Table 51 CTCL-Specific Patient Questionnaire: Composite Score of Feelings (Question 1.b to 1.e) Change From Baseline

(N=63)

Initial Assigned Dose ($mg/m^2/day$)	Study Visit	Composite Score of Feelings					
		No. Pts.	Mean	SE	Min	Median	Max
300	Day 1 Baseline	35	28.1	1.3	11	30	40
	Week 4 Change	34	1.5	1.1	-16	1	22
	Week 8 Change	35	0.8	0.9	-12	0	19
	Week 12 Change	32	0.4	1.2	-15	0	22
	Week 16 Change	28	-0.8	1.5	-17	0	17
	Week 20 Change	21	-1.0	1.3	-10	0	12
	Week 24 Change	13	1.5	1.6	-11	1	10
	Week 28 Change	11	-0.9	1.1	-6	-2	6
	Week 32 Change	11	0.3	1.0	-5	0	6
	Week 36 Change	8	-0.1	2.3	-13	1	8
	Week 40 Change	7	-0.7	1.3	-5	0	5
	Week 44 Change	5	0.2	0.9	-2	1	2
	Week 48 Change	3	-2.3	0.9	-4	-2	-1
>300	Day 1 Baseline	26	27.9	1.6	14	30	40
	Week 4 Change	25	0.5	1.2	-19	0	16
	Week 8 Change	25	-0.7	1.6	-19	0	13
	Week 12 Change	24	-1.5	1.4	-24	-1	11
	Week 16 Change	23	0.7	1.4	-10	0	15
	Week 20 Change	19	1.7	1.7	-15	0	16
	Week 24 Change	16	2.8	1.7	-6	1	16
	Week 28 Change	17	2.6	1.6	-8	1	16
	Week 32 Change	11	4.1	2.4	-5	0	16
	Week 36 Change	10	-0.5	2.3	-10	-2	14
	Week 40 Change	9	0.0	3.0	-12	-1	15
	Week 44 Change	10	3.5	2.9	-9	1	17
	Week 48 Change	8	4.8	3.2	-8	4	16
	Week 52 Change	8	2.5	2.9	-7	0	13
	Week 56 Change	4	7.0	5.1	-3	6	19
	Week ≥60 Change	3	-7.0	4.0	-15	-4	-2

CTCL-specific Questions 2 - 7 investigated changes in itchiness at the skin lesion (Q2); redness, scaling, and/or plaque elevations (Q3); satisfaction with physical appearance (Q4); CTCL interference with normal work activities (Q5); CTCL interference with normal social activities (Q6); and CTCL interference with normal physical activities (Q7) Marginal improvement, was seen in these measures among completers from baseline to Week 16. The same degree of improvement was noted in the >300 $mg/m^2/day$ initial dose group. The patients' self-assessment of their change in CTCL as compared to baseline, taking into account the appearance and all symptoms related to CTCL (Q8), was graded on a five-point scale of 1 (much worse) to 5 (much improved). **Table 52A** shows

the completers patients' assessment of how their CTCL has changed as compared to before participation in the study. For the 300 mg/m^2/day initial dose group from Week 4 until Week 32, at least 73% of patients assessed themselves as either moderately improved or much improved, including 79% at Week 16 (38% rating themselves much improved and 41% rating themselves moderately improved), with a peak of 91% at Week 28. For the >300 mg/m^2/day initial dose group, an even greater percentage of patients rated themselves as moderately or much improved, including at least 75% from Week 4 through the end of the study, including 82% at Week 16, and peaking at 100% at Weeks 32, 40, 44, and 52 (N=6 to 11 patients).

The patients' overall level of satisfaction or dissatisfaction with the drug treatment in this study (Q9) was self-assessed on a five-point scale of 1 (very dissatisfied) to 5 (very satisfied). **Table 52B** shows the completers patients' assessment of their level of satisfaction/dissatisfaction with study drug treatment. For the 300 mg/m^2/day initial dose group from Week 4 until Week 32, at least 72% of patients assessed themselves as either moderately satisfied or very satisfied, including 72% at Week 16 (38% rating themselves very satisfied and 34% rating themselves moderately satisfied), with a peak of 85% at Week 24 (N=13). For the >300 mg/m^2/day initial dose group, a similar percentage of patients rated themselves as moderately or much improved, including at least 71% from Week 4 to Week 60, including 91% at Week 16, peaking at 100% at Weeks 32, 40, 44, and 52 (N=6 to 11 patients).

Table 52A CTCL-Specific Patient Questionnaire: Change in CTCL (Question 8) Compared to Baseline for Completers (N=63)

Initial Assigned Dose ($mg/m^2/day$)	Study Visit	Total No. Pts.	Much Worse N (%)	Moderately Worse N (%)	About the Same N (%)	Moderately Improved N (%)	Much Improved N (%)
300	Week 4	35	1 (2.9)	2 (5.7)	6 (17.1)	16 (45.7)	10 (28.6)
	Week 8	35	0 (0.0)	2 (5.7)	3 (8.6)	21 (60.0)	9 (25.7)
	Week 12	33	0 (0.0)	3 (9.1)	6 (18.2)	14 (42.4)	10 (30.3)
	Week 16	29	1 (3.4)	1 (3.4)	4 (13.8)	12 (41.4)	11 (37.9)
	Week 20	21	1 (4.8)	2 (9.5)	2 (9.5)	9 (42.9)	7 (33.3)
	Week 24	13	0 (0.0)	0 (0.0)	2 (15.4)	3 (23.1)	8 (61.5)
	Week 28	11	0 (0.0)	0 (0.0)	1 (9.1)	5 (45.5)	5 (45.5)
	Week 32	11	0 (0.0)	1 (9.1)	3 (27.3)	1 (9.1)	6 (54.5)
	Week 36	8	0 (0.0)	0 (0.0)	3 (37.5)	1 (12.5)	4 (50.0)
	Week 40	7	0 (0.0)	1 (14.3)	2 (28.6)	1 (14.3)	3 (42.9)
	Week 44	5	0 (0.0)	0 (0.0)	0 (0.0)	2 (40.0)	3 (60.0)
	Week 48	3	0 (0.0)	0 (0.0)	1 (33.3)	1 (33.3)	1 (33.3)
>300	Week 4	24	0 (0.0)	1 (4.2)	5 (20.8)	11 (45.8)	7 (29.2)
	Week 8	26	1 (3.8)	0 (0.0)	5 (19.2)	11 (42.3)	9 (34.6)
	Week 12	24	0 (0.0)	1 (4.2)	2 (8.3)	12 (50.0)	9 (37.5)
	Week 16	22	0 (0.0)	1 (4.5)	3 (13.6)	9 (40.9)	9 (40.9)
	Week 20	19	0 (0.0)	0 (0.0)	2 (10.5)	10 (52.6)	7 (36.8)
	Week 24	16	0 (0.0)	0 (0.0)	1 (6.3)	6 (37.5)	9 (56.3)
	Week 28	16	0 (0.0)	0 (0.0)	1 (6.3)	4 (25.0)	11 (68.8)
	Week 32	11	0 (0.0)	0 (0.0)	0 (0.0)	3 (27.3)	8 (72.7)
	Week 36	10	0 (0.0)	0 (0.0)	1 (10.0)	3 (30.0)	6 (60.0)
	Week 40	9	0 (0.0)	0 (0.0)	0 (0.0)	2 (22.2)	7 (77.8)
	Week 44	10	0 (0.0)	0 (0.0)	0 (0.0)	3 (30.0)	7 (70.0)
	Week 48	8	0 (0.0)	0 (0.0)	2 (25.0)	0 (0.0)	6 (75.0)
	Week 52	6	0 (0.0)	0 (0.0)	0 (0.0)	2 (33.3)	4 (66.7)
	Week 56	4	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	3 (75.0)
	Week≥60	3	1 (33.3)	0 (0.0)	0 (0.0)	1 (33.3)	1 (33.3)

Table 52B CTCL-Specific Patient Questionnaire: Satisfaction/Dissatisfaction with Study Drug Treatment (Question 9) Compared to Baseline for Completers (N=63)

Initial Assigned Dose ($mg/m^2/day$)	Study Visit	No. Pts.	Very Dissatisfied N (%)	Moderately Dissatisfied N (%)	Neutral N (%)	Moderately Satisfied N (%)	Very Satisfied N (%)
300	Week 4	34	1 (2.9)	2 (5.9)	5 (14.7)	12	14 (41.2)
	Week 8	34	0 (0.0)	1 (2.9)	4 (11.8)	(35.3)	9 (26.5)
	Week 12	33	0 (0.0)	1 (3.0)	5 (15.2)	20	10 (30.3)
	Week 16	29	1 (3.4)	2 (6.9)	5 (17.2)	(58.8)	11 (37.9)
	Week 20	21	0 (0.0)	2 (9.5)	2 (9.5)	17	8 (38.1)
	Week 24	13	0 (0.0)	0 (0.0)	2 (15.4)	(51.5)	5 (38.5)
	Week 28	11	0 (0.0)	0 (0.0)	2 (18.2)	10	4 (36.4)
	Week 32	11	0 (0.0)	1 (9.1)	2 (18.2)	(34.5)	6 (54.5)
	Week 36	8	0 (0.0)	0 (0.0)	2 (25.0)	9 (42.9)	4 (50.0)
	Week 40	7	0 (0.0)	1 (14.3)	1 (14.3)	6 (46.2)	3 (42.9)
	Week 44	5	0 (0.0)	0 (0.0)	1 (20.0)	5 (45.5)	3 (60.0)
	Week 48	3	0 (0.0)	0 (0.0)	2 (66.7)	2 (18.2)	1 (33.3)
						2 (25.0)	
						2 (28.6)	
						1 (20.0)	
						0 (0.0)	
>300	Week 4	24	0 (0.0)	0 (0.0)	7 (29.2)	9 (37.5)	8 (33.3)
	Week 8	26	1 (3.8)	2 (7.7)	4 (15.4)	12	7 (26.9)
	Week 12	25	0 (0.0)	1 (4.0)	2 (8.0)	(46.2)	8 (32.0)
	Week 16	22	0 (0.0)	0 (0.0)	2 (9.1)	14	8 (36.4)
	Week 20	19	0 (0.0)	1 (5.3)	2 (10.5)	(56.0)	9 (47.4)
	Week 24	16	1 (6.3)	0 (0.0)	1 (6.3)	12	8 (50.0)
	Week 28	16	0 (0.0)	0 (0.0)	2 (12.5)	(54.5)	8 (50.0)
						7 (36.8)	
						6 (37.5)	
						6 (37.5)	
	Week 32	11	0 (0.0)	0 (0.0)	0 (0.0)	6 (54.5)	5 (45.5)
	Week 36	10	0 (0.0)	0 (0.0)	2 (20.0)	3 (30.0)	5 (50.0)
	Week 40	9	0 (0.0)	0 (0.0)	0 (0.0)	4 (44.4)	5 (55.6)
	Week 44	10	0 (0.0)	0 (0.0)	0 (0.0)	5 (50.0)	5 (50.0)
	Week 48	8	0 (0.0)	0 (0.0)	1 (12.5)	2 (25.0)	5 (62.5)
	Week 52	6	0 (0.0)	0 (0.0)	0 (0.0)	3 (50.0)	3 (50.0)
	Week 56	4	0 (0.0)	0 (0.0)	0 (0.0)	2 (50.0)	2 (50.0)
	Week ≥60	3	0 (0.0)	1 (33.3)	0 (0.0)	1 (33.3)	1 (33.3)

