# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER:
## 21-056

## MEDICAL REVIEW

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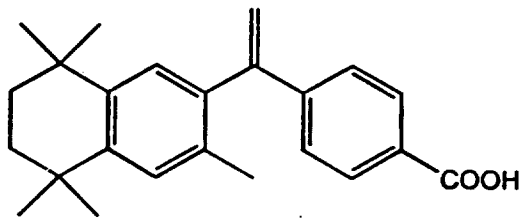
APPEARS THIS WAY
ON ORIGINAL

## GENERAL INFORMATION

Targretin® gel 1% contains bexarotene and is intended for topical application only. Bexarotene is a synthetic compound representing a novel subclass of retinoids that selectively activate retinoid X receptors (RXRs). This subclass of retinoid receptors has biologic activity distinct from that of retinoic acid receptors (RARs).

The chemical name is 4-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthalenyl)vinyl]benzenecarboxylic acid, and the structural formula is as follows:




Bexarotene is an off-white to white powder with a molecular weight of 348.48 and a molecular formula of $C_{24}H_{28}O_2$. It is insoluble in water and slightly soluble in vegetable oils and ethanol, USP.

Targretin® gel is a clear gelled solution containing 1.0% (w/w) bexarotene in a base of dehydrated alcohol, USP, polyethylene glycol 400, NF, hydroxypropyl cellulose, NF, and butylated hydroxytoluene, NF.

**Pharmacologic Category: antineoplastic**

**Proposed indication**

Targretin® (bexarotene) gel 1% is indicated for the 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.

## PHARMACOLOGY/PHARMACOKINETICS/PHARMACODYNAMICS

**General**

The following has been modified from information submitted by Ligand.

Retinoids play critical roles in normal development and physiology by modulating cell growth, division, reproduction, differentiation, and immune function. They are also capable of inhibiting cell growth, inducing differentiation, and inducing apoptosis (programmed cell death) in a variety of tumor cell lines.

The effects which retinoids produce appear to result from changes in gene expression mediated through specific intracellular receptors (IRs). There are two subfamilies of IRs through which retinoids exert their action: the retinoic acid receptors (RARs) and the retinoid X receptors (RXRs). The RARs and RXRs each have three subtypes designated RARα, RARβ, RARγ and RXRα, RXRβ, and RXRγ, respectively. Each receptor subtype is thought to control both unique and overlapping target genes.

Retinoids have been used clinically for the treatment of a wide variety of neoplastic diseases. Clinical response has been observed in patients with acute promyelocytic leukemia (APL), a disease in which a specific chromosomal translocation involving the RAR has been identified. In patients who have this 15:17 chromosomal translocation, all-*trans*-retinoic acid (ATRA) therapy is associated with a high complete remission rate. In addition to APL, significant clinical response rates have been observed in patients with cutaneous T-cell malignancies, juvenile chronic myelogenous leukemia and dermatologic malignancies. The clinical usefulness of topical ATRA for treatment of acne vulgaris and of oral 13-*cis*-retinoic acid for treatment of cystic acne and keratinizing dermatoses is well documented. In addition, 13-*cis*-retinoic acid combined with interferon-α has resulted in significant response rates in patients with squamous cell carcinomas of the head and neck and of the cervix. The concomitant use of topical ATRA with topical 5-fluorouracil significantly enhances the efficacy of this agent in treating patients with either actinic keratosis or basal cell carcinoma.

Targretin drug substance (LGD1069) is a novel synthetic retinoid analogue. Targretin drug substance is a subtype-specific ligand since it binds preferentially to the members of the RXR subclass of receptors. These receptors play a role in the regulation of cell growth and differentiation via their ability to regulate transcription. Evidence is accumulating from *in vitro* studies, experiments in animal models, and from clinical trials to suggest that various retinoids have therapeutic effects on several types of neoplastic diseases, including carcinomas, acute promyelocytic leukemia, AIDS-related Kaposi's sarcoma and multiple myeloma. Molecules which are subtype-specific in the binding and activation of retinoid receptors may have unique biological properties which could translate into useful therapeutic agents.

Several characteristics of targretin drug substance have led Ligand Pharmaceuticals to the development of this compound:

- It has subclass specificity in that it preferentially interacts with the RXR receptor subtypes (RXR-alpha, RXR-beta, and RXR-gamma), which could provide therapeutic specificity and/or reduced toxicities.

- targretin drug substance inhibits the growth of tumor cell lines of both hematopoietic and squamous cell origin.

- targretin drug substance induces apoptosis (programmed cell death) in a number of tumor cell lines.

- Xenografts of primary human squamous cell tumors are inhibited by targretin drug substance.

