

SECONDARY EFFICACY CRITERIA

Body Surface Area (BSA):

The BSA was a key secondary efficacy criterion. The percentage of the body surface covered by plaques or patches were measured at baseline and at each visit.

Tables 14 and 15 summarize the overall BSA involvement and change in BSA involvement respectively for the >300 mg/m²/day initial dose group. The median overall BSA involvement by CTCL was 15% (range 1.0% to 100%) at baseline. After an initial rise at week 2, the change in the median BSA involvement then showed a gradual decrease beginning at Week 4 and reaching a peak of 18% decline as of Week 48 or later. The 6.5 mg/m²/day initial dose group had no appreciable change in BSA involvement.

Table 16 Total Overall CTCL-Involved Body Surface Area for Initial Assigned Dose 300 mg/m²/day

Study Visit	No. Pts. At This Visit	No. Pts. With Area	Total Percent Body Surface Area Involvement				
			Mean	SE	Min	Median	Max
Day 1	28	28	40.1	4.9	2.0	38.5	90.0
Week 2	7	7	47.2	9.0	30.0	32.2	90.0
Week 4	22	22	37.4	5.4	3.0	41.8	90.0
Week 8	22	22	36.3	5.3	0.2	36.0	90.0
Week 12	19	17	36.7	6.0	0.2	40.0	90.0
Week 16	15	14	31.3	6.7	0.2	32.5	90.0
Week 20	8	8	31.8	7.7	1.5	34.5	65.0
Week 24	8	8	23.5	6.6	0.5	34.5	40.0
Week 28	6	6	20.0	8.2	1.0	18.5	40.0
Week 32	4	4	19.7	10.3	1.9	18.5	40.0
Week 36	3	3	6.0	4.5	1.0	2.0	15.0
Week 40	2	2	1.2	0.7	0.5	1.2	1.9
Week 44	1	1	0.5	NA	0.5	0.5	0.5
Week ≥ 48	0	0	NA	NA	NA	NA	NA

Table 17 Total Overall CTCL-Involved Body Surface Area Change From Baseline for Initial Assigned Dose 300 mg/m²/day

Study Visit	No. Pts. At This Visit	No. Pts. With Area	N ⁽⁴⁾	Total Percent Body Surface Area Involvement				
				Mean	SE	Min	Median	Max
Day 1 Baseline	28	28	28	40.1	4.9	2.0	38.5	90.0
Week 2	7	7	7	-4.1	4.0	-26.8	0.0	5.0
Week 4	22	22	22	-5.1	3.6	-56.0	-1.0	43.0
Week 8	22	22	22	-9.4	4.4	-58.8	-0.8	28.0
Week 12	19	17	19	-13.8	5.2	-58.8	-2.3	28.0
Week 16	15	14	15	-16.9	6.5	-58.8	-5.0	28.0
Week 20	8	8	8	-7.9	8.7	-46.0	-4.6	28.0
Week 24	8	8	8	-13.1	10.0	-46.0	-16.5	38.0
Week 28	6	6	6	-7.1	10.0	-29.0	-10.0	38.0
Week 32	4	4	4	-13.0	5.6	-28.0	-10.0	-3.9
Week 36	3	3	3	-19.3	7.8	-29.0	-25.0	-3.8
Week 40	2	2	2	-16.7	12.8	-29.5	-16.7	-3.9
Week 44	1	1	1	-29.5	NA	-29.5	-29.5	-29.5
Week ≥ 48	0	0	0	NA	NA	NA	NA	NA

Area of Individual Index Lesions

The surface area for index lesions measured at each study visit is summarized by initial dose groups in Tables 18. A consistent decrease in the median index lesion aggregate surface area was observed for patients in the 300 mg/m²/day initial dose group, from 99.1 cm² at baseline to 55.1 cm² by Week 16. Similar improvement was observed in the >300 mg/m²/day initial dose group, but mixed changes were noted in the 6.5 mg/m²/day initial dose group. The reduction in aggregate surface area of index lesions correlates with improvement in overall body surface area of involvement by CTCL

Table 18 Index Lesion Area Change From Baseline for Initial Assigned Dose 300
 mg/m²/day

Study Visit	No. Pts. At This Visit	No. Pts. With Area	N	Aggregate Area(cm ²)				
				Mean	SE	Min	Median	Max
Day 1 Baseline	28	28	28	130.4	21.2	4.9	99.1	446.0
Week 2	21	21	21	9.3	16.8	-60.5	0.0	332.0
Week 4	23	23	23	-26.2	13.2	-268.0	-4.5	27.3
Week 8	22	22	22	-26.0	15.1	-294.3	-4.5	46.3
Week 12	19	18	19	-27.4	18.0	-294.3	-4.0	58.8
Week 16	16	16	16	-32.3	20.9	-292.0	-5.4	52.4
Week 20	8	7	8	-17.9	20.7	-101.8	-23.9	78.6
Week 24	8	7	8	-29.0	22.3	-126.4	-25.7	95.2
Week 28	6	5	6	-34.6	8.9	-67.8	-31.1	-5.5
Week 32	4	3	4	-76.6	32.3	-160.1	-69.6	-7.0
Week 36	3	2	3	-29.2	15.1	-58.0	-22.6	-7.1
Week 40	2	1	2	-34.1	11.4	-45.5	-34.1	-22.6
Week 44	1	0	1	-22.6	NA	-22.6	-22.6	-22.6
Week ≥ 48	0	0	0	NA	NA	NA	NA	NA

Pigmentation

Few patients in the study had hypo/hyperpigmentation at baseline, and there was little change in hypo/hyperpigmentation during the study for any initial dose group.

Pruritus

Pruritus was an independent protocol-specified secondary efficacy endpoint in this study. It was however not integrated into the CA primary efficacy endpoint, although the protocol specified that this would be done.

The study drug effects on pruritus were analyzed for all patients regardless of concurrent use of antihistamine/ antipruritic. An analysis was also performed for these two subgroups. The 43% (25/58) of patients with one or more antipruritic medications overlapping with study drug administration comprised the population of patients with concurrent antipruritic therapy. The complementary subset of 57% (33/58) of patients,

with no concomitant antipruritic medication, comprised the data set of patients with no concurrent antipruritic therapy.

The median degree of pruritus of index lesions at baseline was similar for all three initial dose groups, and ranged, on a scale of 0 (none) to 8 (very severe, unrelieved itch, prevents routine activities, awakens patient from sleep), (2 = mild, occasional transient itch on lesions; 4 = moderate, frequent itch every 1-3 hours, reflex scratching).

The change from baseline in pruritus for all patients (both with and without concurrent antipruritics) is summarized for the 300 mg/m²/day initial dose group in Table 17. The median degree of pruritus began to decrease from Week 4.

The median and mean degrees of pruritus at Day 1 (2.1 and 2.3, respectively) had decreased by -1.0 and -1.2 by Week 4, reached -0.9 and -1.6 by Week 16, increased to 0.0 by Week 16, half of the patients assessed had experienced a decrease in pruritus between -0.9 and -4.0 grades.

Table 19 Index Lesion Pruritus Change From Baseline for Initial Assigned Dose 300 mg/m²/day

Study Visit ⁽²⁾	No. Pts. At This Visit ⁽⁴⁾	No. Pts. With Pruritus	Pruritus					
			N ⁽⁴⁾	Mean	SE	Min	Median	Max
Day 1 Baseline ⁽³⁾	28	20	28	2.3	0.4	0.0	2.1	8.0
Week 2	21	14	21	-0.3	0.3	-2.4	0.0	3.0
Week 4	23	10	23	-1.2	0.3	-3.8	-1.0	1.0
Week 8	22	9	22	-1.1	0.4	-3.8	-0.7	3.1
Week 12	19	9	19	-1.3	0.4	-3.8	-0.3	0.6
Week 16	16	5	16	-1.6	0.4	-4.0	-0.9	0.0
Week 20	8	2	8	-0.8	0.6	-4.2	0.0	0.7
Week 24	8	3	8	-0.9	0.7	-4.6	0.0	0.4
Week 28	6	1	6	-1.3	0.8	-4.6	-0.1	0.0
Week 32	4	1	4	-1.3	1.2	-4.8	-0.1	0.0
Week 36	3	1	3	-2.6	1.4	-4.8	-3.0	0.0
Week 40	2	0	2	-1.5	1.5	-3.0	-1.5	0.0
Week 44	1	0	1	-3.0	NA	-3.0	-3.0	-3.0
Week ≥ 48	0	0	0	NA	NA	NA	NA	NA

For the entire study population of patients (those taking and not taking antipruritics), a progressive decrease in index lesion pruritus was observed for patients in the 300

mg/m²/day initial dose group, from a baseline of midway between mild (occasional transient itch) and moderate (frequent itch every 1-3 hours, reflex scratching), to a point midway between no pruritus and mild by Week 16. A much less pronounced pattern of pruritus reduction was observed in the 6.5 and >300 mg/m²/day initial dose groups.

The findings at the 300 mg/m²/day initial dose group were generally supported by data in the 6.5 and >300 mg/m²/day initial dose groups.

Table 20 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

Study Visit	Pruritus									
	Patients <u>Taking</u> Antihistamines/Antipruritics					Patients <u>Not Taking</u> Antihistamines/Antipruritics				
	No. Pts. At This Visit	No. Pts. With Pruritus	Min	Median	Max	No. Pts. At This Visit	No. Pts. With Pruritus	Min	Median	Max
Day 1										
Baseline	10	6	0.0	2.5	5.0	18	14	0.0	2.1	8.0
Week 2	9	6	-2.4	0.0	0.3	12	8	-1.4	-0.1	3.0
Week 4	10	4	-3.6	-1.5	0.0	13	6	-3.8	-0.3	1.0
Week 8	10	4	-3.0	-0.9	0.0	12	5	-3.8	-0.4	3.1
Week 12	7	4	-3.6	-1.8	0.0	12	5	-3.8	-0.1	0.6
Week 16	6	3	-4.0	-1.0	0.0	10	2	-3.8	-0.9	0.0
Week 20	4	2	-4.2	0.0	0.7	4	0	-3.0	0.0	0.0
Week 24	3	2	-4.6	0.0	0.3	5	1	-3.0	0.0	0.4
Week 28	3	1	-4.6	0.0	0.0	3	0	-3.0	-0.3	0.0
Week 32	2	1	-4.8	-2.4	0.0	2	0	-0.3	-0.1	0.0
Week 36	1	1	-4.8	-4.8	-4.8	2	0	-3.0	-1.5	0.0
Week 40	0	0	NA	NA	NA	2	0	-3.0	-1.5	0.0
Week 44	0	0	NA	NA	NA	1	0	-3.0	-3.0	-3.0
Week ≥ 48	0	0	NA	NA	NA	0	0	NA	NA	NA

Pigmentation:

Few patients in the study had hypo/hyperpigmentation at baseline, and there was little change in hypo/hyperpigmentation during the study for any initial dose group.