The CTCL-specific quality of life questionnaire showed consistent improvement for the 300 mg/m²/day initial dose group that was supported by similar findings in the >300 mg/m²/day initial dose group. **Table 53** summarizes the mean changes from baseline to Week 16 for completers in the 300 mg/m²/day initial dose group. The consistent improvement in the patients' self-assessed quality of life change scores could possibly corroborate the sponsor's primary and other secondary efficacy endpoint findings in the study.

Table 53 CTCL-Specific Patient Questionnaire: Summary of Changes to CTCL-Specific Questions for 300 mg/m2/day Initial Dose Group for Completers

Q #	Category	Self-Assessment (Approximated to Descriptors)	
		Baseline	Week 16
Q2	Itchiness	Moderate	Mild
Q3	Redness, scaling and/or plaque elevation	Moderate	Mild
Q4	Physical appearance with respect to CTCL	Moderately Dissatisfied to Neutral	Neutral to Moderately Satisfied
Q5	Work activity interference	Minimally to Mildly Disruptive	Minimally to Mildly Disruptive
Q6	Social activity interference	Minimally to Mildly Disruptive	Minimally to Mildly Disruptive
Q7	Physical activity interference	Minimally to Mildly Disruptive	Minimally to Mildly Disruptive
Q8	Change in CTCL	(N/A - change from baseline question)	79% Moderately to Much Improved
Q9	Overall Satisfaction/ Dissatisfaction with Study Drug	(N/A - change from baseline question)	72% Moderately to Very Satisfied

Survival

Survival was not an efficacy endpoint in this study. This study lacked a concurrent untreated control arm and was not designed to test for a survival advantage. The protocol however required that survival information be collected and analyzed.

As of the date of completion of this clinical study report, a total of 16% (15/94) of patients in the database for this NDA report have died, including four deaths during the protocol-specified treatment and follow-up period, seven deaths after the protocol-specified one-month follow-up period, and four additional deaths after the closure of the database for this report. Among the 13 patients enrolled in the study after the 31 July 1998 cutoff date for inclusion in the NDA database, there have been two deaths (15%, 2/13).

The sponsor claims that all but one of these 15 patient deaths was not related to Targretin capsule treatment. The death of Patient 591 (Center 444) from severe bleeding/hemorrhage, coagulopathy, and liver failure was the only drug-related death in this study and was considered by the Investigator to be "possibly related" to treatment. Ten of the 15 deaths occurred among patients who had been treated in the 300 mg/m^2/day initial dose level and seven occurred among the patients in the >300 mg/m^2/day initial dose level. The most common cause of death for these 15 patients was progression of CTCL, cited as the cause of death for eight patients (the sole cause for seven patients and a contributing cause for another). The next most common cause was infection, cited for five patients (two with sepsis, one with sepsis combined with fever and end-stage CTCL, one with pneumonia, and one with pneumonia combined with pelvic thrombosis and pulmonary embolism). The five remaining causes of death, reported for one patient each, were severe bleeding/hemorrhage, coagulopathy, and liver failure; hepatic hemorrhage secondary to liver biopsy; congestive heart failure; automobile accident; and one unknown at the time of this report.

SAFETY RESULTS

A total of 99 % (93/94) of enrolled patients in the study experienced at least one adverse event (AE). The incidence of AEs increased in relation to increased dose with the initial dose group of >300mg/ms/day having more AEs than the 300mg/m2/day..

The AEs and the frequency of occurrence are as outlined below:

Hypertrigyceridemia	78% (73/94)
Hypercholesterolemia	40%
Hypothyroidism	38%
Pruritus	18%
Nausea	18%
Asthenia	30%
Headaches	29%
Rash	26%
Leukopenia	26%
Pruritus	25%
Chills	11%
Abdominal Pains	11%
Exfoliative dermatitis	21%
Anemia	16%
Pancreatitis	5.2%

The most common laboratory abnormality associated with Targretin treatment was elevation of triglycerides and cholesterol levels. The increased values ocurred within 2 to 4 weeks of initiation of treatment. There was associated abdominal pains and pancreatitis related to the elevated hyperlipidemia. The median values for cholestrol and triglyceride elevations were 293 and 687mg/dl respectively, and remained high during the treatment period for 12 to 16weeks.

Other frequent laboratory abnormalities were, abnormal tests of liver function and thyroid function, leukopenia, anemia.

SAEs: For patients in both initial dose groups, the most serious SAEs were

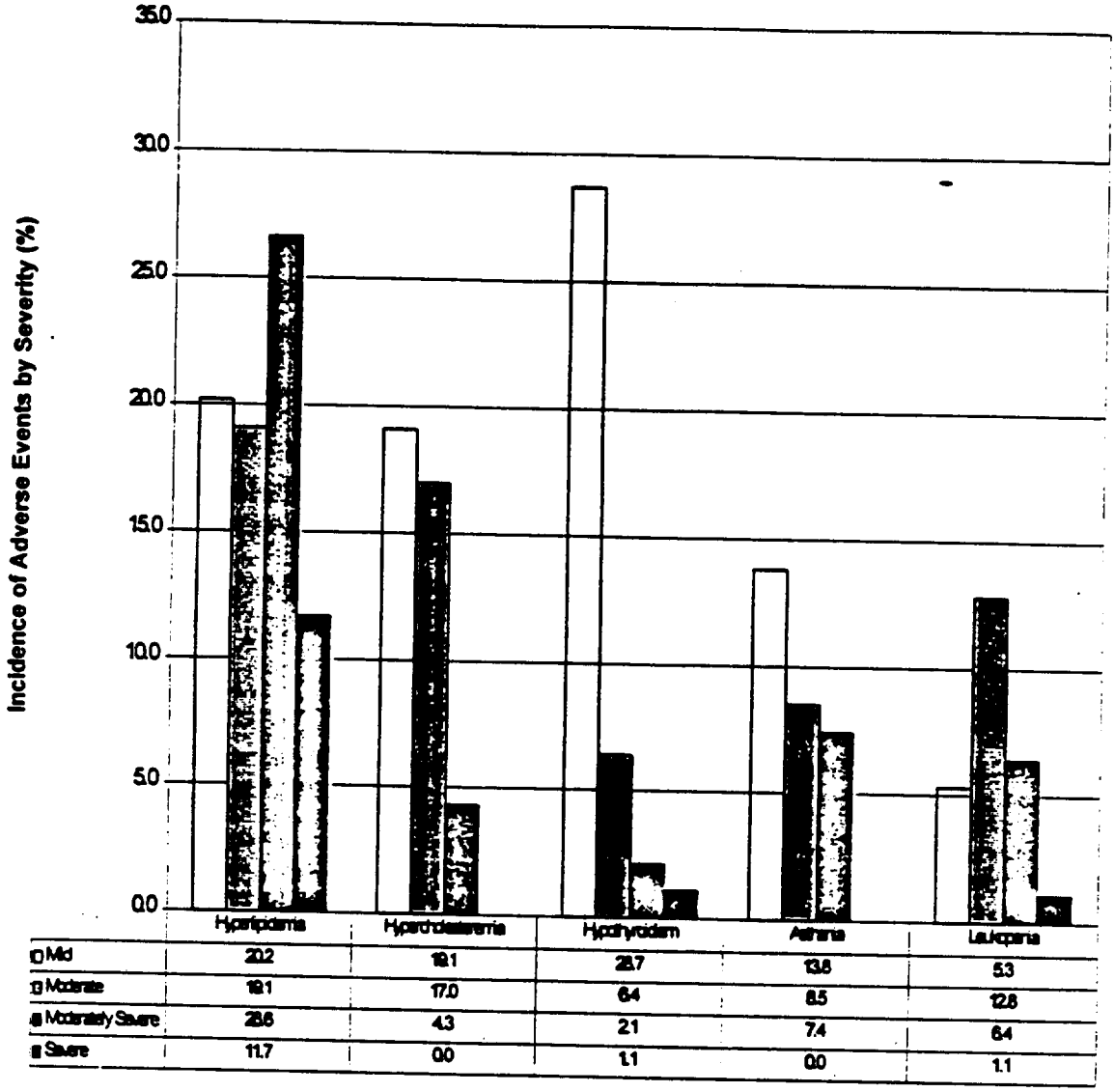
Pneumoia	5.4%	(5/94)
Fever	4.3%	(4/94)
Infection	3.2%	(3/94)
Pruritus	3.2%	(3/94)
Pancreatitis	1.1%	(1/94)

The severity and details of these adverse events are as provided in Table 53 and Figure 2

Table 54 All Adverse Events With Overall Incidence ≥10% (in Both Initial Dose Groups Combined)

