Another example is demonstrated by patients #622, #721, #871, and #1711. The CAPL CRFs were not submitted in the electronic version of the CRF. In response to FDA inquiry, Ligand submitted the forms for the first three patients and wrote that the CAPL was not available for #1711 (Ligand response dated 5/11/2000). The CAPL CRFs submitted were blank for antipuritic therapies; this information was not captured in the ACCESS database (file CMTL) for #622, #871, and #1711. Electronic CAPL and CMTL CRFs were not submitted for patient #702. Ligand submitted the forms (Ligand response dated 5/11/2000). The CAPL CRF was blank and the CMTL contained information found in the ACCESS database. Submission of blank of CRF forms was not unusual.

For patient #805, the ACCESS database and pathology report dates do not match; ACCESS database has the incorrect date for the qualifying biopsy.

Protocol Deviations

Ligand's analysis of protocol deviations is below.

Protocol Deviations by Category of Deviation

Category of Deviation[1]	Targretin® gel 1% N = 50 n (%)
Deviation From Inclusion Criteria	20 (40)
Deviation From Exclusion Criteria	2 (4)
Developed Withdrawal Criteria but Not Withdrawn	0
Received Prohibited Drug/Therapy	25 (50)
Other Deviation	0
Total Number of Deviations[2]	51
Total Number of Patients with at Least One Deviation	33 (66)

(1) Patients are counted no more than once in each category, even if the patient had multiple deviations in each given category.
(2) Patients may contribute multiple deviations in any given category and deviations from multiple categories.

Below are additional protocol deviations.

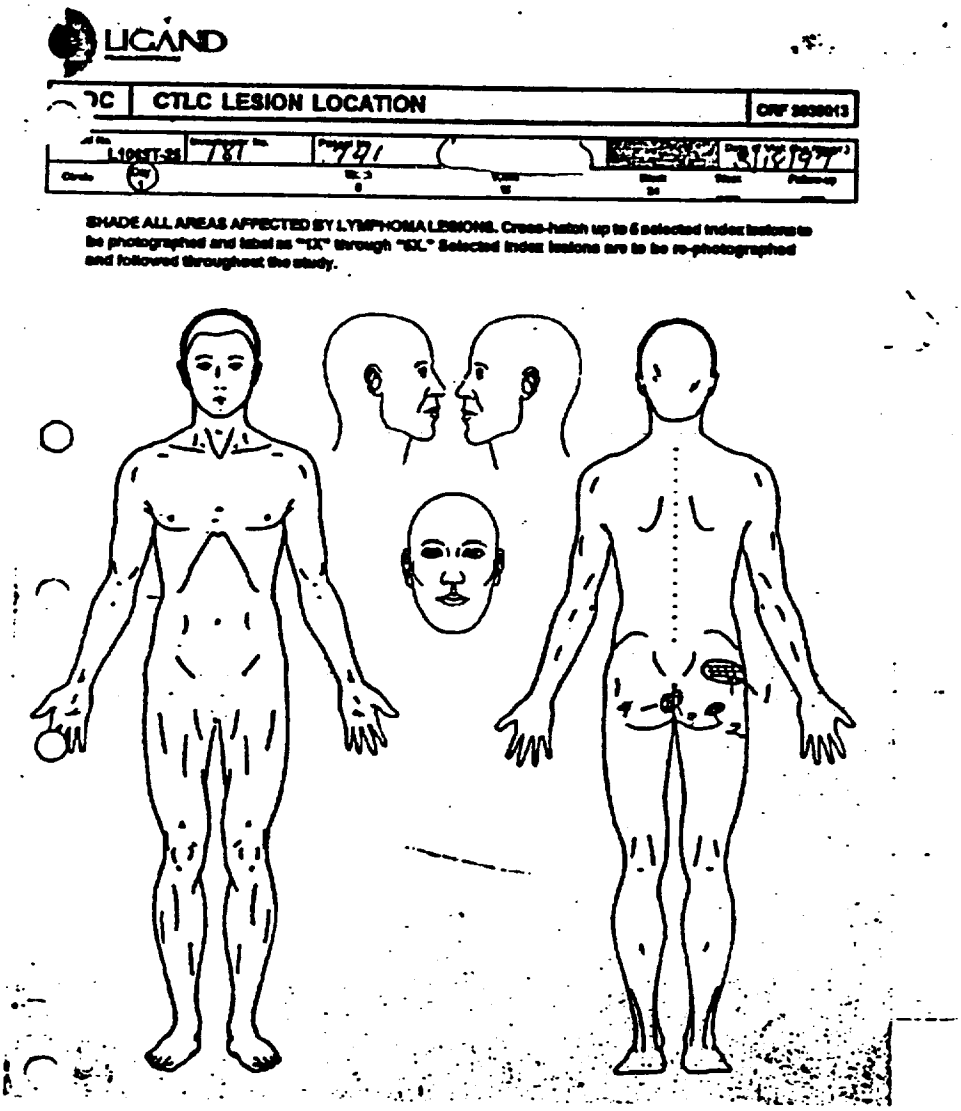
1. According to the protocol, a PGA grade of 6 at two or more consecutive timepoints persisting over at least four weeks defines progressive disease. In the table below are four patients who met the criteria for PD by PGA and continued on study.

PATIENT #	EVALUATION DAYS: PD BY PGA	EVALUATION DAYS CONTINUED; PATIENT SHOULD HAVE BEEN TERMINATED FROM STUDY
621	28, 56	84, 112, 140, 168, 196, 224, 252, 280, 308, 336, 364
701	56, 84	112
802	28, 56	84, 112
842	56, 84, 112	140, 168, 196, 224

