CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
21-056

STATISTICAL REVIEWS

Statistical Review and Evaluation

JUN - 5 2000

NDA#:	21-056
Applicant:	Ligand Pharmaceuticals
Name of Drug:	Targretin (bexarotene) Gel
Indication:	Topical treatment of cutaneous lesions in patients with early stage (IA, IB, & IIA) cutaneous T-cell lymphoma (CTCL) who have not tolerated other therapies or who have refractory or persistent disease.
Documents Reviewed:	Vols. 1.1, 1.69, 1.70, 1.71, 1.80 and 1.81
Medical Officer:	Robert White, M.D.
Statistical Reviewer:	Mark Rothmann, Ph. D.

1. BACKGROUND AND OVERVIEW

In support of Targretin gel as a topical treatment of cutaneous lesions in patients with CTCL (Stage IA, IB, & IIA) who have not tolerated other therapies or who have refractory or persistent disease, the sponsor submitted an NDA that consists of ten clinical studies.

Four of these studies – one phase III study and three phase I-II studies - involved patients with CTCL. Fifty patients were enrolled in the phase III study (L1069T-25). Sixty-seven patients were enrolled in three phase I-II studies (L1069T-11, L1069T-12 and L1069-94-04T).

In addition, six Phase I-II and II clinical studies in patients with non-CTCL cancers were conducted.

2. BRIEF DESCRIPTION OF STUDIES

Study L1069T-25

Study L1069T-25 was a Phase III, open-label, multicenter, multinational, historically-controlled, single-arm study. The principal objectives were to evaluate the safety, tolerability and anti-tumor efficacy of Targretin gel in patients with refractory or persistent early stage (I-IIA) CTCL. Patients were to have been refractory to, intolerant to, or have reached a plateau for at least six months on a least two prior therapies - PUVA, UVB, EBT, photopheresis, interferon, systemic cytotoxic chemotherapy, topical nitrogen mustard, or topical carmustine (BCNU) – where at least one of these topical therapies must have been nitrogen mustard, BCNU, or a phototherapy (UVB, PUVA or EBT). Topical steroids and systemic retinoids did not qualify. For at least one week prior to study, patients were to have avoided systemic or topically-applied antihistamine and antipruritic agents. If such agents could not be avoided, they were to be administered under a stable dose regimen for at least one week prior to initiation of Targretin gel and throughout the study, unless it was determined that a discontinuation or reduction in dose

was indicated. Five or fewer lesions (representative of the overall extent of cutaneous disease) were to be chosen as index lesions. Patients were evaluated prior to treatment (within 14 days) and at baseline (study day 1), and were to have had multiple periodic safety and effectiveness evaluations while on study.

All patients were initially treated with Targretin gel 1% applied topically every other day. The frequency of application was escalated (as tolerated) at one week intervals to 1% once daily, 1% twice daily, 1% three times daily and then 1% four times daily. The frequency of application could independently be adjusted for each lesion. Treatment limiting toxicity (TLT) adjustment guidelines were provided. Patients who experienced TLT and had restarted a reduced exposure regimen after a period of four or fewer weeks off treatment, were to advance the frequency of study drug application by no more than two treatment exposure levels at one time and at intervals of no less than one week. The patient was withdrawn from the study, if no application frequency was tolerated for any of the patient's lesions.

A total of 63 patients were screened and 50 patients were enrolled into the study at 25 study centers through 15 February 1999 (at this date the last entered patient was to have had 16 weeks of therapy). All 50 patients received at least one application of treatment and were included in the ITT (efficacy) and safety populations. Treatment was to have been administered for at least 16 weeks. A patient could receive treatment beyond 16 weeks, if the study was open and active, the investigator deemed the treatment was of potential benefit to the patient, and no unacceptable toxicity occurred. Table 1 below gives the distribution of CTCL stages among the patients.

Table 1. Distribution of CTCL Stages

Stage of CTCL	Number (%)
IA	25 (50)
IB	22 (44)
IIA	2 (4)
IIB[1]	1 (2)

[1] The sponsor considered this patient as a protocol violator.

