure of 360 mg for 8 weeks. All completed the study.

In Study 33, 8 adverse events, amongst 4 patients, were in the "skin" body system. Three adverse events, amongst 2 patients, were observed in the "body as a whole" body system. All other adverse events observed ("digestive" "sensory" and "urogenital") were noted in only one patient each.
All adverse events in Study 33 were mild or moderate in severity; no severe adverse events were noted.

Summary of Adverse Events in Study 33

	Patient Numbers
Patients with at least one adverse event	7
Total adverse events	22
Treatment-related adverse events	5
Serious adverse events	0
Deaths	0
Non-lethal adverse events leading to discontinuation	0

Summary of Treatment-Related Adverse Events (TRAE) * in Study 33

	Patient Numbers

CHARACTERISTICS	N (%) OF PATIENTS TRILUMA (N=569)
Age	
Mean/median/range (years)	43.2/42.3/24 - 76
≤40years	220 (38.7)
>40 years	349 (61.3)
Sex (N% of patients)	
Male	9 (1.6)
Female	560 (98.4)
Race (N% of patients)	
Caucasian	375 (65.9)
Black	16 (2.8)
Asian	24 (4.2)
Other	154 (27.1)
Skin phototype (N% of patients)	
Type I	52 (9.1)
Type II	178 (31.3)
Type III	221 (38.8)
Type IV	118 (20.7)

The demographic and baseline data are consistent with those in Study 28. This was an open-label study with all patients to be using TRI-LUMA Cream, further analysis by prior treatment is not shown here. Such analysis has been presented in the study report and the two prior treatment groups (TRI-LUMA or dyad) appear to be similar.

The number of patients that took at least one concomitant medication while on study medication was 516 (90.7%). The most frequently used concomitant drugs were progestin and estrogen combination therapies (20.7%), propionic acid derivatives such as ibuprofen (20.2%), anilides such as Tylenol and Benadryl (19.9%), multivitamins (13.2%), and selective serotonin re-uptake inhibitors (13.0%).

iii. Efficacy Data

- It is to be noted that for efficacy discussion, the study times given in the presentation that follows are not cumulative treatment times, as the treatment in Study 29 is intermittent. Cumulative treatment times will be specified when this information is available.
- Since Study 29 has not been completed (data cutoff on 10/31/01) at the time of the report, the data must be interpreted with caution, as incomplete information from patients ongoing in the study may bias conclusions.
- Data interpretation for this study has limitations because the study is uncontrolled. Comparison between prior TRI-LUMA and prior dyad treatment groups also has some drawback because the prior treatment information was not blinded.

Despite these drawbacks, it may be possible to gain some useful efficacy information from Study 29, especially in terms of treatment courses and remission/relapse.

(1) Physician's Assessment of Melasma Severity

- The number of patients whose melasma ***cleared*** after TRILUMA treatment during Study 29 was 38 (7%) at Day 0, 115 (23%) at 6 months, and 86 patients (20%) by 10 months of study.

Total adverse events	22
Total TRAE	5
Event[b]:	
Erythema	2
Skin discomfort	1
Pruritus	1
Desquamation	1

[a]Judged by the investigator to be "possibly" or "probably" related to study medication; [b]Investigator terms

Of the five TRAE observed, four events (desquamation, pruritus, discomfort skin, and one case of erythema) were mild, and one was moderate (erythema).Three of the events (pruritus, mild erythema, and skin discomfort) were observed in one patient (Patient 028).

Comments

There are no unexpected adverse event data. The adverse reactions are basically local application site reactions.

2. This cosyntropin stimulation study for testing adrenal suppression is an appropriate response to "Clinical/Statistical" item 3, and the sole Biopharm item on the deficiency list of the NA Letter of 1/20/00.

3. Adequate and Well-Controlled Phase 3 Clinical Trials

Because of identical design, the safety data from Studies 28A and 28B are reviewed together here. As discussed above, data from studies previously submitted (Studies 24 East and 24 West) are not considered because of concerns regarding data quality.

a. 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]

Details on study design have been presented above (Section VI.C.1.a). Patient disposition has also been discussed for the individual studies, 28A and 28B in Section VI.C.1.b.

i. All Adverse Events

A total of 485 of 641 (75.66%) patients experienced at least one adverse event during these studies. The following table summarizes the number of patients with at least one adverse event, serious adverse events, treatment-related adverse events, and adverse events leading to discontinuation. Across all treatment groups, the majority of adverse events were considered mild.

Summary of Adverse Events in Studies 28A and 28B

	Number (%) of Patients			
	Treatment Group			
	TRI-LUMA (N=161)	FA+HQ (N=161)	FA+RA (N=161)	RA+HQ (N=158)
Patients with at least one adverse event	121 (75.16)	95 (59.01)	131 (81.37)	138 (87.34)
Treatment-related adverse events[a]	102 (63.35)	56 (34.78)	105 (65.22)	126 (79.75)
Serious AE	0	0	3 (1.86)	1 (<1.0)
Deaths	0	0	1 (<1.0)	0
Non-lethal adverse events leading to discontinuation	0	1 (<1.0)	3 (1.86)	1 (<1.0)
Severity:				
Mild	301 (78.18)	141(73.44)	290 (81.92)	343 (80.52)
Moderate	73 (18.96)	48 (25.00)	58 (16.38)	71 (16.67)
Severe	11 (2.86)	3 (1.56)	5 (1.41)	11 (2.58)

[a] Designated as probably or possibly related to study medication by the investigator.

There were no deaths, discontinuations due to adverse events or serious adverse events in the TRI-LUMA group. Four serious adverse events occurred in the phase 3 trials, resulting in one death. A patient in the FA+RA group who had depression at enrollment died of overdose with non-study medication 18 days after entry into the study. The other three events are as follows:

- Supraventricular tachycardia (FA+RA group)
- Subarachnoid hemorrhage (HQ+RA group)
- Hospitalization for removal of thyroid growth (FA+RA group)

Patients discontinued in dyad treatment groups due to adverse events overlap with those who had serious adverse events. The three serious adverse events all led to discontinuation. In addition, three other patients discontinued due to application site reactions: acne, dry and cracked lips, and hyperpigmentation. No pregnancies were reported in the phase 3 trials.

In all four treatment groups, the largest percentage of adverse events occurred in the Application Site Conditions grouping. The most common adverse events (those reported by ≥10% in any treatment group) are summarized below.

Summary of Most Common Adverse Events in Studies 28A and 28B

	Number (%) of Patients Treatment Group			
	TRI-LUMA (N=161)	FA+HQ (N=161)	FA+RA (N=161)	RA+HQ (N=158)
Patients with at least one adverse event	121 (75.16)	95 (59.01)	131 (81.37)	138 (87.34)
Total Adverse Events	385	192	354	426
No. of Patients with Most Common adverse events[a]				
Application site:				
Desquamation	61 (37.89)	6 (3.73)	40 (24.84)	97 (61.39)
Erythema	66 (40.99)	26 (16.15)	41 (25.47)	69 (43.67)
Burning	29 (18.01)	5 (3.11)	33 (20.50)	36 (22.78)
Dryness	23 (14.29)	5 (3.11)	23 (14.29)	21 (13.29)
Pruritus	18 (11.18)	5 (3.11)	12 (7.45)	34 (21.52)
Headache NOS	16 (9.94)	17 (10.56)	13 (8.07)	13 (8.23)

[a] Events occurring in at least 10% of patients in at least one treatment group

Adverse Events of Special Interest

Adverse events of special interest included erythema, skin peeling, burning, irritation, telangiectasia, rosacea, dermatitis, atrophy and grayish discoloration of skin or black dots. These events were specifically solicited by the investigator at each visit, and listed and detailed on the adverse event form of the CRF.

Summary of Adverse Events of Special Interest

	Number (%) of Patients Treatment Group			
	TRI-LUMA (N=161)	FA+HQ (N=161)	FA+RA (N=161)	RA+HQ (N=158)
Patients with at least one adverse event	121 (75.16)	95 (59.01)	131 (81.37)	138 (87.34)
Total Adverse Events	385	192	354	426
Application site:				
Erythema	66 (40.99)	26 (16.15)	41 (25.47)	69 (43.67)
Desquamation	61 (37.89)	6 (3.73)	40 (24.84)	97 (61.39)
Burning	29 (18.01)	5 (3.11)	33 (20.50)	36 (22.78)
Irritation	3 (1.86)	2 (1.24)	7 (4.35)	2 (1.27)

Telangiectasia	5 (3.11)	1 (0.62)	1 (0.62)	0 (00.00)
Rosacea	1 (0.62)	0 (00.00)	0 (00.00)	0 (00.00)
Dermatitis	0 (00.00)	0 (00.00)	0 (00.00)	0 (00.00)
Atrophy	0 (00.00)	1 (0.62)	0 (00.00)	0 (00.00)
Grayish discoloration	0 (00.00)	0 (00.00)	0 (00.00)	0 (00.00)

Erythema, desquamation and burning were the most commonly reported adverse events of special interest. The majority of these events were considered to be mild by the investigator, and no patients withdrew from study due to such an adverse event.

ii. Treatment-Related Adverse Events

Three hundred eighty-nine (389) of 641 (60.69%) patients reported 887 adverse events considered by the investigator to be treatment-related. The TRI-LUMA treatment group had fewer patients (63.4%) reporting one or more treatment-related adverse events than the patients in the RA+HQ group (78.3%) or the FA+RA group (65.2%). The FA+HQ treatment group had the lowest rate (34.8%). The most common treatment-related adverse events were "Application Site Conditions": desquamation (204 patients), erythema (202), burning (103), and dryness (72) (see above Table "Summary of Most Common Adverse Events in Studies 28A and 28B"). Treatment-related adverse events reported in body systems other than "Application Site Conditions" were: Infections and Infestations, Application Site Infections (3; none in TRI-LUMA group), and Skin and Subcutaneous Tissue Disorders (2; none in TRI-LUMA group).

iii. Subset Analysis

Treatment-related adverse events in Studies 28A and 28B have been analyzed by age, race, and skin phototype. Analysis by sex was not performed, as there were few males in the studies (between 1-3% in each treatment group; 14/641, or 2% overall).

(1) Treatment-Related Adverse Events by Age

As the number of patients aged 65 or older was very small, the Applicant reported an analysis by age with age 40 as cutoff. There were 285 patients aged ≤40, and 356 patients aged over 40 at study onset. Similar proportions of such events were seen in either age grouping in TRI-LUMA-treated patients.

Summary of Patients Experiencing Treatment-Related Adverse Events By Age

	Number (%) of Patients			
	Treatment Group			
	TRI-LUMA (N=161)	FA+HQ (N=161)	FA+RA (N=161)	RA+HQ (N=158)
Patients with at least one adverse event	121 (75.16)	95 (59.01)	131 (81.37)	138 (87.34)
TRAE[a]	102 (63.35)	56 (34.78)	105 (65.22)	126 (79.75)
Age ≤ 40 years (N= 285)	(N = 73)	(N = 68)	(N = 74)	(N = 70)
	47 (64.38)	24 (35.29)	43 (58.11)	60 (85.71)
Desquamation	31 (42.47)	2 (2.94)	18 (24.32)	46 (65.71)
Erythema	26 (35.62)	12 (17.65)	18 (24.32)	30 (42.86)
Burning	14 (18.18)	1 (1.47)	14 (18.92)	18 (25.71)
Dryness	12 (16.44)	1 (1.47)	11 (14.86)	12 (16.44)
Age > 40 years (N=356)	(N = 88)	(N = 93)	(N = 87)	(N = 88)
	55 (62.50)	32 (34.41)	62 (71.26)	66 (75.00)
Desquamation	30 (34.09)	4 (4.30)	22 (25.29)	51 (57.95)
Erythema	40 (45.45)	14 (15.05)	23 (26.44)	39 (44.32)
Burning	15 (17.05)	4 (4.30)	19 (21.84)	18 (20.45)
Dryness	11 (12.50)	4 (4.30)	12 (13.79)	9 (10.23)

[a] Designated as probably or possibly related to study medication by the investigator.

