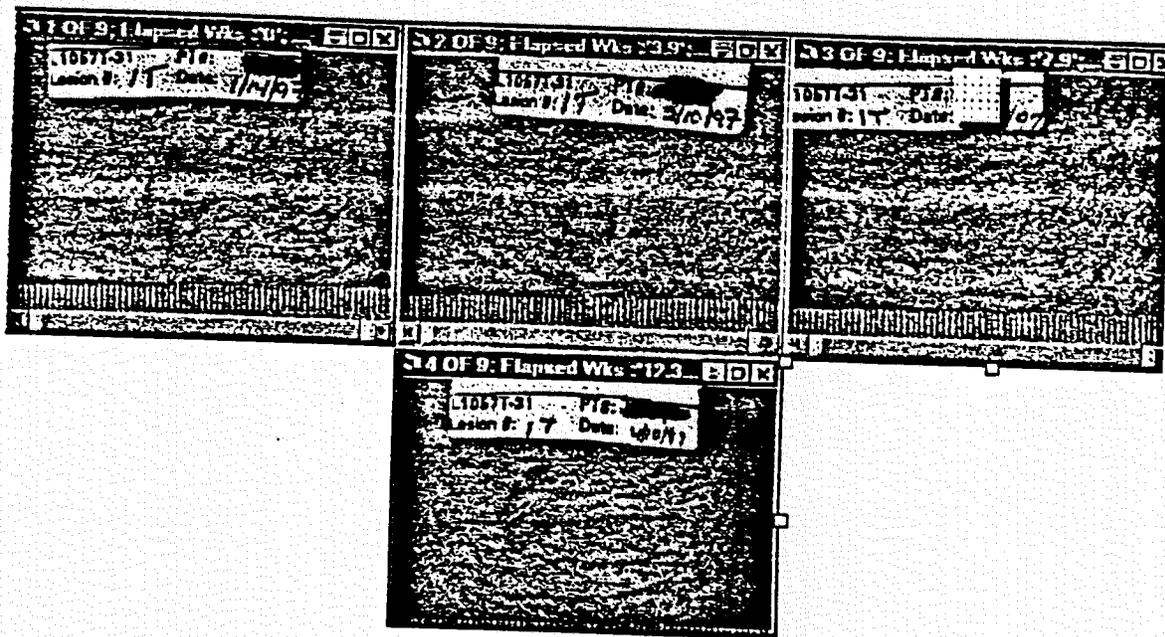
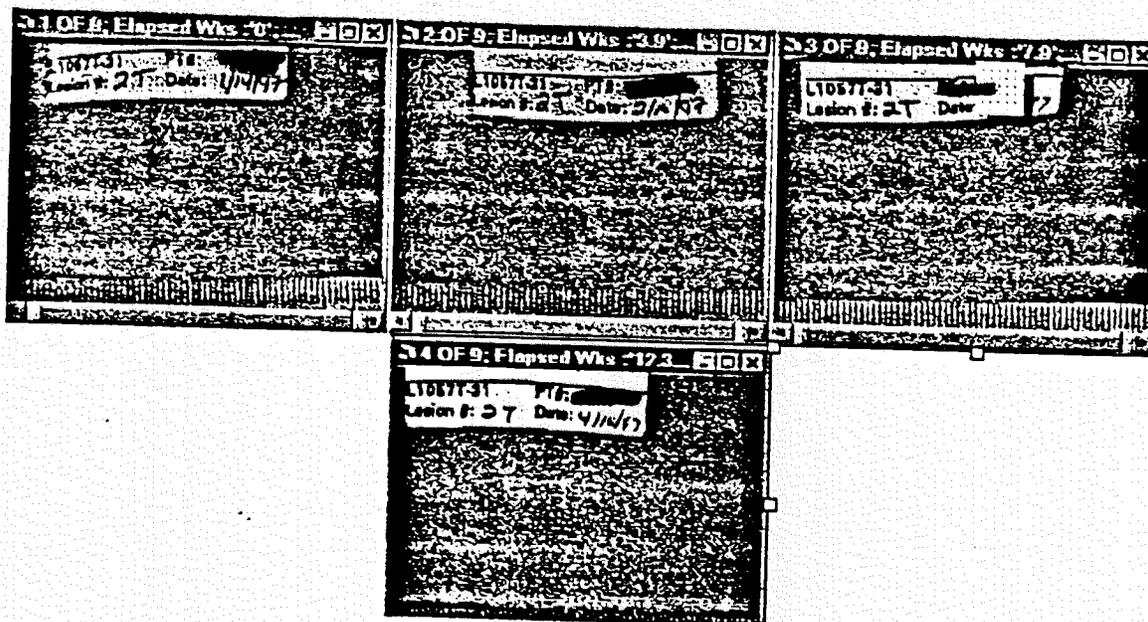