Targretin drug substance is a synthetic retinoid and preferentially interacts with the RXR subtypes. In contrast, ATRA is a naturally occurring hormone that binds with high affinity only to the RAR subtypes, while 9-*cis*-retinoic acid (9-*cis*-RA) is a "pan-agonist" (i.e., it binds and activates all known retinoid receptors, including RAR and RXR families).

Ligand has explored the actions of targretin drug substance in multiple *in vitro* and *in vivo* models. The major findings are outlined below:

- Targretin drug substance induces apoptosis in cell based assays.

- In contradistinction to ATRA, targretin drug substance is not a differentiating agent at levels that do not result in significant RAR activation.

- In a human primary squamous cell xenograft model, targretin drug substance inhibits tumor growth and causes tumor regression in nude mice.

- Neither targretin drug substance nor ATRA inhibits growth of ME-180 tumors in nude mice.

- targretin drug substance has antikeratinizing effects in rhino mice.

- targretin drug substance can modulate lipid metabolism in rats.

**MEDICAL OFFICER NOTE: FDA queried, Do mature helper T-cells and/or CTCL cells have RXR receptors? , Ligand stated that they have not conducted investigations of the expression patterns of the retinoid receptors in either mature helper T-cells or in CTCL cell or cell lines (Ligand response dated 4/24/2000).**

**Levels of RXR-alpha expression in T lymphocytes are coupled to cell cycle progression, and there is tight regulatory control of RXR-alpha expression during the transition from $G_0/G_1$ to S phase of the cell cycle—i.e., RXR-alpha expression is down-regulated during the $G_0/G_1$ to S phase. T cell activation induces expression of transcription factor AP-1. Levels of RXR-alpha in resting T lymphocytes may be inhibitory to AP-1 activity and may prevent AP-1 induced gene transcription and proliferation. RXRs may have a role in the prevention of activation-induced apoptosis in T cell hybridoma and thymocytes. Activation-induced apoptosis can be prevented by treatment with 9-cis retinoic acid can be prevented by treatment with**

9-cis retinoic acid.[1] This action of prevention of apoptosis appears to be the opposite of what Ligand claims targretin does to apoptosis (see bullet above).

**Using Northern blot analysis of the expression of human retinoic acid receptors RAR-alpha and RXR-alpha, T-lymphoid H9 cells express RAR-alpha receptors and not RXR-alpha receptors; the promonocytoid cell, U937 expresses both. Under condition of phorbol myristate acetate (an enhancer of HIV-1 replication by activation of protein kinase C and the nuclear factor kappa-B), H9 cells expressed RXR-alpha.[2]**

Targretin oral capsules at sufficiently high doses may be potentially associated with any of the clinical toxicities observed with hypervitaminosis A syndrome. These include gastrointestinal distress, headache, dizziness, fatigue, irritability, pseudo-tumor cerebri, cheilitis, epidermal desquamation, xerosis, hyperostosis, bone resorption and hairline fractures, hepatosplenomegaly, elevated serum triglycerides and cholesterol, and ocular abnormalities.

Fetal abnormalities are a significant retinoid toxicity and targretin drug substance is a potential teratogen.

## CLINICAL

**Background on Cutaneous T-Cell Lymphoma**

The following has been modified from information submitted by Ligand.

About 1000 new cases of cutaneous T-cell lymphoma (CTCL, mycosis fungoides) are diagnosed every year in the U.S. The disease is typically found in mature adults (40-60 years old) in all races, with men afflicted by the disorder twice as often as women. Lesions of this lymphoma may remain as patches or plaques confined to the skin for many years before development of cutaneous tumors or visceral disease. Cutaneous manifestations of CTCL are present for an average of 2 to 10 years prior to biopsy confirmation of disease.

CTCL is typically a chronic, slowly progressive disease of 10 to 20 years duration classified into four clinical stages. Skin patches and plaques occur in stage I, the presence of clinical lymphadenopathy with negative pathology and/or cutaneous tumors characterize stage II, generalized erythroderma characterizes stage III, and pathologically positive lymph nodes and/or visceral disease characterize stage IV.

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[1] Ishaq M, Zhang Y-M, Natarajan V. J Biol Chem 1998; 273:21210-21216.
[2] Yamaguchi K, Groopman JE, Byrn RA. AIDS 1994; 8:1675-1682.

