Durability of Response

Patients Responding		Responding Patients who Relapsed		Durability of Response (Days)[1,2,3,4]				
n	%	n	%	Min	25th pctl	Median	75th pctl	Max
Primary Endpoint Classification[5] (N=50)								
22	44.0	7	31.8	57	105	NE	NE	204
Physician's Global Assessment (N=50)								
19	38.0	4	21.1	57	172	NE	NE	172
Composite Assessment (N=50)								
18	36.0	4	22.2	64	148	NE	NE	204

(1) Durability of Response is defined as (Date of relapse or for non-relapsed patients, date of last available clinical evaluation – Date of response onset + 1).

(2) Median, 25th, and 75th percentiles are obtained from the Kaplan-Meier method.

(3) NE = Not Estimable.

(4) Min and Max is calculated only from patients who relapsed and represents the minimum and maximum time to relapse from the onset of the response.

(5) The Primary Endpoint Classification is defined as a patient being rated as PR or CCR confirmed over at least 4 study weeks, for either PGA or CA, with no disease progression over the preceding or same time period.

Time to Progression

The table below shows the time to progression. The medians for the respective response criteria have not been reached. Ligand's analysis is based on the disease progression being confirmed. Depending on the response criteria used, between 10% and 16% of patients had disease progression.

Time to Onset of Disease Progression (Protocol Defined)

Patients Progressing		Time to Disease Progression (Days)[1,2,3,4]				
N	%	Min	25th pctl	Median	75th pctl	Max
Primary Endpoint Classification[5] (N=50)						
7	14.0	15	NE	NE	NE	87
Physician's Global Assessment (N=50)						
8	16.0	26	NE	NE	NE	248
Composite Assessment (N=50)						
5	10.0	15	NE	NE	NE	85

(1) Time to Disease Progression is defined as (Date of onset of progression - Day 1) + 1.

(2) Median, 25th, and 75th percentiles are obtained from the Kaplan-Meier method.

(3) NE = Not Estimable.

(4) Min and Max is calculated only from patients who have disease progression and represents the minimum and maximum time to disease progression from the start of the study.

(5) The Primary Endpoint Classification is defined as a patient being rated as PR or CCR confirmed over at least 4 study w eks, for either PGA or CA, with no disease progression over the preceding or same time period.

Time to Disease Progression Without Regard to Confirmation

The FDA requested an analysis of time to disease progression based on the first evidence of progressive disease, without regard to confirmation of, in addition to the protocol-defined analysis in which progression of disease was required to be confirmed over at least four study weeks unless the progression occurred at the last available evaluation in the database (see above). The table below shows the time to progression. The medians for the respective response criteria have not been reached. Depending on the response criteria used, between 22% and 30% of patients had disease progression.

Time to Onset of Disease Progression Regardless of Confirmation

Patients Progressing		Time to Disease Progression (Days)[1,2,3,4]				
N	%	Min	25th pctl	Median	75th pctl	Max
Primary Endpoint Classification[5] (N=50)						
15	30.0	14	64	NE	NE	137
Physician's Global Assessment (N=50)						
11	22.0	26	248	NE	NE	248
Composite Assessment (N=50)						
11	22.0	14	NE	NE	NE	137

(1) Time to Disease Progression is defined as (Date of onset of progression - Day 1) + 1.

(2) Median, 25th, and 75th percentiles are obtained from the Kaplan-Meier method.

(3) NE = Not Estimable.

(4) Min and Max is calculated only from patients who have disease progression and represents the minimum and maximum time to disease progression regardless of confirmation from the start of the study.

(5) The Primary Endpoint Classification is defined as a patient being rated as PR or CCR confirmed over at least 4 study weeks, for either PGA or CA, with no disease progression over the preceding or same time period.

Efficacy: Body Surface Area and Area of Index Lesions

Overall Body Surface Area Involvement by CTCL

The body surface area (BSA) of CTCL involvement, as expressed by percentage of the patient's total body surface area, was to be estimated at baseline and every four weeks during study and at follow-up. In addition, BSA of CTCL involvement was measured for some patients at Week 2. The Involved Body Surface Area (BSA) CRF was designed to collect at each of those visits the percentage BSA involved by CTCL patch and the percentage BSA involved by CTCL plaque. The corresponding values for patch and plaque in the database were summed in order to generate the total, overall BSA involvement by CTCL.

The table below presents the overall (patch plus plaque) CTCL-involved body surface area for targretin® gel 1% through 44 or more weeks on study. The column to the right of the study visit shows the number of patients assessed for BSA involvement at the particular study week (a BSA CRF was submitted for that week), regardless of whether or not the patient had BSA involvement. The next column, the number of patients with area, shows the number of patients who had an assessment of BSA involvement excluding those with a value of zero.

Total Overall CTCL-Involved Body Surface Area for Targretin® Gel 1%

Study Visit[2]	No. Pts. With Data at Visit	No. Pts. Assessed	No. Pts. With Area	Total Percentage Body Surface Area Involvement[1]				
				Mean	SE	Min	Median	Max
Day 1	50	47	47	15.8	2.8	0.9	8.0	90.0
Week 2	49	12	12	24.0	8.2	1.5	9.0	90.0
Week 4	49	43	43	16.1	2.9	1.0	10.0	90.0
Week 8	47	44	44	16.7	3.1	1.0	10.0	90.0
Week 12	44	39	39	14.6	2.9	0.3	6.0	72.0
Week 16	39	36	36	14.7	3.3	0.2	6.6	90.0
Week 20	34	32	30	14.5	3.7	0.3	6.3	90.0
Week 24	23	19	19	14.9	5.3	0.2	3.0	90.0
Week 28	21	19	19	14.7	5.2	0.1	2.0	90.0
Week 32	15	14	14	11.5	5.7	0.0	1.5	80.0
Week 36	12	11	11	14.9	7.5	0.5	2.0	85.0
Week 40	11	9	9	6.0	2.6	0.3	1.6	20.0
Week 44	9	7	7	19.6	11.3	0.5	10.0	85.0
Week >44[3]	8	7	6	21.8	13.0	2.0	11.0	85.0

(1) Total Percentage BSA is the sum of CTCL patch and CTCL plaque assessed at each study visit.

(2) Calculated with Study Visit Interval Algorithm. See Section 11.4.2.11.4.

(3) Last value beyond Week 44.

While this reduction in median BSA, as shown in the table above, could be due to the patients with relatively greater BSA dropping out of the study, the change from Baseline over time in the median percentage BSA involvement in the table below indicate otherwise. Note that the statistics for the BSA in this table are based only on the subset of patients who had a quantitation of BSA both at the given post-baseline visit and at baseline, and therefore may vary from study week to study week. The median BSA involvement remained constant through Week 12. Improvement in the median BSA involvement began at Week 16 (-0.4% absolute change) and began to accelerate at Week 32 (-2.6% absolute change), reaching an absolute change of -6.0% at Week >44, indicating that for the diminishing number of patients still on study at each successive week, this group of patients had progressively greater reductions in BSA involvement that persisted through the last assessment available in the database for this report. The improvement in the mean BSA paralleled the change in the median BSA from Week 16 onwards. Of particular note is that by Week 16, improvements of up to 44% were observed and improvements (absolute change) of up to 47% were observed for Week 32 onwards. The improvements shown in the minimum column suggest that some patients with relatively greater BSA did not drop out of the study.

Total Overall CTCL-Involved Body Surface Area Change From Baseline for Targretin® Gel 1%

Study Visit[3]	No. Pts. With Data at Visit	No. Pts. Assessed	No. Pts. With Area	Change[1] in Total Percentage Body Surface Area Involvement[2]					
				N[4]	Mean	SE	Min	Median	Max
Day 1 Baseline[5]	50	47	47	47	15.8	2.8	0.9	8.0	90.0
Week 2	49	12	12	12	0.6	0.5	-2.0	0.0	5.0
Week 4	49	43	43	43	0.2	0.4	-7.0	0.0	10.0
Week 8	47	44	44	44	0.9	0.7	-10.0	0.0	14.0
Week 12	44	39	39	39	1.3	2.0	-13.0	0.0	65.0
Week 16	39	36	36	36	-2.7	1.4	-44.0	-0.4	10.0
Week 20	34	32	30	32	-3.9	1.4	-32.0	-0.8	5.0
Week 24	23	19	19	19	-5.2	2.6	-42.0	-1.0	5.0
Week 28	21	19	19	19	-5.7	2.5	-42.0	-1.4	3.0
Week 32	15	14	14	14	-8.7	3.5	-47.0	-2.6	1.0
Week 36	12	11	11	11	-9.2	4.4	-47.0	-2.7	0.9
Week 40	11	9	9	9	-9.0	5.0	-47.0	-4.0	0.4
Week 44	9	7	7	7	-10.3	6.4	-47.0	-5.0	1.0
Week >44[6]	8	7	6	7	-12.0	6.1	-47.0	-6.0	0.0

(1) A negative change denotes improvement.
(2) Total Percentage BSA is the sum of CTCL patch and CTCL plaque assessed at each study visit.
(3) Calculated with Study Visit Interval Algorithm.
(4) Number of patients with quantitation of BSA at this visit and at Baseline.
(5) Except for Day 1 baseline values, all values reported are the change from baseline values.
(6) Last value beyond Week 44.

Area of Individual Index Lesions

The surface area for index lesions measured at each study visit is summarized for Targretin® gel 1% in **Table 54 in Section 14.2**. The individual index lesion diameters for each patient at each visit may be found in **Listing 34 in Appendix 16.2.6**.

Index Lesion Area Change From Baseline for Targretin® Gel 1%

Study Visit[3]	No. Pts. With Data at Visit	No. Pts. Assessed	No. Pts. With Area	Change[1] in Aggregate Area (cm^2)[2]					
				N[4]	Mean	SE	Min	Median	Max
Day 1 Baseline[5]	50	46	46	46	234.0	90.6	4.7	86.4	4175.0
Week 2	49	41	41	41	5.0	7.0	-207.4	0.0	117.5
Week 4	49	43	42	43	13.1	15.4	-231.0	3.4	443.2
Week 8	47	42	40	42	-7.6	12.9	-302.0	-1.4	161.3
Week 12	44	38	33	38	-41.6	28.0	-890.0	-18.2	234.2
Week 16	39	34	31	34	-84.8	44.4	-1464.5	-30.7	129.4
Week 20	34	30	27	30	-93.1	61.4	-1740.0	-11.1	240.4
Week 24	23	17	14	17	-127.2	106.2	-1803.0	-21.8	102.4
Week 28	21	17	15	17	-33.3	24.6	-301.5	-5.0	85.7
Week 32	15	12	10	12	-62.7	35.2	-303.0	-25.7	67.2
Week 36	12	11	9	11	-45.5	28.1	-215.3	-13.0	78.2
Week 40	11	11	9	11	-90.1	33.1	-305.0	-23.2	10.1
Week 44	9	8	7	8	-73.5	35.8	-241.7	-30.6	29.9
Week >44[6]	8	7	3	7	-144.5	44.8	-310.5	-139.5	-16.8

(1) A negative change denotes improvement.

(2) The sum of all index lesions for all patients assessed at each visit is computed.

(3) Calculated with Study Visit Interval Algorithm.

(4) Number of patients with quantitation of area at this visit and at Baseline.

(5) Except for Day 1 baseline values, all values reported are the change from baseline values.

(6) Last value beyond Week 44.