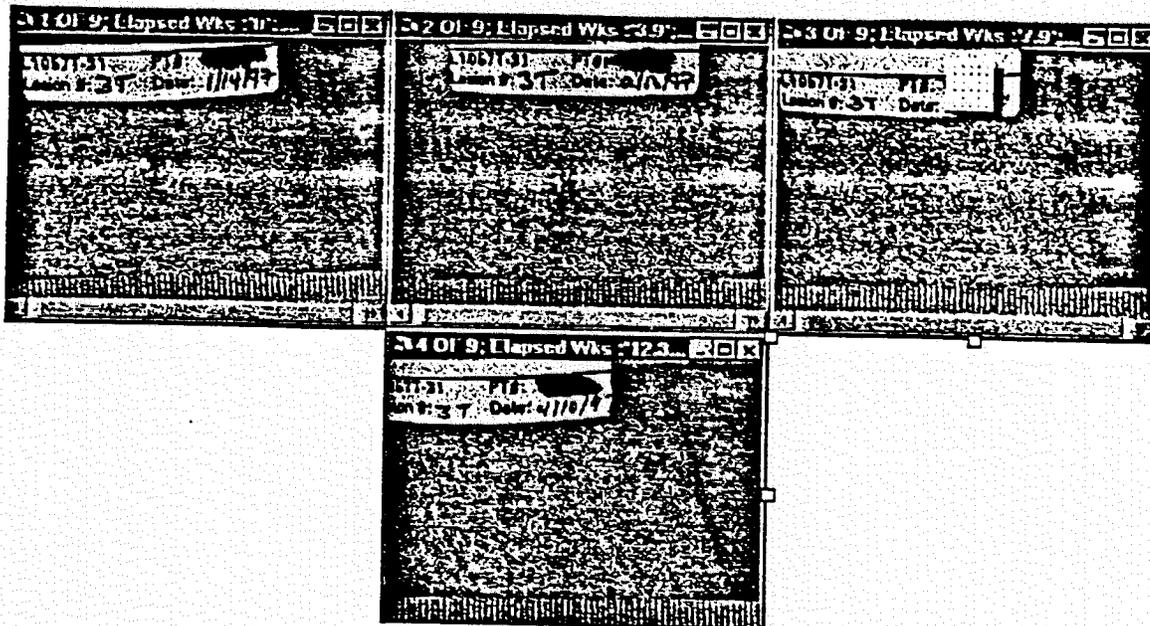
lesion #1
plaque at baseline
flat at 2 wks



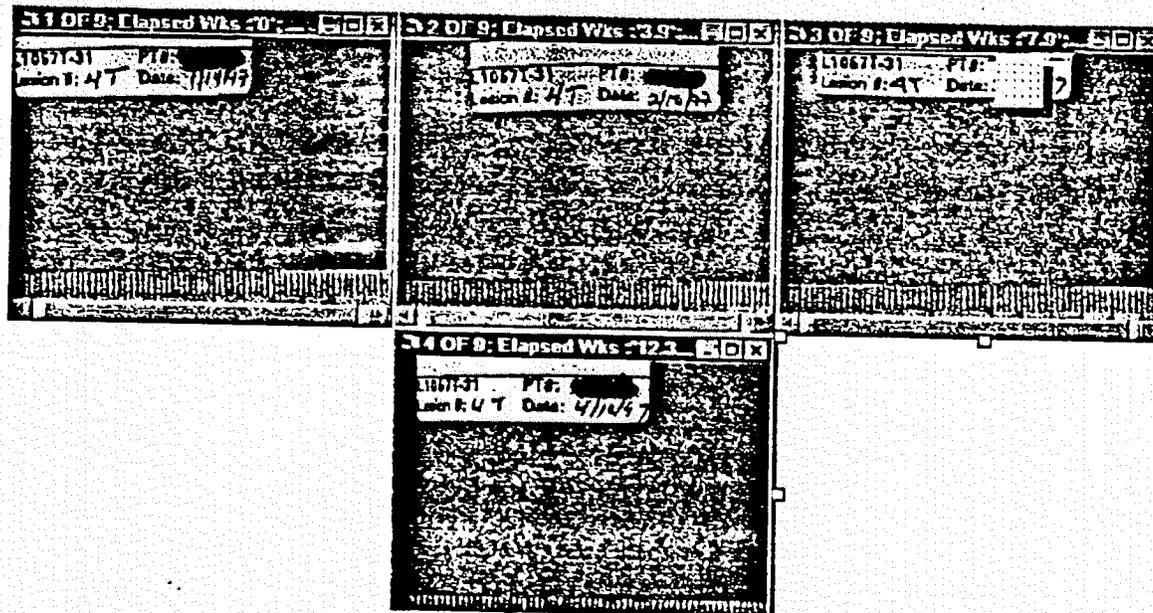
lesion #2:
plaque at baseline
flat at 2 wks