| Stage | TNM Groupings | Description |
|---|---|---|
| IA | T1, N0, M0 | Eczematous patches, papules, or limited plaques covering less than 10% of skin surface. No clinically abnormal peripheral lymph nodes, pathology negative for CTCL. No involvement of visceral organs. |
| IB | T2, N0, M0 | Erythematous patches, papules, or generalized plaques covering 10% or more of the skin surface. No clinically abnormal peripheral lymph nodes, pathology negative for CTCL. No involvement of visceral organs. |
| IIA | T1 or T2, N1, M0 | Eczematous patches, papules, limited or generalized plaques. Clinically abnormal peripheral lymph nodes with pathology negative for CTCL. No involvement of visceral organs. |
| IIB | T3, N0 or N1, M0 | One or more cutaneous tumors. Clinically normal or abnormal peripheral lymph nodes with pathology negative for CTCL. No involvement of visceral organs. |
| III | T4, N0 or N1, M0 | Generalized erythroderma. Clinically normal or abnormal peripheral lymph nodes with negative pathology for CTCL. No involvement of visceral organs. |
| IVA | T1-T4, N2 or N3*, M0 | Eczematous patches, papules, limited or generalized plaques; and/or one or more cutaneous tumors; and/or generalized erythroderma. Clinically normal or abnormal peripheral lymph nodes with pathology positive for CTCL. No involvement of visceral organs. |
| IVB | T1-T4, N0-N3*, M1 | Eczematous patches, papules, limited or generalized plaques; and/or one or more cutaneous tumors; and/or generalized erythroderma. Clinically normal or abnormal peripheral lymph nodes with pathology negative or positive for CTCL. Visceral involvement (must have confirmation of pathology; organ involved must be specified). |

B+ = Positive blood smear
B- = Negative blood smear
*LN3 or LN4 will constitute a N3

The prognosis of CTCL varies with the clinical stage of disease. CTCL patients with superficial skin involvement (stages I and IIA) have a median survival of more than twelve years. Patients with tumors, erythroderma (Sezary syndrome), and lymph node or blood involvement but no visceral involvement (stages IIB, III and IVA) have a median survival of five years. Patients with visceral involvement (stage IVB) have a median survival of 2.5 years or less.

Therapy for cutaneous T-cell lymphoma is frequently given topically, especially in the earlier stages of the disease. Therapies such as topical glucocorticoids, nitrogen mustard (mechlorethamine), carmustine (BCNU), psoralen plus ultraviolet-A radiation (PUVA) and electron beam radiation therapy (EBT) can improve the skin manifestations and induce temporary remissions, but do not alter the patient's long term prognosis. The only

two currently approved therapies for non-advanced CTCL are photopheresis (methoxsalen plus extracorporeal long wave radiation of white blood cells) for the palliative treatment of skin manifestations of CTCL in persons who have not been responsive to other forms of treatment, and systemic mechorethamine (Mustargen®) for the palliative treatment of mycosis fungoides (MF) and targretin capsules for patients who are refractory to at least one prior systemic therapy.

Topical nitrogen mustard, topical BCNU and radiation therapies (EBT and PUVA) carry significant epidermal carcinogenic risk. Environmental exposure of household contacts and health care workers to nitrogen mustard and BCNU is also a concern. Radiation therapies may induce skin aging changes, telangiectasia, edema, radiation dermatitis, permanent alopecia and chronic blepharitis. The incidence of drug hypersensitivity is reported to occur in up to 45% or more of patients treated with topical nitrogen mustard and up to 5% of patients treated with BCNU.

Systemic therapies are generally reserved for more advanced stages of CTCL due to the greater potential for toxicity. In addition to photopheresis as approved therapy, systemic mechorethamine (Mustargen®) is approved for the palliative treatment of mycosis fungoides (MF), vinblastine (Velban®) is approved for advanced stages of MF and methotrexate is approved in combination with other anticancer agents in the treatment of advanced MF. For broader lymphoma indications, Carmustine [BCNU] (BiCNU®) is approved for palliative treatment of non-Hodgkin's lymphoma as secondary therapy in combination with other approved drugs for relapsed and refractory patients and vincristine (Oncovin®) has been shown to be useful in combination therapy with other oncolytic agents for treatment of non-Hodgkin's malignant lymphomas.

Newer therapies have been explored using biological regulators, including interferon $\alpha$ and $\gamma$, 13-*cis*-retinoic acid, etretinate and others. Interferons have been shown to be nearly as active in CTCL as single-agent chemotherapy with less toxicity when used at low doses. Clinical responses have been observed with treatment with retinoids, including 13-*cis*-retinoic acid, arotinoid, and etretinate.

The rationale for using retinoids in cancer therapy is predicated upon the knowledge that these compounds exert a hormone-like control of normal cellular differentiation and proliferation in essentially all epithelia which are target sites for development of invasive carcinoma. Furthermore, it has been demonstrated that retinoids can restore normal cellular differentiation to dysplastic epithelium, both in laboratory and clinical settings.