Data Source: Tables 62 and 219, Section 14.2

Efficacy: Quality of Life

Patient Quality of Life Questionnaires

Two QoL questionnaires were used to evaluate changes in patient well-being: (1) the Spitzer questionnaire, which included six items dealing with the patient's general status and (2) the CTCL-specific questionnaire, which included nine items dealing with the effect of CTCL on the patient's quality of life. These two questionnaires were to be self-administered at baseline and every four weeks during the study. It should be noted that the Spitzer questionnaire is designed for use in hospice patients, who are generally in much later stages of disease than the patients evaluated in this study. Thus, it was anticipated that patients in the current study would score high at Baseline, and would have scores that approached normal. Under these circumstances, it is unlikely that treatment would result in significant improvements in basically normal scores. Further, several of the CTCL-specific scores were designed to validate the Spitzer scores, and were also likely to approach maximal normal values at baseline.

Spitzer Quality of Life Questionnaire

The Spitzer questionnaire consisted of six questions that evaluated changes in general status based on changes in the patients' activity (Question 1), daily living (Question 2), health (Question 3), support (Question 4) and outlook (Question 5). Each of these five questions was scored from 0-2, where 0 indicated the worse response and 2 indicated the best response. A composite of Questions 1-5 was calculated, with a total possible value of 10. Question 6 was recorded on a visual analog scale (VAS) that recorded the patient's perception of their quality of life. Increases in Spitzer item scores represent improvements in QoL and decreases represent deterioration in QoL.

Composite of individual questions change from baseline for completers is shown in the table below. Based on medians, there is no change from baseline in the composite of the individual questions.

General Status Quality of Life Questionnaire (Spitzer Items 1-5): Composite of Individual Questions Change From Baseline for Completers (N=42)

Study Visit[2]	N[3]	Composite of Questions 1 through 5 [1]				
		Mean	SE	Min	Median	Max
Day 1 Baseline[4]	42	9.2	0.18	5	10.0	10
Week 4 Change	42	-0.1	0.14	-3	0.0	2
Week 8 Change	41	0.1	0.18	-2	0.0	4
Week 12 Change	37	-0.1	0.20	-3	0.0	3
Week 16 Change	38	0.0	0.20	-2	0.0	4
Week 20 Change	33	0.5	0.17	-1	0.0	4
Week 24 Change	20	0.5	0.29	-2	0.0	4

Week 28 Change	21	0.6	0.25	-1	0.0	4
Week 32 Change	14	0.6	0.32	0	0.0	4
Week 36 Change	11	0.5	0.41	-1	0.0	4
Week 40 Change	11	0.5	0.41	-1	0.0	4
Week 44 Change	8	0.6	0.42	0	0.0	3
Week >44 Change	8	0.5	0.50	0	0.0	4

(1) Spitzer Items 1 to 5 are on a scale from 0 to 2; Composite has a maximal value of 10. Increases represent improvements in QoL.

(2) Calculated with Study Visit Interval Algorithm.

(3) Number of patients with assessments at Baseline and the specified visit.

(4) Except for Day 1 baseline values, all values reported are the change from baseline.

Question 6 of the Spitzer questionnaire is a visual analogue scale (VAS) that deals with the overall quality of life. The patients' marks to the VAS were converted to millimeter (mm) measurements from the left margin of the VAS box, with a possible range from 0 mm (lowest quality) to 100 mm (highest quality), and entered in the database. Change from baseline for Question 6 for completers is presented in the table below.

At Baseline, the mean score for completers based on Question 6 was 84.3, with a median of 93. The highest score reported was 98 and the lowest 19. Scores decreased after Baseline. For example, at Week 4, the mean change from Baseline was –5.5, at Week 8, –3.3, and at Week 16, - 4.1. The largest mean decrease in score was observed at Week 44 (–10.8), but was based on only 8 patients.

General Status Quality of Life Questionnaire (Spitzer Item 6): Change From Baseline for Completers (N= 42)

Study Visit(2)	N(3)	Spitzer Question 6(1)				
		Mean	SE	Min	Median	Max
Day 1 Baseline(4)	39	84.3	2.63	19	93.0	98
Week 4 Change	36	-5.5	2.55	-52	-4.0	24
Week 8 Change	33	-3.3	2.28	-49	-3.0	29
Week 12 Change	32	-8.5	1.93	-36	-8.0	11
Week 16 Change	34	-4.1	3.06	-49	-2.0	30
Week 20 Change	29	-5.7	2.72	-43	-3.0	37
Week 24 Change	17	-4.9	2.73	-37	-2.0	9
Week 28 Change	20	-8.8	5.29	-90	-4.5	30
Week 32 Change	13	-6.1	2.63	-26	-4.0	8
Week 36 Change	9	-2.2	5.01	-18	-4.0	35
Week 40 Change	10	-4.1	2.81	-21	-3.0	8
Week 44 Change	8	-10.8	2.80	-20	-12.0	-1
Week >44 Change	7	-5.7	2.77	-18	-5.0	4

(1) Question 6 is a visual analog scale on a scale of 0 to 100, where higher scores represent a higher QoL. Decreases represent deteriorations in QoL.
(2) Calculated with Study Visit Interval Algorithm.
(3) Number of patients with assessments at Baseline and the specified visit.
(4) Except for Day 1 baseline values, all values reported are the change from baseline.

Spitzer Questionnaire – Summary

Spitzer questionnaire scores indicate that these CTCL patients had relatively high scores at baseline, leaving little room for improvement. This was not surprising, given that the questionnaire was designed for a generally sicker patient population. There were small changes in individual scores for Questions 1-5 from Baseline to Week 16, while the composite score was unchanged between Baseline and Week 16. However, small improvements were seen in the mean composite score after Week 16.

CTCL-Specific Quality of Life Questionnaire

The first part of the CTCL-Specific QoL questionnaire, Questions 1.a – 1.e, deals with feelings in five categories (overall feelings, physical feelings, emotional feelings, personal life feelings, and feelings about job, respectively). A composite of Questions 1.b –1.e was also used to summarize patients' feelings. Questions 2 and 3 evaluated itchiness and redness/scaling/plaque elevation at the lesion, respectively. Question 4 evaluated satisfaction with general appearance. Questions 5, 6, and 7 evaluated the impact of the disease on work, social activities, and physical activities, respectively. Question 8 evaluated general quality of life and Question 9 evaluated patient satisfaction with treatment.

The table below shows the composite score of feelings (Question 1.b to 1.e) change From baseline for completers. No significant improvement in this CTCL-specific instrument was detected.

CTCL-Specific Patient Questionnaire: Composite Score of Feelings (Question 1.b to 1.e) Change From Baseline for Completers (N = 42)

		Composite Score of Feelings[1]				
Study Visit[2]	N[3]	Mean	SE	Min	Median	Max
Day 1 Baseline[4]	42	32.1	0.89	20	33.5	40
Week 4 Change	42	-0.6	0.82	-11	-1.0	12
Week 8 Change	41	-0.1	0.93	-13	0.0	13
Week 12 Change	37	0.0	0.83	-7	-1.0	12
Week 16 Change	37	-0.4	0.99	-15	0.0	12
Week 20 Change	33	0.1	0.92	-11	0.0	12
Week 24 Change	20	-1.0	1.45	-15	-0.5	12
Week 28 Change	21	-1.2	1.30	-15	-1.0	10

Week 32 Change	14	-3.6	2.23	-25	-4.0	9
Week 36 Change	11	-2.6	2.31	-16	-1.0	12
Week 40 Change	11	-2.1	2.56	-16	-4.0	12
Week 44 Change	8	-2.0	3.12	-20	-1.0	10
Week >44 Change	8	1.5	1.92	-6	-0.5	12

(1) Question 1.b to 1.e are on a scale from 1 to 10 (1 being the very worst and 10 being the very best). Composite has a maximal value of 40. Increases represent improvements in QoL.

(2) Calculated with Study Visit Interval Algorithm.

(3) Number of patients with assessments at Baseline and the specified site.

(4) Except for Day 1 baseline values, all values reported are the change from baseline values.

The table below shows the baseline and changes from baseline: Questions 2 through 7 for completers. No significant improvement in this CTCL-specific instrument was detected. At week 16 there may have been evidence of worsening.

CTCL-Specific Patient Questionnaire: Baseline and Changes from Baseline: Questions 2 through 7 for Completers (N = 42)

	Self-Assessment Mean Values and Approximate Descriptor	
	Baseline Mean Value Descriptor	Week 16 Mean Change from Baseline
Q2 : Itchiness	2.5 (2 = minimal, 3 = mild)	0.1
Q3: Redness, scaling and/or plaque elevation	3.0 (3 = mild, 4 = moderate)	0.2
Q4: Physical appearance with respect to CTCL	2.9 (2 = moderately dissatisfied, 3 = neutral)	0.6
Q5: Work activity interference	1.4 (1 = not at all, 2 = minimally disruptive)	0.2
Q6 : Social activity interference	1.2 (1 = not at all, 2 = minimally disruptive)	0.2
Q7: Physical activity interference	1.3 (1 = not at all, 2 = minimally disruptive)	0.3

Note: Increases indicate deterioration in specified outcome measures.

The table below shows the results of asking patients how their CTCL changed since baseline. Throughout the study patients indicated improvement in their disease status.

CTCL-Specific Patient Questionnaire: Change in CTCL (Q8) Compared to Baseline[1]: Completers (N = 42)

Study Visit[2]	N[3]	Much Worse N (%)	Moderately Worse N (%)	About the Same N (%)	Moderately Improved N (%)	Much Improved N (%)
Week 4	40	3 (7.5)	9 (22.5)	10 (25.0)	16 (40.0)	2 (5.0)
Week 8	40	4 (10.0)	8 (20.0)	5 (12.5)	13 (32.5)	10 (25.0)
Week 12	36	0	6 (16.7)	2 (5.6)	17 (47.2)	11 (30.6)
Week 16	37	1 (2.7)	3 (8.1)	4 (10.8)	15 (40.5)	14 (37.8)
Week 20	33	1 (3.0)	1 (3.0)	7 (21.2)	8 (24.2)	16 (48.5)
Week 24	20	0	0	2 (10.0)	7 (35.0)	11 (55.0)
Week 28	21	0	0	2 (9.5)	7 (33.3)	12 (57.1)
Week 32	14	0	1 (7.1)	2 (14.3)	3 (21.4)	8 (57.1)
Week 36	11	0	0	1 (9.1)	4 (36.4)	6 (54.5)
Week 40	11	0	0	1 (9.1)	3 (27.3)	7 (63.6)
Week 44	8	0	0	0	2 (25.0)	6 (75.0)
Week >44	8	0	0	0	2 (25.0)	6 (75.0)

(1) This question is a comparison to Baseline and was therefore not posed at Baseline.

(2) Calculated with Study Visit Internal Algorithm.

(3) Number of patients with assessments at Baseline and the specified visit.

The table below shows the results of asking patients how about their satisfaction/dissatisfaction with the study-drug.. Throughout the study patients indicated improvement in their satisfaction.

CTCL-Specific Patient Questionnaire: Satisfaction/Dissatisfaction with Study Drug Treatment (Q9) Compared to Baseline[1]: Completers (N = 42)

Study[2] Visit	N[3]	Very Dissatisfied N (%)	Moderately Dissatisfied N (%)	Neutral N (%)	Moderately Satisfied N (%)	Very Satisfied N (%)
Week 4	41	2 (4.9)	4 (9.8)	11 (26.8)	17 (41.5)	7 (17.1)
Week 8	41	1 (2.4)	7 (17.1)	8 (19.5)	15 (36.6)	10 (24.4)
Week 12	36	0	4 (11.1)	6 (16.7)	14 (38.9)	12 (33.3)
Week 16	37	1 (2.7)	3 (8.1)	6 (16.2)	12 (32.4)	15 (40.5)
Week 20	33	0	2 (6.1)	7 (21.2)	10 (30.3)	14 (42.4)
Week 24	20	0	0	4 (20.0)	8 (40.0)	8 (40.0)
Week 28	21	0	0	2 (9.5)	8 (38.1)	11 (52.4)
Week 32	14	0	0	1 (7.1)	5 (35.7)	8 (57.1)
Week 36	11	0	0	0	5 (45.5)	6 (54.5)
Week 40	11	0	0	0	4 (36.4)	7 (63.6)

Week 44	8	0	0	0	1	(12.5)	7	(87.5)
Week >44	8	0	0	0	1	(12.5)	7	(87.5)

(1) This question is a comparison to Baseline and was therefore not posed at Baseline.