The primary efficacy endpoints are tumor response according to Physician's Global Assessment of Clinical Condition (PGA), Composite Assessment of Index Lesion Disease Severity (CA) and the Primary Endpoint Classification (PEC). Patients are followed up to 16 weeks of treatment and beyond if treatment is continued. The CA is determined by a summation of the grades for each index lesion erythema, scaling, plaque elevation, hypopigmentation or hyperpigmentation, and area of involvement of up to five index lesions, and also considered the presence or absence of all extracutaneous disease manifestations. The PGA considers index and non-index cutaneous lesions, clinically abnormal lymph nodes, cutaneous tumors, pathologically positive lymph nodes, visceral disease, and other tumor manifestations. The PGA is an assessment of the extent of improvement/worsening of the patient's overall disease compared to the condition at entry

(at baseline). The PEC is the best response according to either the Composite Assessment of Index Lesion Disease Severity (CA) or the Physician's Global Assessment of Clinical Condition (PGA), unless it was preceded by an assessment of progressive disease.

For PGA and CA primary measures of efficacy, responses required confirmation over at least two assessments that were at least four study weeks apart, and a partial response required at least 50% improvement.

The sponsor deems the study successful if the observed response rate for (CCR+PR) was at least 20% with the corresponding 95% confidence interval lying entirely above 5%.

Secondary endpoints include (1) the response to treatment of the overall extent of cutaneous disease (index and non-index lesions) determined as a percentage involvement of total BSA; (2) the response to treatment of clinically abnormal lymph nodes, if present; (3) the index lesion erythema, plaque elevation, scaling, pruritis, hypopigmentation or hyperpigmentation, and surface area responses to treatment; (4) the time to response; (5) duration of response (duration of disease control and durability of response), (6) time to disease progression, (7) quality of life (questionnaires).

Phase I-II Studies in CTCL Patients

Studies L1069T-11, L1069T-12 and L1069-94-04T were conducted at three independent study centers (under different protocols) as phase I-II, open-label, multiple-doser, safety and efficacy evaluations of Targretin gel and vehicle gel for treatment of CTCL. Up to 65 patients in each study with early stage CTCL were planned to be treated with either Targretin gel only or Targretin gel and vehicle gel (applied on separate lesions). A total of 67 patients were enrolled and analyzed.

Study protocols were amended several times. The original treatment plan starts with Targretin gel 0.1% once daily and then increases to 0.1% twice daily, 0.5% once daily, 0.5% twice daily, 1% once daily, 1% twice daily, 1% thrice daily and 1% four times daily every two weeks as tolerated. The final treatment plan (after protocol amendment) begins with Targretin gel 1% every other day and increases the frequency of applications to four times daily every one or two weeks as tolerated. This final dosing plan is consistent with the phase III study.

The efficacy endpoints were the patient's cutaneous tumor response as determined by the PGA, Overall Severity Assessment of index lesions (OSA), Grading Scales for Clinical Signs, and Grading of Dermal Symptoms. Week 12 was the principal evaluation visit for interpreting data. A decrease from baseline of at least one grade in overall severity of CTCL clinical signs by Week 16 of treatment is regarded as a clinically meaningful response according to Overall Severity Assessment.

Secondary endpoints include (1) the time to response; (2) duration of response (duration of disease control and durability of response); (3) grading scales for clinical signs; and (4) grading of dermal symptoms.

3. SUMMARY OF SOME BASELINE CHARACTERISTICS AND EFFICACY RESULTS

This section summarizes the primary and secondary efficacy analyses and baseline characteristics for study L1069T-25 and the combined phase I-II studies in CTCL patients.

Targretin gel is deemed successful by the sponsor if there is a response rate above 20% and the corresponding confidence interval lies entirely above 5%.

Study L1069T-25

Evaluable Patient Population

A summary of protocol deviations is presented in Table 2 below.

Table 2. Protocol Deviations for Study L1069T-25

Category of Deviation[1]	n (%)
Deviation from Inclusion Criteria	20 (40)
Deviation from Exclusion Criteria	2 (4)
Received Prohibited Drug/Therapy	25 (50)
Other Deviation	0
Total Number of Deviations[2]	51
Total Number of Patients with at Least One Deviation	**33 (66)**

[1] Patients are counted no more than once, unless specified otherwise
[2] Patients may contribute multiple deviations.