(2) Treatment-Related Adverse Events by Race

The majority of patients in all treatment groups were Caucasian (approximately two-thirds overall), making meaningful comparisons by race difficult, especially with Blacks (21/641; 3% overall) and Asians (31/641; 5% overall). The largest non-Caucasian group ("Other") is not a good comparator, as the actual composition of this group is unclear, although most of the patients were of Hispanic origin. The data from race subgroups can be shown as follows, but no specific comments can be made because of the limitations of such data.

Summary of Patients Experiencing Treatment-Related Adverse Events By Race

	Number (%) of Patients			
	Treatment Group			
	TRI-LUMA (N=161)	FA+HQ (N=161)	FA+RA (N=161)	RA+HQ (N=158)
Patients with at least one adverse event	121 (75.16)	95 (59.01)	131 (81.37)	138 (87.34)
TRAE[a]	102 (63.35)	56 (34.78)	105 (65.22)	126 (79.75)
Caucasian (N= 422)	63/103 (61.17)	35/108 (32.41)	67/110 (60.91)	73/101 (72.28)
Black (N= 21)	2 /4 (50.00)	1/6 (16.67)	4/7 (57.14)	4/4 (100.00)
Asian (N= 31)	5/9 (55.56)	4/8 (50.00)	5/6 (83.33)	8/8 (100.00)
Other (N= 167)	32/45 (71.11)	16/39 (41.03)	29/38 (76.32)	41/45 (91.11)

[a] Designated as probably or possibly related to study medication by the investigator.

(3) Treatment-Related Adverse Events by Skin Phototype

The rate of treatment-related adverse events appears to be higher in TRI-LUMA-treated patients with skin phototypes I and lower in similarly treated patients with skin Type IV. These data are also difficult to interpret because of the smaller sample sizes for skin Types I and IV. No such trend in adverse event frequency can be observed in the dyad treatment groups.

Summary of Patients Experiencing Treatment-Related Adverse Events By Skin Phototype

	Number (%) of Patients			
	Treatment Group			
	TRI-LUMA (N=161)	FA+HQ (N=161)	FA+RA (N=161)	RA+HQ (N=158)
Patients with at least one adverse event	121 (75.16)	95 (59.01)	131 (81.37)	138 (87.34)
TRAE[a]	102 (63.35)	56 (34.78)	105 (65.22)	126 (79.75)
Type I (N = 58)	11/14 (78.57)	8/14 (57.14)	10/15 (66.67)	10/15 (66.67)
Type II (N = 197)	31/48 (64.58)	12/50 (24.00)	32/50 (64.00)	36/49 (73.47)
Type III (N = 242)	43/67 (64.18)	26/62 (41.94)	36/56 (64.29)	51/57 (89.47)
Type IV (N = 144)	17/32 (53.13)	10/35 (28.57)	27/40 (67.50)	29/37 (78.38)

[a] Designated as probably or possibly related to study medication by the investigator.

4. Ongoing Long-Term Safety Studies: Studies 29 and 30

The Applicant submitted a "Final" Report for the ongoing long-term safety study, Study 29 on 11/22/01, and resubmitted it, revised, on 12/20/01. The data cutoff date is 10/31/01, and most patients have not completed the study. For Study 30, a similar long-term safety study, limited information is available in the Integrated Summary of Safety submitted on 12/20/01.

Study 29 is a 12-month open-label extension of Studies 28A and 28B, with patients allowed intermittent TRI-LUMA therapy for facial melasma. Details on study design have been presented above (Section VI.C.2.a). Study 30 is similar to Study 29, except for the source of patients. Patients in Study 30 did not previously participate in Studies 28A or 28B. These two studies are an appropriate response to the first "Clinical/Statistical" deficiency item in the NA Letter of 1/20/00.

a. 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]

Details on study design have been presented above (Section VI.C.1.a). As the study is still ongoing, review on this study is based on data submitted in December, 2001 with a cutoff date of 10/30/01. Patient disposition up to this date has been discussed for the in Section VI.C.2.b.

i. All Adverse Events

(1) Summary of Adverse Events

Summary of Adverse Events

	Number (%) of Patients
	Treatment Group
	TRILUMA (N=569)
Patients with at least one AE	460 (80.84)
TRAE[a]	326 (57.29)
Serious adverse events	13 (2.28)
Deaths	0 (0.00)
Non-fatal adverse events s leading to discontinuation	28 (4.92)

[a]Defined as "probably" or "possibly" related to study medication

No deaths were reported. Thirteen serious adverse events and 28 adverse events leading to discontinuation occurred. These are summarized as follows:

Serious Adverse Events (13)	Adverse Events Leading to Discontinuation (28)
Breast cancer Pregnancies 7	
Melanoma-in-situ Hospitalization for salpingo-oophorectomy for ovarian cyst Hospitalization for tonsillectomy Hospitalization for chest pain Hospitalization for ruptured appendix	Pregnancy 3 application site erythema 3 facial redness/tenderness Telangiectasia 2 Flare of rosacea facial flushing facial acne acne-like papules acne worsened irritation facial peeling/burning/tenderness perioral dermatitis increased facial hair growth dry skin "blue saliva"

Although the report and the ISS reports 10 pregnancies, the submission of 11/22/01 updated to give 11 exposed pregnancies in Study 29. 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, but there is no information on the product of conception.

Summary of Most Common Adverse Events

Preferred Term	Number (%) of Patients (N=569)
Total number of patients with at least one AE	478 (84.01)
Application site erythema	217 (38.14)
Application site desquamation	199 (34.97)
Upper respiratory tract infection NOS	87 (15.29)
Application site burning	68 (11.95)
Application site dryness	65 (11.42)
Headache NOS	41 (7.21)
Sinusitis NOS	40 (7.03)
Application site inflammation	39 (6.85)
Application site pruritus	38 (6.68)
Nasopharyngitis	37 (6.50)
Application site reaction NOS	36 (6.33)
Application site rash	31 (5.45)
Influenza	29 (5.10)

The specific adverse events observed in TRILUMA-treated patients in Studies 28 and 29 together were similar to those observed in Study 29 only. The frequency of adverse events was slightly higher in Studies 28 and 29 together, presumably because of the longer duration of both studies combined, compared with Study 29 only.

(2) All Adverse Events by Previous Treatment

The most frequent adverse events (>5% of patients in either the prior TRILUMA or prior Dyad group) observed in Study 29 are summarized by prior (Study 28) treatment group in the table below.

Summary of Most Common Adverse Events By Study 28 Treatment Group

	Number (%) of Patients	
	Study 28 Treatment Group	
Preferred Term	TRILUMA (N=142)	Dyad (N=427)
Total number of patients with at least one AE	115 (80.99)	345 (80.80)
Application site erythema	43 (30.28)	131 (30.68)
Application site desquamation	26 (18.31)	128 (29.98)
Upper respiratory tract infection NOS	18 (12.68)	60 (14.05)
Application site reaction NOS	9 (6.34)	23 (5.39)
Application site dryness	8 (5.63)	38 (8.90)
Application site burning	8 (5.63)	33 (7.73)
Application site inflammation	8 (5.63)	23 (5.39)
Sinusitis NOS	7 (4.93)	32 (7.49)
Nasopharyngitis	7 (4.93)	27 (6.32)
Headache NOS	7 (4.93)	22 (5.15)
Influenza	7 (4.93)	22 (5.15)
Application site rash	3 (2.11)	27 (6.32)

Patients in the prior Dyad group reported similar adverse events, and at a similar frequency, as patients in the prior TRILUMA group, in Study 29.

(3) All Adverse Events by Duration of TRILUMA Use

Analysis of adverse events based on the total cumulative number of treatment days with TRILUMA (1-91, 92-182, 183-273, and 274-365 days) was performed (data not shown).

As it is expected that adverse events regardless of causality would increase with duration in the study, no additional conclusions should be drawn from the analysis.

ii. Treatment-Related Adverse Events

(1) Summary of Treatment-Related Adverse Events

Summary of Most Common Treatment-Related Adverse Events (TRAE) [a]

	Number (%) of Patients		
	Treatment Group		
		TRILUMA	
Preferred Term	All patients (N=569)	Patients with at Least 180 Cumulative Days of TRILUMA Treatment Days (N=314)	Patients with at Least 360 Study Days on TRILUMA (N=172)
Total number of TRAE[a]	326 (57.29)	202 (64.33)	107 (62.21)
Application site erythema	166 (29.17)	105 (33.44)	63 (36.63)
Application site desquamation	145 (25.48)	91 (28.98)	50 (29.07)
Application site dryness	46 (8.08)	27 (8.60)	12 (6.98)
Application site burning	38 (6.68)	25 (7.96)	16 (9.30)
Application site inflammation	31 (5.45)	24 (7.64)	10 (5.81)
Application site reaction NOS	31 (5.45)	17 (5.41)	11 (6.40)
Application site rash	30 (5.27)	18 (5.73)	6 (3.49)
Application site pruritus	24 (4.22)	18 (5.73)	12 (6.98)
Application site pigmentation changes	23 (4.04)	18 (5.73)	9 (5.23)

[a] Defined as "probably" or "possibly" related to study medication

The most common treatment-related adverse events (TRAE) were all at the application site. Patients with at least 180 cumulative days of TRILUMA treatment, and patients with at least 360 study days on TRILUMA, experienced TRAE at approximately the same frequency as all patients. When the prior TRI-LUMA treatment period (from Studies 28A and 28B) is also included in the analysis, the most frequent treatment-related adverse events (reported by at least 5% of patients in any of the three groups) are shown in the Table below. As expected, there is an increase in the incidence of adverse events, but they appear to occur across the board and not confined to specific events.

Summary of Most Common Treatment-Related Adverse Events (TRAE) Including Prior TRI-LUMA Treatment Period in Studies 28A and 28B

	Number (%) of Patients		
Preferred Term	All patients (N=569)	Patients with at Least 180 Cumulative Days of TRILUMA Treatment Days (N=314)	Patients with at Least 360 Study Days on TRILUMA (N=172)
Total number of TRAE	365 (64.15)	223 (71.02)	136 (79.07)
Application site erythema	216 (37.96)	135 (42.99)	95 (55.23)
Application site desquamation	199 (34.97)	123 (39.17)	83 (48.26)
Application site dryness	65 (11.42)	43 (13.69)	30 (17.44)
Application site burning	67 (11.78)	44 (14.01)	35 (20.35)
Application site inflammation	39 (6.85)	26 (8.28)	12 (6.98)
Application site reaction NOS	36 (6.33)	21 (6.69)	15 (8.72)
Application site rash	31 (5.45)	19 (6.05)	7 (4.07)
Application site pruritus	38 (6.68)	26 (8.28)	23 (13.37)
Application site pigmentation changes	26 (4.57)	18 (5.73)	11 (6.40)

(2) Treatment-Related Adverse Events by Severity

Summary of Most Common Treatment-Related Adverse Events (TRAE) By Severity

Preferred Term	Number (%) of Events		
	Severity		
	Mild	Moderate	Severe
Total number of TRAE	602 (82.47)	117 (16.03)	11 (1.51)
Application site erythema	170 (78.34)	42 (19.35)	5 (2.30)
Application site desquamation	173 (89.18)	19 (9.79)	2 (1.03)
Application site dryness	45 (83.33)	8 (14.81)	1 (1.85)
Application site burning	38 (82.61)	7 (15.22)	1 (2.17)
Application site inflammation	24 (72.73)	8 (24.24)	1 (3.03)
Application site reaction NOS	28 (87.50)	3 (9.38)	1 (3.13)
Application site rash	24 (68.57)	11 (31.43)	0 (0.00)
Application site pruritus	25 (89.29)	3 (10.71)	0 (0.00)
Application site pigmentation changes	24 (92.31)	2 (7.69)	0 (0.00)

The majority of TRAE experienced by all patients were mild in severity. The number and percentage of treatment-related adverse events by severity for patients with at least 180 or 360 cumulative days of TRILUMA treatment show a similar pattern as that for all patients in the study.