		Initial Assigned Dose Group		
		300 mg/m²/day N = 56	>300 mg/m²/day N = 38	Overall N = 94
Body System	Adverse Event	N (%)	N (%)	N (%)
Body as a Whole	Altered Hormone Level	6 (10.7)	5 (13.2)	11 (11.7)
	Asthenia	13 (23.2)	15 (39.5)	28 (29.8)
	Fever	4 (7.1)	9 (23.7)	13 (13.8)
	Headache	12 (21.4)	11 (28.9)	23 (24.5)
	Infection	10 (17.9)	8 (21.1)	18 (19.1)
	Pain	10 (17.9)	9 (23.7)	19 (20.2)
Cardiovascular	Edema Peripheral	11 (19.6)	6 (15.8)	17 (18.1)
Digestive	Anorexia	1 (1.8)	9 (23.7)	10 (10.6)
	Diarrhea	4 (7.1)	16 (42.1)	20 (21.3)
Endocrine	Hypothyroidism	16 (28.6)	20 (52.6)	36 (38.3)
Hemic & Lymphatic	Anemia	4 (7.1)	9 (23.7)	13 (13.8)
	Leukopenia	9 (16.1)	15 (39.5)	24 (25.5)
	Lymphadenopathy	7 (12.5)	4 (10.5)	11 (11.7)
Metabolic & Nutritional	Hypercholesteremia	17 (30.4)	21 (55.3)	38 (40.4)
	Hyperlipemia	46 (82.1)	27 (71.1)	73 (77.7)
Skin & Appendages	Dermatitis Exfoliation	5 (8.9)	8 (21.1)	13 (13.8)
	Pruritus	14 (25.0)	5 (13.2)	19 (20.2)
	Rash	10 (17.9)	10 (26.3)	20 (21.3)
	Skin Disorder	9 (16.1)	5 (13.2)	14 (14.9)

Figure 2 Severity of Adverse Events With Overall Incidence of ≥25%
N = 94



	Hyperlipidemia	Hypercholesteremia	Hypothyroidism	Asthenia	Leukopenia
Mild	20.2	19.1	28.7	13.8	5.3
Moderate	19.1	17.0	6.4	8.5	12.8
Moderately Severe	28.6	4.3	2.1	7.4	6.4
Severe	11.7	0.0	1.1	0.0	1.1

Deaths :

There were 17 deaths among patients enrolled in this protocol. One patient died from severe hemorrhage due to coagulopathy and liver failure. The rest of the deaths were believed not to be treatment related.

9.3 FDA ASSESSMENT OF RESULTS: Protocol L-1069-24

Demographics:

The comments made in protocol L 1069-23 concerning median age of patients and long median duration of CTCL manifestation prior to study entry are applicable here as well. The objective of this protocol is to evaluate the safety, tolerability and antitumor efficacy of Targretin in advanced stage cutaneous T-cell Lymphoma.

102 patients were screened and 94 patients were enrolled in the study. The median duration of clinical manifestation of symptoms of CTCL in this patient population was 7.3 years with a range of 9 months to 31 years.

70 of 93 (74.6%) patients were classified as Stage II or III disease. Among the 24 patients clasiffied as Stage IV, very few patients had visceral involvement with CTCL. We therefore are not dealing with a population of patients who truly have advanced CTCL. The issues of violation of protocol entry criteria discussed in Protocol 23 are pertinent here as well.

EFFICACY:

The following tables record FDA findings on review of the data presented by the sponsor. There were no Complete Responders in either dose group.

In the combined 300mg/m2/day and >300mg/m2/day group the CCR+ PR response is 28 of 94 or 30%, and CCR only response rate is 6 of 94(6%). These responses are by Composite Assessment of Index Lesion measures only. The FDA is unable to assess PGA responses, as these are the Investigator's subjective evaluation of the patient's overall clinical status at each evaluation. The absence of half body pictures with front and back views as required by the protocol make FDA confirmation of these assessments of PGA impossible. The Primary Efficacy Endpoint assessment (PEC) is determined by the sponsor utilizing CA and PGA results. The FDA is therefore unable to assess the sponsor's determination of PEC assessments due to the PGA constraints indicated.

The breakdown of the FDA analysis of the Composite Assessment of Index Lesion Disease Severity, CA, for the different response categories is as outlined in the accompanying tables.

Table 55 PROTOCOL L1069-24 Responders by Initial Dose Groups (CA only)

Initial Dose Group	INV.#	PT. ID	RESPONSE. Duration and (Dur.period) in weeks
300MG/M2	Clinical Complete Responders		
	14	309	CCR 16 (4-22)
	14	318	CCR 32 (12-48)
	167	392	CCR 16 (4-20)
	181	442	CCR 36 (4-24)
	Partial Responders		
	14	1472	PR 16 (16-32)*
	14	1474	PR 12 (16-28)*
	15	484	PR 4 (12-16)
	23	572	PR.28 (12-40)*
	34	323	PR.32 (16-48)
	35	562	PR 4 (12-16)*
	282	544	PR 20 (12-32)
	282	546	PR 8 (12-20)
	348	332	PR 16 (12-28)
	349	1463	PR12 (4-16)
			*week censored
>300mg/m2	Clinical Complete Responders		
	14	302	CCR 26 (72-82)
	168	402	CCR 40 (30-70)
	Partial Responders		
	14	301	PR 72 (12-84)
	14	305	PR 12 (4-16)*
	14	306	PR 4 (8-12)
	14	313	PR 4 (8-12)
	35	561	PR 28 (24-52)*
	62	341	PR 4 (16-20)
	168	401	PR 12 (8-20)
	181	441	PR 24 (8-32)
	181	444	PR.8 (12-20)
	205	371	PR 12 (8-20)*
	282	541	PR.32 (8-40)

The FDA had questions about the claimed responses in the six patients listed below, who are included among responders above.

Table 56
PROTOCOL L 1069-24(CA): PATIENTS CONFIRMED WITH QUESTIONS)

INV. ID	PATIENT ID	REVIEWER'S COMMENTS
14	309	Questionable Responses from photographs and CRFs
14	313	Questionable Responses from photographs and CRFs
35	562	Questionable Responses from photographs and CRFs
168	401	Questionable Responses from photographs and CRFs
282	546	Questionable Responses from photographs and CRFs

Table 57 SUMMARY OF TUMOR RESPONSE
PROTOCOL L 1069-24 PGA and CA
COMPARISON OF FDA and LIGAND RESPONSES
300mg/m2/day and >300mg/m2/day

	N	CCR+PR (%)	CCR (%)
PGA (LIG)	94	47 (50)	2 (2)
PGA (FDA)	94	Not Assessable	Not Assessable
CA (LIG)	94	33 (35)	6 (6)
CA (FDA)	94	27 (29)	6 (6)

The FDA could not confirm the responses claimed by Ligand in the six patients listed in the table below.

Table 58 PROTOCOL L 1069-24 PARTIAL RESPONDERS (CA) (Not Confirmed)

INV. ID	PATIENT ID	REVIEWR'S FINDING	COMMENTS
14	312	SD	Photographs provide insufficient support of claim of PR
167	391	SD	Photographs provide insufficient support of claim of PR
167	394	SD INEVALUABLE	Treatment terminated at week 7 due to PD Photographs provide insufficient support of claim of PR No change in abnormal lymph nodes in both axillae and inguinal areas. No prior systemic or topical anti-CTCL therapy. Pt not refractory.
179	431	SD	Photographs provide insufficient support of claim of PR
181	445	SD	Photographs provide insufficient support of claim of PR
312	1341	SD	Criteria for CCR or PR not met by CA. evaluation. PD in abnormal lymph nodes and cutaneous tumors Study terminated after week 20 due to new cutaneous tumors. Photographs provide insufficient support of claim of PR

SUPPORTING EFFICACY CRITERIA: PHOTOGRAPHS:

Full body photographs were required by the protocol as a supportive efficacy requirement. The section of the protocol reads as follows:

Five (5) designated index lesions will be serially photographed at baseline and every four (4) weeks thereafter for the duration of treatment. At the follow-up visit, these five index lesions must be photographed. Global photographs (half-body fields, anterior and posterior) of each patient's CTCL disease will 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 are photographed at baseline must be re-photographed every four (4) weeks, even if the lesions have cleared, until the patient completes the follow-up study visit.

It was the only opportunity available to the FDA to independently verify the PGA and CA claims of the applicant.

The applicant did not comply with protocol specified requirements for full body photographs and no protocol amendment was made to reflect the change.

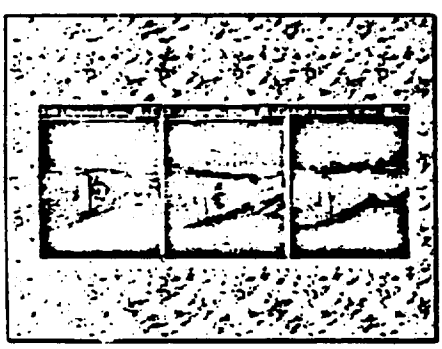
FDA therefore could not assess the sponsor's claimed responses on the PGA.

Some of the photographs of index lesions do not confirm the claimed responses on CA and raise questions on the claimed responses on PGA.

Patient #544

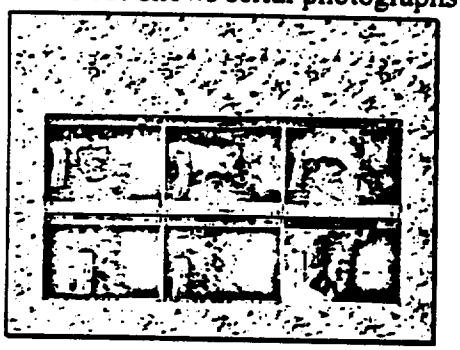
This is an example of a successful treatment. This patient had a response to therapy that began from week 4 and continued until at least week 48 according to the pictures and CRFs.

Lesions in other areas, including the scalp showed impressive responses as well.



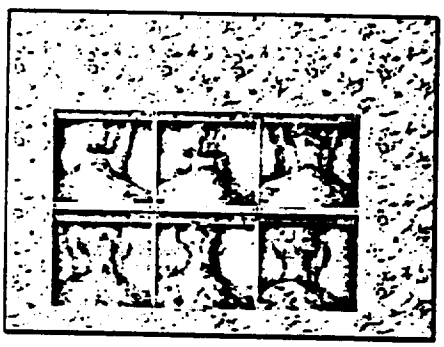
The following patients illustrate the need for full body photographs

Patient #312
This slide shows serial photographs of an index lesion.