Patients that did not meet all of the following criteria were excluded from the evaluable patient population: have satisfied all inclusion criteria and did not satisfy any exclusion criteria; have histopathology either diagnostic of, or consistent with, CTCL by the local pathologist and at least one independent reference dermatopathologist; and have been treated for at least 8 weeks (defined as at least 52 days for analysis purposes) with Targretin gel. Twenty-five patients received prohibited medication, 18 patients had early or late skin biopsy, three patients did not meet other inclusion/exclusion criteria, one patient had an insufficient pathological confirmation and one patient had insufficient qualifying therapy. A total of 34 patients did not satisfy protocol-specified evaluable patient criteria. The remaining 16 patients comprise the evaluable patient population (PP).

The following is an FDA response (from the meeting minutes of Oct. 7, 1998) to Ligand's question "Does the Division concur that the total number of patients in study L1069T-25 and in the Phase 1-2 CTCL studies, N=112, is sufficient to support full approval of the product for the proposed indication:" *"The originally targeted number of 60 evaluable patients is required. Forty five patients may be acceptable, depending on the results."*

Refractory/Persistent CTCL Patient Population

Patients that meet all of the following criteria were included in the refractory/persistent CTCL patient population: have skin biopsy evaluable (at least two dermatopathologist readings at least consistent with CTCL; have qualifying prior CTCL therapy per protocol; and TNM stage within range specified by the protocol. A total of forty-six patients meet those criteria above.

Intolerant (a Subgroup) Patient Population

Twelve patients satisfied conditions for "intolerance." Those medications to which patients where intolerant were: nitrogen mustard (5 patients), PUVA (4 patients), electron beam therapy (1 patient), UVB (1 patient), systemic prednisone (1 patient), and Tigason (1 patient).

Baseline Characteristics

Table 3 below gives descriptive statistics on durations of CTCL (in months) prior to Targretin gel treatment. Medians and ranges are given (statistics suggest that those distributions are skewed to the right).

Table 3. Duration of CTCL Prior to Targretin Gel Treatment

Duration of Disease	
Time (Months) Since First Clinical Manifestation of CTCL	
Median	138.0
Range	15.2-644.7
Time (Months) Since First Clinical Diagnosis of CTCL	
Median	73.1
Range	2.0-278.5
Time (Months) Since First Histopathologic Determination Consistent with CTCL	
Median	69.7
Range	1.8-254.4

Table 4 below gives frequencies and relative frequencies of three forms (Systemic, Topical/Local and Irradiation) of prior anti-CTCL therapies.

Table 4. Most Common Prior Anti-CTCL Therapy

Prior Anti-CTCL Therapy	n (%)
None	0
Any Systemic Agent-Therapy	19 (38)
Any Topical/Local Therapy	44 (88)
Any Irradiation Therapy	47 (94)
Both Systemic and Topical/Local Therapy	14 (28)
Both Systemic and Irradiation Therapy	17 (34)
Both Topical/Local and Irradiation Therapy	41 (82)
Systemic, Topical/Local and Irradiation Therapy	12 (24)

Table 5 below gives frequencies and relative frequencies for the number of prior anti-CTCL therapies (Systemic, Topical/Local or Irradiation).

Table 5. Number of Prior Anti-CTCL Therapies

Number of Prior Anti-CTCL Therapies (Systemic, Topical/Local and Irradiation Combined)	N=50 n (%)
None	0
1 Therapy	0
2 Therapies	22 (44)
3 Therapies	14 (28)
4 Therapies	6 (12)
5 Therapies	5 (10)
6 Therapies	1 (2)
7 Therapies	2 (4)
$\geq$ 8 Therapies	0

Table 6 below gives prior response information for those patients that had received prior anti-CTCL systemic therapy.

Table 6. Response to Prior Anti-CTCL Systemic Agents/Therapies

Prior Anti-CTCL Systemic Agents/Therapies	n (%)
If Systemic Therapy Given, at Least One Response	N=19
Yes	12 (63)
No	5 (26)
Unknown	2 (11)

If Response, at Least One Relapse While Still Receiving Treatment	N=12
Yes	10 (83)
No	1 (8)
Unknown	1 (8)
If Response, Has Response Plateau of at Least 6 Month Duration	N=12
Yes	7 (58)
No	5 (42)
Unknown	0
If Systemic Agents/Therapy Given, Unresponsive to At Least One Therapy	N=19
Yes	9 (47)
No	8 (42)
Unknown	2 (11)
If Systemic Agents/Therapy Given, Intolerant to at Least One Therapy	N=19
Yes	8 (42)
No	11 (58)
Unknown	0

Table 7 below gives prior response information for those patients that had received prior anti-CTCL topical/local therapy.