(3) Treatment-Related Adverse Events by Previous Treatment

The most frequent TRAE (>5% of patients in either the prior TRILUMA or prior Dyad group) observed in Study 29 are summarized by Study 28 treatment group:

Summary of Most Common TRAE By Study 28 Treatment Group

Preferred Term	Number (%) of Patients	
	Study 28 Treatment Group	
	TRILUMA (N=142)	Dyad (N=427)
Total number of patients with at least one TRAE	73 (51.41)	253 (59.25)
Application site erythema	43 (30.28)	30 (30.44)
Application site desquamation	26 (18.31)	128 (29.98)
Application site reaction NOS	9 (6.34)	23 (5.39)
Application site dryness	8 (5.63)	38 (8.90)
Application site burning	8 (5.63)	32 (7.49)
Application site inflammation	8 (5.63)	23 (5.39)
Application site rash	3 (2.11)	27 (6.32)

Patients in the prior Dyad group in Study 28 reported similar TRAE, and at a similar frequency, as patients in the prior TRILUMA group. A higher percentage of patients in the prior Dyad group than in the prior TRILUMA group reported treatment-related application site desquamation in Study 29.

(4) Treatment-Related Adverse Events by Cumulative Days of Treatment

The number and percentage of patients who experienced at least one treatment-related adverse event, as well as the number and percentage of patients experiencing the two most frequent treatment-related adverse events (application site erythema and application site desquamation), are shown by cumulative days of TRILUMA treatment below.

Summary of Two Most Common Treatment-Related Adverse Events (TRAE) By Cumulative Days of Treatment with TRILUMA

Cumulative Days of TRILUMA Treatment	Number (%) of Patients Adverse Event		
	At Least One TRAE[b]	Erythema	Desquamation
1-30 (N=12)	4 (33.33)	3 (25.00)	0 (0.00)
31-60 (N=30)	11 (36.67)	4 (13.33)	7 (23.33)
61-91 (N=48)	28 (58.33)	11 (22.92)	12 (25.00)
92-121 (N=45)	25 (55.56)	12 (26.67)	9 (20.00)
122-151 (N=54)	31 (57.41)	18 (33.33)	12 (22.22)
152-182 (N=52)	27 (51.92)	13 (25.00)	15 (28.85)
183-212 (N=52)	30 (57.69)	16 (30.77)	15 (28.85)
213-242 (N=47)	30 (63.83)	18 (38.30)	14 (29.79)
243-273 (N=60)	35 (58.33)	21 (35.00)	21 (35.00)
274-303 (N=60)	34 (56.67)	17 (28.33)	16 (26.67)
304-333 (N=49)	37 (75.51)	16 (32.65)	11 (22.45)
>=334 (N=44)	34 (77.27)	17 (38.64)	13 (29.55)

There were no unexpected TRAE observed in patients with longer cumulative treatment days with TRILUMA (>180 days), compared with patients treated with shorter treatment. There appears to be a small correlation between cumulative treatment days with TRILUMA and frequency of patients experiencing TRAE early in treatment. There may also be a small increase in TRAE in patients with a high number of cumulative treatment days (at least 304 cumulative treatment days). Combining the prior TRI-LUMA treatment time in Studies 28A and 28B, a similar pattern is observed:

Summary of Two Most Common Treatment-Related Adverse Events (TRAE) By Cumulative Treatment Days Including Prior TRI-LUMA Treatment Time in Studies 28A and 28B

Cumulative Days of TRILUMA Treatment	Number (%) of Patients Adverse Event		
	At Least One TRAE[b]	Erythema	Desquamation
1-30 (N=12)	4 (33.33)	3 (25.00)	0 (0.00)
31-60 (N=30)	12 (40.00)	5 (16.67)	10 (33.33)
61-91 (N=48)	32 (66.67)	18 (37.50)	16 (33.33)
92-121 (N=45)	29 (64.44)	16 (35.56)	13 (28.89)
122-151 (N=54)	36 (66.67)	23 (42.59)	18 (33.33)
152-182 (N=52)	31 (59.62)	16 (30.77)	20 (38.46)
183-212 (N=52)	39 (75.00)	24 (46.15)	17 (32.69)
213-242 (N=46)	31 (67.39)	20 (43.48)	18 (39.13)
243-273 (N=60)	39 (65.00)	24 (40.00)	28 (46.67)
274-303 (N=61)	38 (62.30)	24 (39.34)	22 (36.07)
304-333 (N=48)	36 (75.00)	21 (43.75)	17 (35.42)
>=334 (N=45)	38 (84.44)	22 (48.89)	20 (44.44)

Analysis of treatment-related adverse events based on the total cumulative number of treatment days with TRILUMA (1-91, 92-182, 183-273, and 274-365 days) was also performed (data not shown). This is consistent with the above analysis. The frequencies of adverse events remain relatively stable after an initial lag period. There are no new, unexpected findings.

(5) Treatment-Related Adverse Events by Treatment Course

The most frequent TRAE (observed in >5% of patients who had one or multiple treatment courses) observed during TRILUMA treatment in Study 28 as well as in Study 29 are summarized in the Table below.

Summary of Most Frequent Treatment-Related Adverse Events (TRAE) By Treatment Course, Including Prior TRI-LUMA Treatment Period in Studies 28A and 28B

Preferred Term	Percentage of Patients with Number of Treatment Course(s)				
	1 (N=235)	2 (N=228)	3 (N=72)	4 (N=12)	5 (N=3)
Total number of TRAE	62.13	67.11	69.44	91.67	66.67
Application site desquamation	35.32	32.02	43.06	66.67	33.33
Application site erythema	34.89	38.60	48.61	66.67	66.67
Application site burning	10.21	12.28	15.28	16.67	33.33
Application site dryness	9.79	12.28	19.44	0	0
Application site inflammation	8.09	5.70	4.17	16.67	0
Application site reaction NOS	4.68	7.46	11.11	0	0
Application site pigmentation changes	4.68	4.39	6.94	0	0
Application site pruritus	4.26	6.58	15.28	8.33	33.33
Application site rash	3.83	8.33	2.78	8.33	0

The incidence of specific TRAE in patients who had two treatment courses was not notably higher than the incidence of TRAE in patients who had only one course. The incidence of TRAE increased slightly in patients who had three treatment courses, compared with patients who had only one or two courses. The small number of patients who had treatment courses 4 or 5 preclude meaningful comparison.

iii. Subset Analysis

(1) Treatment-Related Adverse Events by Age

As the number of patients aged 65 or older is very small, a cutoff with age 40 was made for age analysis. There were no notable differences in the frequency of the most common TRAE in patients older than 40 years of age, compared with patients 40 years of age or younger.

Summary of Most Common Treatment-Related Adverse Events (TRAE) By Age and Cumulative Days of Treatment with TRILUMA

Preferred Term	Number (%) of Patients	
	Age Group	
	<= 40 Years[b]	>40 Years[c]
Total number of patients with at least one TRAE[a]		
All patients	123 (55.91)	203 (58.17)
TRILUMA >=180 days[d]	76 (62.30)	126 (65.63)
In Study >=360 days[e]	43 (65.15)	64 (60.38)
Application site erythema		
All patients	65 (29.55)	101 (28.94)
TRILUMA >=180 days	37 (30.33)	68 (35.42)
In Study >=360 days	28 (42.42)	35 (33.02)
Application site desquamation		
All patients	54 (24.55)	91 (26.07)
TRILUMA >=180 days	34 (27.87)	57 (29.69)
In Study >=360 days	21 (31.82)	29 (27.36)
Application site dryness		
All patients	24 (10.91)	22 (6.30)
TRILUMA >=180 days	15 (12.30)	12 (6.25)
In Study >=360 days	6 (9.09)	6 (5.66)
Application site burning		
All patients	9 (4.09)	29 (8.31)
TRILUMA >=180 days	8 (6.56)	17 (8.85)
In Study >=360 days	6 (9.09)	10 (9.43)
Application site inflammation		
All patients	14 (6.36)	17 (4.87)
TRILUMA >=180 days	11 (9.02)	13 (6.77)
In Study >=360 days	6 (9.09)	4 (3.77)
Application site reaction NOS		
All patients	8 (3.64)	23 (6.59)
TRILUMA >=180 days	4 (3.28)	13 (6.77)
In Study >=360 days	4 (6.06)	7 (6.60)
Application site rash		
All patients	9 (4.09)	21 (6.02)
TRILUMA >=180 days	5 (4.10)	13 (6.77)
In Study >=360 days	2 (3.03)	4 (3.77)
Application site pruritus		
All patients	8 (3.64)	16 (4.58)
TRILUMA >=180 days	5 (4.10)	13 (6.77)
In Study >=360 days	4 (6.06)	8 (7.55)
Application site pigmentation changes		
All patients	6 (2.73)	17 (4.87)
TRILUMA >=180 days	4 (3.28)	14 (7.29)
In Study >=360 days	4 (6.06)	5 (4.72)

[a]Defined as "probably" or "possibly" related to study medication
[b]N=220 (all patients); N=122 (patients with at least 180 days of TRILUMA treatment); N=66 (patients with at least 360 study days on TRILUMA)
[c]N=349 (all patients); N=192 (patients with at least 180 days of TRILUMA treatment); N=106 (patients with at least 360 study days on TRILUMA)
[d]Patients with at least 180 days of cumulative TRILUMA treatment
[e]Patients with at least 360 study days on TRILUMA

(2) Treatment-Related Adverse Events by Race

There were insufficient numbers of Blacks [N=16 (all); N=13 (≥180 cumulative days of treatment with TRILUMA), and N=3 (≥360 study days on TRILUMA,)] to conduct any meaningful subgroup analyses. Similarly the number of Asians [N=24 (all); N=14 (≥180 cumulative days of treatment with TRILUMA); and N=6 (≥360 study days on TRILUMA)] was too low for analysis. Therefore, only Caucasians and "Others" were analyzed. The "Other" races included non-Caucasian, non-Black, and non-Asian patients, and were mostly Hispanics.