One of the advances to our understanding of how to apply retinoids in cancer therapy has been documentation that differentiation is a consistent and effective method of treating human cancer. Induction of differentiation is the primary activity of ATRA in remission induction of patients with APL. Thus, retinoids can serve as physiologic rather than cytotoxic drugs to arrest or reverse the process of carcinogenesis. It is also relevant that there is a growing body of evidence that supports a role for retinoids in the induction of apoptosis, and such activities may play a role in the management of cervical cancer by

13-*cis*-retinoic acid plus interferon α. There are also substantial data that associate the growth inhibitory properties of retinoids with their chemopreventive activities.

**Other retinoids:**

At least two retinoids have had success in treating the cutaneous signs of CTCL. etretinate and isotretinoin. Scandinavian investigators demonstrated the utility of retinoids as part of combination therapies in the mid-1980s. They reported complete clearing of skin lesions or partial remissions with isotretinoin, either alone or in combination with PUVA, systemic anticancer drugs or glucocorticoids . In the U.S., researchers working with oral isotretinoin as monotherapy also found complete or partial remissions of CTC. Up to 75% of patients had some clinical response, usually after eight weeks of therapy, with 9% having complete clearing. Isotretinoin was successful when other therapies could not be tolerated. These clinical responses were palliative; although the quality of the patients' lives were much improved, there is no evidence that their prognosis was improved. While retinoids are not recognized as curative therapy, they are successful in treating CTCL in many patients and their use would not adversely affect the patient's outcome by delaying definitive therapy as it is currently known.

# PIVOTAL CLINICAL TRIAL (PHASE 3 EVALUATION OF TARGRETIN™ TOPICAL GEL IN PATIENTS WITH REFRACTORY OR PERSISTENT EARLY STAGE CUTANEOUS T-CELL LYMPHOMA)-- L1069T-25

Up to a total of 72 patients were to be enrolled to provide for a total of 60 evaluable patients. The data from 50 enrolled patients were submitted from this study.

Enrollment in Study –25 was initiated on March 18, 1997 and completed on October 12, 1998. The cut-off date for the Final Report February 15, 1999.

There were 41 investigators at sites located in the United States, Canada, Australia, and Europe (France, Spain, Switzerland, Poland); only 25 sites entered patients on the study (18 of the sites were US).

Data from 50 patients was submitted to the NDA; 40 of the patients were from US sites.

**Protocol review**

Objectives

1. To evaluate the safety and tolerability of targretin topical gel in patients with refractory or persistent early stage cutaneous T-cell lymphoma.

2. To evaluate the antitumor efficacy of targretin topical gel in patients with refractory or persistent early stage cutaneous T-cell lymphoma.

Eligibility

1. Inclusion criteria:

   at least 18 years of age

   a clinical diagnosis of cutaneous T-cell lymphoma (CTCL, mycosis fungoides), stage IA, IB or IIA and confirmed by a current biopsy (within 30 days prior to entry) to be histologically consistent with CTCL by a dermatopathologist.

   refractory to, intolerant to, or reached a response plateau for at least six (6) months on at least two prior therapies from the following list: PUVA, UVB, EBT, photopheresis, interferon, systemic cytotoxic chemotherapy, topical nitrogen mustard or topical carmustine (BCNU). At least one of these qualifying prior treatments must have been topical nitrogen mustard, topical carmustine or a phototherapy (UVB, PUVA, or EBT). Topical steroids and systemic retinoids did not qualify.

Karnofsky performance score of at least 60

Acceptable organ function: hemoglobin ≥9 g/dL and WBC ≥2000/mm$^3$; bilirubin <1.5 times the upper limit of normal; creatinine ≤2 times the upper limit of normal; SGOT (AST) and SGPT (ALT) ≤2.5 times the upper limit of normal; serum calcium ≤11.5 mg/dL; fasting serum triglyceride ≤800 mg/dL

Patients must have been free of serious concurrent illness

Women of childbearing potential must have a negative serum pregnancy test (β-HCG) within seven days prior to initiation of treatment and must have used an effective means of contraception or must have been sexually abstinent for at least four weeks prior to the negative pregnancy test through entry in the study. Female patients and male patients with female partners of child-bearing potential must have agreed to practice an effective method of contraception during the entire period of treatment and for at least three months after treatment was discontinued.

Male patients with female sexual partners who were pregnant or potentially pregnant must have agreed to use condoms during sexual intercourse during the entire period of treatment and for at least three months after treatment was discontinued.

Systemic therapy was not required.

Complete avoidance of systemic or topically-applied antihistamine and antipruritic agents for at least one (1) week, or, if such agents could not be avoided, systemic and topically-applied antihistamine and antipruritic agents must have been using a stable dose regimen for at least one week prior to initiation of study drug treatment and throughout the study, unless it is determined that a discontinuation or reduction in dose is indicated.