Table 7. Response to Prior Anti-CTCL Topical/Local Therapies

Prior Anti-CTCL Topical/Local Therapies	n (%)
If Topical Therapy Given, at Least One Response	N=43
Yes	22 (51)
No	20 (47)
Unknown	1 (2)
If Response, at Least One Relapse While Still Receiving Treatment	N=22
Yes	17 (77)
No	3 (14)
Unknown	2 (9)

If Response, Has Response Plateau of at Least 6 Month Duration	N=22
Yes	8 (36)
No	12 (55)
Unknown	2 (9)
If Topical/Local Therapy Given, Unresponsive to At Least One Therapy	N=43
Yes	28 (65)
No	14 (33)
Unknown	1 (2)
If Topical/Local Therapy Given, Intolerant to at Least One Therapy	N=44
Yes	22 (50)
No	21 (48)
Unknown	1 (2)

Table 8 below gives prior response information for those patients that had received prior anti-CTCL irradiation therapy.

Table 8. Response to Prior Anti-CTCL Irradiation Therapies

Prior Anti-CTCL Irradiation Therapies	n (%)
If Irradiation Therapy Given, at Least One Response	N=47
Yes	32 (68)
No	15 (32)
Unknown	0
If Response, at Least One Relapse While Still Receiving Treatment	N=32
Yes	27 (84)
No	4 (13)
Unknown	1 (3)
If Response, Has Response Plateau of at Least 6 Month Duration	N=32
Yes	9 (28)
No	19 (59)
Unknown	4 (13)

If Irradiation Therapy Given, Unresponsive to At Least One Therapy	N=47
Yes	20 (43)
No	27 (57)
Unknown	0
If Irradiation Therapy Given, Intolerant to at Least One Therapy	N=47
Yes	15 (32)
No	30 (64)
Unknown	2 (4)

Response Rates

Table 9 below lists the sponsor's determined response rates and those corresponding exact 95% confidence intervals based on the ITT population.

Table 9. Response Rates and 95% Confidence Intervals (ITT) for Study L1069T-25

Efficacy Endpoint	Response rate	95% C.I.
PGA	19/50 (38%)	(25%, 53%)
CA	18/50 (36%)	(23%, 51%)
PEC	22/50 (44%)	(30%, 59%)

Fourteen patients were responders according to both PGA and CA. Based on a kappa analysis (from this reviewer's calculations), the agreement between these two response instruments, PGA and CA, is acceptable (kappa =0.609 with a 95% C.I. of (0.330, 0.889)). The earliest time to first response ranged was 28 to 37 days. The latest time to first response ranged was 123 to 155 days with a total of three to six patients responding beyond 100 days. The 25-th percentile (Kaplan-Meier) for durability of response was 105 days for PEC, 172 days for PGA and 148 days for CA. Those rates of relapse were 32% (7/22) for PEC, 21% (4/19) for PGA and 22% (4/18) for CA.

Note that all ITT responders were in the refractory/persistent CTCL patient population.

PGA, CA and PEC responses according to those sponsor's tabulations are given in Table 10 below.

Table 10. PGA, CA and PEC Responses (ITT) for Study L1069T-25

Efficacy Endpoint	PGA	CA	PEC
CCR	1	4	4
PR	18	14	18
SD	20	26	20
PD	8	5	7
Unknown	3	1	1

Median time to disease progression (among those patients who progressed) was 57 days for PEC, 75 days for PGA and 70 days for CA.

Table 11 below lists the sponsor's determined response rates and those corresponding exact 95% confidence intervals based on the evaluable patient population.

Table 11. Response Rates and 95% Confidence Intervals (Evaluable) for Study L1069T-25

Efficacy Endpoint	Response rate	95% C.I.
PGA	7/16 (44%)	(20%, 70%)
CA	8/16 (50%)	(25%, 75%)
PEC	7/16 (44%)	(20%, 70%)

Table 12 below lists the sponsor's determined response rates and those corresponding exact 95% confidence intervals based on the intolerant patient population.

Table 12. Response Rates and 95% Confidence Intervals (Intolerant Patient Population) for Study L1069T-25

Efficacy Endpoint	Response rate	95% C.I.[1]
PGA	3/12 (25%)	(5%, 57%)
CA	3/12 (25%)	(5%, 57%)
PEC	3/12 (25%)	(5%, 57%)

[1] Note: from this reviewer's calculations the lower bounds of these C.I.'s are 5.49%

Note that all response rates were at least 20% with corresponding 95% C.I.'s (no adjustment for multiplicity) lying entirely above 5%.