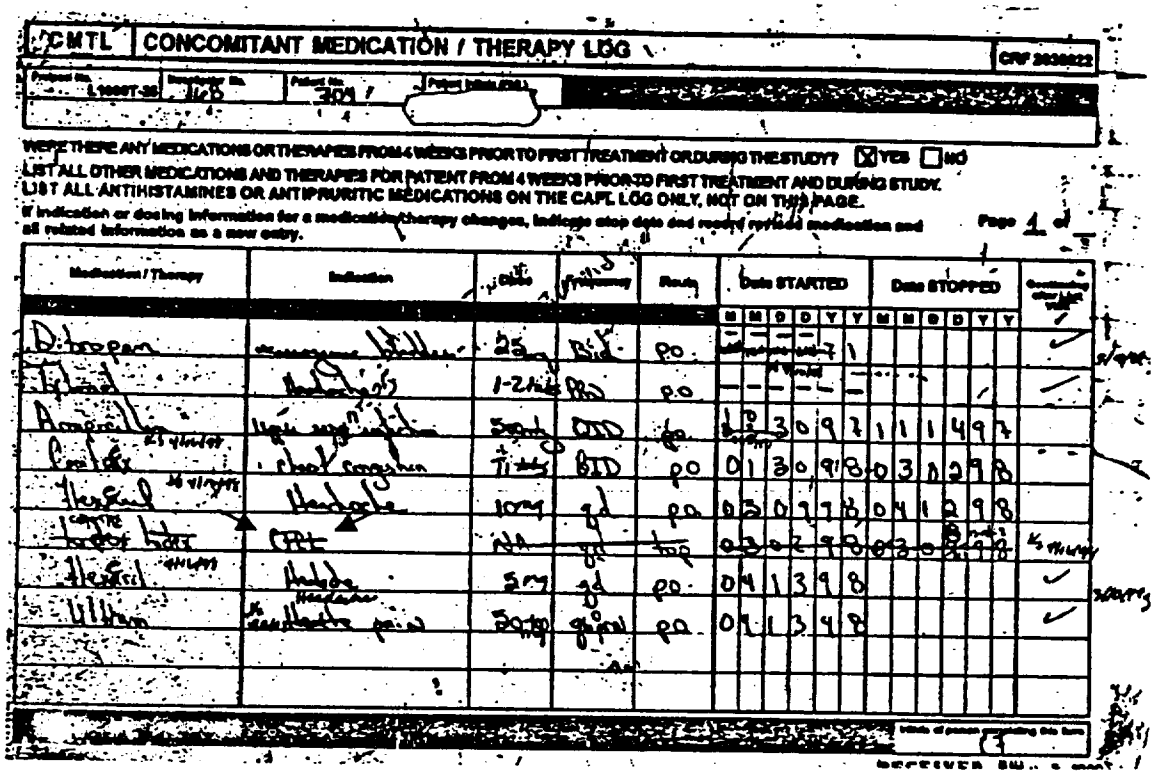
2. Another patient with a protocol violation (#731) was a 13 year-old pediatric patient with Stage IA disease who had previously failed PUVA and interferon therapies. Ligand agreed to a waiver of the age inclusion criterion for this patient. All the other databases (-11, -9403, -9404, -07, -08, -12, -13, -15), the minimum ages were: 30, 33, 33, 23 (next older 33), 30, 34, 36, and 32 (there are 4 other unidentified patients: the youngest could be an infant), respectively. This case was not representative of the expected patient population.

3. Prohibited Medications (see below)

- Ligand describes patient #741 who was prescribed Synalar had a left lower extremity eczematous dermatitis starting on Study Day 85 for a duration of 16 days and for gluteal rash starting on Study Day 25 for a duration of five days (disclosure of order of application of Synalar by Ligand, p. 118 of Study Report). It is of note that the patients index lesions were in the gluteal region (see figure below). This is a protocol disqualification and patient should not be considered a responder.



Below are examples from the CRFS illustrating that the investigators recorded initially CTCL (arrows) as the indication for topical steroid. This was later changed to another indication. The ACCESS database did not record the change in the indication.


CMTL CONCOMITANT MEDICATION / THERAPY LOG

WERE THERE ANY MEDICATIONS OR THERAPIES FROM 4 WEEKS PRIOR TO FIRST TREATMENT OR DURING THE STUDY? ☒ YES ☐ NO

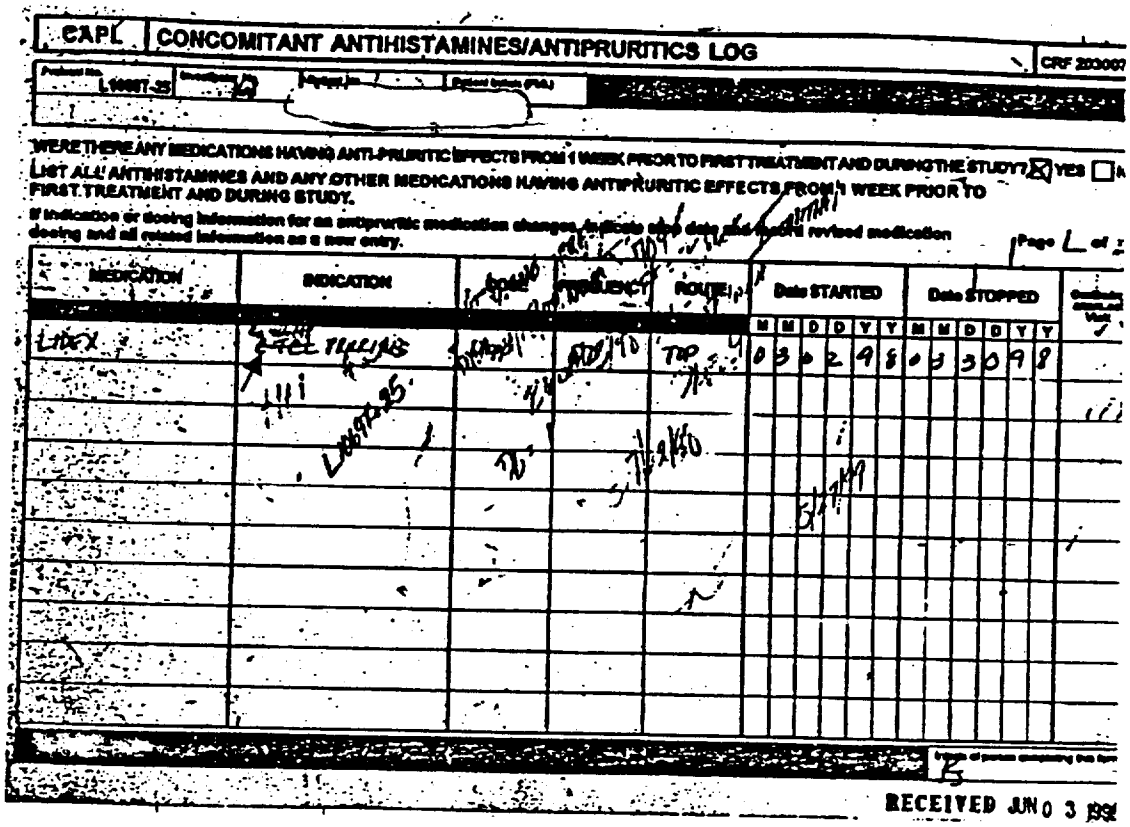
LIST ALL OTHER MEDICATIONS AND THERAPIES FOR PATIENT FROM 4 WEEKS PRIOR TO FIRST TREATMENT AND DURING STUDY.
LIST ALL ANTIHISTAMINES OR ANTIPRURITIC MEDICATIONS ON THE CAPL LOG ONLY, NOT ON THIS PAGE.

If indication or dosing information for a medication/therapy changes, indicate stop date and record revised medication and all related information as a new entry.

Page 1

Medication / Therapy	Indication	Dose	Frequency	Route	Date STARTED	Date STOPPED	Continuing after study visit
Diazepam		25	BID	po			✓
		1-2		po			✓
			QID		12/30/97	1/1/98	
			BID	po	01/30/98	03/29/98	
			qd	po	02/07/98	04/29/98	
					02/27/98	03/29/98	
		5mg	qd	po	04/13/98		✓
			qhs	po	04/13/98		✓

APPEARS THIS WAY
ON ORIGINAL



CAPL | CONCOMITANT ANTIHISTAMINES/ANTIPRURITICS LOG

CRF 200007

L1008T-35

WERE THERE ANY MEDICATIONS HAVING ANTI-PRURITIC EFFECTS FROM 1 WEEK PRIOR TO FIRST TREATMENT AND DURING THE STUDY? ☒ YES ☐ N

LIST ALL ANTIHISTAMINES AND ANY OTHER MEDICATIONS HAVING ANTIPRURITIC EFFECTS FROM 1 WEEK PRIOR TO FIRST TREATMENT AND DURING STUDY.