Lymph Nodes

Clinically Abnormal Lymph Nodes

Clinically abnormal lymph nodes were defined in the protocol as having a minimal diameter of one centimeter. Eight patients enrolled had Stage IIA disease at baseline, indicating the presence of clinically abnormal lymph nodes. Of these, seven patients are shown as having clinically abnormal nodes because; four patients had two lymph nodes, one had one node, one had eight nodes and one with an unknown number of nodes. For the 300 mg/m²/day initial dose group, the two Stage IIA patients had two nodes each. For the 6.5, 300 and >300 mg/m²/day initial dose groups respectively, 13% (2/15), 11% (3/28) (only 7% [2/28] with the number of nodes recorded on CRF), and 13% (2/15) had clinically abnormal lymph nodes at baseline. The number of patients with one or more clinically abnormal nodes never varied more than from zero to three in any one of the three initial dose groups, except for one patient with four nodes later increasing to eight nodes between Study Day 99 to 113 (Patient 273 at Center 023). Some patients had a node appear for one assessment only, then disappear (e.g., Patient 005 at Center 014, Patient 010 at Center 014).

The median lymph node status did not change from baseline during the first 28 weeks of the study. There was very little demonstrable improvement in lymphadenopathy in this group of patients.

Quality of Life Measures

Patient Quality of Life Questionnaires

Two QoL questionnaires were used to track improvements in a patient's well-being: (1) the Spitzer questionnaire, which included six items dealing with a patient's general status, and (2) the CTCL-specific questionnaire, which included nine items dealing with the status of the CTCL condition. These two questionnaires were to be administered at baseline and every four weeks during the study. Questions 8 and 9 of the CTCL-specific questionnaire, that asked about change in comparison to prior to participation in the study and about overall level of satisfaction with study drug treatment were not posed at the baseline, Day 1, visit.

Spitzer Quality of Life Questionnaire

The results from the individual questions in the Spitzer questionnaire at baseline and then the change from baseline at other study time points were summarized separately for patients who did not complete the first 16-week evaluations (non-completers) and those that did (completers). Too few patients in the non-completer group completed questionnaires at times other than baseline, so no conclusions can be drawn from their QoL data. Therefore, only the data from the completers were discussed by the sponsor. Based upon the time-on-study distribution of patients, a cutoff point of 16 weeks was made. The 62% (36/58) of patients who had been on study for 16 weeks or longer as of the database closure for this report were defined as completers. The 38% (22/58) of patients who had not completed 16 weeks on study as of database closure were defined as non-completers.

Overall, there was very little change for nearly all of the questions for all three dose groups. Too few patients in the non-completer group completed questionnaires at times other than baseline, so no conclusions can be drawn from their QoL data. The composite data in Table 21 for the first five questions show that the mean composite scores at baseline, over a possible range of 0 to 10, were 9.5 for the 6.5 mg/m²/day initial dose group, 8.4 for the 300 mg/m²/day initial dose group, and 9.2 for the >300 mg/m²/day initial dose group. Patients in all three initial dose groups rated their general status in all five question areas quite high, leaving very little room for improvement due to drug therapy. The data do show a modest improvement of up to +0.8 (with a possible range of 0, worse, to 10, better) in the mean composite score from Week 4 to 24 for the 300 mg/m²/day initial dose groups, but little change in the other dose groups.

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 by the sponsor to millimeter 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. The mean value at baseline was 94.2 (N=6), 84.3 (N=16), and 76.4 (N=10) for the 6.5, 300, and >300 mg/m²/day initial dose groups, respectively, showing that these early stage patients rated their overall quality of life moderately high. After Day 1 there appeared to be a general but modest downward trend in values for all three initial dose groups, but the

significance of this is unclear. The number of completers in the 300 mg/m²/day initial dose group contributing data at Day 1 (N = 16) drops to 13 at Week 16, then to only seven patients at Week 20, and gradually tapers off to only one patient at Week 44. Overall the patients rated their general status for all six questions on the general status questionnaire quite high in all three initial dose groups, leaving very little room for improvement by the drug treatment. There were no substantial trends for any dose group.

**APPEARS THIS WAY
ON ORIGINAL**

Table 21 General Status Quality of Life Questionnaire (Spitzer Items 1-5): Composite of Individual Questions Change From Baseline for Completers (N=36)

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

Table 22 General Status Quality of Life Questionnaire (Spitzer Item 6): Overall Quality of Life Change From Baseline for Completers (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	89	95	99
	Week 4 Change	6	-10.3	8.2	-50	-5	6
	Week 8 Change	4	-26.0	12.0	-52	-24	-5
	Week 12 Change	4	-24.3	11.0	-53	-21	-3
	Week 16 Change	5	-13.2	9.7	-48	-3	5
	Week 20 Change	4	-16.3	10.6	-48	-7	-3
	Week 24 Change	1	-3.0	na	-3	-3	-3
	Week 28 Change	1	-2.0	na	-2	-2	-2
	Week 32 Change	1	-4.0	na	-4	-4	-4
	Week 36 Change	1	3.0	na	3	3	3
	Week 40 Change	1	4.0	na	4	4	4
	Week 44 Change	1	4.0	na	4	4	4
	Week ≥48 Change	1	2.0	na	2	2	2
300	Day 1 Baseline	16	84.3	3.2	58	89	100
	Week 4 Change	14	-8.3	3.6	-40	-6	9
	Week 8 Change	14	-11.8	4.4	-46	-8	18
	Week 12 Change	15	-5.2	4.1	-28	-7	35
	Week 16 Change	13	-5.7	3.0	-25	-2	13
	Week 20 Change	7	-13.3	4.2	-33	-11	1
	Week 24 Change	6	-19.0	6.4	-46	-18	1
	Week 28 Change	5	-9.0	4.2	-18	-13	3
	Week 32 Change	3	-11.7	10.7	-33	-2	0
	Week 36 Change	2	-20.5	22.5	-43	-21	2
	Week 40 Change	2	-16.0	16.0	-32	-16	0
	Week 44 Change	1	-16.0	na	-16	-16	-16
	>300	Day 1 Baseline	10	76.4	5.3	47	80
Week 4 Change		7	-8.7	7.6	-33	-6	25
Week 8 Change		9	-8.6	6.6	-47	-7	21
Week 12 Change		9	-8.0	5.5	-35	-9	24
Week 16 Change		6	-15.3	12.2	-68	-10	13
Week 20 Change		7	-14.1	8.1	-33	-28	24
Week 24 Change		4	-7.8	12.3	-39	-6	20
Week 28 Change		6	-16.7	8.1	-35	-21	19
Week 32 Change		4	-20.3	15.2	-45	-30	24
Week 36 Change		4	-5.5	12.7	-37	-5	24
Week 40 Change		5	-11.0	10.7	-41	-13	25
Week 44 Change		5	-17.0	10.6	-37	-27	23
Week ≥48 Change		4	-11.0	14.0	-43	-13	25

CTCL-Specific Quality of Life Questionnaire

For the individual questions on the CTCL-specific patient questionnaire, the summaries are also compiled separately for patients who did not complete the first 16-week evaluations (non-completers) and those who did (completers). Too few patients in the non-completer group completed questionnaires at times other than baseline, so no conclusions can be drawn from their QoL data.

The first part of the questionnaire, Questions 1a – 1e, deals with overall feelings in five categories, while Questions 2 – 9 are specific to the patients CTCL condition and study drug treatment. The patients generally rated themselves feeling good in all the categories. On a possible range of 0 (worst) to 40 (best) for this composite, the baseline median composite scores were 34 (mean 34.3) for the 6.5 mg/m²/day initial dose group, 32 (mean 30.3) for the 300 mg/m²/day initial dose group, and 32 (mean 30.5) for the >300 mg/m²/day initial dose group. The composite data for Questions 1a – 1e, showed a mean decrease in the QoL in the range of about –3 to –4 for most weeks for the 6.5 and >300 mg/m²/day initial dose groups, but no consistent change for patients in the 300 mg/m²/day initial dose group.

Patients generally rated themselves feeling good in the categories about overall feelings, with relatively high baseline composite scores in the range of 30 to 34 (over a possible range of 0 to 40). Overall, there was little change in these scores due to study drug therapy. The CTCL disease-specific questions on the CTCL-specific questionnaire showed improvement for the 300 mg/m²/day initial dose group that was often not reflected by the 6.5 mg/m²/day initial dose group or >300 mg/m²/day initial dose group. The sponsor reported improvement for the 300mg/m²/day initial dose group in responses to CTCL disease-specific quality of life questionnaire. This trend was however, not often reflected in the remaining two dose groups.

Table 29 is a summary of the CTCL-Specific Questions for 300 mg/m²/day Initial Dose Group.

Table 23 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	Mild-Moderate	Minimal
Q3	Redness, scaling and/or plaque elevation	Moderate	Minimal-Mild
Q4	Physical appearance with respect to CTCL	Moderately Dissatisfied to Neutral	Moderately Satisfied
Q5	Work activity interference	Minimally to Mildly Disruptive	Not at all to Minimally Disruptive
Q6	Social activity interference	Minimally to Mildly Disruptive	Not at all to Minimally Disruptive
Q7	Physical activity interference	Minimally to Mildly Disruptive	Not at all to Minimally Disruptive
Q8	Change in CTCL	(N/A - change from baseline question)	100% Moderately to Much Improved
Q9	Overall Satisfaction/Dissatisfaction with Study Drug	(N/A - change from baseline question)	100% Moderately to Very Satisfied

Survival / Deaths

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.

3 of the 58 enrolled patients died beyond the protocol-specified follow-up period. One patient (Patient #145 Center 181) with Stage IB CTCL at baseline who started therapy at 500 mg/m²/day initial dose and discontinued therapy at this same dose level was respiratory and circulatory failure due to *Pneumocystis carinii* pneumonia (PCP), on Study Day 108, after discontinuation of study drug. He had been hospitalized on Study Day 30 with cholestatic jaundice with associated hepatitis and acute pancreatitis, both assessed as related to study drug.

A second patient (Patient 183, Center 015) with Stage IIB CTCL on 6.5 mg/m²/day initial dose and then crossed over to 300 mg/m²/day (initial dose on Study Day 57) died reportedly from progression of the underlying CTCL

The third patient (Patient 147 Center 181) with Stage IB CTCL started therapy at 300 mg/m²/day initial dose died of myocardial infarction.

Supportive Efficacy Data

Index Lesion and Regional Index Lesion Photographs

Photographs were obtained for the purpose of providing supporting data for the efficacy endpoint of patient index lesion response.