Quality of Life

Table 13 summarizes the changes in Spitzer quality of life assessments according to the sponsor's calculations. The first five questions of the Spitzer questionnaire concern

respectively, activity, daily living, health, support and outlook. The choices for each question are scored 2, 1 and 0, from highest quality to lowest quality. Question 6 asks "Please mark with an X the appropriate place within the bar to indicate your rating of your quality of life during the past 4 weeks." The left-hand side represents "lowest quality" and the right-hand side represents "highest quality." These marks were then converted to a score to millimeter measurements from the left margin of the bar. The possible values range from 0 mm (lowest quality) to 100 mm (highest quality). All values are according to the sponsor's calculations.

Table 13. Summary of Spitzer Quality of Life Assessments

Characteristics	No.Pts.	Mean, SE	Median	Range
Changes from Baseline in General Status Quality of Life Questionnaire for Spitzer Items 1-5				
Day 1 Baseline	49	9.0, 0.19	9.0	5 to 10
Week 4	47	-0.1, 0.14	0.0	-3 to 2
Week 8	46	0.0, 0.18	0.0	-3 to 4
Week 12	41	-0.1, 0.19	0.0	-3 to 3
Week 16	38	0.0, 0.20	0.0	-2 to 4
Week 20	33	0.5, 0.17	0.0	-1 to 4
Changes from Baseline in Overall Quality of Life for Spitzer Item 6				
Day 1 Baseline	46	83.9, 2.59	93	19 to 98
Week 4	41	-4.2, 2.35	-3	-52 to 24
Week 8	38	-4.2, 2.62	-3	-59 to 29
Week 12	36	-8.3, 1.99	-8	-36 to 22
Week 16	34	-4.1, 3.06	-2	-49 to 30
Week 20	29	-5.7, 2.72	-3	-43 to 37

Question 2 of the CTCL-specific questionnaire concerns itchiness at skin lesions. This question is on a 5-point scale with 1 being no itchiness at all and 5 being extreme itchiness. Change from baseline results are given in Table 14 below.

Table 14. CTCL-Specific Questionnaire: Change from Baseline of Itchiness at Skin Lesions

Characteristics	No.Pts.	Mean, SE	Median	Range
Changes from Baseline				
Day 1 Baseline	49	2.6, 0.18	3.0	1 to 5
Week 4	46	0.4, 0.22	0.0	-2 to 4
Week 8	46	0.2, 0.20	0.0	-4 to 3
Week 12	41	0.2, 0.22	0.0	-4 to 3
Week 16	36	0.1, 0.24	0.0	-2 to 4

Week 20	33	0.0, 0.20	0.0	-3 to 3

At least one patient went from no itchiness at baseline to extreme itchiness at four weeks. At least one patient went from extreme itchiness at baseline to no itchiness at eight (twelve) weeks.

Question 3 of the CTCL-specific questionnaire concerns redness, scaling and/or plaque elevation. This question is on a 5-point scale with 1 being no redness, scaling or plaque elevation and 5 being extreme redness, scaling and/or plaque elevation. Change from baseline results are given in Table 15 below.

Table 15. CTCL-Specific Questionnaire: Change from Baseline of Redness, Scaling and/or Plaque Elevation

Characteristics	No.Pts.	Mean, SE	Median	Range
Changes from Baseline				
Day 1 Baseline	49	3.1, 0.14	3.0	1 to 5
Week 4	46	0.8, 0.18	1.0	-1 to 4
Week 8	46	0.4, 0.17	0.0	-2 to 2
Week 12	41	0.1, 0.17	0.0	-2 to 2
Week 16	37	0.2, 0.21	0.0	-2 to 3
Week 20	33	-0.2, 0.22	0.0	-2 to 3

At 4 weeks after baseline, more than half of the 46 patients went up at least one scale of redness, scaling and/or plaque elevation from baseline. At least one patient went from no redness, scaling or plaque elevation at baseline to extreme redness, scaling and/or plaque elevation at four weeks. At four weeks after baseline, the t-test statistic value for no mean change from baseline is 4.44 with a corresponding two-sided p-value less than 0.0001. Since such a test does not test any pre-specified hypothesis, interpretation of the p-value should be with caution.