(2) Calculated with Study Visit Internal Algorithm.

(3) Number of patients with assessments at Baseline and the specified visit.

Summary of QOL Results

These patients had early-stage CTCL with lesions limited to the skin. Because of the limited extent of their disease, it is not surprising that they had nearly normal QoL scores at baseline. Therefore, a marked improvement in these essentially normal baseline scores was not possible. The results of both questionnaires demonstrated that most scores generally were unchanged at Week 16 or had changed (improved or deteriorated) to a very small extent. There were small improvements in the mean composite Spitzer questionnaire score after Week 16 up to the last assessment after Week 44.

Based on changes in CTCL-specific item scores for Question 8 and Question 9, there were improvements in the patients general CTCL status, based on appearance and all symptoms, and a high degree of satisfaction with treatment. When asked to compare their general CTCL status at Baseline and at Week 16, over 75% of patients were moderately or much improved at Week 16. Similarly, over 70% of patients were moderately or very satisfied with the treatment at Week 16.

Thus, while there were minimal changes in QoL items, this is likely to be due to the high, essentially normal scores seen at baseline. Despite relatively little change seen in most QoL scores, the overwhelming majority of patients reported improvement in their overall CTCL status and were satisfied with treatment.

MEDICAL OFFICER NOTE: The QOL evaluation did not provide the **information the FDA expected. However, Ligand claimed the disease to be worse than their study found, raising the FDA's expectation that this disease would provide valuable QOL information.**

> **"CTCL is a devastating, highly-symptomatic, chronic malignancy characterized by years of deforming symptomatic skin lesions that often culminate in ulceration with secondary infection and visceral tumor invasion. Nearly all patients have symptoms relating to skin lesions, that may itch and cause pain, bleeding, infection, or disfigurement (Vol. 1; p. 60)**

Safety results

Exposure

Eighty-four pe.cent of patients received study-drug for 16 or more weeks. Eight patients received study-drug for less than 16 weeks; five of these patients received study-drug for at least 12 weeks. The median duration of therapy was 165 days. The table for duration of exposure is below.

Duration of Exposure

Duration	Targretin® gel 1% N = 50 n (%)
Duration of Therapy (weeks)[1]	
1-3 Weeks	1 (2)
4-7 Weeks	1 (2)
8-11 Weeks	1 (2)
12-15 Weeks	5 (10)
16-23 Weeks	16 (32)
≥24 Weeks	26 (52)
Duration of Therapy (days)	
N	50
Mean (SE)	199.1 (17.83)
Median	164.5
Range	3 – 687[2]

[1] Duration of therapy (weeks)=(Date of last dose of study medication in the database – Date of first dose of study medication +1) /7.
[2] Patient treated for 687 days was ongoing at the data cut-off date.

Only 44% of the patient achieved QID application of targretin as the maximum dosing frequency.

Maximum Level and Last Level of Drug Exposure by Dose Regimen

Dose frequency	Targretin® gel 1% N = 50	
	Maximum Level n (%)	Last Level n (%)
QOD	1 (2)	6 (12)
QD	2 (4)	10 (20)
BID	9 (18)	12 (24)
TID	16 (32)	11 (22)
QID	22 (44)	11 (22)

The following narrative describes a patient with a high degree of CTCL involvement and a high application of targretin gel.

> Patient #744 had a neutrophil value of 2993/μL at Baseline, and a value that met the criteria as a treatment-emergent abnormal neutrophil count (1494/μL) at Study Day 55 after treatment TID. The plasma bexarotene value at this time was 7.98 ng/mL. This patient had **a 45% BSA involvement and had applied excessive quantities of drug. She had had bexarotene plasma values as high as 54.9 ng/mL** subsequent to this date with no association with abnormal laboratory values. Subsequent assessments of neutrophils at Study Day 97 (neutrophil count 3640/μL, plasma bexarotene values, 21.6 ng/mL) and Study Day 113 (neutrophil count, 2200/μL, plasma bexarotene values 54.9 ng/mL) after treatment TID were within normal limits. The patient had repeat plasma bexarotene concentration values greater than 15 ng/mL, including two samples that had bexarotene levels reaching 47.1 and 54.9 ng/mL. She started applying Targretin® gel TID as soon as Week 4, and used an unusually large number of tubes, as evidenced by 90 tubes being dispensed at her visit to the clinic on Week 16, the study period during which high bexarotene concentrations were observed. All post-dose blood samples collected in this patient had quantifiable bexarotene concentrations, ranging between 1.57 and 54.9 ng/mL (mean = 25.0 ng/mL). The high bexarotene plasma concentration values observed in Patient 181/744 were considered to have been due to the large amounts of Targretin® gel used by this patient.

Treatment-limiting toxicity

Based on the protocol-specified definition, treatment-related local dermal irritations that met the criteria for Grade 3 or Grade 4 events were considered to be TLTs (table below). Grade 3 local dermal irritations (very red, with edema, with or without vesiculation) were to have resulted in a decrease in dose frequency and Grade 4 dermal irritations (deep red, swelling and edema, with or without signs of bullae formation and necrosis) were to have resulted in a 4 week treatment cessation, and re-initiation at a lower frequency. Grades 0, 1 and 2 dermal irritations did not require adjustment of dose frequency, however, application adjustments for lower grade events occurred at the discretion of the investigator.

GRADING OF LOCAL DERMAL IRRITATION

GRADE	DEFINING CLINICAL SIGNS
0 = No Reaction	None
1 = Mild	Definite pink to red coloration
2 = Moderate	Increased redness, possible edema
3 = Severe	Very red, with edema, with or without vesiculation
4 = Very Severe	Deep red, swelling and edema with or without signs of bullae formation and necrosis

Twenty-eight percent of patient had a grade 3 TLT. An additional 34% of patients had TLT recorded but the grades were 1 – 2.

Patients with Local Dermal Irritation Recorded on the TLT CRF

	Targretin® gel 1% N = 50 n (%)
Patients with Any Event Recorded on the TLT CRF	31 (62)
Grade [1]	
Grade 1	5 (10)
Grade 2	12 (24)
Grade 3	14 (28)
Grade 4	0

[1] Summarized by highest grade ever reported by each patient.

The appearance of rash appears to have a dose response with application frequency. The other application site TLTs were infrequent but proportionately increased with frequency of application.

Patients with Local Dermal Irritation Recorded on the TLT CRF (Grade 1, 2 or 3) by Dose Frequency

	Targretin® gel 1% N = 50				
	Dose Frequency				
COSTART 5 Adverse Event	QOD N = 50[1] n (%)	QD N = 49[1] n (%)	BID N = 47[1] n (%)	TID N = 38[1] n (%)	QID N = 22[1] n (%)
Patients with any Event on the TLT CRF[2]	1 (2)	2 (4)	10 (21)	6 (16)	12 (55)
Pain	0 (0)	1 (2)	0	1 (3)	1 (5)
Contact Dermatitis	1 (2)	0 (0)	2 (4)	0	1 (5)
Pruritus	0 (0)	0 (0)	3 (6)	0	0
Rash[3]	0 (0)	3 (6)	8 (17)	4 (11)	9 (41)
Rash Maculopapular	0 (0)	0 (0)	0	0	1 (5)
Skin Disorder NOS	1 (2)	0 (0)	1 (2)	2 (5)	1 (5)
Ulcer Skin	0 (0)	0 (0)	0	0	1 (5)

[1] Number based on patients who ever received specified dose frequency
[2] Patients with multiple occurrences of the same event are summarized by dose regimen at the time of the first occurrence.
[3] One patient, who had rash, had no dose frequency reported at the time of the event and is not included in this table.

Grade 3 TLTs occurred in 14% of patients as rash and appeared to have a dose response with frequency of application of targretin. Grade 3 TLTs were infrequent in other categories of toxicities.

Patients with Grade 3 TLTs by Dose Regimen

	Targretin® gel 1% N = 50				
	Dose Frequency				
COSTART 5 Adverse Event	QOD N = 50[1] n (%)[2]	QD N = 49[1] n (%)[2]	BID N = 47[1] n (%)[2]	TID N = 38[1] n (%)[2]	QID N = 22[1] n (%)[2]
Patients with any Grade 3 TLT	0	0	6 (13)	3 (8)	5 (23)
Pain	0	0	0	0	1 (5)
Dermatitis Contact	0	0	1 (2)	0	0
Pruritus	0	0	2 (4)	0	0
Rash	0	0	4 (9)	2 (5)	3 (14)
Rash Maculopapular	0	0	0	0	1 (5)
Skin Disorder NOS	0	0	0	1 (3)	0
Ulcer Skin	0	0	0	0	1 (5)

(1) Number based on patients who ever received specified dose
(2) Patients with multiple occurrences of the same event are summarized by dose regimen at the time of the first occurrence

Adverse Events

Ninety-eight percent of patients had an adverse event. Seventy-eight percent of the patients had an adverse event at the application site. Only one patient had a severe adverse event. Fourteen percent of the patients withdrew from the study because of an adverse event. The table below summarizes this information.

Summary of Adverse Events

Patients with Adverse Events	Targretin® gel 1% N = 50 n (%)
Patients with	
Any AE	49 (98)
Any Application Site AE	39 (78)
Any Related AE	46 (92)
Any Severe AE	1 (2)
Any Moderately Severe AE	12 (24)
Any SAE	1 (2)
Any Related SAE	0
Patients Who Withdrew Due to AE[1]	7 (14)
Patients who Died	1 (2)

(1) Patients who withdrew from the study and had the primary reason for withdrawal identified as an AE.

The most common adverse events reported to be possibly, probably or definitely related to targretin topical gel therapy included irritation, erythema, scale, pruritus and folliculitis. Patients developed rash (72%), pruritus (36%), contact dermatitis (14%), and rash/maculopapular (6%). Patients developed also pain (30%), infection (18%), headache (14%), hyperlipidemia (10%),

Adverse Events with an Incidence of at Least 5%

COSTART 5 Body System/Preferred Term	Targretin® gel 1% N = 50 n (%)
Patients with Any AE	49 (98)
Body as a Whole	30 (60)
Asthenia	3 (6)
Headache	7 (14)
Infection	9 (18)
Pain	15 (30)
Cardiovascular	12 (24)
Edema	5 (10)
Edema Peripheral	3 (6)
Hemic and Lymphatic	10 (20)
Leukopenia	3 (6)
Lymphadenopathy	3 (6)
WBC Abnormal	3 (6)
Metabolic and Nutritional	9 (18)
Hyperlipemia	5 (10)
Nervous	9 (18)
Paresthesia	3 (6)
Respiratory	8 (16)
Cough Increased	3 (6)
Pharyngitis	3 (6)
Skin and Appendages	46 (92)
Contact Dermatitis	7 (14)
Dermatitis Exfoliation	3 (6)
Pruritus	18 (36)
Rash	36 (72)
Rash Maculo Papular	3 (6)
Skin Disorder (NOS)	13 (26)
Sweat	3 (6)

At the application site, patients developed rash (56%), pruritus (18%), pain (18%), contact dermatitis (8%), and paresthesia (6%).