The applicant reports the observation that the change in appearance of CTCL lesions in the photographs generally followed the trend of responses that were captured in the Investigators' index lesion assessments in the CRFs. Electronic digital images and photographic prints of all index lesions and regional index lesion photographs obtained during the studies for all patients meeting criteria for the Primary Endpoint Classification of response were sorted and catalogued.

9.6 SAFETY RESULTS

A total of 98 % of enrolled patients in the study experienced at least one adverse event (AE). The incidence of AEs increased in relation to increased dose across the three initial dose groups.

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

Hypertriglyceridemia	71%
Hypercholesterolemia	36%
Headaches	36%
Hypothyroidism	29%
Pruritus	18%
Nausea	18%
Asthenia	14%
Chills	11%
Abdominal Pains	11%
Exfoliative dermatitis	11%

Pancreatitis

5.2%

Details of the adverse events and their severity are as indicated in Table 24 and Figure 1

The most common laboratory abnormality associated with Targretin treatment was elevation of triglycerides and cholesterol levels. The increased values occurred within 2 to 4 weeks of initiation of treatment. There was associated abdominal pains and pancreatitis related to the elevated hyperlipidemia. The range of triglyceride level was 222-3,120 mg/dl. Other frequent laboratory abnormalities were, abnormal tests of liver function and thyroid function, leukopenia, anemia.

APPEARS THIS WAY
ON ORIGINAL

**Table 24 All Adverse Events With Overall Incidence $\geq 10\%$
(in All Initial Dose Groups Combined)**

Body System	Adverse Event	Initial Assigned Dose Group (mg/m ² /day)				Overall N = 58 n (%)
		Pre ⁽¹⁾	Pre/Post ⁽²⁾		>300	
		6.5 N = 15 n (%)	6.5 N = 15 n (%)	300 N = 28 n (%)	N = 15 n (%)	
Body as a Whole	Altered Hormone Level	2 (13.3)	2 (13.3)	3 (10.7)	2 (13.3)	7 (12.1)
	Asthenia	5 (33.3)	8 (53.3)	4 (14.3)	9 (60.0)	21 (36.2)
	Chills	0 (0.0)	0 (0.0)	4 (14.3)	3 (20.0)	7 (12.1)
	Headache	3 (20.0)	3 (20.0)	13 (46.4)	11 (73.3)	27 (46.6)
	Infection	2 (13.3)	2 (13.3)	1 (3.6)	4 (26.7)	7 (12.1)
	Pain	0 (0.0)	2 (13.3)	4 (14.3)	5 (33.3)	11 (19.0)
	Pain Abdomen	2 (13.3)	2 (13.3)	4 (14.3)	0 (0.0)	6 (10.3)
Digestive	Diarrhea	1 (6.7)	3 (20.0)	2 (7.1)	6 (40.0)	11 (19.0)
	Nausea	0 (0.0)	0 (0.0)	7 (25.0)	2 (13.3)	9 (15.5)
Endocrine	Hypothyroidism	2 (13.3)	7 (46.7)	8 (28.6)	8 (53.3)	23 (39.7)
Hemic & Lymphatic	Anemia	1 (6.7)	2 (13.3)	1 (3.6)	4 (26.7)	7 (12.1)
	Anemia Hypochromic	1 (6.7)	2 (13.3)	1 (3.6)	3 (20.0)	6 (10.3)
	Leukopenia	2 (13.3)	3 (20.0)	5 (17.9)	8 (53.3)	16 (27.6)
Metabolic & Nutritional	Hypercholesteremia	2 (13.3)	6 (40.0)	10 (35.7)	12 (80.0)	28 (48.3)
	Hyperlipemia	6 (40.0)	11 (73.3)	20 (71.4)	15 (100.0)	46 (79.3)
	LDH Increase	1 (6.7)	3 (20.0)	1 (3.6)	3 (20.0)	7 (12.1)
	SGOT Increase	0 (0.0)	2 (13.3)	2 (7.1)	2 (13.3)	6 (10.3)
	SGPT Increase	0 (0.0)	2 (13.3)	2 (7.1)	2 (13.3)	6 (10.3)
Skin & Appendages	Dermatitis exfoliation	1 (6.7)	2 (13.3)	3 (10.7)	6 (40.0)	11 (19.0)
	Pruritus	3 (20.0)	6 (40.0)	6 (21.4)	3 (20.0)	15 (25.9)
	Rash	3 (20.0)	3 (20.0)	4 (14.3)	2 (13.3)	9 (15.5)
	Skin Disorder	2 (13.3)	3 (20.0)	2 (7.1)	3 (20.0)	8 (13.8)

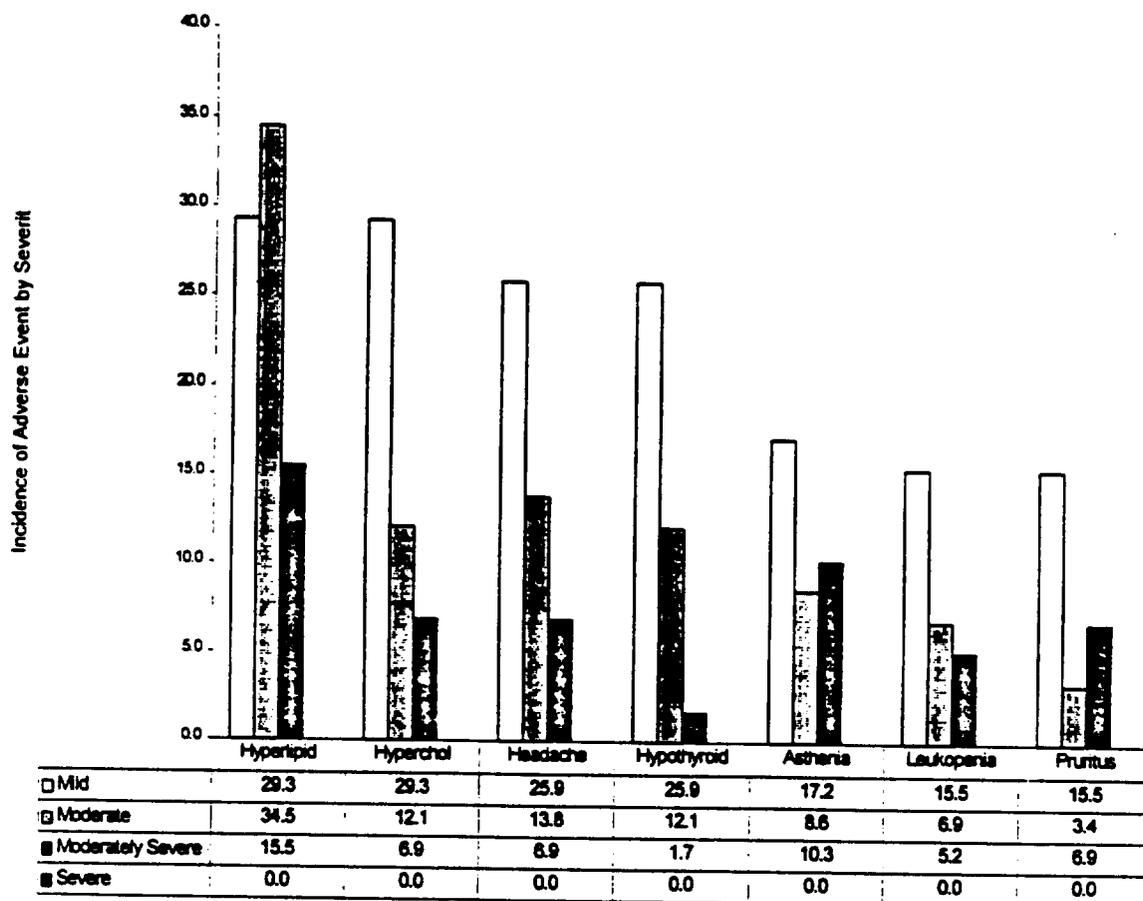
⁽¹⁾ Data prior to cross-over to higher dose.

⁽²⁾ Data from pre and post cross-over periods

**APPEARS THIS WAY
ON ORIGINAL**

Figure 1 Severity of Adverse Events With an Overall Incidence of $\geq 25\%$

N = 58



8.3 FDA REVIEWER'S ASSESSMENT Protocol L-1069-23

Demographics:

65 patients were screened for entry in this study, and 58 were enrolled. 51 of the 58 patients 88% had Stage 1 disease. This implies that the majority of patients enrolled in this study had very minimal disease.

A review of the CRF indicates Patient #91 (Investigator #167) had 13 CTCL skin lesions with no other disease manifestation. Similarly, Patient 147 (Investigator #181) had less than 20 (10) CTCL lesions and "circulating abnormal T cells", but no abnormal T cells are on record. These two patients are therefore more appropriately in Stage 1A disease. This further increases the number of patients in Stage 1A to 53 or 91.4%

The median duration of first manifestation of disease is 10.6 years, with a range of 2 to 59 years. These patients appeared to have extremely indolent disease, in whom a true effect of drug therapy will be difficult to demonstrate in a non-randomized study

Refractoriness of Disease: One of the objectives of the study is to determine activity of Targretin in a population of patients who are, refractory, intolerant or reached a plateau after 6 months on prior anti-CTCL therapies.

There is a question whether all the patients in this study were truly refractory, or reached a response plateau of six months on prior therapy.

One example is, Patient #009 (Investigator 14) who had no prior systemic anti-CTCL therapy, no prior radiation therapy of any sort. The only prior therapy for this patient was topical nitrogen mustard and the duration of topical therapy is recorded as unknown.

As previously indicated, there were numerous protocol violations in this study, and most of the violations involved violation of Inclusion Criteria established in the protocol. The sponsor has also documented five patients who "had a duration of washout from prior therapy that was abbreviated with respect to time required in the protocol (Patients 91, 92, 143, 145 and 1021). The confounding effect of this violation on responses by three of the five patients (91, 92 and 143) cannot be readily determined. Two of the three responding patients (91 and 143) were in the low dose group, with responses after cross over.

The question therefore arises whether the patients in this study truly represented a population that is refractory, intolerant or reached a response plateau of six months on prior therapies.

This reviewer is conducting an analysis of this category of patients in an effort to answer this question. The result of the analysis will be included as a supplement to this review.

Efficacy:

Reviewer's Analysis of Efficacy is as outlined in the accompanying tables:

A breakdown of the 6.5mg/m²/ day dose group is also provided by cross-over; before and after cross-over.