Exclusion Criteria

Systemic antibiotic therapy within two (2) weeks of entry in the study. (Patients with infections requiring antibiotics or likely to require antibiotics should be appropriately treated with a course of antibiotics terminating at least two weeks prior to entry, or if indicated, a chronic suppressive or prophylactic dose of antibiotics stabilized at least two weeks prior to entry. Patients who required initiation of, or changes in, antibiotic therapy during the study will not be considered in violation of this protocol.)

Topical therapy for CTCL including nitrogen mustard, carmustine (BCNU), corticosteroids and others within two (2) weeks of entry in the study.

Psoralen plus UV-A radiation therapy (PUVA) or UVB therapy within three (3) weeks of entry in the study.

Electron beam therapy (EBT) or photopheresis therapy within 30 days of entry in the study.

Systemic anticancer therapy of any kind (e.g., methotrexate, mechlorethamine, vinblastine, corticosteroid, etc.) within thirty (30) days of entry in the study.

Systemic therapy with Vitamin A in doses of greater than 15,000 IU (5,000 mcg) per day (equivalent to approximately three times the RDA) or other retinoid class drugs within thirty (30) days of entry in this study.

Participation in any other investigational drug study within thirty (30) days of entry in this study.

Oral retinoid therapy for any indication within three (3) months of entry in the study.

Oral etretinate therapy for any indication within one (1) year of entry in the study.

Participation in any other study using topical retinoid therapy for CTCL.

Pregnancy or active breast-feeding.

Serious known intercurrent medical illness or infection, including HIV, which could potentially present a safety risk and/or prevent compliance with the requirements of the treatment program.

Unwillingness or inability to avoid prolonged exposure to the sun or UV light sufficient to produce a mild erythema or thought by the Investigator likely to modify the patient's disease.

Known allergy or sensitivity to retinoid class drugs.

Dose and Schedule

Patients began treatment with 1% TARGRETIN gel applied topically every other day (QOD) and then escalated the frequency of application at one week intervals to 1% QD, then 1% BID, then 1% TID and then 1% QID, as tolerated. The frequency of application was adjusted for toxicity.

Although all lesions are to be treated, up to five lesions representative of the overall extent of cutaneous disease were selected as index lesions.

The patient was instructed to apply study drug gel to all CTCL lesions at the assigned frequency by using a finger to place a generous coating of study drug gel on the entire surface of the specified CTCL lesion.

Since there was only one concentration of study drug in the study, adjustments to exposure were made only by adjustments to the frequency of application. All patients were started on a dosing frequency of every other day (QOD) and then escalate the frequency of application at one week intervals to 1% QD, then 1% BID, then 1% TID and then 1% QID, as tolerated. The frequency of application was recorded for each index lesion at every visit on the patient's Case Report Forms.

The frequency of application was to be adjusted for each lesion independently. The goal of treatment adjustments was to have each CTCL lesion treated at the maximum tolerated frequency of application. However, patients who exhibited treatment-limiting toxicity (TLT) had their treatment exposure reduced or discontinued. The frequency of study drug application for any index lesion and for any supplemental (non-index) lesion was advanced, as tolerated by the patient, by no more than two (2) treatment exposure levels at one time and at time intervals of no less than every one week.

If a patient discontinued active involvement in the study (did not continue to be evaluated every four weeks and was withdrawn from the study) but experiences an exacerbation of their cutaneous T-cell lymphoma, treatment could be reinitiated, subject to prior written approval from the study Sponsor. The decision to resume TARGRETIN topical gel treatment included a judgment by the investigator that TARGRETIN topical gel was the optimal treatment for the patient and that the patient continued to meet all protocol eligibility criteria.

Prohibitions and Restrictions

During the study, the following therapies are prohibited and may not be administered to patients being treated on this protocol:

Systemic anti-psoriatic and systemic anticancer drugs and therapies (e.g., methotrexate, bleomycin, cyclophosphamide, prednisone, etc.).

Topical medications (such as corticosteroids or tar baths). However, mineral oil, baby oil, and simple moisturizing lotions were used as emollients.

Systemic use of other retinoid class drugs, beta-carotene compounds, or Vitamin A doses of more than 15,000 IU (5,000 mcg) per day (equivalent to approximately three times the RDA) for any indication.

If systemic and topically-applied antihistamine and antipruritic agents could not be avoided, such agents were administered using a stable dose regimen for at least one (1) week prior to initiation of study drug treatment and throughout the study, unless it was determined that a discontinuation or reduction in dose was indicated.

Localized radiation therapy of specific lesions was to be avoided; however, should such therapy be necessary, then any lesions so treated was considered to have shown progressive disease for the purposes of study endpoints.

Treatment Adjustments

Since there was only one concentration of study drug in this study, adjustments to exposure will be made only by adjustments to the frequency of application.