If indication or dosing information for an antipruritic medication changes, indicate stop date and record revised medication dosing and all related information as a new entry.

Page 1 of 2

MEDICATION	INDICATION	DOSE	FREQUENCY	ROUTE	Date STARTED (M M D D Y Y)	Date STOPPED (M M D D Y Y)	Continuing after Last Visit
LIDEX	ECZEMA			TOP	03 02 98	03 30 98	

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ERE THERE ANY MEDICATIONS OR THERAPIES FROM 4 WEEKS PRIOR TO FIRST TREATMENT OR DURING THE STUDY? ☒ YES ☐ NO

ST ALL OTHER MEDICATIONS AND THERAPIES FOR PATIENT FROM 4 WEEKS PRIOR TO FIRST TREATMENT AND DURING STUDY.
ST ALL ANTIHISTAMINES OR ANTIPRURITIC MEDICATIONS ON THE CAPL LOG ONLY, NOT ON THIS PAGE.

Indication or dosing information for a medication/therapy changes, indicate stop date and record revised medication and related information as a new entry.

Page 1 of 1

Medication/Therapy	Indication	Dose	Frequency	Route	Date STARTED (M M D D Y Y)	Date STOPPED (M M D D Y Y)	Continuing after Last Visit
TYLENOL	MENSTRUAL PAIN	500mg	PRN	PO	- - - - - -		✓
ADVIL	GENERAL PAIN	200mg	PRN	PO	- - - - - -		✓
[illegible]	URINARY TRACT [illegible]	950mg	BID	PO	10 07 98	10 11 98	
TEMOVATE	[illegible]	[illegible]	BID	TO	12 16 98		✓

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4. Evaluation of Baseline Lesions

a. Patients #632, #663, and #811 did not have baseline evaluation of index lesions.

b. There were two patients (Patients 348/631 and 349/1761) who had indicated the presence of more than five total CTCL lesions on the CTCL History (CLHX) CRF, but less than five were designated as index lesions at Baseline. Patient 348/631 had indicated ≥20 CTCL lesions on the CLHX CRF but only two lesions were designated as index lesions. According to the LOC CRF it appeared that the majority of this patient's lesions were confluent. In addition, the patient terminated from the study on Day 9 due to an adverse event (contact dermatitis). Patient 349/1761 had indicated seven discrete cutaneous lesions on the CLHX CRF. However in the AIR CRF it was reported that the patient did not have five CTCL lesions and as a result only three lesions were designated as index lesions.

FDA assessment of efficacy

Demographics

The CTCL is most common in mature adults (45 to 65 years old) and is observed in all races but more commonly in blacks than whites by a ratio of 2:1, and with men afflicted by the disorder more often than women by a ratio of 2:1. The Study –25 patient population is different than this description as follows: 1. One patient was 13 years old when entered; females outnumbered males; and whites outnumbered blacks. The table below shows the demographics.

DEMOGRAPHICS	
Age, median (range)	64 (13[7] – 85 yrs)
Gender	23 males, 27 females
Race	40 whites, 10 blacks
Stage IA IB IIA IIB[8]	 25 22 2 1
Time from original CTCL diagnosis to 1st treatment on study Median Range	 6 years 0.14 – 22.75 years
Circulating abnormal T-lymphocytes % cells median (range)	6[9] 10% (2% - 31%)

Baseline body surface areas (patch and plaque disease) were provided for the patients. The percent body surface area of involvement with CTCL differentiates Stage IA from Stage IIB. Staging as Stage IA (less than 10% of skin surface) matched percent body surface assessment in 84% of cases (21/25). Staging as Stage IB (10% or more of the skin surface) matched percent body surface assessment in 86% of cases (19/22).

[7] Next age 33 yrs
[8] This stage was not eligible.
[9] None of the cases were responders.

The FDA Efficacy Analysis—The Primary Endpoint

Only the composite assessment was acceptable to the FDA as a potential response criteria. The physician's global assessment (PGA) was not reviewable since global photographs as described in the protocol were not provided.

A Composite Assessment of Index Lesion Disease Severity was generated by a summation of the grades for each index lesion erythema, scaling, plaque elevation, hypopigmentation or hyperpigmentation, and area of involvement (see Protocol Review). The Composite Assessment of Index Lesion Disease Severity grade at baseline was divided into the Composite Assessment of Index Lesion Disease Severity grade at each subsequent study visit to determine the patient's response to treatment.

The following table lists the responders according to Ligand (Vol. 1, Critical Patient Reference List; these are also the patients with a CA response for whom the hard copy photographs and electronic CRFs were submitted)[10]. The first set of patients had less than 20 CTCL total lesions (n=10). The second set of patients had 20 or more CTCL total lesions (n=7).

CA Responders Claimed by Ligand

PATIENT #	LIGAND COMPOSITE ASSESSMENT
691	CCR
692	CCR
695	PR
702	PR
704	PR
741	CCR
801	PR
831	PR
841	PR
1761	PR
671	PR
694	PR
703	PR
721	PR

[10] Ligand has 18 CA responders in their analysis in Table 77 of the ITT population. The extra CA responder may be patient #842, but patient #842 was not listed in the Critical Patient Reference List, and hard copy photographs and electronic CRFs were not submitted for this patient. It appears that Ligand believed this patient was not a responder.

PATIENT #	LIGAND COMPOSITE ASSESSMENT
743	CCR
871	PR
1711	PR

Based on this assessment, the response rate is 34% (17/50; 95% confidence intervals, 21%, 47%).

However, the above is the intent-to-treat analysis. There were 34 non-evaluable patients according to Ligand (Listing 30). Among these cases, there were 7[11] CA responders. The response for evaluable patients is 44% (7/16; 95% CI, 19%, 68%).

CA Responders Claimed by Ligand: Dermatopathology

The table below lists the 17 Ligand scored CA responders and the pathology readings of the local and reference dermatopathologist. Readings were required to be either diagnostic of CTCL or consistent with CTCL. Six CA responders had "diagnostic" as the local reading and 10 had "consistent" as the local reading; there was no local reading for one patient. The reference dermatopathologist read the slides as "diagnostic" for 10 patients and "consistent" for 7 patients. Five patients had concordance of the readings with "diagnostic/diagnostic" and six patients had concordance with "consistent/consistent". Four patients had discordant readings with "consistent/diagnostic" and one patient had discordant readings with "diagnostic/consistent".