Table 25 **PROTOCOL L-1069-23**
6.5mg/m²/day (Before and after cross-over)
FDA Confirmed Responses

Initial Dose Group	INV.#	PT. ID	CA RESP.
6.5mg/m ² before cross-over	Clinical Complete Responder		
	168	102	CCR 48 (8-56)
	Partial Responder		
	181	146	PR 12 (4-16)*
	14	005	PR 4 (16-20)
6.5mg/m ² after cross-over	14	005	PR
	14	006	PR 16 (4-20)
	167	91	PR (22-35)*
	181	141	PR 22 (24-46)
	181	143	PR 4 (12-16)

*week censored

Table 26 **PROTOCOL L-1069-23** **FDA Confirmed Responses**

Initial Dose Group	INV.#	PT. ID	CA RESP.
300mg/m ²	Partial Responders. No FDA Confirmed CCR		
	14	010	PR 8 (12-20)
	14	1171	PR 20 (4-24)*
	14	1172	PR 8 (12-16)*
	23	272	PR 8 (16-24)
	167	92	PR 4 (8-12)
	168	104	PR 4 (16-60)*
	204	122	PR 4 (8-12)
	283	242	PR 16 (28-44)*
	348	32	PR 4 (20-24)

>300mg/m ² / day	Clinical Complete Responders		
	14	003	CCR.56 (8-64)
	179	131	CCR 40 (12-52)
	Partial Responders		
	14	008	PR. 12 (12-24)
	14	009	PR.8 (12-20)*

168	103	PR 4 (8-12)
181	142	PR 36 (16-52)*

*week censored

Table 27 PROTOCOL L 1069-23: (CA):PR PATIENTS CONFIRMED BY FDA WITH QUESTIONS

INV. ID	PATIENT ID	REVIEWER'S FINDING
14	1171	Questionable Responses from photographs and CRFs
168	103	Questionable Responses from photographs and CRFs
204	122	Criteria for CCR or PR not met by PGA. Claim of PR is questionable from photographs Pt withdrew consent after week 12 .due to AEs-Dry flaky skin, marked hyperlipidemia (both triglycerides and cholesterol): Triglyceride levels of; 3,120 at week 3, 1,533 at week 7 after drug withdrawal.

Table 28 PROTOCOL L 1069-23 CLINICAL COMPLETE RESPONDERS ON COMPOSITE ASSESSMENT (not confirmed as CCR by FDA but as PR)

INV. ID	PATIENT ID (STAGE)	REVIEWER'S FINDING	COMMENTS
181	142 (1A)	PR	Photographs provide insufficient support of claim of <u>complete clearance of Index lesions</u> . No discernible change in some Global pictures

Table 29 PROTOCOL L 1069-23 PARTIAL RESPONDERS ON COMPOSITE ASSESSMENT (not confirmed as responders by FDA)

INV. ID	PATIENT ID	REVIEWER'S FINDING	COMMENTS
181	148	SD	Criteria for CCR or PR not met . Study terminated after week 8 due to AE (Continued increase in lipid values). Photographs provide insufficient support of claim of PR QOL: No change from baseline.

283	243	SD	Criteria for CCR or PR not met. Photographs provide insufficient support of claim of PR
-----	-----	----	---

**Table 30 SUMMARY OF TUMOR RESPONSE PROTOCOL L 1069-23
COMPARISON OF FDA and LIGAND RESPONSES**

	Higher Dose 300mg/m2/day and >300mg/m2/day			Low Dose (6.5 mg/m2/day) Before and after Cross over		
	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		15	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)

SAFETY:

The Medical Officer's discussion of safety issues in this protocol is combined with the safety report on patients in Protocol L 1069-24.

**APPEARS THIS WAY
ON ORIGINAL**

9.0 PIVOTAL STUDY #2 L-1069-24

Title: A Multicenter International Phase 2-3 Evaluation of TARGRETIN™ Capsules in Patients with Refractory Advanced Stage Cutaneous T-Cell Lymphoma

9.1 STUDY Protocol # L1069-24

OBJECTIVES

The principal objectives of this clinical trial are:

1. To evaluate the safety and tolerability of TARGRETIN capsules in patients with refractory advanced stage cutaneous T-cell lymphoma.
2. To evaluate the antitumor efficacy of TARGRETIN capsules in patients with refractory advanced stage cutaneous T-cell lymphoma.

RATIONALE:

TARGRETIN activity in both the gel and capsule formulation had demonstrated activity in previous Phase 1-2 studies of CTCL patients, conducted by the Applicant using different dose schedules. The lack of other available therapies for patients who have exhausted current standard therapy was the applicant's rationale for conducting a phase II-III study in this disease.

EXPERIMENTAL DESIGN

This is a multicenter, open label, Phase II-III study of patients with stage IIB-IV cutaneous T-cell lymphoma assessing the tolerability, safety, and antitumor efficacy of TARGRETIN capsules. Patients must have been refractory to one or more systemic chemotherapy agents.

PATIENT POPULATION

Inclusion Criteria

Same as L1069-23 except for stage of disease which must be :

- i. stage IIB, III, IVA, IVB and confirmed by a current biopsy (within 30 days prior to entry) to be histologically consistent with CTCL by a dermatopathologist.

Exclusion Criteria for Definition of Study Population

Same as L1069-23

Concomitant Medications or therapy:

Same as L1069-23

Treatment Plan

All patients received 650 mg/m²/day, dose of Targretin capsule under the first version of the protocol. This starting dose was subsequently and continuously adjusted downwards to 500 mg/m²/day, and then to 300 mg/m²/day.

The dose could be further adjusted downward for toxicity by 100 mg/m²/day, decrements to 100 mg/m²/day, as indicated by toxicity concerns. If a patient remained on 300 mg/m²/day, and no response was observed for that patient within eight or more weeks of therapy, the dose could be increased to 400 mg/m²/day, after week 8, provided no unacceptable toxicity was occurring.

Treatment was intended to be administered for a minimum of 16 weeks. Treatment could be continued beyond 16 weeks for any patient as long as the study remained open and active, provided the Investigator deemed treatment was of potential benefit to the patient and no unacceptable toxicity occurred.

Under the final version of the protocol, up to a total of 120 patients could be enrolled to provide for at least 30 evaluable patients starting at 300 mg/m²/day (allowing for the additional patients previously enrolled at the, 650 and 500 mg/m²/day, starting dose levels.)

Patients who developed abnormal triglyceride levels during the study were required to have additional laboratory monitoring of the elevated triglyceride levels. In order to continue in the study, such patients would also require treatment with an antilipemic agent for their abnormal triglycerides. Additionally, based on the degree of abnormal triglycerides, patients could require dose reductions, suspensions or withdrawal from the study.

Treatment Adjustments:

Dose-Limiting Toxicities / Dose Modifications/ Therapeutic prevention/interventions for hypertriglyceridemia

Same as L1069-23

STUDY PROCEDURES

Same as L1069-23

RESPONSE ASSESSMENTS:

Same as L1069-23

9.2 RESULTS: Reported by Applicant: Protocol #L1069-24

Patient Disposition, Comparability

Demographic and Other Baseline Characteristics

Patients enrolled in this study were as identified in Table 30. The median age of patients at time of entry in the study was 64 years, with a range from 27 to 89 years. The ratio of male to female patients is 2:1.

Table 31 Baseline Demographics

Demographics		Initial Assigned Dose (mg/m ² /day)		All Patients N = 94 N (%)
		300 N = 56 N (%) ^a	>300 N = 38 N (%)	
Age	<30	1 (1.8)	0 (0.0)	1 (1.1)
(Years)	30 - 39	2 (3.6)	1 (2.6)	3 (3.2)
	40 - 49	8 (14.3)	3 (7.9)	11 (11.7)
	50 - 59	11 (19.6)	8 (21.1)	19 (20.2)
	60 - 69	19 (33.9)	9 (23.7)	28 (29.8)
	=>70	15 (26.8)	17 (44.7)	32 (34.0)
Min / Median / Max		27 / 62 / 88	35 / 67 / 89	27 / 64 / 89
Sex	Male	30 (53.6)	24 (63.2)	54 (57.4)
	Female	26 (46.4)	14 (36.8)	40 (42.6)
Race	White	44 (78.6)	33 (86.8)	77 (81.9)
	Black	9 (16.1)	4 (10.5)	13 (13.8)
	Hispanic	1 (1.8)	1 (2.6)	2 (2.1)
	Asian	0 (0.0)	0 (0.0)	0 (0.0)
	Other	2 (3.6)	0 (0.0)	2 (2.1)

Baseline CTCL Characteristics

Stage and Duration of CTCL at Study Entry

The majority of patients had Stage II or III disease, 74.5% (70/94), illustrating that this was not a generally poor prognosis group. One patient, (Patient 309 Center 014) originally registered as Stage IVA disease, was switched to Stage IIA since there was no

clinical or pathological lymphadenopathy, cutaneous tumors, or known visceral involvement).

Data on the duration of CTCL for the overall study population are provided in terms of length of clinical manifestation of disease and time of first histopathologic diagnosis prior to entry in the study and are summarized for the two initial-dose groups in Table 31

These data again indicate the very indolent and protracted nature of this disease.

Information is provided on the time of first clinical manifestation of CTCL, and the time of first histopathological determination consistent with CTCL. For all patients, the median time since first clinical manifestation of CTCL was 7.3 years, (range 0.8 to 31 years), the median time since first histopathological determination consistent with CTCL was 3.4 years, range (0 days to 28 years)

The patients had received an average of 3.0 different treatments prior to entry on study.

Table 32 Baseline Patient Characteristics: Stage and Duration of CTCL

	Initial Assigned Dose (mg/m ² /day)		All Patients N = 94 N (%)
	300 N = 56 N (%) ⁽²⁾	>300 N = 38 N (%)	
Duration of Disease			
Time (Months) Since First Clinical Manifestation of CTCL			
No. Pts. with Data	56	38	94
Mean	121.3	102.6	113.7
Min / Median / Max	9 / 102 / 372	13 / 84 / 324	9 / 88 / 372
Time (Months) Since First Histopathologic Determination Consistent with CTCL:			
No. Pts. with Data	56	37	93
Mean	60.4	64.5	62.0
Min / Median / Max	1 / 42 / 336	-1 / 41 / 220	-1 / 41 / 336
Stage of CTCL			
IIA	0 (0.0)	1 (2.6)	1 (1.1)
IIB	23 (41.1)	17 (44.7)	40 (42.6)
III	19 (33.9)	10 (26.3)	29 (30.9)
IVA	9 (16.1)	6 (15.8)	15 (16.0)
IVB	5 (8.9)	4 (10.5)	9 (9.6)

Disposition of Patients:

Patients Screened	102
Patients Enrolled	94
Patients Not Enrolled	8
Study Drug Dispensed	94
Study Drug Not Dispensed	0
300mg/m ² /day Group	
# of patients	56
Completed 16 weeks	34
Withdrawn Prior to 16 weeks	22
>300mg/m ² /day Group	
# of patients	38
Completed 16 weeks	25
Withdrawn Prior to 16 weeks	13

Patient Withdrawal from study:

Table 33 provides a summary of disposition of patients presented above in terms of those who withdrew from study prior to 16 weeks or thereafter.