Summary of Most Common Treatment-Related Adverse Events (TRAE) By Race and Cumulative Days of Treatment with TRILUMA

Preferred Term	Number (%) of Patients	
	Race	
	Caucasian[b]	Other[c,d]
Total number of patients with at least one TRAE[a]		
All patients	200 (53.33)	100 (64.94)
TRILUMA >=180 days[e]	118 (60.82)	67 (72.04)
In Study >=360 days[f]	64 (57.66)	38 (73.08)
Application site erythema		
All patients	100 (26.67)	53 (34.42)
TRILUMA >=180 days	58 (29.90)	37 (39.78)
In Study >=360 days	33 (29.73)	26 (50.00)
Application site desquamation		
All patients	82 (21.87)	48 (31.17)
TRILUMA >=180 days	49 (25.26)	32 (34.41)
In Study >=360 days	29 (26.13)	18 (34.62)
Application site dryness		
All patients	33 (8.80)	10 (6.49)
TRILUMA >=180 days	20 (10.31)	6 (6.45)
In Study >=360 days	10 (9.01)	2 (3.85)
Application site burning		
All patients	13 (3.47)	17 (11.04)
TRILUMA >=180 days	7 (3.61)	12 (12.90)
In Study >=360 days	5 (4.50)	7 (13.46)
Application site inflammation		
All patients	19 (5.07)	6 (3.90)
TRILUMA >=180 days	15 (7.73)	6 (6.45)
In Study >=360 days	6 (5.41)	3 (5.77)
Application site reaction NOS		
All patients	12 (3.20)	16 (10.39)
TRILUMA >=180 days	6 (3.09)	9 (9.68)
In Study >=360 days	6 (5.41)	5 (9.62)
Application site rash		
All patients	20 (5.33)	10 (6.49)
TRILUMA >=180 days	11 (5.67)	7 (7.53)
In Study >=360 days	3 (2.70)	3 (5.77)
Application site pruritus		
All patients	14 (3.73)	8 (5.19)
TRILUMA >=180 days	10 (5.15)	6 (6.45)
In Study >=360 days	8 (7.21)	4 (7.69)
Application site pigmentation changes		
All patients	0 (0.00)	16 (10.39)
TRILUMA >=180 days	0 (0.00)	14 (15.05)
In Study >=360 days	0 (0.00)	7 (13.46)

[a]Defined as "probably" or "possibly" related to study medication
[b]N=375 (all patients); N=194 (patients with at least 180 cumulative days of TRILUMA treatment); N=111 (patients with at least 360 study days on TRILUMA)
[c]N=154 (all patients); N=93 (patients with at least 180 cumulative days of TRILUMA treatment); N=52 (patients with at least 360 study days on TRILUMA)
[d]"Other" includes all races except Caucasians, Blacks, and Asians
[e]Patients with at least 180 cumulative days of TRILUMA treatment
[f]Patients with at least 360 study days on TRILUMA
Data source: Section 14.3, Tables 8.4.1 – 8.7.3)

Patients of "Other" races experienced a slightly higher proportion of TRAE than Caucasian patients. Specific TRAE observed >5% more frequently in "Other" races than in Caucasians were application site erythema, desquamation, burning, reaction not specified, and pigmentation changes.

(3) Treatment-Related Adverse Events by Skin Phototype

Summary of Most Common Treatment-Related Adverse Events (TRAE) By Skin Phototype and Cumulative Days of Treatment with TRILUMA

Preferred Term	Number (%) of Patients by Skin Phototype			
	I[b]	II[c]	III[d]	IV[e]
Total number of patients with ≥1 TRAE[a]				
All patients	28 (53.85)	92 (51.69)	136 (61.54)	70 (59.32)
TRILUMA >=180 days[f]	13 (65.00)	44 (53.01)	91 (67.41)	54 (71.05)
In Study >=360 days[g]	9 (45.00)	39 (62.90)	39 (63.93)	20 (68.97)
Application site erythema				
All patients	15 (28.85)	44 (24.72)	70 (31.67)	37 (31.36)
TRILUMA >=180 days	6 (30.00)	20 (24.10)	47 (34.81)	32 (42.11)
In Study >=360 days	5 (25.00)	20 (32.26)	24 (39.34)	14 (48.28)
Application site desquamation				
All patients	14 (26.92)	39 (21.91)	57 (25.79)	35 (29.66)
TRILUMA >=180 days	7 (35.00)	21 (25.30)	34 (25.19)	29 (38.16)
In Study >=360 days	6 (30.00)	16 (25.81)	15 (24.59)	13 (44.83)
Application site dryness				
All patients	0 (0.00)	14 (7.87)	23 (10.41)	9 (7.63)
TRILUMA >=180 days	0 (0.00)	6 (7.23)	15 (11.11)	6 (7.89)
In Study >=360 days	0 (0.00)	4 (6.45)	5 (8.20)	3 (10.34)
Application site burning				
All patients	3 (5.77)	7 (3.93)	17 (7.69)	11 (9.32)
TRILUMA >=180 days	2 (10.00)	3 (3.61)	11 (8.15)	9 (11.84)
In Study >=360 days	1 (5.00)	4 (6.45)	8 (13.11)	3 (10.34)
Application site inflammation				
All patients	2 (3.85)	10 (5.62)	9 (4.07)	10 (8.47)
TRILUMA >=180 days	2 (10.00)	7 (8.43)	7 (5.19)	8 (10.53)
In Study >=360 days	0 (0.00)	4 (6.45)	2 (3.28)	4 (13.79)
Application site reaction NOS				
All patients	2 (3.85)	7 (3.93)	14 (6.33)	8 (6.78)
TRILUMA >=180 days	0 (0.00)	3 (3.61)	9 (6.67)	5 (6.58)
In Study >=360 days	0 (0.00)	4 (6.45)	4 (6.56)	3 (10.34)
Application site rash				
All patients	1 (1.92)	7 (3.93)	14 (6.33)	8 (6.78)
TRILUMA >=180 days	0 (0.00)	3 (3.61)	9 (6.67)	6 (7.89)
In Study >=360 days	0 (0.00)	0 (0.00)	4 (6.56)	2 (6.90)
Application site pruritus				
All patients	1 (1.92)	7 (3.93)	8 (3.62)	8 (6.78)
TRILUMA >=180 days	0 (0.00)	5 (6.02)	7 (5.19)	6 (7.89)
In Study >=360 days	1 (5.00)	5 (8.06)	3 (4.92)	3 (10.34)
Application site pigmentation changes				
All patients	1 (1.92)	3 (1.69)	7 (3.17)	12 (10.17)
TRILUMA >=180 days	1 (5.00)	2 (2.41)	4 (2.96)	11 (14.47)
In Study >=360 days	1 (5.00)	1 (1.61)	2 (3.28)	5 (17.24)

[a]Defined as "probably" or "possibly" related to study medication
[b]N=52 (all patients); N=20 (patients with at least 180 cumulative days of TRILUMA treatment); N=20 (patients with at least 360 study days on TRILUMA)
[c]N=178 (all patients); N=83 (patients with at least 180 cumulative days of TRILUMA treatment); N=62 (Patients with at least 360 study days on TRILUMA)
[d]N=221 (all patients); N=135 (patients with at least 180 cumulative days of TRILUMA treatment); N=61 (patients with at least 360 study days on TRILUMA)
[e]N=118 (all patients); N=76 (patients with at least 180 cumulative days of TRILUMA treatment); N=29 (patients with at least 360 study days on TRILUMA)
[f]Patients with at least 180 cumulative days of TRILUMA treatment
[g]Patients with at least 360 study days on TRILUMA
Data source: Section 14.3, Tables 8.8.1-8.11.3

There were no obvious differences between skin phototypes I-IV with regard to the most frequent TRAE, although patients of skin phototype IV had somewhat higher frequency of application site pigmentation changes than the other three skin phototypes (I-III).

b. Study 30. 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 without Study Report; data from Integrated Summary of Safety Submitted 12/20/01]

This open-label long-term safety study is ongoing, and the design is almost identical to that of Study 29, except for the fact that patients are not enrolled from a previous study (Studies 28A and 28B for Study 29).

At the data cutoff date, 228 patients have been in the study, with 13 completed, 181 still in the study, and 34 discontinued. Reasons for discontinuation are: patient request 11, adverse event 4, lost to follow-up 15, treatment failure 2 and "other" 2. Demographics in this study is similar to that in Study 29.

There have been no deaths reported in this study. In the ISS submitted on 12/20/01, 5 patients with serious adverse events are reported. Four of them had hospitalizations for unrelated surgical conditions, and one was hospitalized for severe angina. An additonal patient was reported by the Applicant on 12/31/01: hospitalization for bacteremia, peritonsillar abscess, and tonsillitis, considered unrelated to study treatment. There were 4 patients who discontinued from study due to adverse events, two of whom had pregnancy (considered an adverse event). One discontinuation was due to a breast lump, and another due to hyperpigmentation "possibly related to treatment". Since the case report form of this patient (#298) does not have any details on the hyperpigmentation, it is not possible to exclude this as a manifestation of ochronosis.

Limited safety data have been provided in the submission dated 12/20/01. Adverse events have been reported in 74.6% (170/228) of patients and treatment-related adverse events in 47.4% (108/228) of patients. The limited adverse event profile provided to-date is similar to that in Study 29. Most of the treatment-related adverse events were application site reactions: dryness 6%, erythema 21%, pigmentary changes 3%, pruritus 1%, "rash" 5%, atrophy 1%, burning 9%, desquamation 23%, inflammation 4%, irritation 2%, and application site reaction, unspecified, 9%.

(iv) Adverse Events of Special Interest

Details of adverse events of special interest are discussed in Section VII.C.5. Such events include erythema, skin peeling (desquamation), burning, irritation, telangiectasia, rosacea, dermatitis, atrophy and grayish discoloration of skin or black dots. These adverse events have also been reported above under other headings but are summarized here.

As expected, erythema, desquamation and burning were the most commonly reported adverse events of special interest. The great majority of these events were considered to be mild by the investigator, and no patients in the primary clinical studies withdrew from either study due to an adverse event of special interest.

Summary of Adverse Events of Special Interest

Preferred Term	Number (%) of Patients		
	TRILUMA		
	All patients (N=569)	Patients with at Least 180 Cumulative Days of TRILUMA Treatment (N=314)	Patients with at Least 360 Study Days on TRILUMA (N=172)
Total number of patients with at least one AE	460 (80.84)	274 (87.26)	150 (87.21)
Application site erythema	167 (29.35)	105 (33.44)	63 (36.63)
Application site desquamation	145 (25.48)	91 (28.98)	50 (29.07)
Application site burning	40 (7.03)	27 (8.60)	17 (9.88)
Application site irritation	10 (1.76)	5 (0.88)	3 (1.74)
Application site reaction NOS	31 (5.45)	17 (5.41)	11 (6.40)
Application site rash	30 (5.27)	18 (5.73)	6 (3.49)
Application site rosacea	4 (0.20)	0 (0.00)	1 (0.58)
Atrophy	1 (0.18)	0 (0.00)	0 (0.00)
Grayish discoloration	0 (0.00)	0 (0.00)	0 (0.00)

In parallel with the findings of the phase 3 studies, erythema, desquamation and burning were the most commonly reported adverse events of special interest. The majority of these events were considered to be mild. Both the number and the percentages of these events were lower in the long-term study than in the primary clinical studies. However, since patients who enter into the extension study have a selection bias, it is difficult to draw conclusions based on this finding. It is also noted that in Study 29, incidence of treatment-related adverse events remained relatively stable after an expected apparent increase initially.

5. Adverse Events of Special Interest in Clinical Trials

Some adverse events are of special interest because they are related to effects of the active ingredients. They were included in the Investigator Brochure for the IND and sought during the clinical trials: erythema, skin peeling (desquamation), burning, irritation, telangiectasia, rosacea, dermatitis, atrophy and grayish discoloration of skin or black dots. Some do not have corresponding MedDRA preferred terms; rosacea was coded under "Application Site Inflammation", telangiectasia under "Application Site Reaction - NOS", dermatitis under "Application Site Rash", and categorized under "General Disorders". Dermatitis was also reported under "Skin and Subcutaneous Tissue Disorders".

a. Erythema:

i. In phase 3 studies, application site erythema was reported by 66 (40.99%) patients in the TRI-LUMA group. Most cases were mild or moderate in intensity, and considered to be related to study medication by the investigator.