Patient #	local/reference pathology readings
691	consistent/consistent
692	diagnostic/diagnostic
695	consistent/consistent
702	diagnostic/diagnostic
704	diagnostic/diagnostic
741	Consistent/diagnostic
801	Diagnostic/consistent
831	consistent/consistent
841	consistent/consistent
1761	consistent/diagnostic
671	diagnostic/diagnostic

[11] In Table 218, Ligand has 8 CA. As described in the footnote above, the extra patient is patient

Patient #	local/reference pathology readings
691	consistent/consistent
703	diagnostic/diagnostic
721	consistent/diagnostic
743	consistent/diagnostic
671	consistent/consistent
1721	no local pathology; only reference diagnostic

Ligand CA Responders: Qualifying Prior Therapy

The table below lists the Ligand CA responders and the qualify prior therapies.

ca responder patient #	Qualifying prior therapies	basis of qualifying	type of intolerance
691	uvb puva	intolerant refractory	Photoallergy
692	puva ubv	plateau plateau	
695	nitrogen mustard puva	plateau refractory	
702	mtx mtx puva nitrogen mustard	intolerant plateau	pruritus
704	bcnu nitrogen mustard mtx	Plateau Intolerant Intolerant	blistering/pruritus nausea + fatigue

ca responder patient #	Qualifying prior therapies	basis of qualifying	type of intolerance
741	nitrogen mustard puva	Intolerant Intolerant	Increased redness/itching early cataracts
801	nitrogen mustard ebt	refractory intolerant	reached recommended limit
831	nitrogen mustard puva	intolerant plateau	redness, pruritus, severe irritation
841	nitrogen mustard x2 ebt	intolerant intolerant	hives/contact dermatitis radiation changes
1761	mtx nitrogen mustard ebt	plateau plateau plateau	
671	bcnu x 3 nitrogen mustard mtx	refractory plateau refractory	
694	nitrogen mustard puva	intolerant refractory	Allergy
703	nitrogen mustard	refractory-plateau	

[12] PUVA given 1 year before histopathological diagnosis of CTCL was made (hx on surgical path report states CTCL since date of histopath dx)

ca responder patient #	Qualifying prior therapies	basis of qualifying	type of intolerance
	mtx puva[12]	refractory plateau	
721	mtx uvb[13]	Intolerant Refractory	Increased lfts
743	nitrogen mustard uvb/uva[14]	Intolerant Refractory	Increased redness/itching
871	nitrogen mustard ebt	Refractory Plateau	
1711	cytoxan solu-medrol puva	Refractory Refractory Refractory	

The table below illustrates each type of qualifying prior therapy and the number of CA responders refractory, intolerant, or plateau to that type of therapy. Most the qualifying prior therapies were mixtures of types (e.g., refractory + intolerance, intolerance + plateau, refractory and plateau). One patient was refractory to systemic therapy and irradiation therapy; 2 patients were intolerant to topical cytotoxic therapy and irradiation therapy; 2 patients who had disease response plateau had either two irradiation or topical cytotoxic therapy and irradiation therapy.

TYPE OF QUALIFYING PRIOR THERAPY	# OF CA RESPONDERS REFRACTORY	# OF CA RESPONDERS INTOLERANCE	# OF CA RESPONDERS PLATEAU
Radiation	6	4	5
Topical cytotoxic	4	6	6
Systemic	3	2	1

[13] UVB given 5 – 6 months before histopathological diagnosis of CTCL was made
[14] Phototherapy not confined to uvb range and no psoralen was used

Ligand CA Responders: Number of Lesions

The table below shows the number of lesions each of the CA responders had a baseline and the number of lesions evaluated as index lesions. Only patient #1761 did not have the maximum number of lesions treated that were available for study.

PID	NUMBER OF LESIONS @ BASELINE	NUMBER OF LESIONS EVALUATED AS INDEX LESIONS
691	13	5
692	8	5
695	12	5
702	10	5
704	7	5
741	4	4
801	4	4
831	12	5
841	2	2
1761	7	3
671	>= 20	5
694	>= 20	5
703	>= 20	5
721	>= 20	5
743	>= 20	5
871	>= 20	5
1711	>= 20	5

Patients with 20 or more lesions had a 37% response rate (7/19); patients with less than 20 lesions had a response rate of 32% (10/31); 95% CI for difference: -23%, 32%.

Ligand CA Responders: CTCL Stage

The table below shows the CA responders by CTCL stage.

PID	STAGE
691	IA
692	1A
695	IB
702	IA
704	IA

PID	STAGE
741	IA
801	IB
831	IB
841	IA
1761	IB
671	IB
694	IB
703	IA
721	IB
743	IA
871	IA
1711	IA

Stage IA patients had a CA response rate of 40% (10/25); stage IB patients had a CA response rate of 32% (7/22; 95% CI for difference: -19%, 36%). **There were no Stage IIA responders (0 of 2 Stage IIA pts responded) (the label includes Stage IIA in the Indications section).**

Ligand CA Responders: Body Surface Area Involvement

The table below shows the Ligand CA responders with respect to the percent body surface area involved with CTCL.

PID	BSA-% (PATCHES + PLAQUES)
691	2
692	10
695	10
702	5.3
704	0.9
741	3
801	1.5
831	30
841	2
1761	8
671	10
694	12

PID	BSA-% (PATCHES + PLAQUES)
703	2.21
721	67
743	6
871	25
1711	7

Response by CA was trending in favor of patients with less percent body surface area[15] involved with CTCL; BSA < 10%, response: 40% (10/25); BSA ≥ 10%, response: 25% (7/25; 95% CI difference: -14%, 38%).

Ligand CA Responders: Time from Original CTCL Diagnosis to First Treatment

The table below shows the CA responders and time from the original CTCL diagnosis to 1st treatment on study.

PID	Time from original CTCL diagnosis to 1st treatment on study YEARS
691	2.91
692	7.32
695	8.35
702	4.13
704	4.98
741	1.19
801	1.07
831	15.92
841	17.62
1761	22.75
671	12.43
694	3.16
703	5.45
721	0.22
743	5.93
871	9.99
1711	4.2

[15] < 10% and ≥ 10% were used because Stages IA and IIB are determined by that criteria.

For all the patients, the median time from the original diagnosis of CTCL to 1st treatment on study was 6 years. Patients with less than 6 years of CTCL diagnosis had a response rate of 40% (10/25) and patients with a CTCL diagnosis of 6 or more years had a response rate of 28% (7/25; 95% CI for difference: -14%, 38%).

Ligand CA Responders: Geographic Distribution

There were 40 patients accrued to US, 7 patients accrued to European, 2 accrued to Canadian, and 1 accrued to Australian investigator sites. Fifteen CA responders were from the US (38% [15/40]; 95% CI: 23%, 53%) and two CA responders were from foreign sites (Australia and Poland).

Ligand CA Responders: Prior Retinoid Therapy

Seven patients received prior retinoids; 4 of 7 of these patients had an objective response to the prior retinoid. Only 1 of 7 patients had a CA response to targretin gel.

PATIENT #	PRIOR RETINOIDS	RESPONSE TO PRIOR RETINOID	CA RESPONSE TO TARGRETIN GEL
732	targretin oral	SD Relapsed on prior retinoid	no
803	accutane	PD	no
804	accutane	NE	no
1622	soriatone	PR Relapsed on prior retinoid	no
1711	etretinate	PR Relapsed on prior retinoid	yes
1721	tigason	PR Relapsed on prior retinoid	no
1781	retinoide	CR Relapsed on prior retinoid	no

Ligand CA Responders: New Lesions & New Tumors

Fourteen patients[16] developed new lesions (14/50; 28%). Six of these patients were CA responders (#671, #691, #692, #702, #704, & #1761). Four patients[17] developed abnormal lymph nodes (≥ 1 cm diam) (4/50; 8%); one patient (#601) had the lymph node disappear; none of these cases were responders. One patient[18] developed an abnormal cutaneous tumor (1/50; 2%). This information was extracted from CTCLA, AE, LOC, CAPL, CMTL, LNAL, TAL, pathology reports, and monitoring reports.