	Initial Assigned Dose (mg/m ² /day)	
	300	>300
	N = 56	N = 38
	N (%)	N (%)
Completed 16 Weeks	34 (60.7)	25 (65.8)
Withdrawn Prior to 16 weeks	22 (39.3)	13 (34.2)
Withdrawn at or After 16 Weeks	13 (23.2)	15 (39.5)
Re-Initiated Treatment	0 (0.0)	1 (2.6)

Table 34 summarizes those patients who withdrew from the study by time on study and by the initial assigned dose level.

Overall, 67% (63/94) of patients had been withdrawn from the study and 33% (31/94) of patients continued in the study as of the database cutoff for this report.

37% (35/94) of patients discontinued prior to Week 16, the intended initial duration of therapy. Of the 63 patients withdrawn from the study as of the database cutoff for this report, 25% (16/63) remained in the study for at least 24 weeks. 18% (17/94) of all enrolled patients remained on treatment for at least 40 weeks, 10% (9/94) for at least 50

weeks, and the longest duration of therapy was 96.6+ weeks for a patient continuing on treatment at the time of the database closure.

The most common primary reason for withdrawal was progressive disease, cited in 51% (32/63) of patients withdrawn, or 34% (32/94) of patients enrolled. Progressive disease was also the most common primary reason for withdrawal for patients in the 300 mg/m²/day initial dose group, reported in 63% (22/35) of patients withdrawn, or 39% (22/56) of patients enrolled in this dose group.

The second most common primary reason for withdrawal was adverse events which were cited as the reason for 17% (11/63) of patients withdrawn, and 12% (11/94) of all enrolled patients.

The next most common primary reason for withdrawal was withdrawal of consent, recorded for 11% (7/63) of patients withdrawn, and 7% (7/94) of all enrolled patients. For those patients withdrawn for a primary reason of withdrawn consent, adverse event was recorded as the additional reason for three patients, a combination of adverse event and partial response for one patient, and for one patient each, partial response, stable disease, and no additional reason.

Three patients withdrew for a primary reason of partial response, three for death, two for failure to follow appointment schedule, two for administration reasons, and one each for clinical complete response, stable disease, and lost to follow-up.

**APPEARS THIS WAY
ON ORIGINAL**

Table 34 Primary Reason for Withdrawal from Study by Dose Group

Primary Reason	Initial Assigned Dose ⁽¹⁾ (mg/m ² /day)	
	300 N = 56	>300 N = 38
	N (%)	N (%)
Did Not Withdraw	21 (37.5)	10 (26.3)
CTCL Disease Status		
Progressive Disease	22 (39.3)	10 (26.3)
Stable Disease	0 (0.0)	1 (2.6)
Partial Response	2 (3.6)	1 (2.6)
Clinical Complete Response	0 (0.0)	1 (2.6)
Adverse Event	4 (7.1)	7 (18.4)
Withdrew Consent	3 (5.4)	4 (10.5)
Death	1 (1.8)	2 (5.3)
Noncompliance		
Failure to Follow Dosing Regimen	0 (0.0)	0 (0.0)
Failure to Follow Appointment	2 (3.6)	0 (0.0)
Schedule	1 (1.8)	0 (0.0)
Lost to Follow-up	0 (0.0)	2 (5.3)

Protocol Deviations

A summary of protocol deviations by initial dose group are presented in Table 34.

Protocol deviations did not occur at an appreciably higher rate at any one particular study center, as can be seen from the summary of protocol deviations by the individual 25 study centers with at least one deviation in Table 34. For all study centers combined, a total of 90% (85/94) of patients had at least one protocol deviation identified according to these categories of deviations, and contributed a total of 303 deviations.

Table.35 Protocol Deviations by Category of Deviation

Category of Deviation	Initial Assigned Dose (mg/m ² /day)	
	300	>300
	N = 56 N (%) ⁽²⁾	N = 38 N (%)
Deviation From Inclusion Criteria	20 (35.7)	21 (55.3)
Deviation From Exclusion Criteria	15 (26.8)	16 (42.1)
Received Incorrect Treatment or Dose	12 (21.4)	16 (42.1)
Received Prohibited Drug/Therapy	27 (48.2)	30 (78.9)
Other Deviation	10 (17.9)	2 (5.3)
Total Number of Deviations	152	151
Total Number of Patients with at Least One Deviation	47 (83.9)	38 (100.0)

The most common category of protocol deviation was use of a prohibited drug or therapy. A total of 61% (57/94) of all enrolled patients had at least one deviation in this category.

Several patients did take prohibited medications during the study that might potentially have activity against CTCL. The effect of such therapy on the primary efficacy endpoint response determinations for these patients is unknown.

Protocol Revisions and amendments.

The original version of the protocol dated July 8, 1996, was amended nine times in the course of the study. Several of the revisions were presumably necessitated by safety concerns noted by the FDA and the applicant in the course of the trial.

EFFICACY RESULTS

Primary Efficacy Endpoints

The Intent to treat (ITT) analysis of response findings by the applicant represents a total of 102 patients who were screened and 94 patients entered into the study in 26 enrolling centers through July 31, 1998. Table 35 below summarizes the applicants results by initial dose group assignment and response by CA, PGA and PEC within each dose group. There were no Complete Responders (CR) in the study. CCR responses in the 300mg/m²/day dose group were 1.8%, 0% and 1.8% for CA, and PEC respectively, PR responses were 25%, 48.2%, 42.9% respectively. The combined CCR+PR responders were 26.8% 48.2% and 25% respectively. Response rates for the >300mg/m²/day group were; CCR 13.2%, 47.4% 42.1% by CA, PGA, and PEC respectively. PR responses were; 34.2%, 47.4% and 42.1% by CA, PGA, and PEC respectively. The combined CCR+ PR response rates were 47.4%, 52.7% and 45.3% respectively.

Table 36 Overall Response Rate by CA, PGA and CA
Initial Assigned Dose(mg/m²/day)

Response	300 N=56 N (%)			>300 N=38 N (%)		
	CA	PGA	PEC	CA	PGA	PEC
CR	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
CCR	1 (1.8)	0 (0.0)	1 (1.8)	5 (13.2)	2 (5.3)	5 (13.2)
PR	14 (25.0)	27 (48.2)	24 (42.9)	13 (34.2)	18 (47.4)	16 (42.1)
SD	21 (37.5)	19 (33.9)	9 (16.1)	9 (23.7)	14 (36.8)	5 (13.2)
PD	20 (35.7)	10 (17.9)	22 (39.3)	11 (28.9)	4 (10.5)	12 (31.6)

These findings indicate a higher response rate by PGA than CA or PEC in both dose group categories.

SECONDARY EFFICACY CRITERIA

Time to Response:

The time to response for a given patient is defined as the time interval from the first day of Targretin capsule treatment to the time of the first observation when the patient meets criteria for CR, CCR or PR. The time to onset of response was the date of onset of the patient's first confirmed response (CCR, CR, or PR) or the date of last clinical evaluation of lesions for those patients not responding minus the date of first day of study (Day 1), plus one day. All patients were included in the calculation, with patients not achieving a response censored at their date of last clinical evaluation of lesions available in the database for this report.

The applicant's projected time to onset of first response and best response based on the Primary Endpoint Classification for the study for the initial dose groups are summarized in Tables 37 and 38...

According to the Primary Endpoint Classification, the projected median time to onset of both first and best response for the 300 mg/m²/day initial dose group patients was 180 days with a range of 14 to 197 and 15 to 197, respectively. For the >300 mg/m²/day initial dose group, the projected median time to first response was 59 days (range 22 to 169) and for the best response a median of 106 (range 22 to 511).

Table 37- Time to Onset of First Response
According to Primary Endpoint Classification

Initial Assigned Dose (mg/m ² /day)	Total Patients		Patients Responding		Projected Time to Response (days)				
	N	%	N	%	Min	25th pctl	Median	75th pctl	Max
300	56	59.6	25	44.6	14.0	32.0	180.0		197.0
>300	38	40.4	21	55.3	22.0	36.0	59.0		169.0

Table 38. Time to Onset of Best Response According to Primary Endpoint Classification

Initial Assigned Dose (mg/m ² /day)	Total Patients		Patients Responding		Projected Time to Response (days) ⁽¹⁾				
	N	%	N	%	Min	25th pctl	Median	75th pctl	Max
300	56	59.6	25	44.6	15.0	34.0	180.0		197.0
>300	38	40.4	21	55.3	22.0	50.0	106.0	511.0	511.0

Analyzed with Kaplan-Meier Method.

The time to onset of first and best response according to the PGA endpoint, CA endpoint, and the Primary Endpoint Classification for the study for the 300 mg/m²/day initial dose group is presented in Table 39.

According to the PGA endpoint, the projected median time to onset of both first and best response was 100 days (range 20 to 180 days). According to the CA endpoint, the projected time to first and best response ranged 14-15 days to 197 days. For the Primary Endpoint Classification for the study, the projected median time to first and best response was 180 days (range 14-15 days to 197 days). Some responses were observed for the PGA, CA and Primary Endpoint Classification as early as the first, Week 2, post-baseline efficacy assessment, and observed in the range of 14 to 20 days.

Table 39 Time to Onset of First and Best Response According to PGA, CA and Primary Endpoint Classification for All Patients in the 300 mg/m²/day Initial Dose Group (N = 56 Patient in 300 mg/m²/day Initial Dose Group)

Response Category	Time to Response (Days)					
	PGA (N=27 Responders)		CA (N=15 Responders)		Primary Endpoint Classification (N=25 Responders)	
	Median	Min-Max	Median	Min-Max	Median	Min-Max
First Response	100	20 - 180	—	14 - 197	180	14 - 197
Best Response	100	20 - 180	—	15 - 197	180	15 - 197

The sponsor's projected median time to first response was longer for the 300 mg/m²/day initial dose group than for the >300 mg/m²/day initial dose group according to the Primary Endpoint Classification (180 versus 59 days, respectively), but shorter according to the PGA endpoint (100 versus 113 days, respectively). No comparison could be made for the CA endpoint because there was no projected median time to first response for the 300 mg/m²/day initial dose group.

In summary, according to the Primary Endpoint Classification for the study, the sponsor projects a median time to first response and best response based upon both responding and non-responding patients in the 300 mg/m²/day initial dose group of 180 days (range 14 days to 197 days). For the >300 mg/m²/day initial dose group patients the projection is a median time to first response of 59 days (range 22 to 169) and best response of 106 days (range 22 days to 511 days).