Summary of Patients Experiencing Application Site Erythema

	Number (%) of Patients			
	Treatment Group			
	TRI-LUMA (N=161)	FA+HQ (N=161)	FA+RA (N=161)	RA+HQ (N=158)
All patients with at least one adverse event	121 (75.16)	95 (59.01)	131 (81.37)	138 (87.34)
Erythema	66 (40.99)	26 (16.15)	41 (25.47)	69 (43.67)
All patients with ≥1TRAE[a]	102 (63.35)	56 (34.78)	105 (65.22)	126 (79.75)
Erythema	66 (40.99)	26 (16.15)	41 (25.47)	69 (43.67)
TRAE[a] severe	1 (1.33)	0 (00.00)	0 (00.00)	3 (4.00)

[a] Designated as probably or possibly related to study medication by the investigator.

- The mean total duration of all application site erythema episodes was 4.8 days for the TRI-LUMA group, compared to 1.2 days in the FA+HQ group, 1.4 days in the FA+RA group, and 4.0 days in the RA+HQ group.
- For events considered by the investigator to be related to study medication, most of the patients experiencing treatment-related application site erythema did so by Day 21.
- The mean duration of the first treatment-related application site erythema episode in the TRI-LUMA treatment group was 4.3 days, compared to 1.2 days in the FA+HQ group, 1.3 days in the FA+RA group, and 3.9 days in the RA+HQ group.
- Eight (8) patients in the TRI-LUMA treatment group experienced two or more episodes of application site erythema, compared to 6 patients in the RA+HQ treatment group, 1 patient in the FA+HQ treatment group, and 2 patients in the FA+RA treatment group.

Subset Analysis of Patients Experiencing Treatment-related Application Site Erythema

	Number (%) of Patients			
	Treatment Group			
	TRI-LUMA (N=161)	FA+HQ (N=161)	FA+RA (N=161)	RA+HQ (N=158)
Treatment-related AE[a]	102 (63.35)	56 (34.78)	105 (65.22)	126 (79.75)
Erythema	66 (40.99)	26 (16.15)	41 (25.47)	69 (43.67)
Age ≤ 40 years	47 (64.38)	24 (35.29)	43 (58.11)	60 (85.71)
Erythema	26 (35.62)	12 (17.65)	18 (24.32)	30 (42.86)
Age > 40 years	55 (62.50)	32 (34.41)	62 (71.26)	66 (75.00)
Erythema	40 (45.45)	14 (15.05)	23 (26.44)	39 (44.32)
Race: Caucasians	63 (61.17)	35 (32.41)	67 (60.91)	73 (72.28)
Erythema	38 (36.89)	15 (13.89)	21 (19.09)	41 (40.59)
Race: Black	2 (50.00)	1 (16.67)	4 (57.14)	4 (100.00)
Erythema	1 (25.00)	0 (00.00)	1 (14.29)	1 (25.00)
Race: Asian	5 (55.56)	4 (50.00)	5 (83.33)	8 (100.00)
Erythema	5 (55.56)	3 (37.50)	3 (50.00)	5 (62.50)
Race: Other	32 (71.11)	16 (41.03)	29 (76.32)	41 (91.11)
Erythema	22 (48.89)	8 (20.51)	16 (42.11)	22 (48.89)
Type I Skin Phototype	11 (78.57)	8 (57.14)	10 (66.67)	10 (66.67)
Erythema	8 (57.14)	5 (35.71)	4 (26.67)	6 (40.00)
Type II Skin Phototype	31 (64.58)	12 (24.00)	32 (64.00)	36 (73.47)
Erythema	20 (41.67)	5 (10.00)	13 (26.00)	24 (48.98)
Type III Skin Phototype	43 (64.18)	26 (41.94)	36 (64.29)	51 (89.47)
Erythema	24 (35.82)	14 (22.58)	15 (26.79)	21 (36.84)
Type IV Skin Phototype	17 (53.13)	10 (28.57)	27 (67.50)	29 (78.38)
Erythema	14 (43.75)	2 (5.71)	9 (22.50)	18 (48.65)

[A] Designated as probably or possibly related to study medication by the investigator.

- Treatment-related application site erythema was reported by similar percentages of patients in both age groups in all treatment groups. Too few Blacks and Asians were enrolled to provide meaningful comparisons by race, but a higher percentage of "Other" (largely Hispanic) population reported application site erythema than did the Caucasians. In the TRI-LUMA treatment group, patients exhibiting Type I skin phototype exhibited a greater percentage of application site erythema than did those exhibiting the other skin phototypes.

ii. In Study 29, 167 (29.35%) patients reported 213 events of application site erythema, a lower percentage than shown in the short-term studies. Five of these 213 events were considered to be severe

b. Skin peeling (desquamation):

i. In phase 3 studies, application site desquamation was reported by 61 patients (37.89%) in the TRI-LUMA treatment group. Most cases were mild or moderate in intensity, and were considered to be related to study medication by the investigator.

Summary of Patients Experiencing Application Site Desquamation

	Number (%) of Patients

	Treatment Group			
	TRI-LUMA (N=161)	FA+HQ (N=161)	FA+RA (N=161)	RA+HQ (N=158)
All patients with at least one adverse event	121 (75.16)	95 (59.01)	131 (81.37)	138 (87.34)
Desquamation	61 (37.89)	6 (3.73)	40 (24.84)	97 (61.39)
All patients with ≥TRAE[a]	102 (63.35)	56 (34.78)	105 (65.22)	126 (79.75)
Desquamation	61 (37.89)	6 (3.73)	40 (24.84)	97 (61.39)
TRAE[a] severe	1 (1.56)	0 (00.00)	1 (2.33)	1 (0.91)

[a] Designated as probably or possibly related to study medication by the investigator.

Summary of Patients Experiencing Treatment-related Application Site Desquamation

	Number (%) of Patients			
	Treatment Group			
	TRI-LUMA (N=161)	FA+HQ (N=161)	FA+RA (N=161)	RA+HQ (N=158)
Treatment–related adverse events[a]	102 (63.35)	56 (34.78)	105 (65.22)	126 (79.75)
Desquamation	61 (37.89)	6 (3.73)	40 (24.84)	97 (61.39)
Age ≤ 40 years	47 (64.38)	24 (35.29)	43 (58.11)	60 (85.71)
Desquamation	31 (42.47)	2 (0.94)	18 (24.32)	46 (65.71)
Age > 40 years	55 (62.50)	32 (34.41)	62 (71.26)	66 (75.00)
Desquamation	30 (34.09)	4 (4.30)	22 (25.29)	51 (57.95)
Race: Caucasians	63 (61.17)	35 (32.41)	67 (60.91)	73 (72.28)
Desquamation	33 (32.04)	3 (2.78)	29 (26.36)	57 (56.44)
Race: Black	2 (50.00)	1 (16.67)	4 (57.14)	4 (100.00)
Desquamation	1 (25.00)	1 (16.67)	2 (28.57)	2 (50.00)
Race: Asian	5 (55.56)	4 (50.00)	5 (83.33)	8 (100.00)
Desquamation	4 (44.44)	1 (12.50)	0 (00.00)	5 (62.50)
Race: Other	32 (71.11)	16 (41.03)	29 (76.32)	41 (91.11)
Desquamation	23 (51.11)	1 (2.56)	9 (23.68)	33 (73.33)
Type I Skin Phototype	11 (78.57)	8 (57.14)	10 (66.67)	10 (66.67)
Desquamation	8 (57.14)	1 (7.14)	6 (40.00)	8 (53.33)
Type II Skin Phototype	31 (64.58)	12 (24.00)	32 (64.00)	36 (73.47)
Desquamation	18 (37.50)	3 (6.00)	13 (26.00)	31 (63.27)
Type III Skin Phototype	43 (64.18)	26 (41.94)	36 (64.29)	51 (89.47)
Desquamation	25 (37.31)	0 (00.00)	10 (17.86)	36 (63.16)
Type IV Skin Phototype	17 (53.13)	10 (28.57)	27 (67.50)	29 (78.38)
Desquamation	10 (31.25)	2 (5.71)	11 (27.50)	22 (59.46)

[a] Designated as probably or possibly related to study medication by the investigator.

- Treatment-related application site desquamation was reported by similar percentages of patients in both age groups in all treatment groups. Too few Blacks and Asians were enrolled for comparisons by race, but a higher percentage of Caucasians reported application site desquamation than did "Others" (largely Hispanic). In the TRI-LUMA treatment group, patients exhibiting Type I skin phototype exhibited more application site desquamation than did those of other phototypes.

ii. In Study 29, 145 (25.48%) patients reported 185 events of application site peeling (desquamation), a lower percentage than shown in the short term studies. Of these 185 events, 2 were considered severe

c. Burning:

i. In phase 3 studies, application site burning was reported by 29 (18.01%) patients in the TRI-LUMA treatment group. Most cases of application site burning were mild in intensity, and considered to be related to study medication by the investigator.

Summary of Patients Experiencing Application Site Burning

	Number (%) of Patients			
	Treatment Group			
	TRI-LUMA (N=161)	FA+HQ (N=161)	FA+RA (N=161)	RA+HQ (N=158)
All patients with ≥1 AE	121 (75.16)	95 (59.01)	131 (81.37)	138 (87.34)
Burning	29 (18.01)	5 (3.11)	33 (20.50)	36 (22.78)
All patients with ≥1 TRAE[a]	102 (63.35)	56 (34.78)	105 (65.22)	126 (79.75)

Burning	29 (18.01)	5 (3.11)	33 (20.50)	36 (22.78)
TRAE[a] severe	0 (00.00)	0 (00.00)	0 (00.00)	1 (2.78)

[a] Designated as probably or possibly related to study medication by the investigator.

- The mean total duration of all application site burning episodes was 1.2 days for the TRI-LUMA treatment group, compared to 0.5 days in the FA+HQ group, 1.6 days in the FA+RA group, and 2.0 days in the RA+HQ group.
- For those events considered by the investigator to be related to study medication, most of the patients experiencing treatment-related application site burning did so by Day 21.
- The mean duration of the first treatment-related application site burning episode in the TRI-LUMA treatment group was 1.2 days, compared to 0.5 days in the FA+HQ group, 1.6 days in the FA+RA group, and 2.0 days in the RA+HQ group.
- Three patients in the TRI-LUMA treatment group experienced two or more episodes of application site burning, compared to no patients in the RA+HQ group, no patients in the FA+HQ group, and 1 patient in the FA+RA group.

Summary of Patients Experiencing Treatment-related Application Site Burning

	Number (%) of Patients			
	Treatment Group			
	TRI-LUMA (N=161)	FA+HQ (N=161)	FA+RA (N=161)	RA+HQ (N=158)
Treatment–related adverse events[a]	102 (63.35)	56 (34.78)	105 (65.22)	126 (79.75)
Burning	29 (18.01)	5 (3.11)	33 (20.50)	36 (22.78)
Age ≤ 40 years	47 (64.38)	24 (35.29)	43 (58.11)	60 (85.71)
Burning	14 (19.18)	1 (1.47)	14 (18.92)	18 (25.71)
Age > 40 years	55 (62.50)	32 (34.41)	62 (71.26)	66 (75.00)
Burning	15 (17.05)	4 (4.30)	19 (21.84)	18 (20.45)
Race: Caucasians	63 (61.17)	35 (32.41)	67 (60.91)	73 (72.28)
Burning	15 (14.56)	2 (1.85)	19 (17.27)	14 (13.86)
Race: Black	2 (50.00)	1 (16.67)	4 (57.14)	4 (100.00)
Burning	2 (50.00)	0 (00.00)	3 (42.86)	2 (50.00)
Race: Asian	5 (55.56)	4 (50.00)	5 (83.33)	8 (100.00)
Burning	3 (33.33)	0 (00.00)	3 (50.00)	5 (62.50)
Race: Other	32 (71.11)	16 (41.03)	29 (76.32)	41 (91.11)
Burning	9 (20.00)	3 (7.69)	8 (21.05)	15 (33.33)
Type I Skin Phototype	11 (78.57)	8 (57.14)	10 (66.67)	10 (66.67)
Burning	0 (00.00)	0 (00.00)	3 (20.00)	5 (33.33)
Type II Skin Phototype	31 (64.58)	12 (24.00)	32 (64.00)	36 (73.47)
Burning	7 (14.58)	1 (2.00)	12 (24.00)	7 (14.29)
Type III Skin Phototype	43 (64.18)	26 (41.94)	36 (64.29)	51 (89.47)
Burning	15 (22.39)	2 (3.23)	10 (17.86)	14 (24.56)
Type IV Skin Phototype	17 (53.13)	10 (28.57)	27 (67.50)	29 (78.38)
Burning	7 (21.88)	2 (5.71)	8 (20.00)	10 (27.03)

[a] Designated as probably or possibly related to study medication by the investigator.