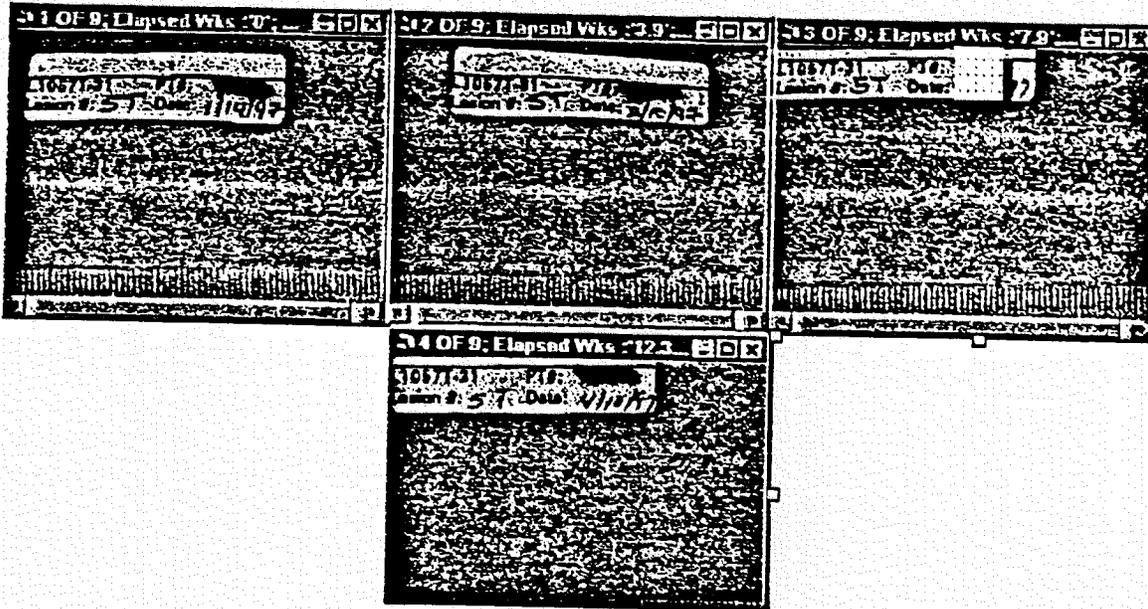
lesion #3:
plaque at baseline
flat at 4 wks