Response Duration / Duration of Disease Control

Response duration for a given patient is defined as the time interval from the first observation when the patient meets criteria for CR, CCR or PR to the time that the patient relapses. For the analysis in this report, the sponsor assessed response duration both as duration of disease control, and as durability of response. Duration of disease control among responding patients was calculated as the date of onset of the patient's relapse minus the date of first day on study (Day 1), plus one day. The sponsor indicates that as of the database closure for this report the relapse for PGA responders was 19% (5/27) of patients in the 300 mg/m²/day initial dose group and 25% (5/20) in the >300 mg/m²/day initial dose group.

Table .40 Duration of Disease Control According to Composite Assessment

Initial Assigned Dose mg/m ² /day	Total Patients		Patients Responding		Responding Patients Relapsed		Projected Duration of Disease Control (days)				
	N	%	N	%	N	%	Min	25th pctl	Median	75th pctl	Max
300	56	59.6	15	26.8	5	33.3	57.0	141.0			147.0
>300	38	40.4	18	47.4	7	38.9	94.0	193.0	456.0	505.0	602.0

Analyzed with Kaplan-Meier Method.

Table 41 Duration of Disease Control According to Physician's Global Assessment

Initial Assigned Dose (mg/m ² /day)	Total Patients		Patients Responding		Responding Patients Relapsed		Projected Duration of Disease Control (days)				
	N	%	N	%	N	%	Min	25th	Median	75th	Max
								pctl		pctl	
300	56	59.6	27	48.2	5	18.5	85.0	299.0			299.0
>300	38	40.4	20	52.6	5	25.0	94.0	339.0	385.0		385.0

Table.42 Duration of Disease Control According to Primary Endpoint Classification

Initial Assigned Dose mg/m ² /day	Total Patients		Patients Responding		Responding Patients Relapsed		Projected Duration of Disease Control (days) ^{(1),(2)}				
	N	%	N	%	N	%	Min	25th	Median	75th	Max
								pctl		pctl	
300	56	59.6	25	44.6	9	36.0	57.0	141.0	299.0		299.0
>300	38	40.4	21	55.3	8	38.1	94.0	336.0	385.0	456.0	456.0

A total of 39% (7/18) of the 18 CA responding patients at the >300 mg/m²/day initial dose group relapsed. The projected median duration of disease control according to CA was 456 days (range 94 to 602 days).

Durability of Response

Response duration for a given patient is defined as the time interval from the first observation when the patient meets criteria for CR, CCR or PR to the time that the patient relapses. As of the database closure for this report, the sponsor reports 19% (5/27) of PGA responding patients in the 300 mg/m²/day initial dose group had relapsed (projected durability of response ranging 57 to 159 days) and 25% (5/20) of PGA responding patients in the >300 mg/m²/day initial dose group had relapsed (projected median durability of response 306 days, range 64 to 306).

The sponsor's projected durability of response based on the CA endpoint range is 29 to 128 days from the onset of response. A total of 39% (7/18) of the CA responding patients

in the >300 mg/m²/day initial dose group had relapsed. The projected median durability of response for this dose group was 372 days (range 55 to 517 days).

The projected durability of response based on the Primary Endpoint Classification for the study as of the database closure for this report, in the 300 mg/m²/day initial dose group, the projected durability of response ranges from 29 to 159 days from the onset of response. For the >300 mg/m²/day initial dose group the projected median durability of response according to Primary Endpoint Classification for the study was 306 days (range 55 to 430 days).

Table. 43 Durability of Response According to Primary Endpoint Classification

Initial Assigned Dose (mg/m ² /day)	Total Patients		Patients Responding ⁽³⁾		Responding Patients Relapsed		Projected Durability of Response (days) ⁽¹⁾				
	N	%	N	%	N	%	Min	25th pctl	Median	75th pctl	Max
	300	56	59.6	25	44.6	9	36.0	29.0	87.0	159.0	
>300	38	40.4	21	55.3	8	38.1	55.0	168.0	306.0	430.0	430.0

The reported projected median durability of response as of the database closure for this report was 5.3 months (159 days) for the 300 mg/m²/day initial dose group and 10.2 months (306 days) for the >300 mg/m²/day initial dose group, with a maximum of 14.3 months (430 days), for Primary Endpoint Classification for the study.

Time to Disease Progression

The time to disease progression for a given patient is defined as the time interval from the first day of Targretin capsule treatment to the time of the first observation when the patient meets criteria for progressive disease (PD). All patients were included in the calculation, with patients not achieving a PD censored at their date of last clinical evaluation of lesions.

The time to disease progression based on CA or PGA is summarized for the 300 and >300 mg/m²/day initial dose groups. According to the PGA or CA endpoints respectively, the rate of progressive disease for the 300 mg/m²/day initial dose group

(18%, 10/56 and 36%, 20/56) was modestly higher than for the >300 mg/m²/day initial dose group (11%, 4/38 and 29%, 11/38). The time to progression ranged from eight days to 400 days.

As with the PGA and CA endpoints individually, the rate of progressive disease according to the Primary Endpoint Classification for the study for the 300 mg/m²/day initial dose group (39%, 22/56) was higher than for the >300 mg/m²/day initial dose group (32%, 12/38). The projected time to progression for the Primary Endpoint Classification for the study ranged from 14 to 141 days for the 300 mg/m²/day initial dose group patients and eight to 206 days for the >300 mg/m²/day initial dose group patients. A median time to progression for either the 300 or >300 mg/m²/day initial dose group could not be projected.

Table 44. Time to Onset of Disease Progression According to Primary Endpoint Classification

Initial Assigned Dose (mg/m ² /day)	Total Patients		Patients Progressing		Projected Time to Disease Progression (days)				
	N	%	N	%	Min	25th	Median	75th	Max
						pctl		pctl	
300	56	59.6	22	39.3	14.0	57.0			141.0
>300	38	40.4	12	31.6	8.0	92.0			206.0

Time to Disease Progression Regardless of Confirmation

An analysis was made of time to disease progression based on the first evidence of progressive disease, without regard to confirmation of progression, in addition to the analysis in which progression must be confirmed over at least four study weeks. The rate of progressive disease without regard to confirmation was similar for the 300 mg/m²/day initial dose group 46%, (26/56) and the >300 mg/m²/day initial dose group 47%, (18/38). The rate of progressive disease without regard to confirmation according to PGA was also comparable between the 300 mg/m²/day initial dose group (32%, 18/56) and the >300 mg/m²/day initial dose group (29%, 11/38).

The projected time to progression without regard to confirmation according to PGA ranged from one to 188 days for the 300 mg/m²/day initial dose group and was a median of 413 days (range eight to 413 days) for the >300 mg/m²/day initial dose group

The projected median time to progression without regard to confirmation according to CA was 147 days (range 14 to 188 days) for the 300 mg/m²/day initial dose group and 281 days (range 13 to 505 days) for the >300 mg/m²/day initial dose group.

The reported rate of progressive disease according to the Primary Endpoint Classification for the 300 mg/m²/day initial dose group was 55% (31/56) and 58% (22/38) for the >300 mg/m²/day initial dose group. The projected median time to progression without regard to confirmation for the 300 and >300 mg/m²/day initial dose groups respectively was 97 days (range one to 188 days) and 206 days (range eight to 456 days).

The rate of progressive disease with the PGA and CA endpoints were similar to the Primary Endpoint Classification for the 300 mg/m²/day initial dose group (39%, 22/56) and it was modestly higher than for the >300 mg/m²/day initial dose group (32%, 12/38). The projected time to progression for the study ranged from 14 to 141 days for the 300 mg/m²/day initial dose group patients and eight to 206 days for the >300 mg/m²/day initial dose group patients.

The projected median time to progression without regard to confirmation according to the Primary Endpoint Classification for the study for the 300 and >300 mg/m²/day initial dose groups respectively was 97 days (range one to 188 days) and 206 days (range eight to 456 days).

**APPEARS THIS WAY
ON ORIGINAL**

Table 45 Time to Onset of Disease Progression According to Primary Endpoint Classification Regardless of Confirmation

Initial Assigned Dose (mg/m ² /day)	Total Patients		Patients Progressing		Projected Time to Disease Progression (days) ⁽¹⁾				
	N	%	N	%	Min	25th pctl	Median	75th pctl	Max
300	56	59.6	31	55.4	1.0	35.0	97.0		188.0
>300	38	40.4	22	57.9	8.0	29.0	206.0	413.0	456.0

Total Body Surface Area Involvement

Table 46 presents the overall (patch plus plaque) CTCL-involved body surface area for the 300 mg/m²/day initial dose group up through 48 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 greater than 0%.

Table 46 The median overall BSA involvement by CTCL for those patients with area greater than zero was 70% (range 1% to 100%) at baseline. The diminishing group of patients at each study visit had a gradual reduction in their median area from 70% to 40% at Week 16, and to 16% at Week 44 for the last four patients begin assessed. A similar reduction was noted in the mean BSA. Also noted is a gradual reduction in the maximum BSA from 100% after Week 20 to the range of 60% to 85% to Week 44 at which time it was 23% for the last four patients assessed.

Table.46 Total Overall CTCL-Involved Body Surface Area for Initial Assigned Dose 300 mg/m²/day(N = 56)

Study Visit	No. Pts. At This Visit	No. Pts. With Area	Total Percent Body Surface Area Involvement ⁽¹⁾				
			Mean	SE	Min	Median	Max
Day 1	54	53	58.2	5.4	1.0	70.0	100.0
Week 2	20	20	55.5	9.2	1.0	57.5	100.0
Week 4	51	50	50.4	5.3	0.3	50.0	100.0
Week 8	46	45	48.8	5.7	0.3	45.0	100.0
Week 12	37	37	48.7	6.0	0.3	45.0	100.0
Week 16	27	27	43.7	7.6	0.3	40.0	100.0
Week 20	20	20	38.8	7.9	0.3	38.0	100.0
Week 24	13	12	43.0	8.4	1.0	41.0	85.0
Week 28	12	12	30.4	7.7	1.1	25.0	85.0
Week 32	10	10	31.6	8.5	1.0	22.5	85.0
Week 36	7	7	28.9	7.4	7.0	23.0	60.0
Week 40	6	6	32.8	12.1	7.0	21.5	85.0
Week 44	4	4	16.8	2.8	12.0	16.0	23.0
Week ≥48	2	2	50.0	30.0	20.0	50.0	80.0

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

Table 47 Total Overall CTCL Involved Body Surface Area Change From Baseline for Initial Assigned Dose 300 mg/m²/day (N = 56)

Study Visit	No. Pts. At This Visit	No. Pts. With Area	Total Percent Body Surface Area Involvement					
			N	Mean	SE	Min	Median	Max
Day 1 Baseline	54	53	54	57.1	5.4	0.0	67.5	100.0
Week 2	20	20	19	-2.1	1.7	-30.0	0.0	5.0
Week 4	51	50	50	-6.8	1.7	-60.0	0.0	1.0
Week 8	46	45	46	-6.2	2.2	-60.0	0.0	30.0
Week 12	37	37	37	-9.6	3.7	-90.0	0.0	30.0
Week 16	27	27	27	-16.0	4.8	-90.0	-4.5	7.0
Week 20	20	20	20	-23.1	5.9	-75.0	-10.5	5.0
Week 24	13	12	13	-32.4	8.3	-85.0	-20.0	5.0
Week 28	12	12	12	-31.1	9.1	-75.0	-23.8	5.0
Week 32	10	10	10	-31.3	10.0	-80.0	-26.4	5.0
Week 36	7	7	7	-34.3	11.6	-70.0	-40.0	5.0
Week 40	6	6	6	-20.8	12.6	-62.0	-7.5	5.0
Week 44	4	4	4	-28.8	18.1	-62.0	-29.0	5.0
Week ≥48	2	2	2	2.5	2.5	0.0	2.5	5.0

Total Percent BSA is sum of CTCL patch and CTCL plaque assessed at each study visit.