Application Site AEs with an Incidence of at Least 5%

COSTART 5 Body System/Preferred Term	Targretin® gel 1% N = 50 n (%)
Any Application Site AE	39 (78)
Body As a Whole	12 (24)
Pain	9 (18)
Nervous	3 (6)
Paresthesia	3 (6)
Skin and Appendages	36 (72)
Contact Dermatitis	4 (8)
Pruritus	9 (18)
Rash	28 (56)
Skin Disorder (NOS)	9 (18)

The non-application site adverse events included: rash (28%), infection (16%), headache (14%), pain (12%), pruritus (10%), and hyperlipidemia (10%).

Non-Application Site AEs with an Incidence of at Least 5%

COSTART 5 Body System/Preferred Term	Targretin® gel 1% N = 50 n (%)
Any Application Site AE	41 (82)
Body As a Whole	23 (46)
Asthenia	3 (6)
Headache	7 (14)
Infection	8 (16)
Pain	6 (12)
Cardiovascular	9 (18)
Edema	5 (10)
Edema Peripheral	3 (6)
Hemic and Lymphatic	10 (20)
Leukopenia	3 (6)
Lymphadenopathy	3 (6)
WBC Abnormal	3 (6)
Metabolic and Nutritional	9 (18)
Hyperlipemia	5 (10)
Respiratory	8 (16)
Cough Increased	3 (6)
Pharyngitis	3 (6)
Skin and Appendages	24 (48)
Contact Dermatitis	3 (6)
Pruritus	5 (10)
Rash	14 (28)
Skin Disorder (NOS)	6 (12)
Sweat	3 (6)

Moderately severe application site adverse events were rash (8%) and pruritus (4%). Non-application site adverse events were below 5% except for rash (10%).

Incidence of Moderately Severe Application Site and Non-Application Site Adverse Events

COSTART 5 Body System/Preferred Term	Targretin® gel 1% N = 50	
	Moderately Severe Application Site Aes n (%)	Moderately Severe Non-Application Site AEs n (%)
Any Moderately Severe AE	5 (10)	9 (18)
Body	0	2 (4)
Headache	0	1 (2)
Pain	0	1 (2)
Metabolic and Nutritional	0	1 (2)
LDH increased	0	1 (2)
Respiratory	0	1 (2)
Laryngitis	0	1 (2)
Skin and Appendages	5 (10)	7 (14)
Contact Dermatitis	0	1 (2)
Pruritus	2 (4)	1 (2)
Rash	4 (8)	5 (10)
Rash Maculo Papular	0	1 (2)

Safety Conclusions

The analysis of safety data revealed that Targretin® gel 1% was generally well tolerated in the study over median treatment duration of 164.5 days (23.5 weeks) with a range of 3 days to 687 days (98 weeks).

One of the objectives of this study was to evaluate the tolerability of Targretin® gel 1%. All patients were initially treated with Targretin® gel 1% QOD, and the frequency of treatment was escalated at one week intervals sequentially to QD, BID, TID and QID. The frequency of application could be decreased by the patient or the investigator if a toxicity occurred. All patients except one escalated above the initial QOD treatment frequency. There were 22 patients (44%) who reached the maximum QID treatment regimen and another 16 patients (32%) who reached the TID treatment regimen.

There were no deaths during treatment or within 4 weeks of the cessation of treatment. One patient died of small cell carcinoma of the lung 51 days after treatment; this event was categorized as not related to study medication. There were no treatment-related serious AEs. One patient had a serious AE (hospitalization for tachycardia) during the study. This event was not related to study medication, and the patient continued treatment with study medication.

Treatment-limiting toxicities (TLTs) were evaluated as AEs of special interest. There were 14 patients (28%) with a treatment-limiting toxicity, defined as a Grade 3 or above treatment-related local dermal irritation. No Grade 4 events were reported. Most frequently, TLTs started during the QID dose regimen. There was no association between the occurrence of TLTs and plasma bexarotene concentrations. Most patients with these events were successfully managed with dose frequency adjustments. Only two patients (4%) withdrew from the study in association with a TLT.

The majority of patients (49 patients, 98%) in this study experienced at least one treatment-emergent AE, and at least one treatment-related AE (46 patients, 92%). Although AEs and related AEs were common, most were mild to moderate in intensity, and did not lead to withdrawal from the study. Moderately severe and severe AEs related to study medication occurred in 10 patients (20%). However, as was true with TLTs, there was no indication that patients with moderately severe or severe related AEs had unusually high plasma bexarotene levels.

Overall, the most common AEs were rash (36 patients, 72%), pruritus (18 patients, 36%), pain, primarily a burning sensation at the application site, (15 patients, 30%), skin disorder NOS (13 patients, 26%), infection, primarily upper respiratory infections, (9 patients, 18%), headache (7 patients, 14%) and contact dermatitis (7 patients, 14%). The majority of AEs were related to study medication. The most common treatment-related AEs were rash (36 patients, 72%), pruritus (16 patients, 32%), pain (11 patients, 22%), and skin disorder NOS (8 patients, 16%). The majority of AEs and AEs related to study medication were mild to moderate in severity. There were no clinically significant systemic AEs.

The majority of patients who experienced an AE continued in the study; only seven (14%) withdrew due to an AE prior to the data cut-off date. The majority of these patients withdrew for mild to moderately severe rash related to study medication.

There were few notable laboratory abnormalities. Five patients had treatment-emergent low lymphocyte counts (<1000/μL). However, most of these patients had low normal counts at Baseline, and none required treatment or had any clinical consequence. No patient withdrew from the study for a treatment-emergent laboratory abnormality or a laboratory abnormality reported as an AE. A review of other laboratory data, vital sign data and physical exam findings did not reveal any safety concerns in these patients.

In conclusion, the primary AEs related to study medication with Targretin® gel 1% were mild to moderate rash, pruritus, pain and skin disorder. The majority of these events were related to study medication. Generally, these events were without sequelae, and patients who experienced these events were able to maintain the assigned dose regimen or continue in the study with dose frequency modifications. Relatively few of these events led to discontinuation from the study. There were no treatment-related serious AEs or deaths. A review of laboratory, vital sign and physical exam findings did not raise any additional safety concerns.

Drug Discontinuations

Only 14% of patients withdrew from the study due to an adverse event. Ten percent of patients withdrew consent.

Primary Reason for Withdrawal from Study Prior to Data Cut-off Date

	Targretin® gel 1% N = 50 n (%)
Did Not Withdraw Prior to Data Cut-off Date	22 (44)
Withdrew Prior to Data Cut-off Date	28 (56)
Primary Reason[1]	
CTCL Disease Status	
Progressive Disease	5 (10)
Stable Disease	5 (10)
Partial Response	4 (8)
Clinical Complete Response	1 (2)
Adverse Event	7 (14)
Withdrew Consent	5 (10)
Death	0
Noncompliance	0
Lost to Follow-up	1 (2)
Administrative	0

[1] Each patient had one primary reason for discontinuation.

APPEARS THIS WAY
ON ORIGINAL

FDA Assessment of Study -25

FDA assessment of study conduct

Number of patients: accrued and evaluable

In the last version of the protocol (1/8/98), the plan was to accrue up to a total of 72 patients to provide for a total of 60 evaluable patients. The Intent-to-Treat (ITT) population for efficacy was defined as those patients who were enrolled and dispensed at least one dose of targretin® gel. The "evaluable" patient population was to be comprised of patients who: satisfied all inclusion criteria and did not satisfy any exclusion criteria (regardless of whether waivers were granted) except for the inclusion criterion regarding use of antihistamines or antipruritics; have histopathology either diagnostic of, or consistent with, CTCL by the local pathologist and at least one independent reference dermatopathologist; and have been treated for at least eight weeks with targretin® gel (defined for the purposes of analysis as ≥ 52 days).

A total of 34 (68%) patients from the ITT population did not satisfy all of the above - protocol-specified evaluable patient criteria, and so the evaluable patient population was comprised of the remaining 16 patients. According to Ligand's analysis, the reasons for exclusion from evaluable patients were: receiving prohibited medication (25 patients), skin biopsy early or late (18 patients), did not meet other inclusion/exclusion criteria (3 patients), had not been treated for at least 8 weeks (2 patients), insufficient pathological confirmation (1 patient), and insufficient qualifying therapy (1 patient). Many patients were excluded for more than one reason.

This is different than what the FDA believed they would receive in the NDA—i.e., 50 evaluable patients out of 60 to 70 intent-to-treat patients. Since this was a single arm trial, without a control arm, it is more difficult to determine the clinical relevance of the evaluability problems and protocol deviations cited in the table and narratives below.

Below is a table that lists the patients with evaluability problems. The shaded rows are CA responders according to Ligand. "Xs" derived from Ligand's Listing 30: Patients excluded from evaluable patient population. Narrative provided by FDA if information available. **Bolded inserts were added by FDA.**

	PROHIBITED DRUG[4]	INSUFFICIENT PATHOLOGIC CONFIRMATION	QUALIFYING SKIN BIOPSY—EARLY OR LATE# DAYS	*DID NOT MEET OTHER INCLUSION/EXCLUSION CRITERIA	HAVE NOT BEEN TREATED FOR AT LEAST 8 WEEKS	INSUFFICIENT QUALIFYING PRIOR THERAPY
601	X During a lapse in Targretin application. patient applied triamcinolone 0.1% to an area of irritation	biopsy performed 10/21/97 reference dematopathologist report dated 4/14/97 CRF: patient enrolled and started on study 2/98 (protocol :current biopsy within 30 days prior to entry on study) 2/5/98 biopsy no reference dermatopathology review.	X 104 days			**PUVA given 7 years (1988) before histopathological diagnosis of CTCL was made (1995)** **Other QPTs: nitrogen mustard**
621	X		X			X PUVA but no second qualifying therapy
622	**Pramosone & triamcilone topicals prescribed on 7/30/97 (wk 10)**		X 45 days			
631		**Ligand acknowledges protocol violation; biopsies done 1993 & 1994 (and these slides not**	X 1225 days		X	

[4] 5.5. Prohibitions and Restrictions: during the study, the following therapies are prohibited and may not be administered to patients being treated on this protocol: topical medications (such as corticosteroids or tar baths.

	PROHIBITED DRUG[4]	INSUFFICIENT PATHOLOGIC CONFIRMATION	QUALIFYING SKIN BIOPSY—EARLY OR LATE# DAYS	DID NOT MEET OTHER INCLUSION/EXCLUSION CRITERIA	HAVE NOT BEEN TREATED FOR AT LEAST 8 WEEKS	INSUFFICIENT QUALIFYING PRIOR THERAPY
		sent to reference dermatopathologist)				
632	X		X			
641	X Pramosone and Triamcinolone on Study Day 73					
661	X					
671	X Temovate topical wk 16.1 for new hyperpigmented lesions (CTCL crossed-out) Response started day 51		X 83 days			
691	X PRN Westcort topical since 3 wks prior to entry Response started day 57		X 35 days			
693					X	
695			X			Nitrogen mustard

	PROHIBITED DRUG[4]	INSUFFICIENT PATHOLOGIC CONFIRMATION	QUALIFYING SKIN BIOPSY—EARLY OR LATE# DAYS	DID NOT MEET OTHER INCLUSION/EXCLUSION CRITERIA	HAVE NOT BEEN TREATED FOR AT LEAST 8 WEEKS	INSUFFICIENT QUALIFYING PRIOR THERAPY
						given at least 2 months before histopathological diagnosis of CTCL was made Other QPTs: PUVA
701	X		X 49 days	X		
702	X					
703						PUVA given 1 year before histopathological diagnosis of CTCL was made (hx on surgical path report states CTCL since date of histopath dx) Other QPTs: nitrogen mustard, MTX
704	X+ Lidex started about wk 23 for 28 days for pruritus (no pruritus recorded by CA		X 33 days			

	PROHIBITED DRUG[4]	INSUFFICIENT PATHOLOGIC CONFIRMATION	QUALIFYING SKIN BIOPSY—EARLY OR LATE# DAYS	DID NOT MEET OTHER INCLUSION/EXCLUSION CRITERIA	HAVE NOT BEEN TREATED FOR AT LEAST 8 WEEKS	INSUFFICIENT QUALIFYING PRIOR THERAPY
	grading and CTCL crossed-out on CRF) Response started day 124 Duration of response terminates on day Lidex started					
711			X			
						UVB given 5 – 6 months before histopathological diagnosis of CTCL was made Only one QPT
731				X Age 13 years old		PUVA given 2 months before histopathological diagnosis of CTCL was made Only one QPT
732[5]	X		X 144 days	X Stage IIB		

[5] Received local radiation treatment received during the study.