Chronology of Response Listing

The FDA reviewed the Chronology of Responses According to Composite Assessment (Vol. 1.31; Listing 35).

PATIENT #	LIGAND COMPOSITE ASSESSMENT	FDA REVIEW OF CA LISTINGS
691	CCR	PR (confirmed then relapse x 6 before CCR)
692	CCR	CCR
695	PR	PR
702	PR	PR
704	PR	Relapse at confirmation
741	CCR	CCR
801	PR	PR
831	PR	PR
841	PR	PR
1761	PR	PR
671	PR	PR
694	PR	PR
703	PR	PR
721	PR	PR
743	CCR	CCR
871	PR	PR
1711	PR	PR

[16] 601, 641, 644, 661, 671, 691, 692, 702, 704, 732, 842, 851, 1761, 1781
[17] 601, 632, 701, 711
[18] 711

Based on this assessment, the FDA response rate is 32% (16/50; 95% confidence intervals, 19%, 45%).

Re-Calculation of CA Response

The FDA re-calculated the composite assessment for each of the CA responders. Individual index lesion clinical signs and symptoms were to be graded at each visit according to the scales found in the tables above. A Composite Assessment of Index Lesion Disease Severity will be generated by a summation of the grades for each index lesion erythema, scaling, plaque elevation, hypopigmentation or hyperpigmentation, and area of involvement. The Composite Assessment of Index Lesion Disease Severity grade at baseline were divided into the Composite Assessment of Index Lesion Disease Severity grade at each subsequent study visit to determine the patient's response to treatment. Any ratio of Composite Assessment of Index Lesion Disease Severity grades <1.0 will indicate improvement in disease and a ratio >1.0 will indicate worsening of disease. An improvement or worsening in the Composite Assessment of Index Lesion Disease Severity grade must have been confirmed by two or more consecutive observations over at least four (4) weeks.

PATIENT #	LIGAND COMPOSITE ASSESSMENT	FDA REVIEW OF CA LISTINGS	FDA calculation of CA response
691	CCR	PR (confirmed then relapse x 6 before CCR)	PR
692	CCR	CCR	CCR
695	PR	PR	PR
702	PR	PR	PR
704	PR	Relapse at confirmation	PR
741	CCR	CCR	CCR
801	PR	PR	PR
831	PR	PR	PR
841	PR	PR	NR Calculations OK but no lesion area measurements
1761	PR	PR	PR

PATIENT #	LIGAND COMPOSITE ASSESSMENT	FDA REVIEW OF CA LISTINGS	FDA calculation of CA response
671	PR	PR	PR
694	PR	PR	PR
703	PR	PR	PR
721	PR	PR	PR
743	CCR	CCR	CCR
871	PR	PR	PR
1711	PR	PR	NR Calculations by Ligand did not include pigment grade

Based on this assessment, the FDA response rate is 30% (15/50; 95% confidence intervals, 17%, 43%).

The FDA Efficacy Analysis—The Secondary Endpoints

Secondary Endpoint: Time to Response

The table below illustrates the time to response by FDA re-calculation of CA response. The median time to response was 87.5 days (range: 36 – 154). The median time to CCR (n = 1) was 174 days.

PATIENT #	FDA CA RESPONDERS TIME TO RESPONSE BEST RESPONSE (DAYS)
691[19]	
692	92 174 to CCR
695	56
702	141
704	123
741[20]	

[19] Disqualified response; see CA Responders & Evaluability section.

PATIENT #	FDA CA RESPONDERS TIME TO RESPONSE BEST RESPONSE (DAYS)
801	83
831	36
841	
1761	154
671	50
694	85
703	90
721	110
743[21]	
871	84
1711	

Secondary Endpoint: Duration of Response

The table below illustrates the duration of response by FDA re-calculation of CA response. The median duration of response has not been reached.

PATIENT #	FDA CA RESPONDERS DURATION OF RESPONSE BEST RESPONSE (DAYS)
691[22]	
692	342+ 260+ for CCR

[20] Disqualified response; see CA Responders & Evaluability section.
[21] Disqualified response; see CA Responders & Evaluability section.
[22] Disqualified response; see CA Responders & Evaluability section.

PATIENT #	FDA CA RESPONDERS DURATION OF RESPONSE BEST RESPONSE (DAYS)
695	70+
702	63+
704	53[23]
741[24]	
801	149+
831	337+
841	
1761	182+
671	63+
694	189+
703	259+
721	205
743[25]	
871	63+
1711	

Secondary Endpoint: Area of Index Lesions

To determine the area of index lesions, and then graded as in the table below.

The area of the index lesions was assessed for response. The longest diameter and the longest diameter perpendicular to the diameter of each index lesion were to the nearest millimeter. The lesion areas were the products of these two diameters. A 50% reduction in the area of the index lesions was considered a response if confirmed in 28 days.

PATIENT #	LIGAND COMPOSITE ASSESSMENT	FDA REVIEW OF CA LISTINGS	FDA calculation of CA response	**FDA evaluation of response by area of index lesions**

[23] Duration of response halted with prohibited treatment.
[24] Disqualified response; see CA Responders & Evaluability section.
[25] Disqualified response; see CA Responders & Evaluability section.

PATIENT #	LIGAND COMPOSITE ASSESSMENT	FDA REVIEW OF CA LISTINGS	FDA calculation of CA response	FDA evaluation of response by area of index lesions
691	CCR	PR (confirmed then relapse x 6 before CCR)	PR	PR
692	CCR	CCR	CCR	CCR
695	PR	PR	PR	PR
702	PR	PR	PR	NR
704	PR	Relapse at confirmation	PR	PR
741	CCR	CCR	CCR	CCR
801	PR	PR	PR	PR
831	PR	PR	PR	PR
841	PR	PR	NR Calculations OK but no lesion area measurements	NR not evaluable; no measurements
1761	PR	PR	PR	PR
671	PR	PR	PR	NR no confirmation
694	PR	PR	PR	PR
703	PR	PR	PR	PR
721	PR	PR	PR	PR
743	CCR	CCR	CCR	CCR
871	PR	PR	PR	PR
1711	PR	PR	NR Calculations by Ligand did not include pigment grade	NR

Based on this assessment of index lesion area, the FDA response rate is 26% (13/50; 95% confidence intervals, 14%, 38%).

Secondary Endpoint: Body Surface Area Involvement

The area of the patient's palm was be defined as 1% of that patient's total body surface area. The extent of involvement of disease was determined as multiples of the patient's palm area and expressed as a percentage of that patient's total body surface area at baseline (Day 1), every four weeks thereafter during treatment and at the follow-up visit. Body surface area (BSA) measurements of plaques plus patches were summed. A 50% reduction in the body surface area of CTCL was considered a response if confirmed at least 28 days later. If all the patients are examined the BSA response rate is 34% (16/47).

For the purposes of this review only the CA responders were examined further for BSA response. Response by BSA did not always coincide with the FDA CA response; the timing of the BSA response in comparison to the FDA CA response is indicated when they do not match.