The overall BSA involvement and change in BSA involvement respectively for the >300 mg/m²/day initial dose group suggests that the number of patients assessed for BSA involvement at each visit but who had BSA of 0% increased from one patient at baseline, to three patients at Week 4, to four patients at Weeks 8 and 12. The median overall BSA involvement by CTCL for all patients with area greater than zero was 50% (range 2.3% to 100%) at baseline. The diminishing group of patients at each study visit had minor fluctuations in median area in the range of 50% to 64.5% until Week 20, at which time the median area dropped to 33% and then to 25% from Week 24 to Week 36. The reported median BSA involvement from a baseline of 45% began at Week 8 (-1.3%) and increased at Week 12 (-6.6%), peaking at -39.3% at Week 40. The improvement in the mean BSA paralleled the change in the median BSA, but started earlier with a -4.4% reduction at Week 4, and reaching -10.6% at Week 16 and -26.1% at Week 32. The improvement in total BSA observed in the 300 mg/m²/day initial dose group was also observed in the >300 mg/m²/day initial dose group.

Individual Index Lesions Signs and Symptoms

The grading of individual index lesion clinical signs comprised the core of the CA primary efficacy endpoint assessment. Each individual clinical sign for the designated index lesions was prospectively identified as an independent secondary efficacy endpoint. The CTCL Index Lesion Clinical Assessment Log (CTCLA) CRF was designed to record the longest diameters and the assessed grading of each of the clinical signs and symptoms of erythema, scaling, plaque elevation, hyper-/hypo-pigmentation, and surface area of involvement and .Up to five index lesions per patient were measured at baseline and at each on-study assessment.

Erythema

Erythema was recorded for at least one index lesion at baseline for the 300 and >300 mg/m²/day initial dose groups respectively for 100% (56/56) and 89% (34/38) of patients. The median degree of erythema of index lesions at baseline was similar for the two initial dose groups, and ranged, on a scale of 0 (none) to 8 (very severe), from 4.2 to 4.4 (4 = moderate: red lesion).

A decrease in median index lesion erythema was observed for patients in the 300 mg/m²/day initial dose group, from a baseline of moderate (very red lesions), to mild (light red lesions) by Week 16, and approaching a point midway between no erythema and mild during subsequent weeks. This pattern was also observed in the >300 mg/m²/day initial dose groups.

Scaling

Scaling was graded on a scale of 0 (none) to 8 (very severe). Scaling was recorded for at least one index lesion at baseline for the 300 and >300 mg/m²/day initial dose groups respectively for 95% (53/56) and 87% (33/38) of patients. The median degree of scaling of index lesions at baseline was similar for the two initial dose groups, and ranged, on a scale of 0 (none) to 8 (very severe), from 3.0 (2 = mild, mainly fine scales, lesions partially covered; and 4 = moderate, somewhat coarser scales, lesions partially covered) for the 300 mg/m²/day initial dose group to 2.8 for the >300 mg/m²/day initial dose group.

A similar pattern and magnitude of decreasing index lesion scaling over time was also seen in the >300 mg/m²/day initial dose group. A progressive decrease in index lesion scaling was observed for patients in the 300 mg/m²/day initial dose group, from a baseline of the midpoint between mild (mainly fine scales, lesions partially covered) and moderate (somewhat coarser scales, lesions partially covered), to less than mild at Week 16, to a point just higher than no scaling by Week 32 for the five patients with scaling at that visit. This pattern of improvement was also observed in the >300 mg/m²/day initial dose group.

Plaque Elevation

A progressive decrease in index lesion plaque elevation was observed for patients in the 300 mg/m²/day initial dose group, from a baseline of just above slight plaque elevation (≥ 0.5 to < 1 mm), to an average point midway between minimal but definite plaque elevation above normal skin level (≥ 0 to < 0.5 mm) and slight but definite plaque elevation (≥ 0.5 to < 1 mm) by Week 16, and reaching a range of absence or near absence

of plaque elevation by Week 32. Approximately the same magnitude of improvement was observed in the >300 mg/m²/day initial dose group.

Hypo/Hyperpigmentation

Very few patients in the study had hypo/hyperpigmentation at baseline, compared to other index lesion clinical signs, and there was little change in the median or mean degree of hypo/hyperpigmentation during the study for either dose group.

Pruritus

Pruritus was an independent protocol-specified secondary efficacy endpoint in this study. It was however not integrated into the CA primary efficacy endpoint, although the protocol specified that this would be done. The study drug effects on pruritus were analyzed for all patients regardless of concurrent use of antihistamine/ antipruritic. An analysis was also performed for these two subgroups

The change from baseline in pruritus for all patients (both with and without concurrent antipruritics) is summarized for the 300 mg/m²/day initial dose group in Table 48. The median degree of pruritus began to decrease from Week 4.

The 62% (58/94) of patients with one or more antipruritic medications overlapping with study drug administration comprised the population of patients with concurrent antipruritic therapy. The complementary subset of 38% (36/94) of patients, with no concomitant antipruritic medication, comprised the data set of patients with no concurrent antipruritic therapy. Pruritus was recorded for at least one index lesion at baseline for the 300 and >300 mg/m²/day initial dose groups respectively for 91% (51/56) and 76% (29/38) of patients. The median degree of pruritus of index lesions at baseline for those patients with pruritus was similar for the two initial dose groups, and on a scale of 0 (none) to 8 (very severe, unrelieved itch, prevents routine activities, awakens patient from sleep), was 3.4 and 2.8 (2 = mild, occasional transient itch on lesions; and 4 = moderate, frequent itch, every 1-3 hours, reflex scratching), respectively.

Table 48 Index Lesion Pruritus Change From Baseline for Initial Assigned Dose
300 mg/m²/day
(N = 56)

Study Visit	No. Pts. At This Visit	No. Pts. With Pruritus	Pruritus					
			N	Mean	SE	Min	Median	Max
Day 1 Baseline	56	51	56	3.4	0.3	0.0	3.2	8.0
Week 2	53	42	53	-1.0	0.2	-7.8	-0.6	1.8
Week 4	51	37	51	-1.4	0.3	-8.0	-1.3	2.4
Week 8	47	33	47	-1.5	0.3	-8.0	-1.0	5.0
Week 12	37	26	37	-1.1	0.4	-8.0	-1.2	6.0
Week 16	27	20	27	-1.5	0.3	-4.8	-1.0	1.2
Week 20	20	13	20	-2.5	0.4	-8.0	-2.1	0.0
Week 24	13	7	13	-3.1	0.6	-8.0	-2.8	-0.4
Week 28	12	6	12	-2.7	0.7	-8.0	-2.4	0.6
Week 32	10	3	10	-2.9	0.7	-8.0	-2.2	-0.4
Week 36	7	3	7	-3.0	0.9	-8.0	-2.2	-1.6
Week 40	6	3	6	-3.7	1.0	-8.0	-2.8	-1.6
Week 44	4	1	4	-3.3	1.7	-8.0	-2.5	0.0
Week ≥48	2	0	2	-3.6	1.8	-5.4	-3.6	-1.8

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).

33 patients took concurrent antipruritics and 20 patients did not do so. The entire study population of patients (taking and not taking antipruritics), all showed a decrease in index lesion pruritus. A progressive decrease in index lesion pruritus was observed for patients in the 300 mg/m²/day initial dose group, from a baseline of midway between mild (occasional transient itch) and moderate (frequent itch, every 1-3 hours, reflex scratching), to a point between no complaint of itching and mild pruritus by Week 16, and approaching the absence of pruritus during subsequent weeks. A similar pattern of pruritus reduction was observed in the >300 mg/m²/day initial dose

Clinically Abnormal Lymph Nodes

Clinically abnormal lymph nodes were defined in the protocol as having a minimal diameter of one centimeter. For the 300 and >300 mg/m²/day initial dose groups, 46% (26/56) and 26% (10/38) of patients, respectively, had clinically abnormal lymph nodes

recorded at baseline. These numbers closely approximate the 52% (29/56) of patients in the 300 mg/m²/day initial dose group and the 24% (9/38) of patients in the >300 mg/m²/day initial dose group who were noted as having a baseline history of clinically abnormal lymph nodes.

For those patients with one or more clinically abnormal nodes recorded at baseline, the median and mean number of clinically abnormal nodes was 2.5 and 3.6 (range one to 13), respectively, for the 300 mg/m²/day initial dose group and two and 2.4 for the >300 mg/m²/day initial dose group (range one to six). The mean number of lymph nodes for all 56 patients was 1.7 at Day 1 (baseline) and fluctuated between no change and a change by -0.5 from Week 2 until Week 32, at which time only ten patients were assessed and the number of patients with clinically abnormal nodes being assessed had decreased from 26 to four.

Therefore, there were few clinically abnormal lymph nodes per patient at baseline as indicated by a mean of 1.7 nodes (range one to 13) for the 56 patients in the 300 mg/m²/day initial dose group and mean of 2.4 nodes (range one to six) for the 38 patients in the >300 mg/m²/day initial dose group. There was little demonstrable population change in the number of clinically abnormal lymph nodes.