- Treatment-related application site burning was reported by similar percentages of patients in both age groups in all treatment groups. Too few Blacks and Asians were enrolled to provide meaningful comparisons by race, but a higher percentage of "Other" (largely Hispanic) population reported application site burning than did the Caucasian population. In the TRI-LUMA treatment group, patients exhibiting Type III skin phototype appear to show a greater percentage of application site burning than did those exhibiting the other skin phototypes.

ii. In Study 29, 40 (7.03%) patients reported 46 events of application site burning, a lower percentage than shown in the short term studies. Of these 46 events, one was considered to be severe.

d. Irritation:

i. In phase 3 studies, application site irritation was reported by 3 (1.86%) patients in the TRI-LUMA treatment group. Most cases of application site irritation were mild, and all were considered related to study medication by the investigator. Because of the small number of events, no meaningful subset analysis by demographics or skin types is possible.

Summary of Patients Experiencing Application Site Irritation

	Number (%) of Patients			
	Treatment Group			
	TRI-LUMA (N=161)	FA+HQ (N=161)	FA+RA (N=161)	RA+HQ (N=158)
All patients with at least one adverse event	121 (75.16)	95 (59.01)	131 (81.37)	138 (87.34)
Irritation	3 (1.86)	2 (1.24)	7 (4.35)	2 (1.27)
All patients with ≥1 TRAE[a]	102 (63.35)	56 (34.78)	105 (65.22)	126 (79.75)
Irritation	3 (1.86)	2 (1.24)	7 (4.35)	2 (1.27)
TRAE[a] severe	0 (00.00)	0 (00.00)	0 (00.00)	0 (00.00)

[a] Designated as probably or possibly related to study medication by the investigator.

ii. In Study 29, 10 (1.76%) patients reported 10 events of application site stinging (irritation). Of these 10 events, none was considered to be severe.

e. Telangiectasia:

i. In phase 3 studies, application site telangiectasia was reported by 5 patients in the TRI-LUMA treatment group, 1 patient in the FA+HQ group, and 1 patient in the FA+RA group. These cases of application site telangiectasia were mild in intensity, and considered to be related to study medication by the investigator. Because of the small number of events, no meaningful subset analysis by demographics or skin types is possible.

ii. In Study 29, 31 (5.45%) patients reported 32 events of application site telangiectasia. Of these 32 events, only one was considered to be severe.

f. Rosacea:

i. In phase 3 studies, application site rosacea was reported by 1 (0.62%) patient in the TRI-LUMA treatment group. This case of application site rosacea was of unknown intensity, and was considered to be related to study medication by the investigator. No meaningful subset analysis by demographics or skin types is possible with a single case. It is noted that under "application site inflammation", an item "**acne**" is reported in similar numbers across treatment groups (8-11; 6%-9%), and there was a case of "**acne-like rash**" in the TRI-LUMA and one in the FA+HQ treatment groups. It is unclear whether there are reporting biases in cases of "application site inflammations".

Summary of Patients Experiencing Application Site Rosacea

	Number (%) of Patients			
	Treatment Group			
	TRI-LUMA (N=161)	FA+HQ (N=161)	FA+RA (N=161)	RA+HQ (N=158)
All patients with at least one adverse event	121 (75.16)	95 (59.01)	131 (81.37)	138 (87.34)
All patients with ≥1 TRAE[a]	102 (63.35)	56 (34.78)	105 (65.72)	126 (79.75)
Application site inflammation:	10 (6.2)	10 (6.2)	13 (8.1)	11 (7.0)
Acne	8	9	10	11
Rosacea	1 (0.62)	0 (00.00)	0 (00.00)	0 (00.00)
Chapping mouth	0	0	1	0
Seborrheic keratosis	0	0	1	0
Superficial abrasions	0	0	1	0
Acne-like rash	1	1	0	0

[a] Designated as probably or possibly related to study medication by the investigator.

ii. In Study 29, four (0.70%) patients reported four events of application site rosacea. Of these four events, none were considered to be severe.

g. Dermatitis:

i. In phase 3 clinical studies, application site dermatitis was reported under "Application Site Rash". Retinoid dermatitis to the face was reported in one patient in the RA+HQ group.

ii. In Study 29, 30 patients reported 35 events of application site dermatitis. Of these 35 events, none was considered to be severe.

h. Atrophy: Skin atrophy is an adverse effect from prolonged corticosteroid treatment and was specifically sought in the clinical studies.
i. In phase 3 studies, application site atrophy was reported by no patients in the TRI-LUMA treatment group, and only one patient, in the FA+HQ treatment group.

ii. In Study 29, 1 (0.18%) patient reported 1 event of application site atrophy. It was considered by the investigator to be mild.

i. Grayish discoloration of skin or black dots: One of the adverse effects of hydroquinone is the development of exogenous ochronosis. This was not reported in the phase 3 trials or Study 29. However, it is not clear whether there might have been reporting bias for such data collection, as exogenous ochronosis, a rare condition, could have been reported as "hyperpigmentation". In the absence of more information about instructing the evaluators or patients in the clinical trials, this issue remains open.

i. In phase 3 studies, 3 cases of pigmentary changes were reported in TRI-LUMA Cream-treated patients. One patient had mild increase in pigmentation in the treated area, another developed mild "post-inflammatory hyperpigmentation", and the third observed hypopigmentation surrounding hyperpigmented area.

ii. In Study 29, there were 23 additional cases of "pigmentary changes". However, because of lack of detailed descriptions by the Investigators other than "hyperpigmentaiton" or "hypopigmentation", no conclusions can be drawn as to whether exogenous ochronosis has been observed.

6. Summary of Adverse Events in Clinical Studies

1. 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%).
2. When considering treatment-related adverse events, the proportions of patients in all four treatment groups were similar to those who experienced all adverse events.
3. Analyses for safety by age (with cutoff at 40), race and skin phototypes have been performed. With age analysis, similar proportions of adverse events were observed in the $\leq$40 and the above 40 age groups. Because of the smaller sample sizes by race and skin phototype analysis, it is difficult to draw conclusions
4. Safety data from earlier studies submitted in the original NDA (Studies 24 East and 24 West) have been considered inadequate, due to the lack of reporting of many anticipated adverse events. However, findings from the phase 3 trials in the current response to NA Letter are consistent with the overall data from these previous studies. Most of the adverse effects from the use of TRI-LUMA Cream have been found to be application site reactions, and were of mild or moderate in intensity.
5. Patients in Study 29, the long-term extension of the phase 3 studies, had a similar profile of adverse events of special interest 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. A

D. Adequacy of Safety Testing

1. The Applicant has conducted both short-term and long-term studies to determine the safety of TRI-LUMA Cream in the treatment of facial melasma. In these studies, the anticipated adverse events have been specifically queried and reported in the case report forms. The coding uses MedDRA terminology, but some events may not necessarily be well covered with the MedDRA system. Despite this, the adverse event data are consistent with application site effects of the active ingredients, and no unexpected findings have surfaced to-date. An adequate sample size has been exposed to the product for at least 6 months to comply with the recommendations of the ICH Guidance E1A.

2. In one of the phase 3 trials (Study 28A), and in the long-term safety study, Study 29, clinical laboratory tests were conducted at selected centers: CBC, serum chemistry, and urinalysis. There have been 210 patients (51 on TRI-LUMA) tested in Study 28A and 189 (all on TRI-LUMA) tested in Study 29, and no consistent, clinically significant abnormalities observed with such testing. Laboratory data in Study 28A were similar across the treatment groups (TRI-LUMA and dyads). In Study 29, serum glucose was the analyte with the greatest number of shifts from normal to abnormal (15 patients); however, a similar number of patients (22) had a shift from abnormal to normal over the same time period. No patient withdrew due to abnormal laboratory findings, or to an adverse event related to changes in lab parameters in either study.

3. The clinical studies also included pregnancy test in women of childbearing potential. Eleven patients developed pregnancy in Study 29 ——— Most pregnancy outcomes are not yet available at the time of this review. It is premature to draw conclusions, and the Applicant should make efforts to follow-up the pregnancies and update the outcome data when available.

4. Systemic availability of the active ingredients in TRI-LUMA Cream has been evaluated in a PK study, Study 104479-70. The assays for the active ingredients have been validated, 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.

5. 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.

- Thus, the safety evaluation as presented in this NDA resubmission, together with previous findings, appears to be adequate to support the conclusion that TRI-LUMA Cream is safe for the treatment of facial melasma if used under proper labeling.

E. Summary of Critical Safety Findings and Limitations of Data

- A summary of the adverse event data has been presented in Section VII.C.6.

- As discussed above, the long-term safety studies have not been completed, and updates should be made upon completion of these studies to yield a complete picture of long-term safety.

- The coding of adverse events by the MedDRA system presents some difficulty, as some events do not have proper MedDRA terms, and this could affect the frequency of events presented.

- The dermal safety studies show that TRI-LUMA Cream is an irritant, and may be a contact sensitizer. Although the sensitization potential has not been adequately clarified, labeling may be sufficient to address this risk. TRI-LUMA Cream does appear to have an advantage over the dyad combination of hydroquinone and tretinoin in terms of irritancy potential.

- Systemic bioavailability appears to be low as determined by the PK study involving maximal exposure, and with the HPA axis suppression testing. The HPA axis suppression testing is not optimal, since the baseline response before TRI-LUMA therapy was inadequate in most patients as judged by the Cortrosyn® label criteria. However, there is no significant change from the baseline response after 8 weeks of TRI-LUMA application, and it appears that at least this glucocorticoid systemic effect is minimal with TRI-LUMA use. More sensitive measures may yet demonstrate a glucocorticoid effect, but do not seem to be warranted at this time.

- The pregnancy outcome information for most of the pregnancies exposed to TRI-LUMA is still not available. This would require follow-up to yield complete information.

VIII. Dosing, Regimen, and Administration Issues

The proposed dosing and regimen in the draft label:

> "TRI-LUMA Cream should be applied once daily, approximately 30 minutes before bedtime, at night. 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 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, the patient is directed to use a sunblock or sunscreen and wear protective clothing. Avoidance of sun exposure would be ideal. Patients may use moisturizers and/or cosmetics during the day."