Schedule of Dose Escalation

| Exposure Level | Week of Treatment | Frequency of Application |
|---|---|---|
| A | 1 | QOD |
| B | 2 | QD |
| C | 3 | BID |
| D | 4 | TID |
| E | ≥5 | QID |

QOD = Every Other Day
QD = Once Daily
BID = Twice Daily
TID = Three Times Daily
QID = Four Times Daily

Adjustments to the frequency of application were necessitated because of toxicity or if under the judgment of the Investigator it was in the best interests of the patient not to advance to the next higher dose level. However, patients who exhibited treatment-limiting toxicity (TLT) should have their treatment exposure reduced or discontinued. The frequency of study drug application for any index lesion and for any supplemental (non-index) lesion were advanced, as tolerated by the patient, by no more than two (2) treatment exposure levels (see Table above) at one time and at time intervals of no less than every one week. Specific guidelines for treatment adjustments necessitated by local dermal treatment-limiting toxicity are specified in Table below

The treatment modifications in the Table below were intended as a set of guidelines for dosing frequency adjustments. Patients may need to be restarted on a reduced exposure regimen after a period of up to two (2) weeks off treatment. If no frequency of study drug application was tolerated for any of the patient's lesions, then the patient was to be withdrawn from the study.

TABLE. ADJUSTMENT GUIDELINES FOR TREATMENT-LIMITING TOXICITY

| TYPE AND DEGREE OF TOXICITY | TREATMENT ADJUSTMENTS |
|---|---|
| **LOCAL DERMAL IRRITATION** | |
| Grade 0, 1 or 2 | • No action required; observation; treatment continues. |
| Grade 3 | • Treatment frequency for that lesion should be reduced or suspended for up to four (4) weeks*. If after irritation improves to Grade 2 or lower, and treatment is restarted, treatment frequency may be increased every week as tolerated. |
| Grade 4 | • Treatment for that lesion must be discontinued until irritation improves to Grade 2 or lower (this must occur within four (4) weeks)*; treatment may then be restarted at ≤QD for at least one week before increasing frequency, as tolerated. Treatment should not be restarted if Grade 4 toxicity occurred at ≤QD. |
| **SYSTEMIC TOXICITY** (Graded per NCI Criteria) | Should a systemic adverse event occur that is thought to be possibly or more related to the study drug administration and possibly treatment-limiting, the study site should immediately confer with the Ligand physician monitor for the study. |

***If irritation does not subside to Grade two (2) or lower within four weeks, a waiver from Ligand Pharmaceuticals must be obtained to continue the patient.**

Treatment interruptions for non-medical reasons were at times unavoidable and were permissible under this protocol but were documented. However, every attempt was made to avoid any non-medical treatment delays. Patients who required frequent or prolonged treatment interruptions were withdrawn from the study.

Diagnosis

Each patient's histopathology specimens used to meet entry criteria were sent to a reference dermatopathologist for the study who read the biopsy slides. If this reference dermatopathologist concluded that the specimens were either diagnostic of or consistent with CTCL, the patient will have met this test of evaluability for study endpoints. However, if this reference dermatopathologist concluded that the specimens were neither diagnostic of nor consistent with CTCL, the specimens were sent to a second reference dermatopathologist who then read the biopsy slides. If this second reference dermatopathologist concluded that the specimens were either diagnostic of or consistent with CTCL, (2 of 3 pathology reports) the patient met this test of evaluability for study endpoints. However, if this second reference

dermatopathologist also concluded that the specimens were neither diagnostic of nor consistent with CTCL, the patient were considered unevaluable for study endpoints.

Duration of Therapy

Treatment was intended to be administered for a minimum of 16 weeks. Treatment 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..

If a patient reached a confirmed complete clinical response or a partial response plateau with a duration of at least twelve weeks, and decided to discontinue treatment with targretin topical gel, the patient continued to be evaluated every four weeks for at least an additional twelve weeks after treatment discontinuation. The patient continued to be considered an active patient in the study, even though treatment has been discontinued and could resume treatment as needed.

If a patient discontinued active involvement in the study (did not continue to be evaluated every four weeks and was withdrawn from the study) but experienced an exacerbation of their cutaneous T-cell lymphoma, treatment may have been reinitiated, subject to prior written approval from the study Sponsor. The decision to resume targretin topical gel treatment included a judgment by the investigator that targretin topical gel was the optimal treatment for the patient and that the patient continued to meet all protocol eligibility criteria. Women of childbearing potential must have had a negative serum pregnancy (β-HCG within seven (7) days prior to reinitiation of treatment and must have used an effective means of contraception or must have been sexually abstinent for at least four (4) weeks prior to the negative pregnancy test through reinitiation of treatment.

Treatment would be reinitiated at the last tolerated dosing frequency the patient was using prior to discontinuing treatment and continued to follow the dose modification guidelines. Patients continued to be identified by the original patient number assigned at the baseline visit.