Table 16 summarizes the sponsor's tabulations of the responses to question 8 of the CTCL-specific patient questionnaire.

Question 8 of the CTCL-specific questionnaire: Taking into account the appearance and all symptoms related to your cutaneous t-cell lymphoma (mycoses), how has your cutaneous t-cell lymphoma (mycoses) changed as compared to before your participation in this study? (1= 'Much worse' to 5= 'Much improved')

Table 16. CTCL-Specific Patient Questionnaire: Change in CTCL (Question 8) Compared to Baseline

Study Visit	Total No.Pts.	Much Worse	Moderately Worse	About the Same	Moderately Improved	Much Improved
Week 4	46	3	12	11	18	2
Week 8	46	4	11	7	14	10
Week 12	41	2	8	2	18	11
Week 16	37	1	3	4	15	14
Week 20	33	1	1	7	8	16

Table 17 summarizes the sponsor's tabulations of the responses to question 9 of the CTCL-specific patient questionnaire.

Question 9 of the CTCL-specific questionnaire: What has been your overall level of satisfaction or dissatisfaction with the drug treatment in this study? (1= 'Very dissatisfied' to 5= 'Very satisfied')

Table 17. CTCL-Specific Patient Questionnaire: Satisfaction/Dissatisfaction with Study Drug Treatment (Question 9) Compared to Baseline

Study	Study Visit	Total No.Pts.	Very Dissatisfied	Moderately Dissatisfied	Neutral	Moderately Satisfied	Very Satisfied
	Week 4	47	2	5	14	18	8
	Week 8	47	1	10	9	17	10
	Week 12	41	2	6	6	15	12
	Week 16	37	1	3	6	12	15
	Week 20	33	0	2	7	10	14

Phase I-II Studies in CTCL Patients

Eighteen of the 67 patients initially received Targretin 1% gel (vol. 1.69 pages 75-76). Eight of these 18 patients had a response according to PGA.

Table 18 below gives frequencies and relative frequencies by dose group of two forms (Systemic and Topical/Local) of prior anti-CTCL therapies.

Table 18. Prior Anti-CTCL Therapy by Dose Group

Prior Anti-CTCL Therapy	Patients Who Reached 1% Targretin (N=58) n (%)	All Patients (N=67) n (%)
None	14 (24)	15 (22)
Any Systemic Agent Therapy	15 (26)	18 (27)
Any Topical/Local Therapy	44 (76)	52 (78)
Both Systemic and Topical/Local Therapy	15 (26)	18 (27)

Table 19 below gives frequencies and relative frequencies by center (study) of two forms (Systemic and Topical/Local) of prior anti-CTCL therapies.

Table 19. Prior Anti-CTCL Therapy by Center

Prior Anti-CTCL Therapy	L1069T-11 (N=33) n (%)	L1069T-12 (N=13) n (%)	L1069-94-04T (N=21) n (%)
None	5 (15)	5 (38)	5 (24)
Any Systemic Agent Therapy	6 (18)	4 (31)	8 (38)
Any Topical/Local Therapy	28 (85)	8 (62)	16 (76)
Both Systemic and Topical/Local Therapy	6 (18)	4 (31)	8 (38)

Table 20 below lists the sponsor's determined response rates and those corresponding exact 95% confidence intervals for the ITT population.

Table 20. Response Rates and 95% Confidence Intervals for Phase I-II studies in CTCL patients (ITT analyses)

Efficacy Endpoint	All Patients Response rate	95% C.I.
PGA	42/67 (63%)	(50%, 74%)
OSA	34/67 (51%)	(38%, 63%)

PGA and OSA responses, by whether 1% Targretin was reached (according to the sponsor's tabulations), are given in Table 21 below.

Table 21. PGA and OSA Responses for those Phase I-II studies in CTCL patients

Efficacy Endpoint	Patients Who Reached 1% Targretin (N=58)	Patients Who Did Not Reach 1% Targretin (N=9)	All Patients (N=67)
PGA Response			
CCR	14	0	14
PR	23	5	28
SD	13	1	14
PD	8	3	11
OSA Response			
CSR	31	3	34

The earliest time to first response was 29 days. The latest time to first response was 390 to 601 days (patients that reached 1% Targretin gel and all patients respectively).