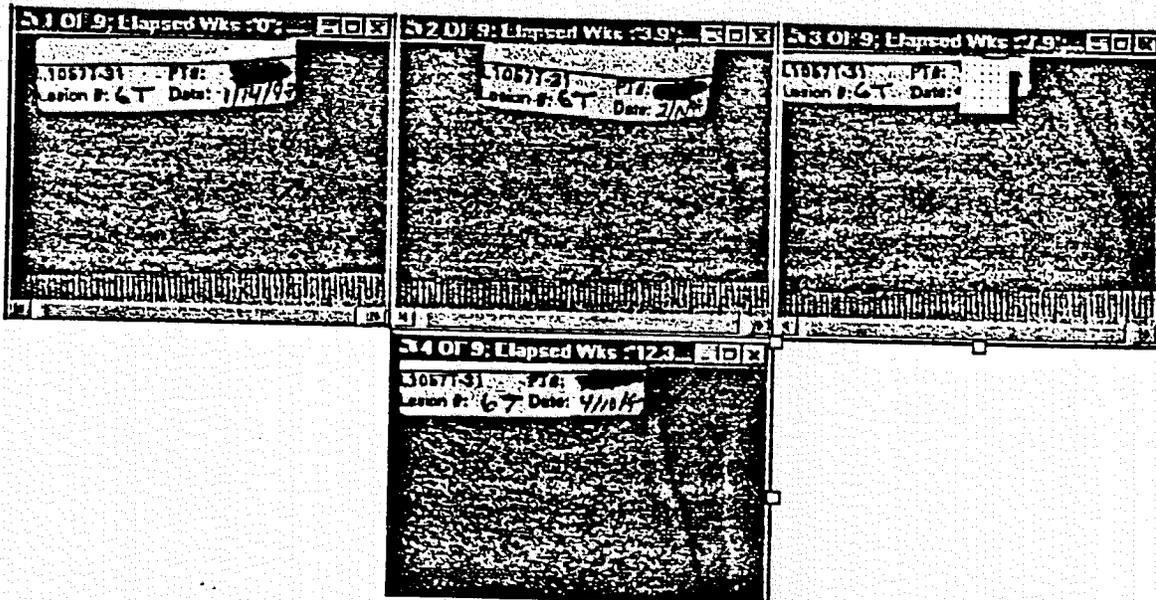
lesion #4:
flat at baseline
no activity on CRF



lesion #5:
flat at baseline
no activity on CRF



lesion #6:
flat at baseline
no anti-KS activity



There were PI changes in this patient, at 1-2 mos., while on-study (crixivan, saquinavir).

SUMMARY of Patient

- Modified ACTG: PR
- Physician's global assessment: SD
- Patient satisfaction with the KS lesions treated: neutral
- Cosmetically beneficial response: YES

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**4.3.3 SUMMARY OF RESPONSE EFFICACY IN STUDY -31
DURING THE INITIAL BLINDED PHASE (12 WEEKS)**

Ligand	PANRETIN	PLACEBO
Modified ACTG Response (6 index lesions) FDA	47/134 (35%) 1 CR	24/134 (18%) p = 0.002
Modified ACTG Response (6 index lesions) FDA	46/134 (34%) 1 CR	22/134 (16%) p= 0.0012
Ligand Physician's Global Assessment (all rxed lesions) FDA	26/134 (19%)	5/134 (4%) p = 0.00014
Beneficial Response Photographs (index lesions only) FDA	20/134 (15%)	5/134 (4%) p =0.0026
*Beneficial Response Photographs (index lesions only)	23/134 (17%)	Not Applicable
Ligand *Patient's Overall Satisfaction with KS Lesion Drug Effect (all rxed lesions)	P=.0001 Favoring Panretin	

*Entire Study both Blinded Phase and Post Blinded Phase

The disparity between the modified ACTG response and the Physician's Global Assessment is noted. The table below for the panretin responders shows that about two thirds of the partial responders by the modified ACTG criteria were evaluated as stable disease by the PGA.

Best response: ACTG					
Best response: PGA	CCR	PR	SD	PD	TOTAL
CCR	1	0	0	0	1
PR ³⁷	0	15	9	1	25
SD ³⁸	0	31	58	16	105
PD	0	0	0	3	3
TOTAL	1	46	67	20	134
P=0.0017; kappa correlation 0.213					

The tables below attempt to explain the disparity between the modified ACTG response and the PGA. The 47-panretin responders were divided into two groups. One group responded by reduction in the height of index lesions only. The second group responded by reduction in area of index lesions—more potent criteria—plus or minus reduction in the height of index lesions. Only 5 out of 33 or 15% of the modified ACTG panretin responders scored with height reduction only agreed with the physician's global assessment. Interestingly, 11 out of 14 or 79% of the modified ACTG panretin responders scored with area reduction agreed with the physician's global assessment. A similar pattern was seen with the vehicle arm. It appears that the physician-investigators were impressed with area reduction as a response criteria.

³⁷ Grades 1, 2, or 3

³⁸ Grades 3, 4, or 5. Note: grade 3 is included in both response criteria (vol. 1.73, p. 219); on p. 294 SD did not include grade 3.