Pathologically Positive Lymph Nodes and Visceral Tumor :

There are insufficient post-baseline data and no pre-study to post-baseline comparison data in the database upon which to base any conclusions about the pathologically positive lymph nodes or visceral tumor activity of Targretin capsules. Only three patients had post-baseline lymph node biopsies, and none of these three patients had a pre-study lymph node biopsy reported:

Cutaneous CTCL Tumors

Cutaneous tumors are defined as having minimal bidimensional skin surface diameters of 10 mm by 10 mm and a height above the surrounding skin surface of at least 5 mm. .35% (33/94) of all enrolled patients and 36% (20/56) of patients in the 300 mg/m²/day initial

dose group were noted at baseline to have cutaneous tumors. For these patients combined, the median number of cutaneous tumors was two (range one to 50)

For the patients with cutaneous tumors in the 300 mg/m²/day initial dose group, there was no meaningful change in the number of tumors until Week 24, when the median and mean number of tumors increased based on two patients with tumors being assessed for the rest of the study. The baseline median and mean aggregate cutaneous tumor volume for patients with measures of volume recorded was 4.0 cm³ and 59.2 cm³ for the 300 mg/m²/day initial dose group (N=12, range 0.4 to 255.3 cm³) and 12.5 cm³ and 12.5 cm³ (N=2, range 5.0 to 20.0 cm³) for the >300 mg/m²/day initial dose group, respectively. There was no meaningful change in the median and mean aggregate cutaneous tumor volume for the groups of patients with tumor measures in either initial dose group, especially in consideration of the small sample sizes.

The generally low number of cutaneous tumors make it difficult to demonstrate clinical improvement on a population basis.

Circulating Sezary Cells:

Measurement of Sezary cells was obtained on very few patients as the sponsor did not consider it a protocol requirement.

Five patients had a pre-study and at least one post-baseline Sezary determination. The Sezary counts appeared to improve for two patients, and no meaningful change to increase in number in others. There was no clear correlation between changes in Sezary counts and response according to primary endpoints for these five patients. For three other patients who lacked a pre-study determination but had serial post-baseline determinations, the Sezary counts improved for two and worsened in the third. No meaningful conclusion can therefore be drawn on the efficacy of Targretin in ameliorating circulating Sezary cells in this disease.

Patient Quality of Life Questionnaires

Two QoL questionnaires were used to track improvements in a patient's well-being: (1) the Spitzer questionnaire, which included six items dealing with a patient's general status, and (2) the CTCL-specific questionnaire, which included nine items dealing with the status of the CTCL condition. These two questionnaires were to be administered at baseline and every four weeks during the study. Questions 8 and 9 of the CTCL-specific questionnaire, that asked about change in comparison to prior to participation in the study and about overall level of satisfaction with study drug treatment were not relevant at baseline, and therefore were not posed at baseline, Day 1, visit.

Spitzer Quality of Life Questionnaire

The results from the individual questions in the Spitzer questionnaire at baseline and then the change from baseline at other study time points are summarized in Tables 49 and 50. The summaries are compiled separately for patients who did not complete the first 16-week evaluations (non-completers) and those that did (completers). Too few patients in the non-completer group completed questionnaires at times other than baseline, so no conclusions can be drawn from their QoL data. Therefore, only the data from the completers were presented.

The 67% (63/94) of patients who had been on study for 16 weeks or longer as of the database closure for this report were defined as completers. The 33% (31/94) of patients who had not completed 16 weeks on study as of database closure were defined as non-completers.

Overall, there was very little change for nearly all of the questions for both initial groups. Too few patients in the non-completer group completed questionnaires at times other than baseline, so no conclusions can be drawn from their QoL data. Table 49 summarizes the change from baseline in the composite of responses to Spitzer Questions 1 - 5 for the 63 patient completers

The composite data for the first five questions show that the mean composite scores at baseline, over a possible range of 0 to 10, were 8.0 for the 300 mg/m²/day initial dose group and 8.2 for the >300 mg/m²/day initial dose group. This indicates that patients in both initial dose groups rated their general status in all five question areas quite high,

leaving very little room for improvement. For the 300 mg/m²/day initial dose group, the data do show a modest improvement of up to +0.5 (with a possible range of 0, worse, to 10, better) in the mean composite score at Week 8, and +0.2 at Week 16, then ranging +0.5 to +0.8 from Week 28 until Week 40. The patients initially assigned to the >300 mg/m²/day initial dose group also reported a modest improvement, ranging from +0.1 to +0.8 from Week 20 until Week 44.

In assessing the five individual questions making up these composite data, it appears that most of this modest improvement derived from Question 1 about Activity, followed by Question 3 about Health. None of the other individual questions showed any meaningful changes.

**APPEARS THIS WAY
ON ORIGINAL**

Table 49. General Status Quality of Life Questionnaire (Spitzer Items 1-5):
Composite of Individual Questions Change From Baseline for Completers
(N=63)

Initial Assigned Dose (mg/m ² /day)	Study Visit	Composite of Individual Questions					
		No. Pts.	Mean	SE	Min	Media n	Max
300	Day 1 Baseline	35	8.0	0.3	4	8	10
	Week 4 Change	34	0.3	0.2	-2	0	3
	Week 8 Change	35	0.5	0.3	-2	0	5
	Week 12 Change	32	-0.1	0.3	-6	0	3
	Week 16 Change	28	0.2	0.3	-3	0	4
	Week 20 Change	21	0.0	0.3	-2	0	3
	Week 24 Change	13	0.2	0.6	-5	0	3
	Week 28 Change	11	0.8	0.3	-1	1	2
	Week 32 Change	11	0.5	0.3	-1	0	3
	Week 36 Change	8	0.6	0.5	-1	0	3
	Week 40 Change	7	-0.3	0.2	-1	0	0
	Week 44 Change	5	-0.2	0.5	-2	0	1
	Week 48 Change	3	0.0	0.0	0	0	0
>300	Day 1 Baseline	26	8.2	0.4	5	9	10
	Week 4 Change	25	-0.1	0.4	-5	0	4
	Week 8 Change	25	0.1	0.3	-4	0	4
	Week 12 Change	24	-0.2	0.4	-7	0	3
	Week 16 Change	22	0.0	0.3	-2	0	4
	Week 20 Change	18	0.7	0.4	-3	0	4
	Week 24 Change	16	0.8	0.3	-1	0	3
	Week 28 Change	17	0.3	0.3	-1	0	4
	Week 32 Change	11	0.7	0.7	-2	0	4
	Week 36 Change	10	0.1	0.5	-2	0	3
	Week 40 Change	9	0.3	0.7	-3	0	4
	Week 44 Change	10	1.0	0.4	0	1	3
	Week 48 Change	8	1.0	0.7	-2	1	4
	Week 52 Change	8	1.0	0.7	-1	0	4
	Week 56 Change	4	1.8	0.9	0	2	4
Week \geq 60 Change	3	-1.3	1.3	-4	0	0	

Spitzer Items 1 to 5 are on a scale from 0 to 2.

Question 6 of the Spitzer questionnaire is a visual analogue scale (VAS) that deals with the overall quality of life, and so it is discussed separately. The data for that question for the group of completers demonstrate a mean value at baseline of 78.9 (N=33) and 75.9 (N=26) for the 300 and >300 mg/m²/day initial dose groups, respectively, showing that these patients rated their overall quality of life moderately high. After Day 1 there

appeared to be a general but mild downward trend in values for both initial dose groups, but less noticeable in the >300 mg/m²/day initial dose group. The significance of this trend is unclear.

These CTCL patients generally rated their general status for all six questions in the general status (Spitzer) questionnaire high in both initial dose groups, leaving very little room for improvement. Overall there were no substantial changes for either initial dose group except for a trend to mild improvement in the composite of the first five questions and a trend to modest worsening in the VAS question about overall quality of life.

Table 50 General Status Quality of Life Questionnaire (Spitzer Item 6): Overall Quality of Life Change From Baseline for Completers (N=63)

Initial Assigned Dose (mg/m ² /day)	Study Visit	Overall Quality of Life ⁽¹⁾					
		No. Pts.	Mean	SE	Min	Median	Max
300	Day 1 Baseline	33	78.9	3.6	35	89	100
	Week 4 Change	31	-3.7	3.5	-53	-1	38
	Week 8 Change	31	-5.4	4.2	-49	-6	49
	Week 12 Change	28	-7.6	3.2	-54	-5	28
	Week 16 Change	26	-10.7	5.0	-80	-10	27
	Week 20 Change	20	-12.7	5.0	-86	-8	14
	Week 24 Change	13	-4.8	6.1	-55	-1	19
	Week 28 Change	11	-6.6	4.2	-32	-4	14
	Week 32 Change	11	-8.1	7.0	-71	-6	12
	Week 36 Change	8	-2.5	4.7	-22	-2	14
	Week 40 Change	7	-4.6	5.7	-28	0	12
	Week 44 Change	5	-6.6	7.3	-34	-3	10
	Week 48 Change	3	-12.3	8.4	-29	-5	-3
	>300	Day 1 Baseline	26	75.9	5.0	21	85
Week 4 Change		21	-1.5	3.3	-47	-2	27
Week 8 Change		23	-6.4	5.3	-90	-2	33
Week 12 Change		24	-1.9	5.6	-78	-4	61
Week 16 Change		22	-1.4	4.9	-50	-5	52
Week 20 Change		19	4.6	4.7	-22	-1	53
Week 24 Change		16	2.6	7.3	-77	2	55
Week 28 Change		16	6.1	4.9	-13	1	53
Week 32 Change		11	6.7	7.2	-17	-2	57
Week 36 Change		8	-7.1	8.8	-45	-9	42
Week 40 Change		9	-0.6	7.3	-23	1	44
Week 44 Change		10	2.5	6.7	-27	0	49
Week 48 Change		8	4.8	9.3	-25	2	64
Week 52 Change		8	-1.1	9.0	-35	-4	50
Week 56 Change		4	-2.3	19.7	-35	-15	55
Week ≥6 Change		3	-28.7	25.2	-78	-13	5

CTCL-Specific Quality of Life Questionnaire

For the individual questions on the CTCL-specific patient questionnaire, the results at baseline and the changes reported at different study times are reported for completers and non-completers. Too few patients in the non-completer group completed questionnaires at times other than baseline, so no conclusions could be drawn from their QoL data.

The first part of the questionnaire, Questions 1a - 1e, deals with overall feelings in five categories, while Questions 2 - 9 are specific to the patient's CTCL condition and study drug treatment. Table 51 summarizes for completers the mean changes from baseline in the composite responses to the CTCL-specific patient Questions 1b - 1e.

On a possible range of 0 (worst) to 40 (best) for this composite, the baseline mean composite scores were 28.1 for the 300 mg/m²/day initial dose group and 27.9 for the >300 mg/m²/day initial dose group. The composite data showed no consistent change or trends for patients in either initial dose group..

Similarly, there were no meaningful changes or trends observed in any of the four individual questions making up this composite for either initial dose group.

**APPEARS THIS WAY
ON ORIGINAL**