These instructions are consistent with those in the phase 3 trials and the long-term safety study (Study 29). On December 28, 2001, the Applicant has provided the names of the sunscreens (Pre-Sun SPF 30 or Vanicream SPF 35) and the mild cleanser (Cetaphil gentle skin cleanser) provided to patients for mandatory use in the studies. The use of moisturizer (Cetaphil Moisturizing Lotion) is not mandatory. The information on the use of these proprietary products may be placed in the clinical studies section of the label. The following may be recommended for the DOSAGE AND ADMINISTRATION Section:

> 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.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

- The clinical trials have enrolled primarily females (97-98% in phase 3 and long-term safety studies), as melasma occurs mostly in women. Gender effect analysis is not practical because of the small number of males studied, and has not been performed.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

- Age analysis has been performed on the safety data of the phase 3 studies (Section VII.C.3.a.iii) using age 45 as cutoff. Age analysis has also been performed on the safety data of the long-term study, Study 29. No significant age effect has been observed for safety. For efficacy, age analysis has not been performed. The Applicant tried to use age 65 as cutoff, and noted that there were too few patients aged 65 or over to yield a meaningful analysis (Section VI.C.1.b.v).

- Analysis by race is difficult because there have been few Black or Asian patients in the clinical trials. The great majority of the patients were Caucasians, followed by "Other", which contained mostly Hispanics. However, because of the lack of breakdown within this "Other" race group, it may be misleading to simply use it as an entity. Nevertheless, analysis of treatment-related adverse events by race has been conducted, and no clear-cut effect by race is observed (Section VII.C.3, 4 and 5). Race analysis for efficacy has similarly not led to any clear-cut conclusions (Section VI.C.1.b.v), although TRI-LUMA Cream appears to be effective in both Caucasians and non-Caucasians. 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 (Section VI.C.1.b.v).

- It must be noted that the clinical studies were not powered to detect any demographic effect. Post-hoc analysis is primarily for hypothesis generation, and an effect is not expected to be observed unless it is large.

C. Evaluation of Pediatric Program

- The clinical development of TRI-LUMA Cream has not included a pediatric program. Melasma is not a pediatric indication. A waiver has been requested by the Applicant and may be granted.

D. Comments on Data Available or Needed in Other Populations

- Because of low systemic availability, and the lack of a signal in the clinical laboratory tests conducted in the phase 3 study, Study 28A, and in the long-term safety study, Study 29, specific toxicity in the presence of renal or hepatic hypofunction is not anticipated. Additional evaluation in such populations is not warranted.

- 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 (Section VI.C.1.b.v).

- Because melasma is a condition that often occurs in women of child-bearing potential, it is expected that there will be pregnancies exposed to the drug product. In the clinical studies, 11 pregnancies from Study 29 and have been presented. 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. Patients exposed to TRI-LUMA in pregnancy have been discontinued from treatment, and the pregnancies are being followed up to yield outcomes. Because of the limited number of exposures in pregnant women, analysis on safety and efficacy data from these patients would not be meaningful, especially since they have been discontinued and may not have had optimal treatment. However, it is most important to have follow-up information on the pregnancy outcome, and the progress of the children, if live born. This may be a good case for pregnancy registry to determine whether any suspected human reproductive toxicity can be confirmed.

- The issue of use of TRI-LUMA Cream in pregnant women is the subject of very serious concern in the Agency. An internal meeting was conducted on January 7, 2001 to discuss this. As the concern is almost entirely over the teratogenicity of tretinoin in TRI-LUMA Cream, only this specific ingredient is being addressed here. Although some might argue that corticosteroids also have teratogenic potential, and the combination of three ingredients may alter absorption of the ingredients, these

arguments are largely theoretical. Fluocinolone acetonide plasma levels were below quantitation limit after even excessive dosing in melasma patients, and application of TRI-LUMA Cream to melasma lesions involves intact, non-inflamed skin. The irritation due to tretinoin and hydroquinone is reduced by the presence of corticosteroid.

This review cannot address exhaustively the factors that contribute to the ultimate recommendations put forth here, but the ideas and viewpoints from many in and out of the Division are gratefully acknowledged. For the sake of convenience, the following outline will be used in the derivation of the recommendations:

- Arguments for approving TRI-LUMA Cream with Pregnancy Category X
- Arguments against approving TRI-LUMA Cream with Pregnancy Category X
- Conclusions
- Recommendations to manage the risks arising from the use of TRI-LUMA Cream in pregnant women

Arguments for approving TRI-LUMA Cream with Pregnancy Category X

1. Developmental toxicity has been demonstrated with tretinoin in animals, and with the to-be-marketed formulation in the studies conducted by the Applicant. The Pharm/Tox Reviewer recommends Pregnancy Category X, 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."

Comments:

a. It is well known that tretinoin is a teratogen, and developmental toxicity is expected if exposure is adequate. However, the exposure in the animal studies by the Applicant was through the dermal route, and thus this may lend credence to the importance of the animal data when extrapolated to humans.

b. The animal studies conducted by Hill were judged to be inadequate by design by the Pharm/Tox Reviewer. Yet, it is unclear why the positive findings on developmental toxicity are unquestionably accepted. It is noted that of the 6 studies presented, only 4 were under GLP. Among the GLP studies, it is not exactly clear how the animals were prevented from ingesting the drug applied. Semi-occlusive dressing was used in the rat studies, and a collar was used in the rabbit studies. Such measures were not likely to prevent ingestion through contamination of the cage and environment with test drug, because, as the Pharm/Tox Reviewer acknowledges, the quantity applied to skin was in great excess than would normally be applied (20x). The excessive material is expected to contaminate all over the cage, including the animal food. Indeed, in all studies, maternal systemic effects have been described, but discounted. In the human studies, there is no signal of systemic effects upon the use of TRI-LUMA Cream in the treatment of melasma.

*c. Category X is not an assignment that can be based on data alone. Clearly the regulations place the conjunction "AND" between evidence and risk-benefit analysis. It is perfectly appropriate for the Pharm/Tox Reviewer to make judgment regarding risk based on the toxicolgy data presented by the Applicant. Yet, it may not be appropriate to assign Category X based on risk alone, as one must consider what "**any possible benefit**" is for that drug.*

2. Teratogenic risks from the use of TRI-LUMA Cream for a cosmetic indication clearly outweigh any benefit. Safer alternative treatments are available.

Comments:

a. Pregnancy Category X requires that the risks clearly outweigh any possible benefit. As agreed by the Acting Office Director, one should not trivialize the benefit from treating a cosmetic indication. The teratogenic risks from the use of topical tretinoin w ill be discussed below. However, it can be challenged that such risks CLEARLY outweigh ANY POSSIBLE benefit.
b. Risk-benefit analysis is best done by the prescriber in conjunction with the patient. It is not the regulator's role to make risk-benefit analysis ***FOR*** *the prescriber or the patient. That would both be paternalistic and interfere with the practice of medicine. It is* ***impossible*** *for a regulator to determine whether for* ***any specific patient*** *the use of TRI-LUMA Cream CLEARLY outweighs ANY POSSIBLE benefit. If the regulator cannot determine whether the risks are such that they do not CLEARLY outweigh ANY POSSIBLE benefit, the drug should not be Category X. For more detailed considerations on this analysis, see below. The regulator actually has a more important role to play, viz. to make a risk-benefit analysis in terms of public health: whether the teratogenic risks are balanced by the benefits to society.*
c. The regulations have not elaborated on how this analysis can be conducted, except for giving one example - where safer drugs or other forms of treatment are available. Comparative safety is very tricky, and is only appropriate when the comparison is based on similar efficacy. TRI-LUMA Cream is an advance over existing bleaching agents, and has been demonstrated in the clinical studies to be superior over dyad combinations of its three active ingredients in the treatment of melasma. Thus, it is ***NOT CLEAR*** *that there are safer drugs or other forms of treatment available to treat melasma with similar efficacy.*

3. A conservative approach will bring the least amount of harm over the years, especially since negative human findings may be due to under-reporting, and some potential developmental toxicity may not be apparent at birth and takes a long time to show.

Comments:
a. See below for potentially serious harm from a conservative approach.
b. Both under-reporting and late effects are serious limitations of epidemiologic studies on adverse pregnancy outcome. However, under-reporting will not be remedied by Category X. Category X may deter reporting because of medico-legal consequences. For late effects, see discussion below.

4. There are precedents of drugs given Category X despite low systemic absorption, and there are many low-risk drugs that have been labeled with Category X.

Comments:
a. Among all arguments for Category X, this is the weakest. It is the responsibility of the regulator to judge each case on its own merits, based on science and the regulations. This Medical Officer will not abdicate his responsibility to shadows of the past for the sake of "consistency". If the Agency has assigned Category X rightfully to another drug in the past, that would have served the interest of the public. If such assignment has been misplaced, the Agency should have the courage to correct it. Currently, the Agency is indeed considering revising pregnancy labeling altogether, and this is a positive step.
b. Topical 5-fluorouracil has been quoted as an example where Pregnancy Category X is assigned despite little prospect of teratogenesis. First, the population using the drug for the approved indication is not likely to get pregnant, and therefore the benefit in pregnant women is extremely unlikely. Secondly, systemic availab ility of 5-FU upon topical application can be substantial, because the treatment would likely result in non-intact, inflamed skin. In the label for one of the formulations (Carac ®), it is described that serious systemic reaction has occurred in DPD deficiency in association with the use of topical 5-FU. Thus, because of considerable systemic bioavailability, it is not unreasonable to conclude that the risk for teratogenesis from topical use of 5-FU clearly outweighs any benefit in pregnant women. This is not necessarily the case with topical tretinoin.
c. Much has been quoted about another topical product containing tretinoin which was assigned Category X. This Medical Officer will not question the judgment previously made by another

clinical reviewer. However, the product is for use in a population very different from that intended for TRI-LUMA Cream. At least in this respect, the risk-benefit analysis is not comparable.

5. One should prevent as many pregnant women use TRI-LUMA as possible. Giving a Pregnancy Category C to this product would encourage similar products to be used in pregnancy without precaution. This view is propounded by the Acting Dermatology Team Leader.

Comments:
a. Pregnancy Category X does not prevent use in pregnancy (see below). It may confer a feeling to the regulator that something is being done, but there are other ways of achieving this without incurring the harm from a Category X assignment.
b. It is unclear whether there are any data to support the contention that Category C encourages use in pregnancy without precaution. From the Part 15 hearing dated September 12, 1997 it is public knowledge, and it is the experience of many counselors and physicians that even Category C provokes anxiety about "safety" of a drug exposure in pregnancy. Many publications attest to the perception by patients and some physicians that the teratogenic risk of a "safe" drug is high. Most drug exposures in pregnancy are unintended, and inadvertent exposure in pregnancy is virtually certain for TRI-LUMA Cream (see below). Assigning Category X can only provoke even greater anxiety in the target population for this drug product.

Arguments against approving TRI-LUMA Cream with Pregnancy Category X

1. Both the Agency and many interested parties who take care of, or counsel pregnant women believe that the Pregnancy Categories are inadequate as tools of risk communication. The Agency is in the process of overhauling the Pregnancy subsection in prescription labels. Category X is particularly misleading because it conveys a sense of high risk to the prescriber and the patient, in the same league as teratogens like thalidomide and isotretinoin, even though the real risk may be substantially lower than the risks of those teratogens. To categorize TRI-LUMA Cream in the same way as thalidomide and isotretinoin trivializes the seriousness of Pregnancy Category X.

2. The assignment of Category X hinges on risk-benefit analysis in this particular case, since the teratogenicity potential of tretinoin is undisputed. The regulation requires consideration of "any" benefit to be weighed against the risks. If it is considered that the risks ***clearly*** outweigh ***any possible*** benefit in pregnancy, Category X should be assigned. Perhaps this criterion is somewhat below the high bar of "beyond any reasonable doubt", but still it is a tall order. The patient and the prescriber together are in the best position to make that judgment. A cosmetic indication per se does not necessarily mean that the benefit in pregnancy in ***any specific patient*** is so low that the teratogenicity risk of topical tretinoin ***clearly outweighs*** it. This begs the question of: what is the teratogenicity risk of topical tretinoin.