This is the same patient with a wider view of the skin lesions.
The areas surrounding the index lesion appears to be worsening.

This patient was scored as a Partial Response on the PGA.

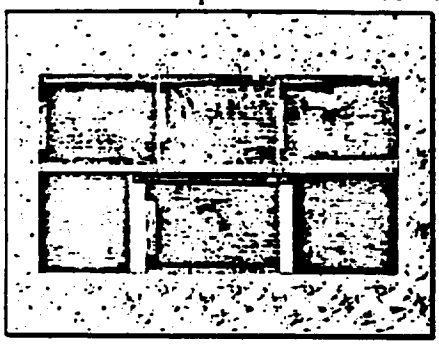


This shows the need for full body photographs to confirm the claimed PGA response

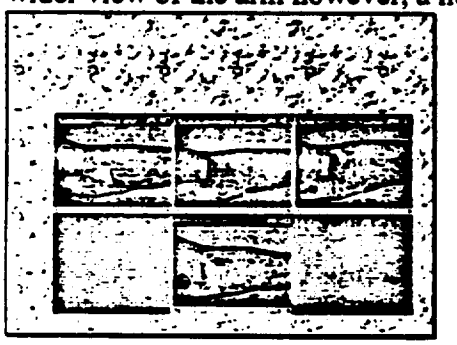
APPEARS THIS WAY
ON ORIGINAL

Patient #1464

This is another patient with close-up pictures of an index lesion.



With a wider view of the arm however, a new tumor is rapidly developing near the index lesion.

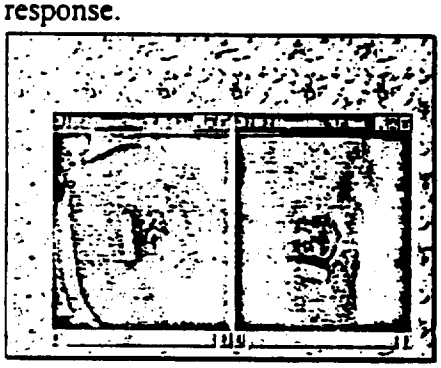


This again indicates the need for full body photographs to confirm the claimed PGA response.

Patient # 1341.

This is yet another patient. This patient was called a responder by PGA and Stable Disease by CA. A huge ulcer is developing. Unfortunately we have no further pictures on this patient beyond the 2nd visit.

Again this illustrates the need for full body photographs to confirm the claimed PGA response.



SAFETY:

This section reviews the safety profile in the 152 patients enrolled in both protocols.

FDA'S review of safety generally agrees with Ligand's report. The following however represents areas in which this reviewer feels the sponsor has not adequately addressed some important safety issues.

Hyperlipidemia and its Clinical Sequelae:

Gastrointestinal Complications: 4 patients in the database of 152 patients had clinical pancreatitis and required hospitalization. Serum amylase was however obtained in 17 of 58 patients in protocol L-23 and 37 of 94 patients in protocol L-24. There were 4 other patients (#313, #394, #1341, #1461), with abdominal and gastrointestinal complaints on whom serum amylase was not obtained. Patient #1341 died.

Cardiovascular complications: Complications of cardiac disease were attributed to drug therapy in some patients in this study. While the patients in the study are in the age range for cardiovasular events, a direct association with hyperlipidemia cannot readily be made, but the potential exists.

Patient #005 (Investigator #14) had coronary heart disease requiring bypass surgery. He had drug induced hypertriglyceridemia and hypothroidism, as well as impotence believed by the investigator to be treatment related.

Patient #306 (Investigator #14) died from Congestive Heart Failure. He had drug induced hypothyoidism, fluid retention and abnormal liver function tests.

Patient 147 (Investigator#181) died of myocardial infarction. The death was considered treatment related by the Investigator.

Patient # 546 (Investigator # 283/282) died from hepatic hemorrhage, which the investigator believed was treatment related. The patient had elevated triglycerides, abnormal thyroid function and worsening pleural effusion.

Quality of life issues: All the patients in this study are on numerous other medications for control of various other co-morbid medical problems. Each patient in the 300mg/m2/day dose group enrolled in this study takes approximately seven pills of Targretin a day. Those in the higher dose groups take more. The need to take additional lipid lowering drugs and thyroid supplements, among other drugs meant to counteract the other adverse effects of Targretin provide an added burden for these patients to carry. About 50%of patients required lipid lowering agents and about 25% of patients required thyroid hormone replacement therapy. The potential problems with drug-drug interaction becomes very high as well.

Worsening of Cataracts: Visual problems, including cataracts, are common in this age group of patients. 79 patients in both protocols (32 patients in early disease and 47 patients I advanced disease) had slit lamp examination at least two times during the study. 5/32 (15.6%) patients in early disease and 10/47 (21.3%) patients in advanced disease protocol developed new or worsening cataracts in the course of the study. The number of these patients who had worsening of cataracts in existence prior to protocol entry is not clearly documented . An example however was Patient # 546 (Investigator # 283/282) mentioned above. While the number does not appear very high, it remains a hazard of concern in individuals in this age group.

Patient withdrawal due to Adverse Effects as a measure of Safety:
In protocol L-23, 17 of 58 (30%) patients withdrew from study or withdrew consent prior to a planned 16 weeks of treatment due to adverse effects. Many of the patients who withdrew consent appeared to do so due to lack of desire to tolerate the adverse effects or rigors involved with the study. 33 of 94 (35%) patients did so in protocol L-24.
This high rate of withdrawals undermine the integrity of conclusions that can be drawn from these studies.

10.0 FDA OVERALL CONCLUSIONS

The following conclusions can be made concerning this submission:

The patients in the early stage disease protocol, mostly had truly early disease Stage I while most of the patients in the advanced disease protocol had Stage IIB or III disease. Additionally, the median duration of initial manifestation of disease in protocol 23 was 10 years and in the protocol 24 was 7.3 years. The longest initial manifestation of disease were 59 years and 31 years respectively. Most of the patients enrolled in the advanced disease protocol do not have visceral disease. The question therefore arises if the design of these studies in the population of patients enroled, truly answer the questions of the antitumor activity of Targretin in all stages (IA-IVB) of CTCL patients.

Lack of half body (anterior and posterior) photographs as previously agreed and as required by the protocols is a serious deficiency and also a violation of the IND regulations. The PGA response is the most important efficacy endpoint in the protocols.. Without the half body photographs (front and back), the FDA is unable to confirm the claimed PGA tumor responses. The study thus becomes an evaluation of selected skin lesions rather than an evaluation of patients, since there is no objective way for anyone, to truly confirm the responses and the degree of responses in these patients. Half body photographs would assess changes in all skin lesions, both index and non-index lesions.

The method of analyzing the effect on secondary efficacy endpoints, such as measurements of BSA involvement, pruritus, Quality of life measures is sub-optimal. The claimed improvement over time may be misleading because patients who are not doing well have dropped out and only the patients who are doing well are assessed.

There were many flaws in the execution of these studies: There were numerous protocol violations, numerous amendments to the original protocol, many patients withdrew consent to continue participation in the studies, many patients who were still within the "washout" period of their prior therapies prior to enrolment on study.

In the context of the design of these studies, this drug does have activity in this disease. The degree of activity is however not particularly overwhelming . All the responses that the FDA can confirm, occur exclusively in the skin, and in extremely few cases, in the peripheral lymph nodes. The fact that several responses could not be confirmed or were confirmed by the FDA with some question probably indicates that at best the responses in these patients were not very dramatic.

There is little evidence of effect on non cutaneous disease. Given the circumstances of the studies outlined above, as well as their design, one wonders whether these responses are more than a series of anecdotes.

There are significant safety issues, especially the need for lipid lowering agents in approximately half of the patients and thyroid hormone replacement in approximately 25% of patients. The 4 cases of pancreatitis are of concern. There are also other toxicities, including patients with gastrointestinal complaints, in whom serum amylase was not obtained, and at least 3 deaths that are possibly attributable to drug therapy.

11.0 REVIEW of Supplemental Report: Summary of Efficacy in patients enrolled in early stage CTCL (Protocol l-1069-23) after NDA Cutoff Date. Date of Report May 10, 1999. Date received June 23, 1999

This study describes the PEC (Primary Endpoint Response Classification) for 26paiets enrolled in early stage CTCL (Protocol l-1069-23) after the cut off date of July 31, 1998.

ANALYSIS OF DATA:

This was a randomized study of an initial dose of 6.5mg/m2/day (N=14) and 300mg /m2/day (N=12).

The responses were determined according to the Physician Global Assesment (PGA) and the Composite Assessment (CA) criteria previously described. There are no supportive photographs for verification of claimed responses in this group of patients.

Only the CTCL Index Lesion Clinical Assessment and PGA Log were provided. There were no data on patients with clinically abnormal lymph nodes. No other secondary response data such as assessment of QOL and pruritus were submitted.

PEC Responses:

6.5mg/m2/day before cross-over: 0/14 PR

after cross-over 2/11 PR(18%)

300mg/m2/day: 7/12 PR (58%)

These results are not substantially different from results provided in the original study. The absence of any photographs and other secondary efficacy measures make these data non-verifiable and do not materially add to previous information.

12.0. REVIEW of 120-DAY SAFETY UPDATE (Received October 18, 1999)

The safety update provided information derived on study patients beyond the July 30, 1999.The database consisted of 193 CTCL patients (152 in ISS) and 420 non-CTCL patients. When compared to the ISS safety database, the information provided does not reveal new safety issues.

13.0 Statement of Financial Disclosure by Clinical Investigators

The applicant submitted a statement of financial certification for all clinical investigators involved in NDA 21-055.

The applicant certified that no investigator was a full-time or part-time employee of Ligand, and that the applicant did not enter into any financial arrangement with the investigators where the value of the compensation could be affected by the outcome of the study. No investigator was the recipient of significant payments of other sorts.

The applicant could not obtain financial disclosure information from 16 investigators (3 from US sites and 13 from European sites) in the early disease protocol, and 13 investigators (4 from US and 9 from European sites) in the advanced disease protocol. None of the investigators in both studies had patients who were responders in either study.