PATIENT #	LIGAND COMPOSITE ASSESSMENT	FDA REVIEW OF CA LISTINGS	FDA calculation of CA response	FDA evaluation of response by area of index lesions	FDA response by BSA
691	CCR	PR (confirmed then relapse x 6 before CCR)	PR	PR	**PR 2 months after FDA CA**
692	CCR	CCR	CCR	CCR	**CCR 2 months after FDA CA**
695	PR	PR	PR	PR	**PR 1 month after FDA CA**
702	PR	PR	PR	NR	**No**
704	PR	Relapse at confirmation	PR	PR	**No**
741	CCR	CCR	CCR	CCR	**CCR**
801	PR	PR	PR	PR	**PR**
831	PR	PR	PR	PR	**No**
841	PR	PR	NR Calculations OK but no lesion area measurements	NR not evaluable; no measurements	**No**
1761	PR	PR	PR	PR	**PR 3 months**

PATIENT #	LIGAND COMPOSITE ASSESSMENT	FDA REVIEW OF CA LISTINGS	FDA calculation of CA response	FDA evaluation of response by area of index lesions	FDA response by BSA
					before FDA CA
671	PR	PR	PR	NR no confirmation	No
694	PR	PR	PR	PR	PR 1 month before FDA CA
703	PR	PR	PR	PR	PR 1 month after FDA CA
721	PR	PR	PR	PR	PR 2 months after FDA CA
743	CCR	CCR	CCR	CCR	PR 1 month after FDA CA
871	PR	PR	PR	PR	PR
1711	PR	PR	NR Calculations by Ligand did not include pigment grade	NR	PR

Based on this assessment, requiring both CA response and BSA response, the FDA response rate is 24% (12/50; 95% confidence intervals, 12%, 36%).

Secondary Endpoint: Photographs

FDA evaluation of photographs

PATIENT #	LIGAND COMPOSITE ASSESSMENT	FDA REVIEW OF CA LISTINGS	FDA REVIEW OF CA LISTINGS	FDA calculation of CA response	FDA evaluation of response by area of index lesions	FDA evaluation of photographs for response
691	CCR	PR (confirmed then relapse x 6 before CCR)	PR (confirmed then relapse x 6 before CCR)	PR	PR	Response
692	CCR	CCR	CCR	CCR	CCR	Response
695	PR	PR	PR	PR	PR	No response
702	PR	PR	PR	PR	NR	Response
704	PR	Relapse at confirmation	Relapse at confirmation	PR	PR	Response
741	CCR	CCR	CCR	CCR	CCR	Response
801	PR	PR	PR	PR	PR	Response
831	PR	PR	PR	PR	PR	Response
841	PR	PR	PR	NR Calculations OK but no lesion area measurements	NR not evaluable; no measurements	Response
1761	PR	PR	PR	PR	PR	Response
671	PR	PR	PR	PR	NR no confirmation	No response
694	PR	PR	PR	PR	PR	No response
703	PR	PR	PR	PR	PR	Response
721	PR	PR	PR	PR	PR	Response
743	CCR	CCR	CCR	CCR	CCR	Response
871	PR	PR	PR	PR	PR	Response
1711	PR	PR	PR	NR Calculations by Ligand did not include pigment grade	NR	Response

Based on this assessment, requiring both CA response and confirmation of CA response , based on photographs, the FDA response rate is 28% (14/50; 95% confidence intervals, 16%, 40%).

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CA Responders & Evaluability

Below is a table illustrating the evaluability problems of CA responders. This information is taken from the FDA Assessment of Study Conduct section of this Review. The basis for non-evaluability in CA responders was: qualify skin biopsy (4), prohibited medication (6), and qualifying prior therapy (4). The impact on the status of the CA responders would be: disqualification of response (3), termination of duration of response (2), and disqualification of patient (5).

PATIENT #	LIGAND COMPOSITE ASSESSMENT	FDA REVIEW OF CA LISTINGS	FDA calculation of CA response	FDA evaluation of response by area of index lesions	FDA evaluation of photographs for response	NON-EVALUABLE CATEGORY
691	CCR	PR (confirmed then relapse x 6 before CCR)	PR	PR	Response	**1. QUALIFYING SKIN BIOPSY—EARLY (-) OR LATE (+) # DAYS: -35 DAYS** **2. PRN Westcort topical since 3 wks prior to entry and continued** **Response started day 57** **RESPONSE DISQUALIFIED**
692	CCR	CCR	CCR	CCR	Response	
695	PR	PR	PR	PR	No response	**Nitrogen mustard given at least 2 months before histopathological diagnosis of CTCL was made** **Other QPTs: PUVA**

PATIENT #	LIGAND COMPOSITE ASSESSMENT	FDA REVIEW OF CA LISTINGS	FDA calculation of CA response	FDA evaluation of response by area of index lesions	FDA evaluation of photographs for response	NON-EVALUABLE CATEGORY
						PATIENT DISQUALIFIED
702	PR	PR	PR	NR	Response	
704	PR	Relapse at confirmation	PR	PR	Response	**1. QUALIFYING SKIN BIOPSY—EARLY(-) OR LATE (+) # DAYS: -33 DAYS** **2. Lidex started about wk 23 for 28 days for pruritus (no pruritus recorded by CA grading and CTCL crossed-out on CRF)** **Response started day 124** **Duration of response terminates on day Lidex started**
741	CCR	CCR	CCR	CCR	Response	**1. QUALIFYING SKIN BIOPSY—EARLY (-) OR LATE (+) # DAYS: -437 DAYS** **2. Synalar topical prescribed 6/10/97 (wk 12) to 6/25/97** **Response started 5/30/97 (day 74)**

PATIENT #	LIGAND COMPOSITE ASSESSMENT	FDA REVIEW OF CA LISTINGS	FDA calculation of CA response	FDA evaluation of response by area of index lesions	FDA evaluation of photographs for response	NON-EVALUABLE CATEGORY
						RESPONSE DISQUALIFIED PATIENT DISQUALIFIED
801	PR	PR	PR	PR	Response	
831	PR	PR	PR	PR	Response	
841	PR	PR	NR Calculations OK but no lesion area measurements	NR not evaluable; no measurements	Response	**Diprosone cream for psoriasis on day 169** **Response at day 63 by CA** **Duration of response should halt on day 169**
1761	PR	PR	PR	PR	Response	
671	PR	PR	PR	NR no confirmation	No response	**1. QUALIFYING SKIN BIOPSY—EARLY (-) OR LATE (+) # DAYS: -83 DAYS** **2. Temovate topical wk 16.1 for new hyperpigmented lesions (CTCL crossed-out)** **response started day 51**
694	PR	PR	PR	PR	No	