PGA and OSA responses according to those sponsor's tabulations are given in Table 22 below.

Table 22. PGA and OSA Responses by Study

Response	L1069T-11 (N=33) n (%)	L1069T-12 (N=13) n (%)	L1069-94-04T (N=21) n (%)
PGA Response			
CCR+PR	28 (85)	7 (54)	7 (33)
95% C.I.	(68, 95)	(25, 81)	(15, 57)
CCR	10 (30)	4 (31)	0
PR	18 (55)	3 (23)	7 (33)
SD	3 (9)	4 (31)	7 (33)
PD	2 (6)	2 (15)	7 (33)
OSA Response			
CSR	21 (64)	6 (46)	7 (33)
95% C.I.	(45, 80)	(19, 75)	(15, 57)

Note that all response rates were at least 20% with corresponding 95% C.I.'s (no adjustment for multiplicity) lying entirely above 5%.

4. REVIEWER'S COMMENTS

- These were poorly conducted studies. For study L1069T-25 only 16 of 50 patients were evaluable patients. Among the 50 patients in study L1069T-25, 20 had protocol

deviations from inclusion criteria, two patients had protocol deviations from exclusion criteria and twenty-five patients received prohibited drug/therapy. For the combined phase I-II studies, only 18 of 67 patients initially received Targretin 1% gel. Fifty-eight of 67 patients would reach Targretin 1% gel.

The following is an FDA response (from the meeting minutes of Oct. 7, 1998) to Ligand's question "Does the Division concur that the total number of patients in study L1069T-25 and in the Phase 1-2 CTCL studies, N=112, is sufficient to support full approval of the product for the proposed indication:" *"The originally targeted number of 60 evaluable patients is required. Forty five patients may be acceptable, depending on the results."*

- Since the response rates were quite different across centers for those phase I-II studies, it is inappropriate to combine response data for a single analysis.

- For the combined phase I-II studies, it is inappropriate to compare results for vehicle gel and Targretin gel since randomization was not involved.

- The changes from baseline in overall quality of life are in opposite directions for question 6 of the Spitzer questionnaire and questions 8 and 9 of the CTCL-specific questionnaire (see tables 13, 16 and 17).

- At 4 weeks after baseline, more than half of the 46 patients went up at least one scale of redness, scaling and/or plaque elevation from baseline. At least one patient went from no redness, scaling or plaque elevation at baseline to extreme redness, scaling and/or plaque elevation at four weeks. At four weeks after baseline, the t-test statistic value for no mean change from baseline is 4.44 with a corresponding two-sided p-value less than 0.0001. Since such a test does not test any pre-specified hypothesis, interpretation of the p-value should be with caution.

5. SUMMARY AND CONCLUSIONS

Summary: These are single armed studies, which use historical controls. In each study there were patients that received Targretin 1% gel. The sponsor deems these studies successful; the response rates (whether PGA, CA, PEC or OSA) were above 20% with confidence intervals which lied entirely above 5%.

The FDA informed the sponsor of the benefits of comparative randomized trials. The following FDA response is from the minutes of an August 7, 1996 meeting with the sponsor: *"While indicating that single-arm studies in refractory patients might support an NDA (depending on the results obtained) the FDA emphasized the advantages of comparative randomized trials and suggested that the sponsor consider conducting randomized trials in early disease comparing Targretin with the current accepted therapies. It was emphasized that response would have to [be, sic] meticulously documented. The sponsor may propose that a 20% response rate is indicative of efficacy*

but the FDA cannot guarantee that this will be adequate until the data is reviewed. ... The proposed use of historical control response rate of no more than 5% in two of the studies was discussed. The sponsor restated that this indicated that no more that [sic] 5% of the patients will have a spontaneous response. Dr. DeLap noted the advantages of comparative trials and emphasized to the sponsor that it is always risky to conduct uncontrolled trials." The FDA re-emphasized the advantages of comparative randomized trials in an October 7, 1996 letter to the sponsor.

Conclusions: In study L1069T-25 and also the combined phase I-II trials in CTCL patients, the response rates (whether PGA, CA or PEC) were above 20% with confidence intervals which lied above 5%. Very few patients were in the evaluable patient population and initially received Targretin 1%. Results of one-armed studies are exploratory. Conclusions should be based on clinical judgement.

/S/

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cc:

Archival NDA #21-056
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This review consists of seventeen pages of text.