14.0: ONCOLOGY DRUG ADVISORY COMMITTEE (ODAC) MEETING:

On Monday December 13 1999, the application was presented to members of the Oncology Drug Advisory Committee. The questions asked, and the votes of the committee members are as indicated below

Two clinical trials were conducted in patients with Cutaneous T Cell Lymphoma (CTCL). One trial in 58 patients with Early Stage disease
(IA, IB and IIA) was planned as a randomized trial comparing low dose and high dose with respect to two primary endpoints: 1) a global measurement, the Physicians Global Assessment (PGA), based on all aspects of the patient's disease and scored on a scale of 0 to 6. It was planned that full body front and back photographs would be used to support the physician's ratings. 2) A Composite Assessment of Index Lesion Severity (CA), also to be supported by photographs. The photographs were considered important because the study was unblinded and the assessments subjective. To enter the trial patients must have failed to respond to, reached a response plateau after 6 months to or been intolerant to at least two prior qualifying therapies. Only 15 patients were randomized to the low dose. This dose was abandoned because of "poor response". The low dose control group, had it been completed, could have provided a direct measure of the natural history of the index lesions.

The other trial was in 94 patients with Advanced Stage disease (IIB, III, IVA and IVB). This trial was not randomized, but the same photographic support was planned. Patients must have been refractory to at least one prior systemic therapy.

The reported tumor response rates in these two studies are shown in Tables 1 and 2 below. The claimed Physician Global Assessment (PGA) tumor responses can not be confirmed by the FDA because the full body front and back photographs specified in the protocols were not done. Generally FDA was able to confirm most of the claimed tumor responses based on Composite Assessment of Selected Index Lesion Severity (CA) by examining the photographs of the index lesions.

Quality of life (QOL) was assessed in both studies using the Spitzer QOL instrument and a CTCL specific QOL of life instrument developed by Ligand. Both of these QOL instruments have a Global question (CTCL specific has 2 Global questions) assessing the patient's overall condition. The results were disparate in both the Early Disease and

Advanced Disease studies with worsening on the Spitzer Global QOL question, but improvement on the CTCL specific Global QOL questions.

Table 1

Tumor Response Early Disease

PGA and CA

	Dose 300			Dose 6.5		
	N	CCR+PR (%)	CCR (%)	N	CCR+PR (%)	CCR (%)
PGA (Lig)	43	23 (53)	3 (7)	15	1 (7)	0 (0)
PGA (Fda)	43	Not Reviewable Without Full Body Photographs				
CA (Lig)	43	17(40)	4(10)	15	3(20)	1(7)
CA (Fda)	43	15 (35)	3 (7)	15	3 (20)	1 (7)
Both PGA&CA*		14				
PGA Not CA*		9				
CA* Not PGA		3				

* Using Ligand Response Assessments

Table 2

Tumor Response Advanced Disease

PGA and CA

	N	CCR+PR (%)	CCR (%)
PGA (Lig)	94	47 (50)	2 (2)
PGA (Fda)	94	Not Reviewable Without Full Body Photographs	
CA (Lig)	94	33(35)	6(6)
CA (Fda)	94	27 (29)	6 (6)
Both PGA&CA*		29	
PGA Not CA*		18	
CA Not PGA*		4	

* Using Ligand Response Assessments

Questions to the Committee

1 Does the Committee believe that a clinically meaningful tumor response rate using acceptable tumor response criteria has been adequately demonstrated?

YES – 11 NO – 4 Abstain – 1

2 Has clinical benefit other than tumor response been adequately demonstrated?

YES – 0 NO – 14 Abstain – 2

3 Are the patient populations in the Early Disease study and the Advanced Disease study adequately characterized in terms of the following:

a) Prior therapies?

YES – 15 NO – 1 Abstain – 0

b) Response to prior therapies?

YES – 1 NO – 14 Abstain – 1

c) Reason for discontinuing or not repeating prior therapies?

YES – 1 NO – 13 Abstain – 2

4 Given the availability of other systemic chemotherapy agents active in this disease, should Targretin Capsules be compared to another systemic therapy in a randomized controlled clinical trial? (Question 4 was answered AFTER Questions 5 & 6)

a) in Early Disease? YES-5 NO-6 Abstain-5

b) in Advanced Disease? YES-8 NO-4 Abstain-4

The Committee indicated that randomized controlled clinical trials would be useful in determining the true benefit of the drug in this very heterogeneous disease. The trials should be done before approval in early disease and must be done after approval as a condition of approval in advanced disease. The randomized controlled study should be directed toward demonstration of clinical benefit as well as tumor response.

5 In view of the risks are the benefits adequate to warrant approval of Targretin Capsules for treatment of the patient population in the Early Disease study?

YES – 5 NO – 7 Abstain – 4

6 In view of the risks are the benefits adequate to warrant approval of Targretin Capsules for treatment of the patient population in the Advanced Disease study?

YES – 13 NO – 2 Abstain – 1

15.0 RECOMMENDATION

The sponsor has conducted two studies of Targretin (Bexarotene) 75mg Capsules in patients with early and late stage of CTCL.

The findings of the Medical Officer's review of these studies and the recommendations of the ODAC Advisory Committee members, are as provided in this document. The Medical Officer therefore makes the following recommendations:

1) Targretin is NOT approvable for patients with [

]Additional reasons for this decision are as follows:

i) Disease Characteristics and Study Design in this patient population. This patient population has a very indolent disease which has waxed and waned on various therapies for a median duration of at least 1 decade on various therapies. The non-randomized nature of the study conducted has not provided convincing evidence that any change seen in index lesions in this patient population can be solely ascribed to this drug, or that none of the currently existing drugs can proveide the same degree of efficacy.

ii) Dose concerns: The appropriate dose of Targretin in terms of efficacy and toxicity have not been demonstrated in this study. This concern will make the use of Targretin inappropriate in this patient population.

iii) Toxicity concerns: In view of the indolent and chronic nature of this disease, this category of patients may be on Targretin for a prolonged duration, measurable in years. While this would be a satisfactory development if one were convinced that this benefit were primarily due to Targretin, the lack of such confidence makes the toxicity of Targretin of considerable importance in this population of patients. The sponsor uses 400mg/dl as an acceptable level of triglycerides. This is a highly artherogenic lipid level with increased risk of cardiovascular events with long term use. The risk of other known AEs increase as well. These include, hypothyroidism cataracts and gastrointestinal problems such as pancreatitis. The risk of potential AEs increase as well. These risks are unknown because of inadequate pre-clinical information on hepatic drug disposition and drug interactions. The issue of dose mentioned above poses unknown, but real risk concerns as well.

2) Targretin is approvable in patients with cutaneous manifestations of advanced CTCL

Approval in this category of patients should therefore be conditional on commitment by the sponsor to conduct a phase IV study that addresses the issues raised above. The study should be a randomized control study of two dose levels of Targretin and an agent with activity in this disease. This reviewer will suggest 300mg/m2/day and 100mg/m2/day. The sponsor can select the comparator, but this reviewer will suggest either oral methotrexate or alpha interferon. The patient population needs only to have failed topical therapy.

This design will provide information concerning the appropriate dose of Targretin. It will determine the true activity of Targretin and duration of that activity. It will also appropriately position Targretin in the efficacy "pecking order" of useful drugs in this disease.

Approval is also conditional on satisfactory resolution of drug-drug interaction issues raised by the Biopharmaceutics group concerning the Targretin effect on CYP3A4 in combination with drugs that enhance or inhibit the substrate of this enzyme

/S/

OLUWOLE O. ODUJINRIN, MD
MEDICAL OFFICER
December 23, 1999

See my Clinical Team Leader Supplement to medical officer review.

/S/
12-23-99

CLINICAL TEAM LEADER SUPPLEMENT TO MEDICAL OFFICER REVIEW OF NDA 21055

NDA 21055

DRUG Targretin Capsules

APPLICANT Ligand Pharmaceuticals

DATE RECEIVED 6-23-99

This review is a supplement to the medical officer review and should be read in conjunction with the medical officer review. It is not a stand alone review. The medical officer is the only person who does a complete detailed review of an NDA. However, I have done some additional analyses not performed by Ligand or the medical officer and it is appropriate that they be included in the record. In addition my Recommendation differs from the medical officer's Recommendation and this must be recorded.

Two clinical trials were conducted in patients with Cutaneous T Cell Lymphoma (CTCL). One trial was in 58 patients with early stage disease [ ] This was a randomized trial between low dose and high dose. However, only 15 patients were randomized to the low dose because of poor response. The other trial was in 94 patients with advanced stage disease [ ] This trial was not randomized.

The primary efficacy endpoints were tumor response using the Physicians Global Assessment criteria and using the Composite Tumor Assessment of Index Lesion criteria. There were some secondary efficacy endpoints the most important of which are described below.

1. PHYSICIANS GLOBAL ASSESSMENT OF TUMOR RESPONSE

The most impressive efficacy result in the two clinical studies is the Physician's Global Assessment of tumor response (PGA). All manifestations of the disease are considered by the physician. If all

disappear, it is a CCR and if there is a 50% improvement, it is a PR. All responses require confirmation at least 4 weeks later.

The FDA is unable to confirm the PGA tumor response rate claimed by Ligand because the full body photographs agreed on at the End of Phase II meeting and required by the protocol are not provided. This is a serious deficiency.

At the end of Phase II meeting with FDA Ligand agreed to provide full body front and back photographs at baseline and every 4 weeks while on study to document tumor response just as they had done in another recent NDA for Panretin in treatment of AIDS-related Kaposis sarcoma. The protocol clearly specified this and was never amended. After the study was completed Ligand told FDA these photographs were not obtained even though the protocol had never been amended to cover this important change.

Without these photographs the FDA is unable to confirm Ligand's claim of PGA tumor responses in these 2 clinical trials. Patients with early disease had only cutaneous disease. Patients with advanced disease had no apparent improvement in tumor other than cutaneous manifestations with the possible exception of clinically abnormal lymph nodes (not histologically involved). Thus the PGA could have been confirmed by the FDA in almost all patients by viewing total body photographs, supplemented by review of the case report forms. The lack of full body photographs is a serious deficiency.