Study Evaluations

FLOW CHART OF STUDY ACTIVITIES

| ASSESSMENT TO BE COMPLETED | At Any Time Prior to Entry | Pre-Study (1) Up to 14 Days Before Day 1 | Day 1 "Baseline" 1st Rx Day | Every 2 Wks to Week 4, then every 4 Weeks | Follow-Up Visit |
|---|---|---|---|---|---|
| CTCL Confirmed by Biopsy | x | | | | |
| Age ≥18 years | | x | | | |
| Women - Neg. β-HCG | | x (2) | | | |
| Symptoms and/or Aes | | x | x | x | x |
| Med History/Physical Exam, Weight | | x (include height) | x | x | x |

| ASSESSMENT TO BE COMPLETED | At Any Time Prior to Entry | Pre-Study (1) Up to 14 Days Before Day 1 | Day 1 "Baseline" 1st Rx Day | Every 2 Wks to Week 4, then every 4 Weeks | Follow-Up Visit |
|---|---|---|---|---|---|
| Karnofsky Performance | | ≥60 | x | x | x |
| Chest X-Ray | | X(6) | | | |
| No Serious Concurrent Illness or Infection | | | x | √ | √ |
| Agree to Use Contraception (2) | | X (2) | √ | √ | √ |
| LABORATORY | | | | | |
| Drug Monitoring Samples (3) | | | x | x (3) | |
| Chemistry Panel and CBC, Including Tests Below (1): | | X (1) | x (1) | x | x |
| Hemoglobin | | ≥9.0 g/dL | X | x | x |
| WBC | | ≥2000/mm$^3$ | X | x | x |
| Total Bilirubin | | <1.5 X ULN | X | x | x |
| SGOT and SGPT | | ≤2.5 X ULN | X | x | x |
| Creatinine | | ≤2.0 X ULN | X | x | x |
| Total Triglycerides (4) | | ≤800 mg/dL (4) | x (4) | x (4) | x (4) |
| Serum Calcium | | ≤11.5 mg/dL | X | x | x |
| Serum Amylase | | ≤1.5 X ULN | | | |
| Electrolytes, BUN and Glucose | | | X | x | x |
| Urinalysis | | | X | x | x |
| HDL, LDL, Total Cholesterol (5) | | | x (5) | | |
| CPK | | | X | | |
| TSH, T4 | | | X | | |
| PT, APTT | | | x | | |
| EFFICACY | | | | | |
| Index Lesion Signs & Symptoms | | | X | x | x |
| Body Surface Area Involvement | | | x | x (3) | x |
| Physician's Global Assessment | | | | x (3) | x |
| Lymph Node and Other Tumor Assessments | | | X | x (3) | x |
| Patient QOL Questionnaires | | | X | x (3) | x |
| CTCL Lesion Photographs | | | X | x (3) | x |

"X" = Required "√" = Check on Status ULN = Upper Limit of Normal

**NOTE 1:** "Pre-study" assessments must be obtained and results known within two (2) weeks prior to the first application of TARGRETIN gel. A set of "baseline" labs must be obtained just prior to the first dose (results do not need to be available to start therapy).

**NOTE 2:** For women of childbearing potential, a serum (β-HCG) pregnancy test must be negative within seven (7) days before starting treatment. Pregnancy is strictly contraindicated during treatment and within three (3) months after treatment discontinuation. All female patients must agree to use an effective contraceptive method or remain sexually abstinent during those periods.

**NOTE 3:** Completed every four (4) weeks during the study.

**NOTE 4:** Lipids should be obtained fasting pre-study, and at any other times when lipid levels are found to be significantly elevated.

**NOTE 5:** Baseline measurements from fasting blood sample. May be repeated during the study if clinically indicated.

**NOTE 6:** Chest X-Ray must have been done within 30 days prior to entry in the study.

Criteria for removing patient from study

Progression of disease
Deleterious changes in the patient's health
Intercurrent illness which prevented further treatment
Several instances of treatment-limiting toxicity
Severe systemic toxicity

Criteria for evaluation and endpoint definitions

Definition of evaluable:

Patients were deemed evaluable for efficacy endpoints if they have met all inclusion and exclusion criteria for defining the study population, have histopathology either diagnostic or consistent with CTCL by the local pathologist and by at least one independent reference dermatopathologist, and have remained on targretin topical gel treatment for at least eight (8) weeks. In addition, patients were deemed evaluable for pruritus if they have met the last inclusion criterion as indicated above. All patients enrolled and receiving at least one dose of targretin topical gel were evaluable for safety and toxicity.