ACTG RESPONSE CRITERIA	# MATCH WITH PGA
<p>PANRETIN 47 RESPONDERS</p> <p><u>HEIGHT REDUCTION only</u> N=33</p> <p>Plaque to macule Nodule reduced Nodule reduced + plaque to macule</p>	5 (15%)
<p><u>AREA REDUCTION alone or area plus height reduction</u> N=14</p> <p>Area Area + plaque to macule Area + nodule reduced Area + nodule reduced + plaque to macule</p>	11 (79%)
	95% CI diff: 39%, 88%

ACTG RESPONSE CRITERIA	# MATCH WITH PGA
<p>VEHICLE 24 RESPONDERS</p> <p><u>HEIGHT REDUCTION only</u> N=18</p> <p>Plaque to macule Nodule reduced Nodule reduced + plaque to macule</p>	2 (11%)
<p><u>AREA REDUCTION alone or area plus height reduction</u> N=6</p> <p>Area Area + plaque to macule Area + nodule reduced Area + nodule reduced + plaque to macule</p>	3 (50%)
	95% CI diff: -4%, 82%

However, since the physician-investigator were to assess both the treated index lesions and the treated non-index, the disparity between the modified ACTG response and the PGA, may

mean that the activity seen in the treated index lesions and scored by the modified ACTG response was not evident in the treated non-index lesions.

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4.3.4 FDA Assessment of Safety

This review of safety discusses dermal toxicity, dermal toxicity in cutaneous T-cell lymphoma, cellulitis, and study termination due to dermal toxicity.

The following safety assessment is from the Ligand MS ACCESS database (panel AE).

SEVERE SKIN ADVERSE EVENTS

Severe Skin Adverse events	North American Phase 3 Study (L1057-31)	
	Panretin Gel N=134 Pts.	Vehicle Gel N=134 Pts.
Severe, General 1 st 12 wks	16 (12%)	1 (1%)
Severe At treatment site 1 st 12 wks	14 (10%)	0 (0%)
Severe, General, Entire study	19 (14%)	-
Severe At treatment site Entire study	18 (13%)	-

ADVERSE EVENTS WITH AN INCIDENCE OF AT LEAST 5% AT THE APPLICATION SITE IN PATIENTS RECEIVING PANRETIN GEL IN BLINDED PHASE

Adverse event	North American Phase 3 Study (L1057-31)	
	Panretin Gel N=134 Pts. %	Vehicle Gel N=134 Pts. %
Rash	77	17
Pain	34	7
Pruritus	11	4
Exfoliative dermatitis	9	2

	North American Phase 3 Study (L1057-31)	
Skin disorder	8	1
Paresthesia	3	0
Edema	8	3

ADVERSE EVENTS WITH AN INCIDENCE OF AT LEAST 5% IN THE SKIN OF PATIENTS (APPLICATION SITE AND/OR NON-APPLICATION SITE) RECEIVING PANRETIN GEL IN BLINDED PHASE

Adverse event	North American Phase 3 Study (L1057-31)	
	Panretin Gel N=134 Pts.	Vehicle Gel N=134 Pts.
Rash	105 (78%)	31 (23%)
Pain	59 (44%)	26 (19%)
Pruritus	17 (13%)	7 (5%)
Exfoliative dermatitis	13 (10%)	4 (3%)
Skin disorder	14 (10%)	4 (3%)
Paresthesia	8 (6%)	3 (2%)
Edema	25 (19%)	20 (15%)
Infection	8 (6%)	3 (2%)

In addition, the following analyses were done.

Treatment limiting toxicity was local grade 3 or higher local dermal irritation and/or very red with edema, with or without vesiculation. The KS index lesions were evaluated for this toxicity. All treatment limiting toxicities were to be recorded on the "adverse events" CRF. Twenty-eight patients on panretin had grade 3 dermal treatment limiting toxicity. These patients were panretin patients (blinded phase and open-label panretin) and vehicle patients who were crossed-over to panretin or who were treated with open-label panretin. Six patients on panretin had 2 episodes; 3 patients had 3 episodes; and 2 patients had 4

episodes; and the rest of the patients had one episode recorded. The median time to the first treatment limiting toxicity was 8 weeks (range: weeks).

In the investigators' evaluation of response of KS index lesions, they graded the lesions for erythema. Grade 2 erythema was a lesion with increased redness, possible edema; grade 3 was a lesion very red, with edema, with or without vesiculation. Nine panretin patients had grade 3 erythema during the initial blinded phase treatment; two patients had two episodes. The median time to first grade 3 erythema was 8 weeks (range: weeks). Sixty-six patients on panretin had grade 2 erythema during the initial blinded phase treatment. Thirty-four patients on panretin had 2 episodes; 6 patients had 3 episodes; and 3 patients had 4 episodes; and the rest of the patients had one episode recorded. The median time to first grade 2 erythema was 4 weeks (range: weeks). One patient on vehicle gel had grade 2 erythema at week one.