2. TUMOR RESPONSE BY COMPOSITE ASSESSMENT OF INDEX LESION SEVERITY

The other primary efficacy endpoint is tumor response based on the Composite Assessment of Index Lesions (CA). It is based on selected index lesions (usually five). Each lesion is scored based on scaling, pigmentation, area, pruritus, erythema and plaque/tumor elevation. It was later decided not to use the pruritus score in calculating the CA tumor response because many patients were on antipruritics. All scores for all lesions for each visit were summed for a total for each visit. If the total score improved by $\geq$ 50% on consecutive visits at least 4 weeks apart, it was a PR. All non cutaneous disease was considered in the CA tumor response. Extracutaneous disease that progressed could negate a CA tumor response, but a response could not be based on improvement in extracutaneous disease.

In general I was able to confirm the tumor responses claimed by Ligand

based on the Composite Assessment of the Index Lesions by examining the photographs.

The results of the PGA and CA tumor response assessments are shown in Tables 1 and 2.

Table 1
Tumor Response Early Disease
PGA and CA

	Dose ≥ 300			Dose 6.5		
	N	CCR+PR (%)	CCR (%)	N	CCR+PR (%)	CCR (%)
PGA (Lig)	43	23 (53)	3 (7)	15	1 (7)	0 (0)
PGA (Fda)	43	Not Reviewable Without Full Body Photographs				
CA (Lig)	43	17(40)	4(10)	15	3(20)	1(7)
CA (Fda)	43	15 (35)	3 (7)	15	3 (20)	1 (7)
Both PGA&CA*		14				
PGA Not CA*		9				
CA* Not PGA		3				

* Using Ligand Response Assessments

Table 2
Tumor Response Advanced Disease
PGA and CA

	N	CCR+PR (%)	CCR (%)
PGA (Lig)	94	47 (50)	2 (2)
PGA (Fda)	94	Not Reviewable Without Full Body Photographs	
CA (Lig)	94	33(35)	6(6)
CA (Fda)	94	27 (29)	6 (6)
Both PGA&CA*		29	
PGA Not CA*		18	
CA Not PGA*		4	

* Using Ligand Response Assessments

3. TUMOR RESPONSE BY % INVOLVED BSA

The Ligand analysis is suboptimal for tumor response based on involved BSA and other secondary efficacy endpoints such as QOL and pruritus. The claimed improvements may be misleading because patients who do poorly drop out so that only patients who are doing well are assessed at later followup visits.

For analysis of tumor response based on involved BSA I have used a more conventional approach that assesses each patient's best response while on study. This analysis includes all patients in the study.

Tables 3 and 4 show the FDA analysis of tumor response rate based on involved BSA. A ≥ 50% decrease in involved BSA on at least two visits at least 4 weeks apart is a response.

Table 3
Tumor Response Early disease
% BSA Tumor Involvement
Dose ≥ 300

	N	Response (%)
BSA	43	16 (37)
Both BSA&PGA		16
BSA Not PGA		0
PGA Not BSA		7

Table 4
Tumor Response Advanced Disease
% BSA Tumor Involvement
Dose ≥ 300

	N	Response (%)
BSA	94	31 (33)
Both BSA & PGA		29
BSA Not PGA		2
PGA not BSA		18

4. QUALITY OF LIFE ASSESSMENT

There is an unexplained discrepancy in results on the Spitzer and CTCL Specific Global QOL asessments. There is worsening on the Spitzer QOL Global assessment (Question #6), but good improvement on the CTCL Specific QOL Global assessment (Questions #8 and #9).

The Spitzer QOL instrument (6 questions) and a Ligand developed CTCL specific QOL instrument (questions 1a-1e and 2-9) were used to assess QOL. Question #6 on the Spitzer and Questions #8 and #9 on the CTCL Specific QOL Instrument were Global questions.

The following describes the Ligand and Spitzer Global QOL questions.

Ligand Question #8 "Taking into account the appearance and all symptoms related to your cutaneous T-cell lymphoma (Mycosis), how has your cutaneous T-cell lymphoma (Mycosis) changed as compared to before your participation in this study?

Ligand Question #9 "What has been your overall level of satisfaction or dissatisfaction with the drug treatment in this study?

The Ligand CTCL Specific Questions #8 and #9 are categorical as follows.

Much Worse (1) Moderately Worse (2) About the Same (3)
Moderately Improved (4) Much Improved (5)

Spitzer Question #6 "Please mark an x in the appropriate place within the bar to indicate your rating of your quality of life during the last 4 weeks.

Lowest quality applies to someone completely dependent physically on others, seriously impaired mentally, unaware of surroundings and in a hopeless position.

Highest quality applies to someone physically and mentally independent, communicating well with others, able to do most things enjoyed, pulling own weight, with a hopeful yet realistic attitude."

The Spitzer question #6 is a visual analogue scale with 0 the lowest score and 10 the highest score.

Tables 5-16 show the results of the QOL analyses.

Table 5
QOL Question #8 Response = Category 4 or 5
Early Disease

	N	Response (%)
QOL 8	40	33 (83)
BothQOL8&PGA		21
QOL8 Not PGA		12
PGA Not QOL8		2

Table 6
QOL Question #8 Response =Category 5
Early Disease

	N	Response (%)
QOL 8	40	16 (40)

Table 7
Qol Question #8 Response = Category 4 or 5
Advanced Disease

	N	Response (%)
QOL 8	87	60 (69)
Both QOL 8 & PGA		45
QOL 8 Not PGA		15
PGA Not QOL 8		2

Table 8
Qol Question #8 Response = Category 5
Advanced Disease

QOL 9	N	Response (%)
	87	34 (39)

Table 9
QOL Question #9 Response = Category 4 or 5
Early Disease

	N	Response(%)
QOL 9	40	29 (73)
Both QOL 9 & PGA		19
QOL 9 Not PGA		10
PGA Not QOL9		4

Table 10
Qol Question #9 Response = Category 5
Early Disease

QOL9	N	Rersponse (%)
	40	13 (33)

Table 11
Qol Question #9 Response = Category 4 or 5
Advanced Disease

	N	Response (%)
QOL 9	88	58 (66)
Both QOL 9 & PGA		44
QOL 9 Not PGA		14
PGA Not QOL 9		3

Table 12
Qol Question #9 = Category 5
Advanced Disease

QOL 9	N	Response (%)
	88	29 (33)

Table 13 General Status Quality of Life Questionnaire (Spitzer Items 1-5): Composite of Individual Questions Change From Baseline for Completers Early Disease (N=36) *

Initial Assigned Dose(mg/m^2/day)	Study Visit	Composite of Individual Questions[1] No. Pts.	Mean	SE	Min	Median	Max
6.5	Day 1 Baseline	6	9.5	0.3		10	
	Week 4 Change	6	0.0	0.5		0	
	Week 8 Change	6	-0.3	0.6		-1	
	Week 12 Change	6	-0.2	0.5		0	
	Week 16 Change	6	0.2	0.4		0	
	Week 20 Change	4	0.0	0.8		0	
	Week 24 Change	1	2.0	na		2	
	Week 28 Change	1	2.0	na		2	
	Week 32 Change	1	2.0	na		2	
	Week 36 Change	1	2.0	na		2	
	Week 40 Change	1	2.0	na		2	
	Week 44 Change	1	2.0	na		2	
	Week ≥48 Change	1	2.0	na		2	
300	Day 1 Baseline	17	8.4	0.4		8	
	Week 4 Change	16	0.3	0.4		0	
	Week 8 Change	17	0.4	0.4		0	
	Week 12 Change	16	0.6	0.4		0	
	Week 16 Change	14	0.8	0.5		0	
	Week 20 Change	7	0.3	0.5		0	
	Week 24 Change	6	-0.3	0.2		0	
	Week 28 Change	5	0.4	0.7		0	
	Week 32 Change	3	0.0	1.2		0	
	Week 36 Change	2	-2.0	2.0		-2	
	Week 40 Change	2	-0.5	0.5		-1	
	Week 44 Change	1	-1.0	na		-1	
>300	Day 1 Baseline	11	9.2	0.5		10	
	Week 4 Change	11	-0.7	0.5		-1	
	Week 8 Change	10	-1.0	0.4		-1	
	Week 12 Change	10	-0.6	0.5		-1	
	Week 16 Change	9	-0.6	0.5		-1	
	Week 20 Change	8	-1.0	0.5		-1	
	Week 24 Change	5	-0.8	0.4		-1	
	Week 28 Change	7	-0.7	0.5		0	
	Week 32 Change	5	-0.2	0.4		0	
	Week 36 Change	5	-0.2	0.7		0	
	Week 40 Change	5	0.0	0.8		0	
	Week 44 Change	5	-0.8	1.1		-1	
	Week ≥48 Change	4	-0.5	1.0		-1	

*From NDA

Table 14 General Status Quality of Life Questionnaire (Spitzer Item 6): Overall Quality of Life Change From Baseline for Completers Early Disease (N=36) *

Initial Assigned Dose(mg/m^2/day)	Study Visit	Overall Quality of Life No. Pts.	Mean	SE	Min	Median	Max
6.5	Day 1 Baseline	6	94.2	1.5		95	
	Week 4 Change	6	-10.3	8.2		-5	
	Week 8 Change	4	-26.0	12.0		-24	
	Week 12 Change	4	-24.3	11.0		-21	
	Week 16 Change	5	-13.2	9.7		-3	
	Week 20 Change	4	-16.3	10.6		-7	
	Week 24 Change	1	-3.0	na		-3	
	Week 28 Change	1	-2.0	na		-2	
	Week 32 Change	1	-4.0	na		-4	
	Week 36 Change	1	3.0	na		3	
	Week 40 Change	1	4.0	na		4	
	Week 44 Change	1	4.0	na		4	
	Week ≥48 Change	1	2.0	na		2	
300	Day 1 Baseline	16	84.3	3.2		89	
	Week 4 Change	14	-8.3	3.6		-6	
	Week 8 Change	14	-11.8	4.4		-8	
	Week 12 Change	15	-5.2	4.1		-7	
	Week 16 Change	13	-5.7	3.0		-2	
	Week 20 Change	7	-13.3	4.2		-11	
	Week 24 Change	6	-19.0	6.4		-18	
	Week 28 Change	5	-9.0	4.2		-13	
	Week 32 Change	3	-11.7	10.7		-2	
	Week 36 Change	2	-20.5	22.5		-21	
	Week 40 Change	2	-16.0	16.0		-16	
	Week 44 Change	1	-16.0	na		-16	
>300	Day 1 Baseline	10	76.4	5.3		80	
	Week 4 Change	7	-8.7	7.6		-6	
	Week 8 Change	9	-8.6	6.6		-7	
	Week 12 Change	9	-8.0	5.5		-9	
	Week 16 Change	6	-15.3	12.2		-10	
	Week 20 Change	7	-14.1	8.1		-28	
	Week 24 Change	4	-7.8	12.3		-6	
	Week 28 Change	6	-16.7	8.1		-21	
	Week 32 Change	4	-20.3	15.2		-30	
	Week 36 Change	4	-5.5	12.7		-5	
	Week 40 Change	5	-11.0	10.7		-13	
	Week 44 Change	5	-17.0	10.6		-27	
	Week ≥48 Change	4	-11.0	14.0		-13	