	PROHIBITED DRUG[4]	INSUFFICIENT PATHOLOGIC CONFIRMATION	QUALIFYING SKIN BIOPSY—EARLY OR LATE# DAYS	DID NOT MEET OTHER INCLUSION/EXCLUSION CRITERIA	HAVE NOT BEEN TREATED FOR AT LEAST 8 WEEKS	INSUFFICIENT QUALIFYING PRIOR THERAPY
				Oral retinoid within 3 mos. Prior to study Psoralen plus UVA or UVB therapy within three weeks prior to study entry		
741	X Synalar topical prescribed 6/10/97 (wk 12) to 6/25/97 Response started 5/30/97 (day 74)		X 437 days			
742	X					
743	X Elocon topical prescribed wk 3.7 x 8 days Triamcinolone topical wk7 x 8 days & wk 10 x 3 days Indications irritant intertrigo					**Phototherapy: not confined to the UVB range and was not used with a psoralen**

	PROHIBITED DRUG[4]	INSUFFICIENT PATHOLOGIC CONFIRMATION	QUALIFYING SKIN BIOPSY—EARLY OR LATE# DAYS	DID NOT MEET OTHER INCLUSION/EXCLUSION CRITERIA	HAVE NOT BEEN TREATED FOR AT LEAST 8 WEEKS	INSUFFICIENT QUALIFYING PRIOR THERAPY
	and contact dermatitis; no pruritus recorded Response started day 50					
744	X					
802						**UVB given 6 - 11 years (1984 – 1989) before histopathological diagnosis of CTCL was made (1995)** **Other QPTs: nitrogen mustard**
803	X					
805	X		**982 days**			
811	X		X 31 days			
831	X					
832		X Specimen not sent to reference dermatopathologist ; local reading: "may represent" not consistent with CTCL	X			
841	tX Diprosone cream for psoriasis on		X			

	PROHIBITED DRUG[4]	INSUFFICIENT PATHOLOGIC CONFIRMATION	QUALIFYING SKIN BIOPSY—EARLY OR LATE# DAYS	DID NOT MEET OTHER INCLUSION/EXCLUSION CRITERIA	HAVE NOT BEEN TREATED FOR AT LEAST 8 WEEKS	INSUFFICIENT QUALIFYING PRIOR THERAPY
	day 169 Response at day 63 by CA Duration of response should halt on day 169					
851	X		X 60 days			
871						EBT given 11 months before histopathological diagnosis of CTCL was made Other QPTs: nitrogen mustard
891	X					
1621	X Biafine for erythema starting on Study Day 76 for 38 days					
1622	X					
1711			X			
1721						X Systemic retinoid (tigason/etretinate) PUVA
	X					

Thirty-seven patients (74%) were not evaluable patients for the following reasons: received prohibited medication, skin biopsy early or late, did not meet other inclusion/exclusion criteria , had not been treated for at least 8 weeks, insufficient pathological confirmation, and insufficient qualifying therapy. Twelve of the 38 patients were CA responders. The table below illustrates the number patients and the reasons for non-evaluability (as extracted from the table above); the column to the right is Ligand's analysis. According to the FDA analysis, only 26% of the 50 patients provided in this pivotal trial are evaluable. It is remarkable that seven patients appear to have received a qualifying prior therapy (i.e., irradiation) before the 1st histological diagnosis of CTCL was made in the patient.

REASON NON-EVALUABLE	FDA ANALYSIS # OF PATIENTS (%)	LIGAND'S ANALYSIS # OF PATIENTS (%)
prohibited medication	26 (52%)	25 (50%)
insufficient pathological confirmation	3 (6%)	1 (2%)
skin biopsy early or late	19 (38%)	18 (36%)
did not meet other inclusion/exclusion criteria	3 (6%)	3 (6%)
had not been treated for at least 8 weeks	2 (4%)	2 (4%)
insufficient qualifying therapy	6 (12%)	1 (2%)
TOTAL # OF PATIENTS WITH AT LEAST ONE OF ABOVE CRITERIA	37[6] (74%)	34 (68%)
# CA RESPONDERS not evaluable	12	10

Prohibited topical medications were the most common reason for non-evaluablity. Most of the prohibited topical medications received by patients were corticosteroids which could be expected to have some anti-CTCL activity and could potentially influence the evaluation of some of the efficacy endpoints in this study. Some suppression of local inflammation and itching would likewise be predicted.

According to the protocol (Prohibitions and Restrictions section), topical corticosteroids were prohibited during study and may not be administered to patients being treated on this protocol. The prescription of topical corticosteroids disqualified or decreased the duration of the response.

[6] Patient #703 was not disqualified because of receipt of PUVA one year before the histopathological diagnosis of CTCL was made; there were two other QPTs.

Photographs

The five (5) designated index lesions were to be serially photographed. On Day 1 (baseline), every four (4) weeks thereafter for the duration of treatment, and again at the follow-up visit, these five index lesions were be photographed. Global photographs (half-body fields, anterior and posterior) of each patient's CTCL disease were to be obtained on Day 1 (baseline), every four (4) weeks during treatment and again at the patient's follow-up visit. All index lesion and global areas, which were photographed at baseline, must have been re-photographed every four (4) weeks, even if the lesions have cleared, until the patient completed the follow-up study visit.

Ligand Pharmaceuticals Inc. was to provide or the use of a standardized photographic system, film, processing and development along with detailed instructions and training. Each area being photographed will be photographed with the patient in a consistent pose and with a technique using a consistent combination of camera, film, light, angle and distance from the patient.

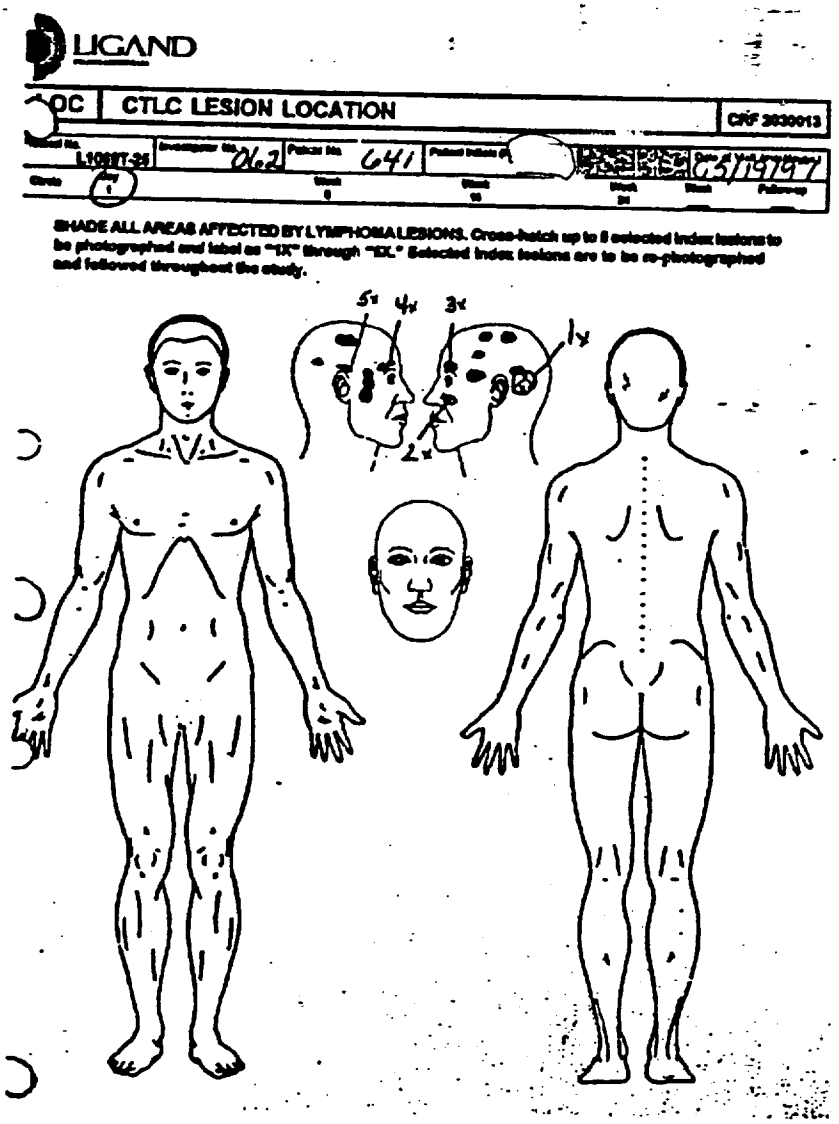
There were two problems with the photographs as submitted to the NDA:

First, the procedures for the taking of the photographs submitted in the NDA was different than described in the protocol. Instead of global photographs, as described above, wider-view photographs of the index lesions were submitted. There was no amendment to the protocol, indicating this change and there was ample opportunity to make that change (Versions of Protocol: OCT 7, 1996, NOV 25, 1996, FEB 25, 1997, 08 APR 97, 30 JULY 1997, and 8 JAN 1998). Because there were no global photographs, FDA is unable to assess the status of other lesions that the patient may have treated and the Physician's Global Assessment.

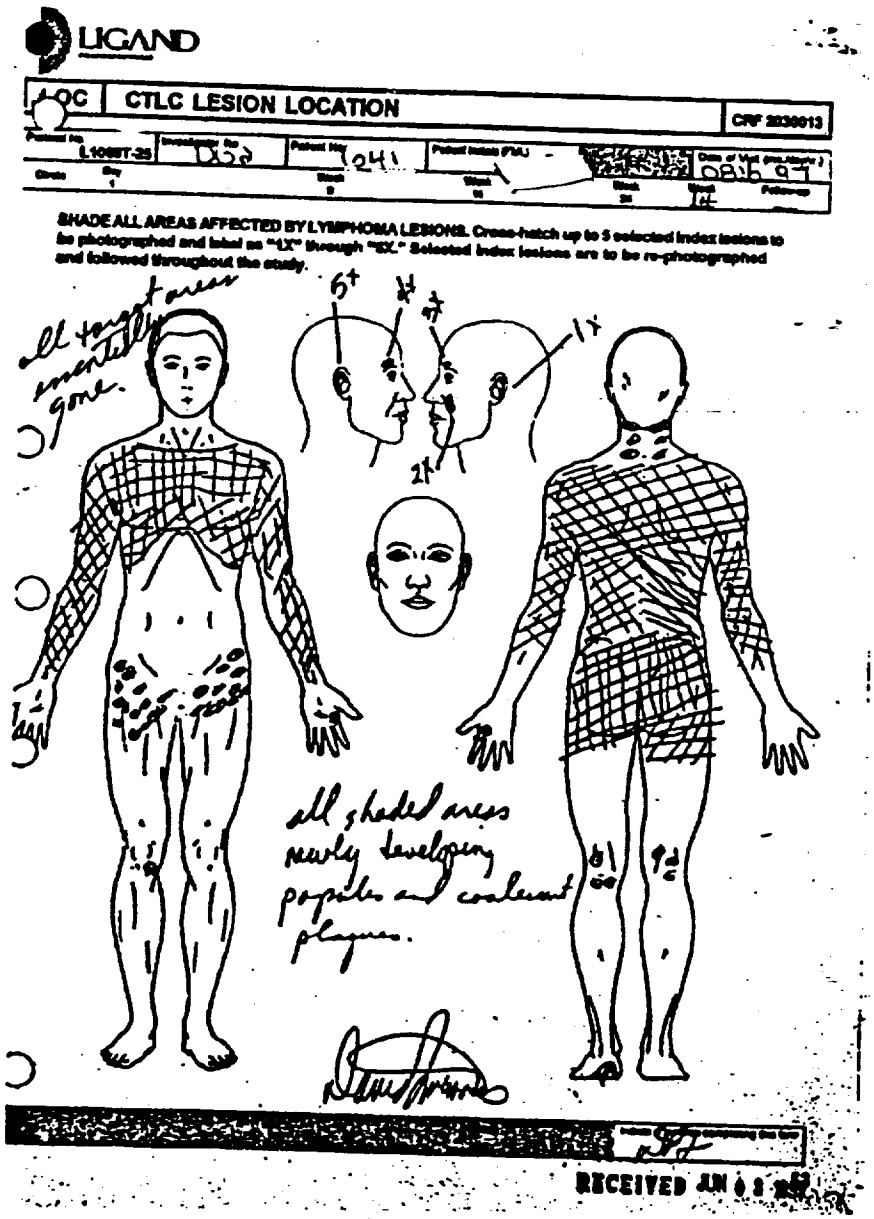
The following are examples of what information global photographs may have provided is demonstrated by serial examination of the CTCL lesion location diagrams.