3. At the concentration in the final formulation (0.05%) of TRI-LUMA Cream, systemic availability of tretinoin in the treatment of facial melasma would not alter plasma levels sufficiently to make them above the normal range. Pharmacokinetic modeling has shown that the actual systemic exposure is 3 to 4 orders of magnitude below that required for teratogenicity. In addition, there has not been good human data to support congenital malformation in humans arising from the use of topical tretinoin since the approval of the first topical formulation in 1971. On the contrary, there are at least 6 study reports with negative results. Reports of holoprosencephaly associated with use of topical tretinoin have been analyzed and re-analyzed without clearly implicating causality. Indeed, OPDRA presented an abstract "Signal Evaluation in Pharmacoepidermiology: the case of topical tretinoin and birth defects" which concludes that there is no evidence between use of topical tretinoin and birth defects [2].

4. Other arguments based on pharmacokinetics have been tretinoin's (a) isomerization into other teratogens and (b) depot in tissues rather than in plasma.

[2] La Grenade LA et al. Signal Evaluation in Pharmacoepidermiology: the case of topical tretinoin and birth defects. *Abstracts of FDA Science Forum, 2000.*

(a) First, tretinoin itself is more potent in terms of teratogenesis than its isomers or metabolites, and indeed the binding to RAR receptors (for tretinoin itself) has been touted as the key to understanding the teratogenic effect of tretinoin. Transformation into other isomers or metabolites tends to lessen teratogenicity rather than enhance it. Secondly, tretinoin, as the *trans-* isomer, is the most stable form, towards which all others tend to isomerize. It is **NOT** reasonable to believe that there are higher levels of other teratogenic isomers when the drug administered is the most stable isomer.
(b) There is a fixed relationship between plasma tretinoin levels and depot contents (confirmed by the Biopharm Team Leader). It is theoretically possible for a sudden efflux of tretinoin from fat depot to plasma to occur, but this conjecture is not based on data. Furthermore, such a scenario would also predispose to the removal of tretinoin from the embryo-fetal tissues and lessen teratogenicity. It is even more important to emphasize that, like vitamin A, ***tretinoin is essential in embryo-fetal development***. Although the threshold level of tretinoin for teratogenesis is not known, morphogenesis is clearly related to the proportion of tretinoin relative to other morphogens present at the critical time for the organogenesis of that particular organ. Tretinoin is bound by CRABP in the cytoplasm, and its access to the nucleus to affect gene expression is regulated. Assuming that slight fluctuations in plasma tretinoin can cause malformations totally ignores the body's control of tretinoin to its site of action, the nucleus.

5. **The critical time for organogenesis** is in the first trimester. Melasma develops gradually in pregnancy, and generally manifests in the second and third trimesters. To inform the prescriber about the teratogenic effect of TRI-LUMA Cream by labeling with Category X misleads the prescriber with the message that this drug product can cause teratogenesis in later pregnancy. An argument has been made that reproductive toxicity is not limited to congenital anomalies, and retinoids have been shown to affect live borns in the long-term, with neurologic and intelligence defects. The following are considerations on this point:

a. The regulations intended such reproductive toxicities that are not congenital malformations to be placed under the ***non-teratogenic effects*** sub-subsection. Although there are labels that contraindicate drugs in later pregnancy because of non-teratogenic effects, it would not be proper to contraindicate them on the basis of Category X. One should not follow improper precedents even if there were one (see above discussion).

b. Such data on neurologic and intelligence deficits were obtained with systemic administration of isotretinoin. Again, one has to refer to the above item (item 4) concerning the unlikelihood of tretinoin effect arising from topical administration when the systemic bioavailability is minimal (3 to 4 logs below levels expected to show teratogenic potential).

Thus, contraindicating the use of TRI-LUMA Cream in pregnancy is based neither on science nor on the intent of the regulations.

6. Pregnancy Category X cannot deter usage in pregnancy. In the clinical trials for TRI-LUMA Cream, where the environment was controlled, and the patients, who received clear-cut instructions to have effective birth control, were better supervised than in real clinical practice, 13 women became pregnant. Since melasma is a condition that develops in pregnancy, this is an almost expected finding, and it is simply anticipated that exposed pregnancies will occur if this product is approved for marketing. Thus, if one is extremely concerned about pregnancy exposure, the only way to stop such exposure is **NOT to approve TRI-LUMA Cream for marketing**. This will deny patients of the potential benefit from its use. As most pregnancy exposures will likely be inadvertent if the drug is marketed, the hortatory language with Category X does nothing to help these exposed women. On the contrary, it only instills unreasonable fear, because patients and prescribers are encouraged by this category to have the perception that the risk of having a malformed fetus is in the order as that for thalidomide or isotretinoin exposure. The fact that subtle, unintended influences can affect serious decision making by patients has been well discussed by Wilkin[3].

[3] Wilkin J. A theory of pregnancy labeling with practical implications: a reviewer's proposal. *The Virtual Journal. http://cdernet/*

7. It has been documented in multiple publications that patients, and even prescribers, have a high risk perception of teratogenesis with respect to drug exposure in pregnancy. Even safe drugs are likely regarded as unsafe. Two examples can be given:

(a) Loebstein *et al* have reported that despite the lack of increased rates of major malformations due to exposure to fluoroquinolones, there was a higher rate of therapeutic abortions in quinolone-exposed women, secondary to the misconception of a major risk related to quinolone use in pregnancy[4].

(b) In a study on the safety of Rubella vaccine, 5 of 7 cases of pregnancy termination were due to perceived risk, as the label lists pregnancy as a contraindication for vaccination [5].

Because of the unreasonable fear associated with exaggerated risk perception arising from Pregnancy Category X, it is anticipated that elective termination of healthy pregnancies will occur if TRI-LUMA Cream is launched with this category. In the clinical trials to-date, although the exact reason is not clear, there has been a case of premature termination of pregnancy in a pregnant woman who was exposed to TRI-LUMA Cream. In the interest of society and public health, one has to determine which is the greater risk: teratogenic risk due to tretinoin exposure or the risk of elective termination of pregnancy due to misinformation by Category X. The answer can only be obvious in retrospect. However, it is reasonable to conclude that under Category X, the latter risk can be expected to be far greater than the former, because the risk of teratogenesis due to use of TRI-LUMA Cream in the treatment of facial melasma is so very low. It is clear that Category X will incur an unacceptably high risk of fetal death due to elective termination of pregnancy, which cannot be balanced by the reduction of malformations that arise from topical tretinoin exposure. In this sense, and **for the sake of public health** , the risk of assigning Pregnancy Category X to TRI-LUMA Cream truly and ***clearly*** outweighs ***any*** possible benefit.

Conclusions

1. It is not in public health interest to assign Pregnancy Category X to TRI-LUMA Cream.

2. Assigning Category X would be based neither on science nor on the intent of the regulations.

3. It is appropriate to label TRI-LUMA Cream under Pregnancy Category C.

Recommendations to manage the risks arising from the use of TRI-LUMA Cream in pregnant women

1. The Agency is promulgating new pregnancy labeling. However, at this time, it is still necessary to label TRI-LUMA Cream with a Pregnancy Category. Nevertheless, it is important that the label be as consistent as possible to the new approach, in order to achieve proper risk communication and help manage both the risk of teratogenesis and the risk of elective termination of pregnancy. The label should address each of two decision modes[3]: whether to starting drug and whether to use birth control when using drug. It is not appropriate for a label to advise whether to continue or terminate a pregnancy upon exposure to drug, but the risk of congenital malformation associated with exposure should be presented.

2. Drug use in pregnancy should be discouraged in general. The prescriber should be informed in the INDICATIONS AND USAGE section of the package insert that the safety and efficacy of TRI-LUMA Cream in pregnant women has not been established, and that the clinical trials were conducted in a setting where pregnant women were excluded, and women of child-bearing potential were to use effective birth control. Thus, there will be discouragement for prescribing TRI-LUMA Cream in women who are or may be pregnant. Although in the clinical trials, TRI-LUMA Cream appears to be effective in both users and non-users of hormonal methods of contraception, as melasma is often associated with the use of hormonal birth control, this information should be forthcoming in the label. Some

[4] Loebstein R et al. Pregnancy outcome following gestational exposure to fluoroquinolones: a multicenter prospective controlled study. Antimicrob Agent Chemother 1998; 42:1336-9.
[5] Koren G. submitted for publication.

patients may be able to have improvement without drug therapy simply by changing the method of contraception.

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4. To be able to more accurately inform prescribers and patients in future, there should be a phase 4 commitment to collect pregnancy outcome data. The design of such an undertaking 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.

X. Conclusions and Recommendations

A. Conclusions

1. The Applicant has responded adequately to the "Clinical/Statistical" items in the NA Letter of 1/20/00 by providing 4 sets of clinical studies to address the four deficiencies:

- Long-term safety studies to comply with ICH E1A Guidance
- A modified Draize test with 221 patients to assess sensitization potential
- An HPA axis suppression study with cosyntropin stimulation to assess adrenal suppression potential
- Two adequate and well-controlled trials comparing TRI-LUMA Cream to dyad components to determine the safety and efficacy of TRI-LUMA Cream in the treatment of facial melasma.

2. The phase 3 trials, Studies 28A and 28B, together with the data from long-term safety studies, Studies 29 and 30, to-date, have demonstrated the safety and efficacy of TRI-LUMA Cream in the treatment of melasma of the face, in the presence of measures for sun avoidance, including the use of sunscreens. The benefits are essentially cosmetic, and the risks are application site reactions, and the potential for teratogenicity due to the component tretinoin. One way to manage the risk/benefit ratio is to approve the product for moderate to severe facial melasma, so that patients with mild melasma are not exposed to this triple therapy.

3. 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.

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

[6] 21 CFR 208.1(c) (1) The drug product is one for which patient labeling could help prevent serious adverse effects. (2) The drug product is one that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decision to use, or to continue to use, the product.

have TRI-LUMA cream as initial therapy, followed by maintenance with a single depigmenting agent. This may incur less exposure to unneeded drugs than with chronic intermittent therapy. The label should clearly indicate that TRI-LUMA Cream is a combination product, and is intended for short-term, [redacted] . treatment of melasma.

5. The risk of human reproductive toxicity from topical use of TRI-LUMA Cream is not believed to be high. However, melasma is an indication that occurs quite often in pregnancy. Further data collection in the post-marketing phase for pregnancy outcome will be useful to determine the real risk of birth defects and other adverse pregnancy effects arising from the use of TRI-LUMA Cream in the treatment of facial melasma. Labeling, including labeling for patients, should carefully communicate the risks to the prescriber and patient. Because of the low systemic bioavailability of the active ingredients in the treatment of melasma and the low likelihood of teratogenesis, Pregnancy Category X is not recommended. At the same time, use in pregnancy should be discouraged, as safety and efficacy of TRI-LUMA Cream in pregnancy has not been established. Because the risk/benefit information on TRI-LUMA Cream may affect patients' decision making, this product is qualified to have a Medication Guide.

B. Recommendations

1. 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.

2. The Applicant should revise the draft label as recommended in Appendix A.

3. 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.

4. 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.

5. A waiver for pediatric study requirements may be granted.

XI. Appendix

A. Recommended Labeling

TRI-LUMA™ Cream
(fluocinolone acetonide 0.01%, hydroquinone 4%, tretinoin 0.05%)

For External Use Only
Not for Ophthalmic Use

Rx only

DESCRIPTION

Number of Pages Redacted 33

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Draft Labeling
(not releasable