PATIENT #	LIGAND COMPOSITE ASSESSMENT	FDA REVIEW OF CA LISTINGS	FDA calculation of CA response	FDA evaluation of response by area of index lesions	FDA evaluation of photographs for response	NON-EVALUABLE CATEGORY
					response	
703	PR	PR	PR	PR	Response	1. **INSUFFICIENT QUALIFYING PRIOR THERAPY: PUVA given 1 YEAR before histopathological diagnosis of CTCL was made** **Other QPTs: nitrogen mustard, MTX**
721	PR	PR	PR	PR	Response	2. **INSUFFICIENT QUALIFYING PRIOR THERAPY: UVB given 5 – 6 months before histopathological diagnosis of CTCL was made** **Other QPTs: MTX** **PATIENT DISQUALIFIED**
743	CCR	CCR	CCR	CCR	Response	1. **INSUFFICIENT QUALIFYING PRIOR THERAPY: Phototherapy: not confined to the UVB range and was not used with a psoralen** **Other QPTs: nitrogen mustard** 2. **Elocon topical prescribed wk 3.7 x 8 days**

PATIENT #	LIGAND COMPOSITE ASSESSMENT	FDA REVIEW OF CA LISTINGS	FDA calculation of CA response	FDA evaluation of response by area of index lesions	FDA evaluation of photographs for response	NON-EVALUABLE CATEGORY
						Triamcinolone topical wk7 x 8 days & wk 10 x 3 days **Indications: irritant interigo and contact dermatitis; no pruritus recorded** **Response started day 50** **RESPONSE DISQUALIFIED**
871	PR	PR	PR	PR	Response	**EBT given 11 months before histopathological diagnosis of CTCL was made (9 months before the 1st clinical manifestation of CTCL)** **Other QPTs: nitrogen mustard** **PATIENT DISQUALIFIED**
1711	PR	PR	NR Calculations by Ligand did not include pigment grade	NR	Response	

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The data in the table below is extracted from the last table. Two patients had their response disqualified because of use of topical steroids (a prohibited drug). Two patients were not eligible because of insufficient qualify prior therapy, i.e., the irradiation therapy had been administered months before the histological diagnosis of CTCL had been made. One patient had the response disqualified and was not eligible because of topical steroid use and the qualifying biopsy was performed over a year before entry on study. Two patients had the duration of their responses terminated because of topical steroid use.

The FDA CA responders (15) minus the 3 disqualified responders = 12. The FDA CA response (- disqualified responders) is 24%; 12/50 (95% CI: 12%; 36%). The evaluable patient denominator is 16 minus 3 (one of three patients had already been deleted from the evaluable patients plus patient #802—a nonresponder); the numerator is 7 minus 2 (one of three patients had already been deleted from the evaluable patients). The FDA evaluable response rate is 39%; 5/13 (95% CI:12%, 65%).

PATIENT #	REASONS FOR DISQUALIFICATION OR CESSATION OF RESPONSE
691	1. QUALIFYING SKIN BIOPSY—EARLY (-) OR LATE (+) # DAYS: -35 DAYS 2. PRN Westcort topical since 3 wks prior to entry and continued Response started day 57 RESPONSE DISQUALIFIED
695	Nitrogen mustard given at least 2 months before histopathological diagnosis of CTCL was made Other QPTs: PUVA

PATIENT #	REASONS FOR DISQUALIFICATION OR CESSATION OF RESPONSE
	PATIENT DISQUALIFIED
741	1. QUALIFYING SKIN BIOPSY— EARLY (-) OR LATE (+) # DAYS: -437 DAYS 2. Synalar topical prescribed 6/10/97 (wk 12) to 6/25/97 Response started 5/30/97 (day 74) RESPONSE DISQUALIFIED PATIENT DISQUALIFIED
721	1. INSUFFICIENT QUALIFYING PRIOR THERAPY: UVB given 5 – 6 months before histopathological diagnosis of CTCL was made Other QPTs: MTX PATIENT DISQUALIFIED
743	1. INSUFFICIENT QUALIFYING PRIOR THERAPY: Phototherapy: not confined to the UVB range and was not used with a psoralen Other QPTs: nitrogen mustard

PATIENT #	REASONS FOR DISQUALIFICATION OR CESSATION OF RESPONSE
	2. Elocon topical prescribed wk 3.7 x 8 days Triamcinolone topical wk7 x 8 days & wk 10 x 3 days Indications: irritant interigo and contact dermatitis; no pruritus recorded Response started day 50 RESPONSE DISQUALIFIED
841	
871	EBT given 11 months before histopathological diagnosis of CTCL was made (9 months before the 1st clinical manifestation of CTCL) Other QPTs: nitrogen mustard PATIENT DISQUALIFIED
704	1. QUALIFYING SKIN BIOPSY—EARLY(-) OR LATE (+) # DAYS: -33 DAYS 2. Lidex started about wk 23 for 28 days for pruritus (no pruritus recorded by CA

PATIENT #	REASONS FOR DISQUALIFICATION OR CESSATION OF RESPONSE
	grading and CTCL crossed-out on CRF) Response started day 124 Duration of response terminates on day Lidex started
841	1. NR by re-calculation of CA Calculations OK but no lesion area measurements 2. Diprosone cream for psoriasis on day 169 RESPONSE DISQUALIFIED
1711	NR by re-calculation of CA Calculations by Ligand did not include pigment grade RESPONSE DISQUALIFIED

CA Responders & QOL Responders

Thirty-seven patients had improvement on QOL question #25 (HOW HAS CTCL CHANGED SINCE STUDY START?); five patients were excluded because an improvement in QOL was recorded only once (i.e., no confirmation). All the CA responders had an improvement in QOL question #25, except patient #671. Thirty-two percent of all the patients had both a CA response and a QOL response on question #25.

Thirty-five patients had improvement on QOL question #26 (LEVEL OF SATISFAC/DISSATISFAC WITH DRUG TREATMENT?); five patients (including two CA responders) were excluded because an improvement in QOL was recorded only once (i.e., no confirmation). All the CA responders had an improvement in QOL question #26, except patients #671 and #702; 30% response rate. Thirty percent of all the patients had both a CA response and a QOL response on question #26.

In the table below "yes" means there was an improvement in QOL that lasted at least 28; "no" means there was no improvement in QOL

PATIENT #	LIGAND COMPOSITE ASSESSMENT	FDA REVIEW OF CA LISTINGS	FDA calculation of CA response	FDA evaluation of response by area of index lesions	FDA evaluation of photographs for response	NON-EVALUABLE CATEGORY	QOL Questions #25 (HOW HAS CTCL CHANGED SINCE STUDY START?)/ #26 (LEVEL OF SATISFAC/DISSATISFAC WITH DRUG TREATMENT?
691	CCR	PR (confirmed then relapse x 6 before CCR)	PR	PR	Response	• QUALIFYING SKIN BIOPSY—EARLY OR LATE# DAYS: 35 DAYS • PRN Westcort topical since 3 wks prior to entry	Yes/yes

PATIENT #	LIGAND COMPOSITE ASSESSMENT	FDA REVIEW OF CA LISTINGS	FDA calculation of CA response	FDA evaluation of response by area of index lesions	FDA evaluation of photographs for response	NON-EVALUABLE CATEGORY	QOL Questions #25 (HOW HAS CTCL CHANGED SINCE STUDY START?)/ #26 (LEVEL OF SATISFAC/DISSATISFAC WITH DRUG TREATMENT?
						Response started day 57	
692	CCR	CCR	CCR	CCR	Response		Yes/yes
695	PR	PR	PR	PR	No response		Yes/yes
702	PR	PR	PR	NR	Response		Yes/no
704	PR	Relapse at confirmation	PR	PR	Response	• QUALIFYING SKIN BIOPSY—EARLY OR LATE# DAYS: 33 DAYS • Lidex started about wk 23 for 28 days for pruritus (no pruritus recorded by CA grading and CTCL crossed-out on CRF) Response started day 124	Yes/yes
741	CCR	CCR	CCR	CCR	Response	• QUALIFYING SKIN BIOPSY—EARLY OR LATE# DAYS: 437 DAYS • Synalar topical prescribed 6/10/97	YES/YES