Evaluation of non-index lesions and new lesions.

Below is the lesion locator diagram for patient #6[illegible]1. Note that there were only lesions on the head at baseline.



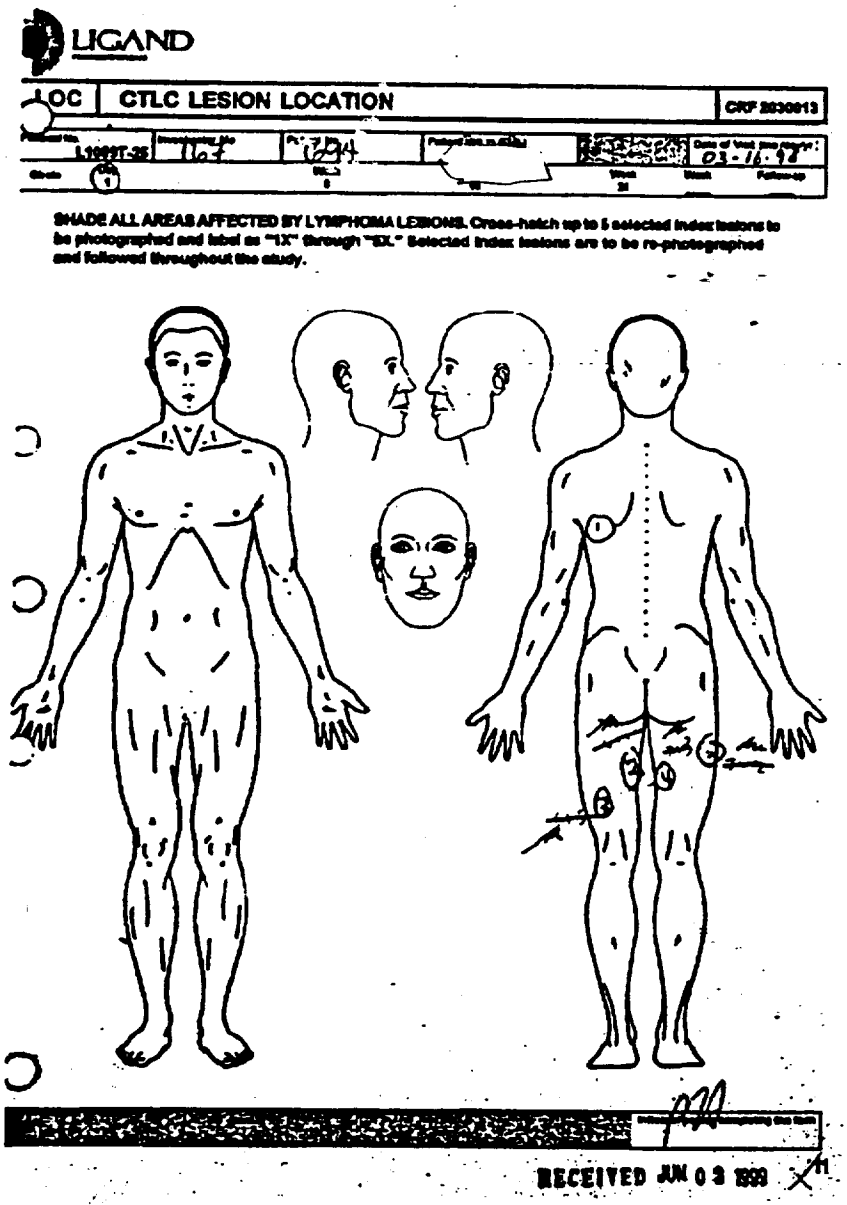
Patient #641 at a time point when by PGA the patient was scored a PR and by CA a PR. New lesions were developing at a time when the index lesions were responding. There were no further evaluations by PGA or CA for this patient; it is unknown if new lesions were treated with targretin.



Anatomical recognition of the area treated

For patient #694 only indicator lesions were mapped at baseline. The medical officer thought the lesions were mislabeled @ week 24 (see second diagram below). According to Ms. P. Murphy (FDA DSI auditor) who visited the investigator site, new lesions were chosen as indicator lesions and followed when the prior indicator lesions had cleared.

+



LIGAND

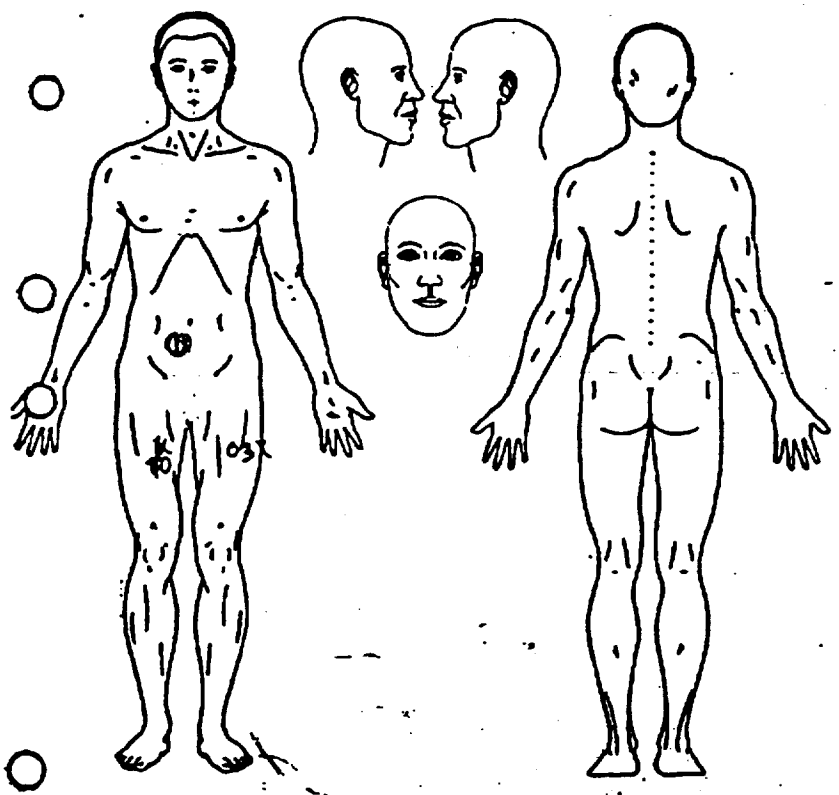
CTLC LESION LOCATION

CRF 2030913

Protocol No. L1069T-35 | Investigator No. 767 | Patient No. 691 | Patient Initials | Date of Visit/Procedure (dd/mm/yy) 10/01/96

Circle: Day 1 | Week 8 | Week 16 | Baseline | Follow-up

SHADE ALL AREAS AFFECTED BY LYMPHOMA LESIONS. Cross-hatch up to 6 selected index lesions to be photographed and label as "1X" through "6X." Selected index lesions are to be re-photographed and followed throughout the study.

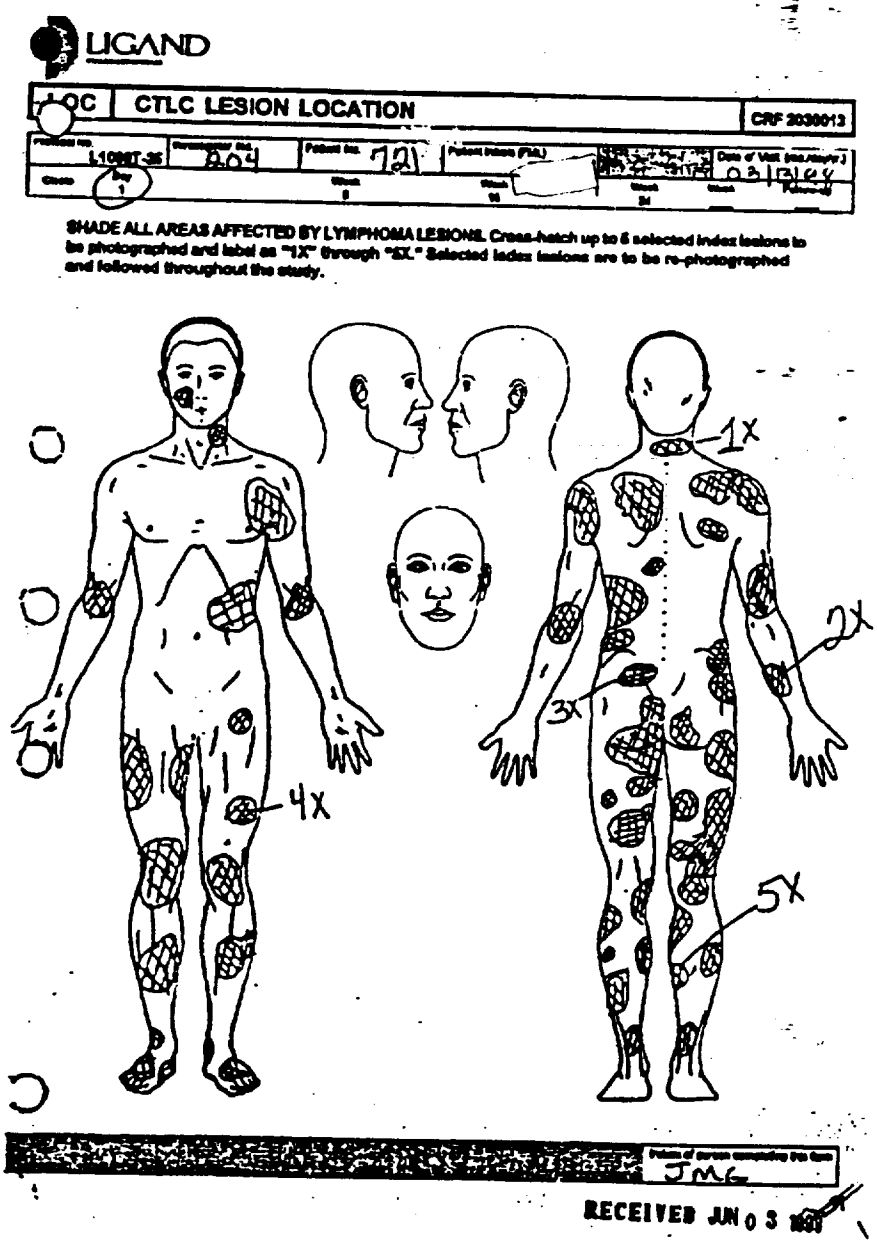


Printed Name of Person Completing this Form

RECEIVED JAN 13 1998

Consistency and Reliability

Patient #721 ...y PGA and CA. It appears what the evaluator drew on CRF was consistent with what was recorded by PGA and CA. This was an example of consistency and reliability.