* From NDA

Table 15 General Status Quality of Life Questionnaire (Spitzer Items 1-5): Composite of Individual Questions Change from Baseline for Completers Advanced Disease *

Initial Assigned Dose (mg/m^2/day)	Study Visit[2]	Composite of Individual Questions[1]					
		No. Pts.	Mean	SE	Min	Median	Max
300	Day 1 Baseline[3]	35	8.0	0.3		8	
	Week 4 Change	34	0.3	0.2		0	
	Week 8 Change	35	0.5	0.3		0	
	Week 12 Change	32	-0.1	0.3		0	
	Week 16 Change	28	0.2	0.3		0	
	Week 20 Change	21	0.0	0.3		0	
	Week 24 Change	13	0.2	0.6		0	
	Week 28 Change	11	0.8	0.3		1	
	Week 32 Change	11	0.5	0.3		0	
	Week 36 Change	8	0.6	0.5		0	
	Week 40 Change	7	-0.3	0.2		0	
	Week 44 Change	5	-0.2	0.5		0	
	Week 48 Change	3	0.0	0.0		0	
>300	Day 1 Baseline[3]	26	8.2	0.4		9	
	Week 4 Change	25	-0.1	0.4		0	
	Week 8 Change	25	0.1	0.3		0	

1. Spitzer items 1 to 5 are on a scale from 0 to 2.
2. Calculated with Study Visit Interval Algorithm.
3. Except for Day 1 baseline values, all values reported are the change from baseline values.

Note: na = Not applicable.

* From NDA

Table 15 Continued General Status Quality of Life Questionnaire (Spitzer Items 1-5): Composite of Individual Questions Change from Baseline for Completers
Advanced Disease *

Initial Assigned Dose (mg/m^2/day)	Study Visit[2]	Composite of Individual Questions[1]					
		No. Pts.	Mean	SE	Min	Median	Max
>300	Week 12 Change	24	-0.2	0.4		0	
	Week 16 Change	22	0.0	0.3		0	
	Week 20 Change	18	0.7	0.4		0	
	Week 24 Change	16	0.8	0.3		0	
	Week 28 Change	17	0.3	0.3		0	
	Week 32 Change	11	0.7	0.7		0	
	Week 36 Change	10	0.1	0.5		0	
	Week 40 Change	9	0.3	0.7		0	
	Week 44 Change	10	1.0	0.4		1	
	Week 48 Change	8	1.0	0.7		1	
	Week 52 Change	8	1.0	0.7		0	
	Week 56 Change	4	1.8	0.9		2	
	Week =>60 Change	3	-1.3	1.3		0	

1. Spitzer Items 1 to 5 are on a scale from 0 to 2.
2. Calculated with Study Visit Interval Algorithm.
3. Except for Day 1 baseline values, all values reported are the change from baseline values.
Note: na = Not applicable.
* From NDA

Table 16 General Status Quality of Life Questionnaire (Spitzer Item 6): Overall Quality of Life Change from Baseline for Completers Advanced Disease *

Initial Assigned Dose (mg/m^2/day)	Study Visit[2]	Overall Quality of Life[1]					
		No. Pts.	Mean	SE	Min	Median	Max
300	Day 1 Baseline[3]	33	78.9	3.6		89	
	Week 4 Change	31	-3.7	3.5		-1	
	Week 8 Change	31	-5.4	4.2		-6	
	Week 12 Change	28	-7.6	3.2		-5	
	Week 16 Change	26	-10.7	5.0		-10	
	Week 20 Change	20	-12.7	5.0		-8	
	Week 24 Change	13	-4.8	6.1		-1	
	Week 28 Change	11	-6.6	4.2		-4	
	Week 32 Change	11	-8.1	7.0		-6	
	Week 36 Change	8	-2.5	4.7		-2	
	Week 40 Change	7	-4.6	5.7		0	
	Week 44 Change	5	-6.6	7.3		-3	
	Week 48 Change	3	-12.3	8.4		-5	
>300	Day 1 Baseline[3]	26	75.9	5.0		85	
	Week 4 Change	21	-1.5	3.3		-2	
	Week 8 Change	23	-6.4	5.3		-2	

1. Overall Quality of Life is from a visual analogue scale from lowest quality to highest quality converted to scale of 0 to 100 respectively.
2. Calculated with Study Visit Interval Algorithm.
3. Except for Day 1 baseline values, all values reported are the change from baseline values.

Note: na = Not applicable.

* From NDA

Table 16 Continued General Status Quality of Life Questionnaire (Spitzer Item 6): Overall Quality of Life Change from Baseline for Completers
Advanced Disease *

Initial Assigned Dose (mg/m^2/day)	Study Visit[2]	Overall Quality of Life[1]					
		No. Pts.	Mean	SE	Min	Median	Max
>300	Week 12 Change	24	-1.9	5.6		-4	
	Week 16 Change	22	-1.4	4.9		-5	
	Week 20 Change	19	4.6	4.7		-1	
	Week 24 Change	16	2.6	7.3		2	
	Week 28 Change	16	6.1	4.9		1	
	Week 32 Change	11	6.7	7.2		-2	
	Week 36 Change	8	-7.1	8.8		-9	
	Week 40 Change	9	-0.6	7.3		1	
	Week 44 Change	10	2.5	6.7		0	
	Week 48 Change	8	4.8	9.3		2	
	Week 52 Change	8	-1.1	9.0		-4	
	Week 56 Change	4	-2.3	19.7		-15	
	Week =>60 Change	3	-28.7	25.2		-13	

1. Overall Quality of Life is from a visual analogue scale from lowest quality to highest quality converted to scale of 0 to 100 respectively.
2. Calculated with Study Visit Interval Algorithm.
3. Except for Day 1 baseline values, all values reported are the change from baseline values.
Note: na = Not applicable.
From NDA

5. ASSESSMENT OF EFFECT ON PRURITUS

The Applicant's analyses of the effect of Targretin capsules on pruritus is shown in the following Tables 17-19.

In the Early Disease study the median baseline pruritus was 2.5 and 2.1 respectively in patients taking and not taking antipruritics. A score of 2 is a "mild occasional transient itch". Thus a decrease in the median at week 16 by 1 and 0.9 points respectively in patients taking and not taking antipruritics does not represent a clinically significant change in what was not a very clinically significant pruritus at baseline.

Table 17 Early Disease. Index Lesion Pruritus Change From Baseline for Patients Taking and Not Taking Antihistamines/Antipruritics as Concurrent Medication During Study for Initial Assigned Dose 300 mg/m²/day *

	Pruritus[1]								
	Patients Taking Antihistamines/Antipruritics					Patients Not Taking Antihistamines/Antipruritics			
Study Visit[2]	No. Pts. At This Visit[4]	No. Pts. With Pruritus	Min	Median	Max	No. Pts. At This Visit[4]	No. Pts. With Pruritus	Min	Median	Max
Day 1 Baseline[3]	10	6	0.0	2.5	5.0	18	14		2.1	
Week 2	9	6	-2.4	0.0	0.3	12	8		-0.1	
Week 4	10	4	-3.6	-1.5	0.0	13	6		-0.3	
Week 8	10	4	-3.0	-0.9	0.0	12	5		-0.4	
Week 12	7	4	-3.6	-1.8	0.0	12	5		-0.1	
Week 16	6	3	-4.0	-1.0	0.0	10	2		-0.9	
Week 20	4	2	-4.2	0.0	0.7	4	0		0.0	
Week 24	3	2	-4.6	0.0	0.3	5	1		0.0	
Week 28	3	1	-4.6	0.0	0.0	3	0		-0.3	
Week 32	2	1	-4.8	-2.4	0.0	2	0		-0.1	
Week 36	1	1	-4.8	-4.8	-4.8	2	0		-1.5	
Week 40	0	0	NA	NA	NA	2	0		-1.5	
Week 44	0	0	NA	NA	NA	1	0		-3.0	
Week ≥ 48	0	0	NA	NA	NA	0	0		NA	

[1] The average of all index lesions for all patients assessed at each visit is computed. Pruritus graded on a scale of 0 (none) to 8 (very severe).
[2] Calculated with Study Visit Interval Algorithm.
[3] Except for Day 1 baseline values, all values reported are the change from baseline values.
[4] Number of patients with quantitation of pruritus at this visit and at baseline.
* From NDA

In the Advanced Disease study the median pruritus score at baseline was 4.2 and 1.4 respectively in patients taking and not taking antipruritics. The decrease in the median at 16 weeks is 1.0 and 1.8 for patients taking and not taking antipruritics. This does not represent a clinically important change.