PATIENT #	LIGAND COMPOSITE ASSESSMENT	FDA REVIEW OF CA LISTINGS	FDA calculation of CA response	FDA evaluation of response by area of index lesions	FDA evaluation of photographs for response	NON-EVALUABLE CATEGORY	QOL Questions #25 (HOW HAS CTCL CHANGED SINCE STUDY START?)/ #26 (LEVEL OF SATISFAC/DISSATISFAC WITH DRUG TREATMENT?
						(wk 12) to 6/25/97 Response started 5/30/97 (day 74)	
801	PR	PR	PR	PR	Response		Yes/yes
831	PR	PR	PR	PR	Response		Yes/yes
841	PR	PR	NR Calculations OK but no lesion area measurements	NR not evaluable; no measurements	Response	Diprosone cream for psoriasis on day 169 Response at day 63 by CA	Yes/yes
1751	PR	PR	PR	PR	Response		Yes/yes
671	PR	PR	PR	NR no confirmation	No response	• QUALIFYING SKIN BIOPSY—EARLY OR LATE# DAYS: 83 DAYS • Temovate topical	NO/NO

PATIENT #	LIGAND COMPOSITE ASSESSMENT	FDA REVIEW OF CA LISTINGS	FDA calculation of CA response	FDA evaluation of response by area of index lesions	FDA evaluation of photographs for response	NON-EVALUABLE CATEGORY	QOL Questions #25 (HOW HAS CTCL CHANGED SINCE STUDY START?)/ #26 (LEVEL OF SATISFAC/DISSATISFAC WITH DRUG TREATMENT?
						wk 16.1 for new hyperpigmented lesions (CTCL crossed-out) response started day 51	
694	PR	PR	PR	PR	No response		Yes/yes
703	PR	PR	PR	PR	Response	• INSUFFICIENT QUALIFYING PRIOR THERAPY: PUVA given 1 YEAR before histopathological diagnosis of CTCL was made	Yes/yes
721	PR	PR	PR	PR	Response	• INSUFFICIENT QUALIFYING PRIOR THERAPY: UVB given 5 – 6 months before histopathological diagnosis of CTCL was made	
743	CCR	CCR	CCR	CCR	Response	• INSUFFICIENT QUALIFYING PRIOR THERAPY: Phototherapy: not confined to the UVB range and	Yes/yes

PATIENT #	LIGAND COMPOSITE ASSESSMENT	FDA REVIEW OF CA LISTINGS	FDA calculation of CA response	FDA evaluation of response by area of index lesions	FDA evaluation of photographs for response	NON-EVALUABLE CATEGORY	QOL Questions #25 (HOW HAS CTCL CHANGED SINCE STUDY START?)/ #26 (LEVEL OF SATISFAC/DISSATISFAC WITH DRUG TREATMENT?
						was not used with a psoralen • Elocon topical prescribed wk 3.7 x 8 days Triamcinolone topical wk7 x 8 days & wk 10 x 3 days Indications: irritant interigo and contact dermatitis; no pruritus recorded Response started day 50	
871	PR	PR	PR	PR	Response	EBT given 11 months before histopathological diagnosis of CTCL was made	Yes/yes
1711	PR	PR	NR	NR	Response		Yes/yes

Summary of the Analyses of Response

The shaded row represents the final FDA response rate.

RESPONSE CRITERIA	RESULTS % (# of responders/50[26]) 95% CI
LIGAND CA INTENT-TO-TREAT	34% (17/50) 21%, 47%
LIGAND CA EVALUABLE	44% (7/16) 19%, 68%
FDA REVIEW OF CA LISTINGS ITT	32% (16/50) 19%, 45%
FDA calculation of CA response[27] ITT	30% (15/50) 17%, 43%
FDA evaluation of response by area of index lesions ITT	26% (13/50) 14%, 38%
FDA response by BSA ITT	24% (12/50) 12%, 36%
FDA evaluation of photographs for response ITT	28% (14/50) 16%, 40%
FDA CA response (minus disqualified responders[28,29]) ITT	24% (12/50) 12%, 36%
FDA response evaluation of evaluable	39% (5/13) 12%, 65%

[26] The number evaluable patients will be much lower.
[27] Patients #841 & #1711 were disqualified as responders because of missing data.
[28] patients #691, #741, & #743 disqualified as responders because of a prohibited medication (i.e., topical steroids)
[29] No patients were disqualified as responders based on photographs although 3 claimed responders could not be confirmed by photographs.

RESPONSE CRITERIA	RESULTS % (# of responders/50[26]) 95% CI
FDA both CA response & QOL: question #25 ITT	32% (16/50) 19%, 45%
FDA both CA response & QOL: question #26 ITT	30% (15/50) 17%, 43%
FDA Median time to CA response ITT Median time to CCR	87.5 days range (36 – 154) 174 days

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FDA assessment of safety

General

The incidence of all adverse events* and application site adverse events with incidence ≥5% for all application frequencies of targretin® gel in the Phase III CTCL Study is shown below.

	All Adverse Events	Application Site Adverse Events
COSTART 5 Body System/Preferred Term	N = 50 n (%)	N = 50 n (%)
Patients with AE	49 (98)	39 (78)
Skin and Appendages		
Contact Dermatitis[1]	7 (14)	4 (8)
Exfoliative Dermatitis	3 (6)	0
Pruritus[2]	18 (36)	9 (18)
Rash[3]	36 (72)	28 (56)
Maculopapular Rash	3 (6)	0
Skin Disorder (NOS)[4]	13 (26)	9 (18)
Sweat	3 (6)	0
Body as a Whole		
Asthenia	3 (6)	0
Headache	7 (14)	0
Infection	9 (18)	0
Pain	15 (30)	9 (18)
Cardiovascular		
Edema	5 (10)	0
Edema Peripheral	3 (6)	0
Hemic and Lymphatic		
Leukopenia	3 (6)	0
Lymphadenopathy	3 (6)	0
WBC Abnormal	3 (6)	0
Metabolic and Nutritional		
Hyperlipemia	5 (10)	0
Nervous		
Paresthesia	3 (6)	3 (6)
Respiratory		
Cough Increased	3 (6)	0
Pharyngitis	3 (6)	0

* Regardless of association with treatment

Includes Investigator Terms Such As:

[1]Contact dermatitis, irritant contact dermatitis, irritant dermatitis

[2]Pruritus, itching, itching of lesion

[3]Erythema, scaling, irritation, redness, rash, dermatitis

[4]Skin inflammation, excoriation, sticky or tacky sensation of skin; NOS = Not Otherwise Specified

Treatment-Limiting Toxicity

Treatment-Limiting Toxicity (TLT) is defined as any treatment-related Grade 3 or higher local dermal irritation as defined in the table.