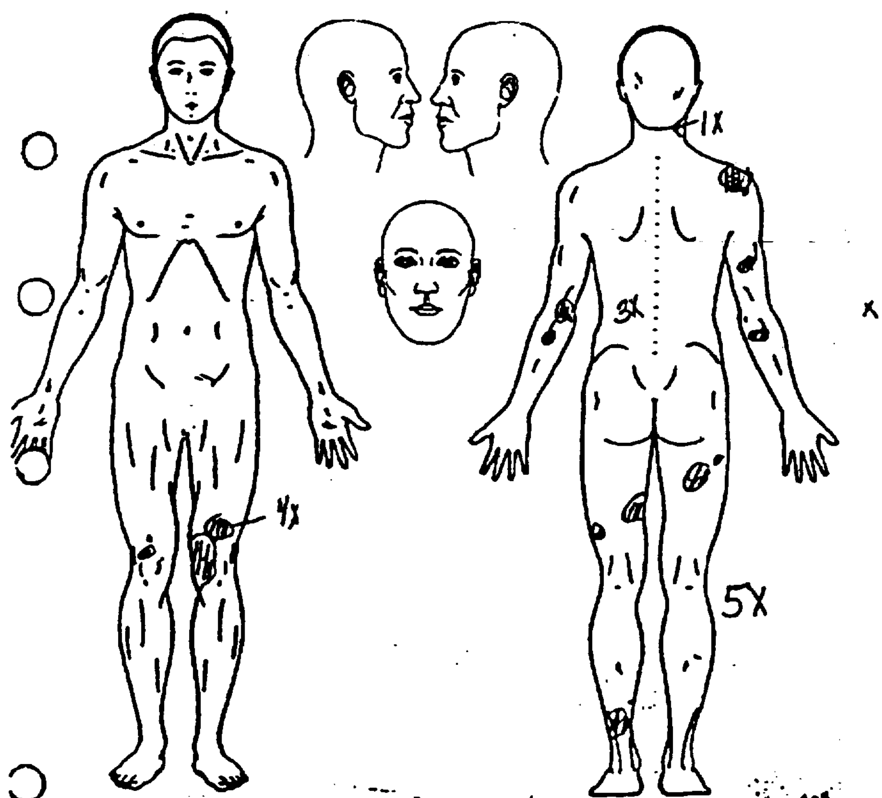
LIGAND

C	CTLC LESION LOCATION	CRF 3030313

Protocol No. L1069T-25	Investigator No. 204	Patient No. 221	Patient Initials [illegible]	Date 8/23/95

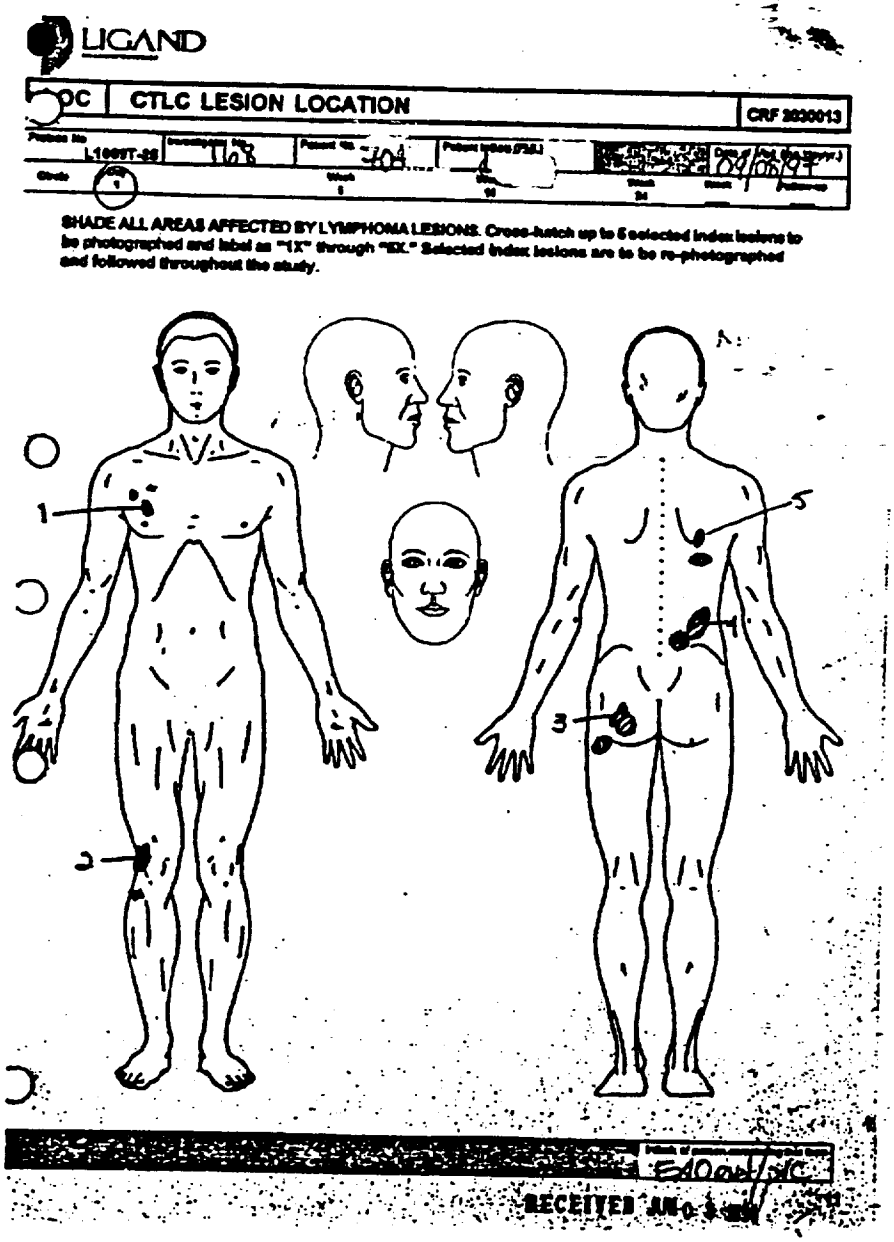
Circle	Day 1	Week 8	Week 16	Week 24	Week	Follow-up

SHADE ALL AREAS AFFECTED BY LYMPHOMA LESIONS. Cross-hatch up to 5 selected index lesions to be photographed and label as "1X" through "5X." Selected index lesions are to be re-photographed and followed throughout the study.



[redacted] Initials of person completing this form JJH

Patient #704 was scored SD by PGA and PR by CA. It appears what the evaluator drew on CRF was not consistent with what was seen on PGA. The patient had a total of 7 lesions.

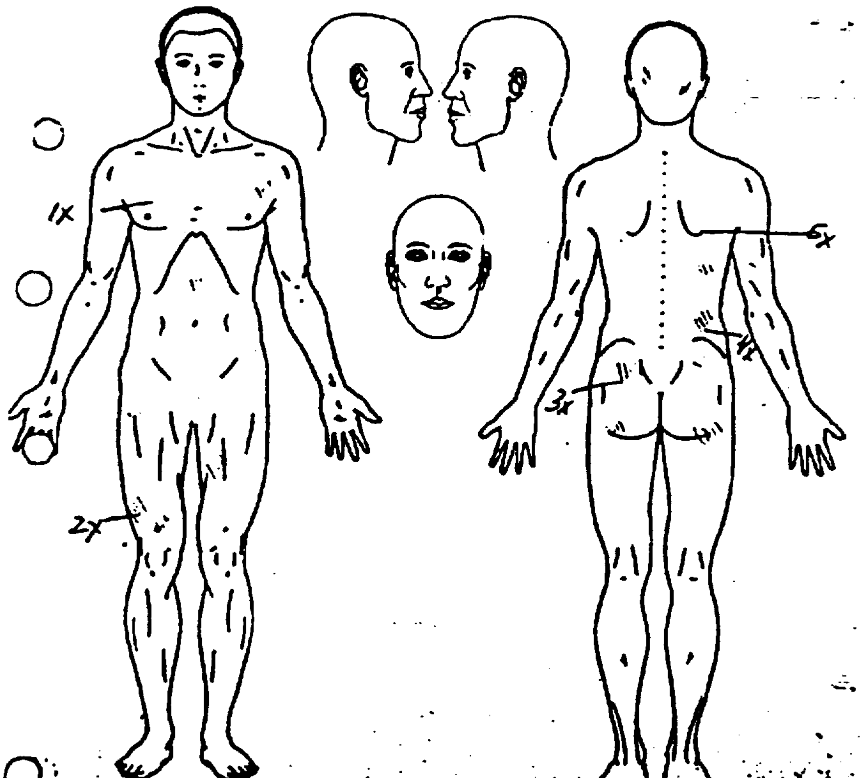


LIGAND

QC	CTLC LESION LOCATION	CRF 2030013

Protocol No.	Investigator No.	Patient No.	Patient Initials (F.M.L.)		Date of Visit (mo./day/yr.)
L1069T-25	161	704			12/21/26
Circle:	Day 1			Week 24	Visit / Follow-up

SHADE ALL AREAS AFFECTED BY LYMPHOMA LESIONS. Cross-hatch up to 5 selected index lesions to be photographed and label as "1X" through "5X." Selected index lesions are to be re-photographed and followed throughout the study.



Initials of person completing this form: [illegible]