Under grade 3 erythema in the adverse event section of the CRF, there were twenty-one patients on panretin with grade 3 erythema. Similar to the foregoing discussion on treatment limiting toxicity, these patients were from panretin patients (blinded phase and open-label panretin) and vehicle patients who were crossed-over to panretin or who were treated with open-label panretin.

Although the three toxicity groups have common panretin patients, there were patients who were not included in all the groups. The final classification combines all the panretin patients with grade 3 dermal toxicity.

CLASSIFICATION OF TOXICITY	PROPORTION OF PATIENTS
TREATMENT LIMITING TOXICITY (GRADE 3) N=234 ³⁹	28/234 (12%)
LESION CLINICAL ASSESSMENT (INITIAL BLIND): ERYTHEMA	

³⁹ This represents 134 pts. in the panretin blinded phase (16 TLT pts), 15 pts. from the vehicle arm crossed-over to blinded panretin (5 TLTs pts), and 85 pts. from the vehicle arm transferred to open-label panretin (7 TLTs pts).

CLASSIFICATION OF TOXICITY	PROPORTION OF PATIENTS
(GRADE 3)	9/134 (7%)
(GRADE 2)	66/134 (49%)
N=134	
ADVERSE EVENT: ERYTHEMA	
(GRADE 3)	21/234 (9%)
N=234	
All patients on panretin with grade 3 dermal toxicity	35/234 (16%)
N=234	

Patients with cutaneous T-cell lymphoma had problems tolerating topical panretin gel. In cutaneous T-cell lymphoma trials, the starting dose of 0.05% panretin gel was reduced to 0.01% due to investigator perception that the former starting dose was too irritating. A planned 30 patient study was stopped after 7 patients were enrolled because panretin gel was more topically irritating in treating CTCL than another retinoid gel in clinical investigation. Five patients had 6 episodes of treatment-limiting toxicities—grade 3 dermal irritation.

In many of the photographs, the panretin-associated erythema appeared strikingly similar to cellulitis. The ACCESS database was probed for this in the concomitant medications section (e.g., specific antibiotics and cellulitis) and in the adverse events section (e.g., infection, cellulitis, purulent drainage). From patients randomized to blinded panretin there were eight patients and 14 episodes of skin infections (e.g., cellulitis, skin infection, boil, pyoderma, folliculitis, bx site #2 infection, purulent drainage to treated non-index lesions). From patients randomized to vehicle gel and then treated on open-label panretin, there were two patients and three episodes of skin infections; these episodes occurred while on panretin. From patients randomized to vehicle gel and crossed-over to blinded panretin, there were five patients and six episodes; these episodes occurred while on

panretin. Six percent (15/234) of patients⁴⁰ on panretin developed a skin infection; three patients had treatment limiting toxicity between ten and three weeks prior to the skin infection. From patients randomized to vehicle, there were three patients and 4 episodes of skin infections; these episodes occurred while on vehicle. Two percent (3/134) of patients randomized to vehicle gel developed a skin infection. The 95% confidence interval for difference was 0.2% and 8%.

Twenty patients, who were either randomized to panretin or randomized to vehicle but on open-label panretin, were terminated from Study -31 with an adverse event most responsible for study drug termination. Ten of these patients had dermal toxicity as the adverse event (e.g., erythema, rash, crusting, pain & irritation, skin burning, and cellulitis). Twenty-three patients, who were terminated, had an adverse event as an additional reason for termination. Fifteen of the patients had dermal toxicity (e.g., very irritated, erythema, redness, stinging, ulceration, and cellulitis) as an additional reason for study termination; one patient was a duplicate from the preceding group.

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⁴⁰ This represents 134 pts. in the panretin blinded phase, 15 pts. from the vehicle arm crossed-over to blinded panretin, and 85 pts. from the vehicle arm transferred to open-label panretin.

EXAMPLES OF DERMAL TOXICITY TO PANRETIN

This is the foot of patient (lesion #2). This patient was considered a modified ACTG criteria responder to panretin (this patient was not a considered a cosmetically beneficial responder). The plaque lesion at baseline became flat at 4 wks. In the physician-investigator's evaluation of this lesion, no erythema was recorded. These photographs demonstrate both erythema and edema in this patient's foot, starting at week 6.