Table 18. Advanced Disease Index Lesion Pruritus Change From Baseline for Patients Taking Antihistamines/Antipruritics As Concurrent Medication During Study for Initial Assigned Dose 300 mg/m^2/day *

(N = 33)

			Pruritus[1]					
Study Visit[2]	No. Pts. At This Visit	No. Pts. With Pruritus	N[4]	Mean	SE	Min	Median	Max
Day 1 Baseline[3]	33	31	33	4.4	0.4		4.2	
Week 2	32	28	32	-1.1	0.3		-0.5	
Week 4	31	25	31	-1.5	0.4		-1.4	
Week 8	28	22	28	-1.6	0.5		-1.4	
Week 12	24	19	24	-1.2	0.6		-1.5	
Week 16	17	14	17	-1.2	0.4		-1.0	
Week 20	11	9	11	-2.7	0.6		-1.8	
Week 24	9	6	9	-3.2	0.7		-2.4	
Week 28	9	5	9	-2.8	0.9		-2.0	
Week 32	8	3	8	-3.1	0.8		-2.2	
Week 36	5	2	5	-3.1	1.2		-2.0	
Week 40	4	1	4	-4.2	1.5		-3.6	
Week 44	2	0	2	-4.9	3.1		-4.9	
Week ≥48	2	0	2	-3.6	1.8		-3.6	

[1]The average of all index lesions for all patients assessed at each visit is computed. Pruritus graded on a scale of 0 (none) to 8 (very severe).

[2]Calculated with Study Visit Interval Algorithm.

[3]Except for Day 1 baseline values, all values reported are the change from baseline values.

[4]Number of patients with quantitation of pruritus at this visit and at baseline.

* From NDA

Table 19. Advanced Disease. Index Lesion Pruritus Change From Baseline for Patients Not Taking Antihistamines/Antipruritics As Concurrent Medication During Study for Initial Assigned Dose 300 mg/m²/day *

(N = 23)

Study Visit[2]	No. Pts. At This Visit	No. Pts. With Pruritus	Pruritus[1]					
			N[4]	Mean	SE	Min	Median	Max
Day 1 Baseline[3]	23	20	23	1.9	0.3		1.4	
Week 2	21	14	21	-0.8	0.2		-0.6	
Week 4	20	12	20	-1.3	0.3		-0.8	
Week 8	19	11	19	-1.4	0.4		-0.8	
Week 12	13	7	13	-1.0	0.7		-0.4	
Week 16	10	6	10	-1.9	0.5		-1.8	
Week 20	9	4	9	-2.2	0.6		-2.8	
Week 24	4	1	4	-2.8	0.8		-3.4	
Week 28	3	1	3	-2.5	1.1		-3.0	
Week 32	2	0	2	-1.8	1.4		-1.8	
Week 36	2	1	2	-2.7	0.5		-2.7	
Week 40	2	2	2	-2.8	0.2		-2.8	
Week 44	2	1	2	-1.6	1.6		-1.6	
Week ≥48	0	0	0	NA	NA		NA	

[1] The average of all index lesions for all patients assessed at each visit is computed. Pruritus graded on a scale of 0 (none) to 8 (very severe).
[2] Calculated with Study Visit Interval Algorithm.
[3] Except for Day 1 baseline values, all values reported are the change from baseline values.
[4] Number of patients with quantitation of pruritus at this visit and at baseline.
NA = Not applicable.

* From NDA

6. ASSESSMENT OF EFFECT ON NON CUTANEOUS CTCL

Targretin Capsules are not shown to have much impact on the non cutaneous aspects of CTCL with the possible exception of clinically abnormal (not histologically positive) lymph nodes.

7. EFFECT ON SERUM TRIGLYCERIDES

The following Tables 20 and 21 show the extent of elevated serum triglycerides in the studies in early and advanced disease. In the early disease study 30 of 58 patients had a serum triglyceride of ≥ 800 mg/dL on one or more occasions during the study. In the advanced disease study 53 of 94 patients had a serum triglyceride of ≥ 800 mg/dL on one or more occasions during the study.

Table 20
Patients With
Triglycerides ≥ 800 mg/dL

	N	Pts with TG ≥ 800 (%)	Median	Mean	Max	Min
Early Dis	58	32 (55)	1234	1458	4290	806
Advanced Dis	94	53 (56)	1223	1491	5440	801

Table 21
Number Determinations with
Triglycerides ≥ 800 mg/dL
Per Patient

	N	Median	Mean	Max	Min
Early Disease	32	2	2.8	12	1
Advanced Disease	53	3	3.4	11	1

8. SUMMARY

- The lack of full body photographs as required by the protocol makes it impossible to confirm the claimed PGA tumor responses. This is the most important aspect of the efficacy evaluation and the lack of photographs is a serious deficiency.

- Ligand's claimed tumor responses using the Composite Assessment of Index lesions are generally confirmed by the FDA by examining the photographs. Many of the FDA confirmations and non conformations of Ligand's claimed tumor responses on the Composite Assessment of Index Lesions represent close calls, indicating the tumor responses in some patients were at best marginal.

- Assessment of tumor response based on Composite Assessment of Index Lesions and Physicians Global Assessment criteria differs from the tumor response assessment criteria used in most published studies of CTCL. Thus it is difficult to compare the results in the Targretin studies with the results of other treatments.

- For assessment of tumor response rate based on % of BSA involved I have used more standard criteria than those used by Ligand. Response rates (at least a 50% reduction for two visits) were 37% and 33% in Early and Advanced Disease respectively. Again the full body photographs are needed to confirm this.

- There is an unexplained discrepancy between results on the Spitzer and CTCL Specific Global QOL Assessments. The Spitzer Global shows worsening while the CTCL Specific Global shows improvement.

- Targretin is not shown to have much effect on the non cutaneous aspects of CTCL with the possible exception of clinically abnormal (not histologically positive) lymph nodes.

- There were elevated serum triglycerides ≥ 800 mg/dL in more than half of the patients in the Early and Advanced Disease studies.

  Sixty per cent of patients taking Targretin Capsules in the 300 mg/m2 initial dose group (the proposed dose for marketing) required lipid lowering agents.

  There were 4 patients with acute pancreatitis requiring hospitalization.

9. ODAC MEETING

Questions to the Committee on December 13, 1999

1. Does the Committee believe that a clinically meaningful tumor response rate using acceptable tumor response criteria has been adequately

demonstrated?

YES – 11 NO – 4 Abstain – 1

2. Has clinical benefit other than tumor response been adequately demonstrated?

YES – 0 NO – 14 Abstain – 2

3. Are the patient populations in the Early Disease study and the Advanced Disease study adequately characterized in terms of the following:

a) Prior therapies?

YES – 15 NO – 1 Abstain – 0

b) Response to prior therapies?

YES – 1 NO – 14 Abstain – 1

c) Reason for discontinuing or not repeating prior therapies?

YES – 1 NO – 13 Abstain – 2

4. Given the availability of other systemic chemotherapy agents active in this disease, should Targretin Capsules be compared to another systemic therapy in a randomized controlled clinical trial? (Question 4 was answered AFTER Questions 5 and 6.)

a) in Early Disease?

YES – 5 NO – 6 Abstain – 5

b) in Advanced Disease?

YES – 8 NO – 4 Abstain – 4

The Committee indicated that randomized controlled clinical trials would be useful in determining the true benefit of the drug in this very heterogeneous disease. The trials should be done before approval for Early Disease and be directed toward demonstration of clinical benefit as well as tumor response. For Advanced Disease, the trial could be done post-approval.

5. In view of the risks are the benefits adequate to warrant approval of Targretin Capsules for treatment of the patient population in the Early Disease study?

YES – 5 NO – 7 Abstain – 4

6. In view of the risks are the benefits adequate to warrant approval of Targretin Capsules for treatment of the patient population in the Advanced Disease study?

YES – 13 NO – 2 Abstain – 1

The Committee considers that this is an active agent to treat a rare disease and that it will be beneficial to some patients. There were concerns about the long term risks, especially of the significant hypertriglyceridemia, and would like to see careful followup on the patients who use the drug chronically.

10. RECOMMENDATIONS

A) I concur with the Advisory Committee's recommendation to approve Targretin Capsules treatment of cutaneous manifestations of Advanced CTCL in patients who are refractory to at least one prior systemic therapy. I would expand the indication slightly to include cutaneous manifestations of Early CTCL in patients who are refractory to at least one prior systemic therapy. There were 12 such patients in the 43 patients in the Early Disease study at the ≥ 300 mg/m2 initial dose and 8 had a tumor response. This indication expansion would appropriately accommodate a few selected Early disease patients. It would also accommodate the Committee's concern that most Early disease patients should not be treated with Targretin Capsules because of the safety concerns with prolonged Targretin Capsule administration.

Regarding the rationale for approval I believe the results of the Early Disease and Advanced Disease studies support each other even though the risk/benefit ratio does not support approval for most patients with Early Disease. I believe that a tumor response in this miserable cutaneous disease can be assumed to indicate clinical benefit, especially in the population recommended for approval. It is disappointing that clinical benefit was not demonstrated in the clinical trials. That is one of the

reasons for requiring a commitment for a Phase IV randomized controlled clinical trial as a condition of approval.

The rationale for not approving Targretin capsules for patients with Early disease who are not refractory to at least one prior systemic therapy is the concern for the safety of prolonged administration of Targretin Capsules in patients who have a prolonged disease course and who have less severe disease than the Advanced Disease patients.

B) I concur with the Committee's recommendation to require a commitment from Ligand to conduct a Phase IV randomized controlled clinical trial in patients with CTCL. This will address the best dose of Targretin Capsules, better delineate the tumor response rate and assess the effect on pruritus, other tumor related symptoms and quality of life. The wording for this requirement is as follows:

As a condition of approval Ligand must commit to conduct a randomized controlled clinical trial in patients with cutaneous T cell lymphoma. At the time of the commitment at a minimum a synopsis of the protocol for this trial must be submitted along with estimated dates for initiating the trial, completing patient accrual, a cut off date for study analysis and for submitting the study results and analysis to the FDA. The trial should compare two dose levels of Targretin. We suggest 100 and 300 mg/m2. The primary endpoint should be tumor response according to the Physician's Global Assessment, the Composite Assessment of Index Lesion Severity and the percent of Body Surface Area Involvement with tumor. Tumor responses must be documented with photographs of Index lesions and full body photographs (front and back). Time to tumor response, time to tumor progression and tumor response duration should also be assessed. The effect on pruritus and other tumor specific symptoms should be assessed. Quality of life should also be assessed.

C) The Package Insert and Patient Package Insert require revision. Please see the documents submitted by Ligand with revisions by all of the FDA review disciplines.

/S/

John R. Johnson, M.D.
December 23, 1999