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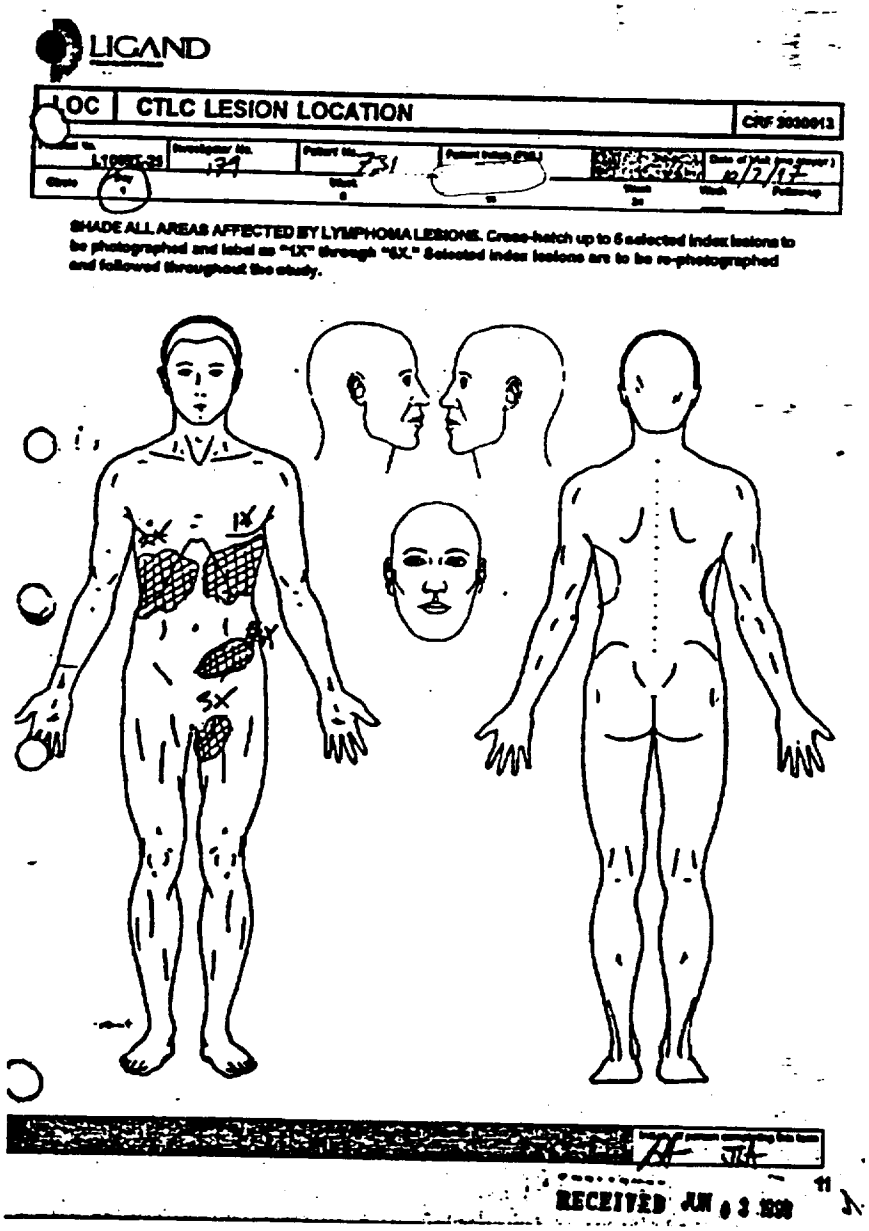
Patient #731: PR by PGA and SD by CA. It appears what the evaluator drew on CRF was not consistent with what was calculated by CA. The patient had a total of 4 lesions.

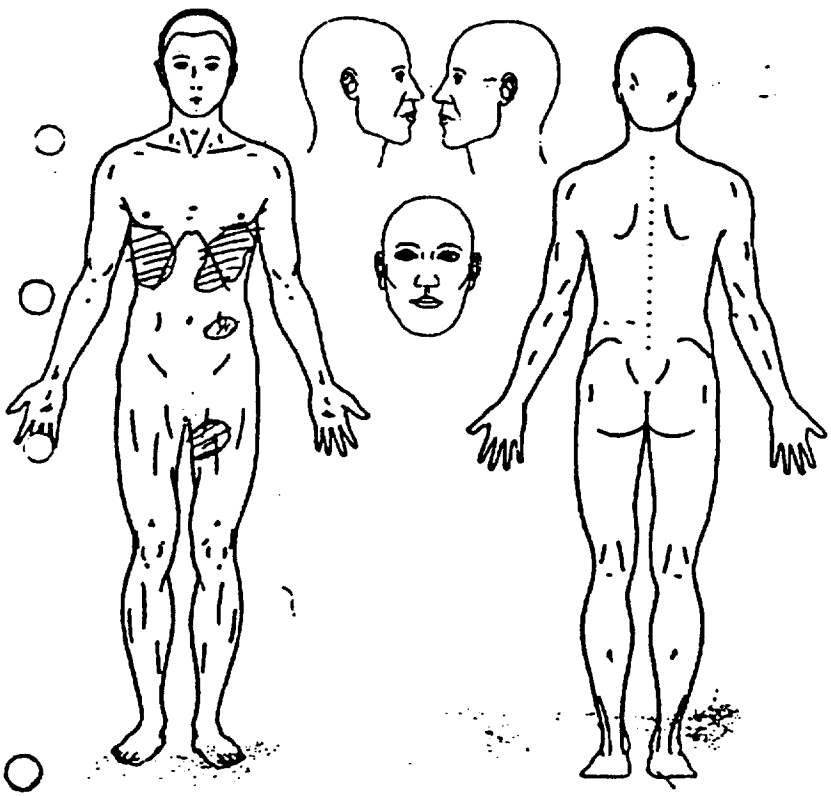


LIGAND

LOC	CTLC LESION LOCATION	CRF 2030913

L1069T-25

SHADE ALL AREAS AFFECTED BY LYMPHOMA LESIONS. Cross-hatch up to 6 selected index lesions to be photographed and label as "1X" through "6X." Selected index lesions are to be re-photographed and followed throughout the study.



RECEIVED JUN 0 3 1995

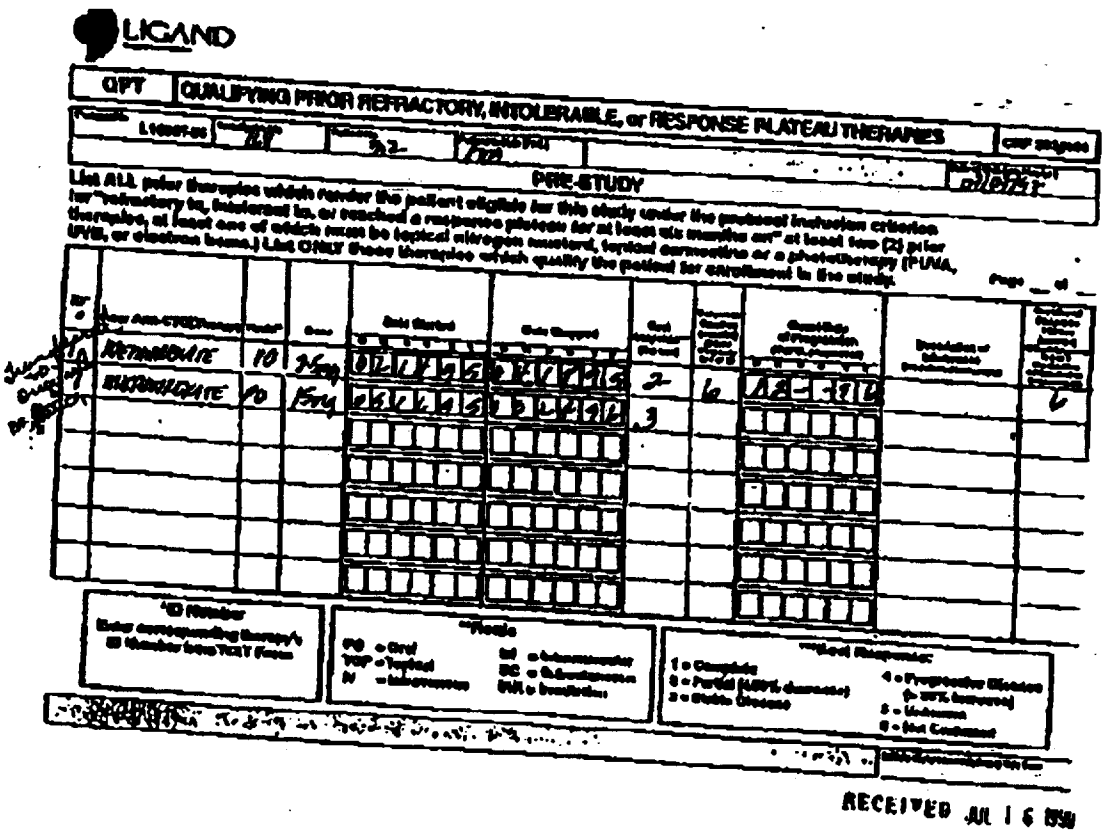
Second, among the 17 composite assessment responders claimed by Ligand from Study - 25, 11 patients had photographs missing or the wrong area was photographed (as indicated on the hard-copies of the photographs: "Shift in Target Area Photographed"). In the case of investigator site #167, when an index lesion regressed, the investigator followed a different lesion (this is according to the DSI audit of this site). It is not known whether this was an isolated practice or whether other investigators also shifted to a different lesion.

APPEARS THIS WAY
ON ORIGINAL

Electronic Discrepancies

The electronic version of the CRF in some instances was not complete or did not match other areas of the electronic CRF or other parts of the NDA where identical information was to be recorded.

For example, the electronic version of the QPT for patient #702 is shown below. Based on the information on this form, the patient has insufficient qualifying prior therapy and is not eligible for the study. No TCLT was submitted in the electronic version of the CRFs. The FDA requested the TCLT from Ligand.



Below is a copy of the TCLT for this patient (sent by Ligand 5/12/2000). According to Listing 14 in the NDA, this patient's qualifying therapies were PUVA and topical nitrogen mustard; the ACCESS database has similar information; the TCLT has similar information. The basis for qualification for study was intolerance (pruritus) and plateau,

respectively. This information was not recorded on the electronic QPT form.

0019

LIGAND

COPY

TCLT | PREVIOUS CUTANEOUS T-CELL LYMPHOMA THERAPY | CRF 2030073

Protocol No. L1058T-25 | Investigator No. 142 | Screen No. 17[illegible]38 | Patient Initials (First, Last) | Date of Visit (mm/dd/yy) 07/07/97

PRE-STUDY

PRIOR CUTANEOUS T-CELL LYMPHOMA SYSTEMIC AGENTS/THERAPIES ☒ YES (list all) ☐ NO

ID #	ANTI-CTCL SYSTEMIC AGENTS/THERAPIES (List most recent first)	Total # of cycles administered (if applicable)	Duration of Therapy (weeks)	**Limits to Therapy (list one if applicable)	*Best Response (list one)	Relapsed? Complete only if Best Response is 1, 2 or 3 — Yes / No / Unknown
1	METHOTREXATE	NAP	44-54	3	2	☒ ☐ ☐
2			5 Weeks			☐ ☐ ☐
3						☐ ☐ ☐
4						☐ ☐ ☐
5						☐ ☐ ☐

PRIOR CUTANEOUS T-CELL LYMPHOMA TOPICAL/LOCAL AGENTS/THERAPIES ☒ YES (list all) ☒ NO

ID #	ANTI-CTCL TOPICAL THERAPIES (List most recent first)	AREA TREATED: % BSA	AREA TREATED: # of Lesions Treated	Frequency of Therapy	Duration of Therapy (weeks)	**Limits to Therapy (list one if applicable)	*Best Response (list one)	Relapsed? Complete only if Best Response is 1, 2 or 3 — Yes / No / Unknown
6	PUVA Emol			Tiw	4		2	☐ ☐ ☐
7	PUVA K5 7/11/97			Biw	8		1	☒ ☐ ☐
8	PUVA			Qw	20	3	3	☒ ☐ ☐
9	Nitrogen Mustaid	100	UNK	Biw	62	3	2	☒ ☐ ☐
10								☐ ☐ ☐

PRIOR CUTANEOUS T-CELL LYMPHOMA IRRADIATION THERAPIES ☒ YES (list all) ☒ NO

ID #	ANTI-CTCL IRRADIATION THERAPIES (List most recent first)	AREA TREATED: % BSA	AREA TREATED: # of Rads	# of Treatments	Duration of Therapy (weeks)	**Limits to Therapy (list one if applicable)	*Best Response (list one)	Relapsed? Complete only if Best Response is 1, 2 or 3 — Yes / No / Unknown
11	PUVA	100	UNK	46-93	82	2	2 1	☒ ☐ ☐
12				15 Weeks	42 3/97		5 3/97	☐ ☐ ☐
13								☐ ☐ ☐
14								☐ ☐ ☐
15								☐ ☐ ☐

**Limits to Therapy
1 = Refractory to therapy
2 = Intolerant to therapy
3 = Response plateau (no further improvement) after at least 6 months on therapy

* Best Response:
1 = Complete
2 = Partial (≥50% decrease)
3 = Stable Disease
4 = Progressive Disease (> 25% increase)
5 = Unknown
6 = Not Evaluated

Initials of person completing this form: [illegible]

5A