Endpoint definitions

The primary efficacy endpoints were the tumor responses (CCR + PR) determined by the Composite Assessment (CA) of Index Lesion Disease Severity and by the Physician's Global Assessment (PGA) of Clinical Condition follow up to sixteen (16) weeks of treatment and beyond if treatment was continued.

Secondary efficacy endpoints included the tumor response (CCR + PR) to treatment, the extent of cutaneous disease (index and non-index lesions treated from baseline) determined as a percentage of total body surface area; the response to treatment of clinically abnormal lymph nodes, if present; the index lesion erythema, plaque elevation, scaling, itching, hypopigmentation or hyperpigmentation, and area responses to treatment; the time to response; the response duration; the time to disease progression; and the responses to the patient quality of life questionnaires. Survival information was to be collected. Index lesion photographs, global photographs and histologic analyses of any CTCL lesion biopsies obtained were to be considered as supporting data to the above evaluations.

Grading Scales for Index Lesion Clinical Signs and Symptoms (Composite Assessment): a Response Criteria

Individual index lesion clinical signs and symptoms were be graded at each visit according to the scales found in the table below. A Composite Assessment (CA) of Index Lesion Disease Severity was generated by a summation of the grades for each index lesion erythema, scaling, plaque elevation, hypopigmentation or hyperpigmentation, and area of involvement. The Composite Assessment of Index Lesion Disease Severity grade at baseline was divided into the Composite Assessment of Index Lesion Disease Severity grade at each subsequent study visit to determine the patient's response to treatment.

At every evaluation, each of the index lesion clinical symptoms and signs were graded on the scales as in two tables that follow. These evaluations would made with non-leading (non-directive) questions of symptoms to the patient. Examples of symptom-related events would be elicited from the patient to substantiate grading severity. Observations of index lesion clinical signs and determination of the index lesion areas would be made with the patient as fully undressed as necessary to evaluate all index lesion areas.

To determine the area of index lesions, the longest diameter and the longest diameter perpendicular to this diameter of each index lesion were to be measured to the nearest millimeter. The lesion areas were the product of these two diameters and then graded as in the table below. If there was central clearing of an index lesion (clearing of disease within the outer boundaries of the lesion), then the product of the largest perpendicular diameters of the area(s) of clearing were subtracted from the area determined from the outer boundary diameters before assigning the appropriate grade as in table below.

The degree of hypopigmentation or hyperpigmentation of lesions as seen in occasional CTCL patients would be considered independently of lesion erythema, scaling and plaque elevation for those patients in whom hypopigmentation or hyperpigmentation was the clinical manifestation of CTCL. Erythema, scaling and plaque elevation were to continue to be assessed and graded as in the table below. The greatest elevation of plaque within a given index lesion would be used in assessing the plaque elevation of that index lesion. If pigmentation obscured all signs of possible erythema, then erythema would be recorded as grade 0.

Grading Scales for COMPOSITE ASSESSMENT
Index Lesion Clinical Signs and Symptoms

| | |
|---|---|
| **SCALING** | 0 – No evidence of scaling on the lesion<br>1*<br>2 – Mild: Mainly fine scales; lesion partially covered<br>3*<br>4 – Moderate: Somewhat coarser scales; lesion partially covered<br>5*<br>6 – Severe: Coarse, thick scales; virtually all of the lesion covered; rough surface<br>7*<br>8 – Very severe: Coarse, very thick scales; all of the lesion covered; very rough surface |
| **ERYTHEMA** | 0 – No evidence of erythema, possible brown hyperpigmentation<br>1*<br>2 – Mild: Light red lesion<br>3*<br>4 – Moderate: Red lesion<br>5*<br>6 – Severe: Very red lesion<br>7*<br>8 – Very severe: Extremely red lesion |

| | |
|---|---|
| **PLAQUE ELEVATION** | 0 - 0 mm: No evidence of plaque above normal skin level<br>1* - ≥0 to <0.5 mm: Minimal but definite plaque elevation above normal skin level<br>2 - ≥0.5 to <1 mm: Slight but definite plaque elevation<br>3* - ≥1 to <1.5 mm: Mild elevation<br>4 - ≥1.5 to <2 mm: Moderate elevation<br>5* - ≥2 to <2.5 mm: Moderate to marked elevation<br>6 - ≥2.5 to <3 mm: Marked elevation<br>7* - ≥3 to <3.5 mm: Very marked elevation<br>8 - ≥3.5 mm: Extreme elevation |

* Intermediate intervals 1,3,5 and 7 are to serve as mid-points between the defined grades 0,2,4,6 and 8.Table. (continued)

| | |
|---|---|
| **HYPO-/HYPER-PIGMENTATION** | To be used only when hypopigmentation or hyperpigmentation is the clinical manifestation of CTCL.<br><br>0 – No evidence of pigmentation change.<br><br>1*<br><br>2 – Mild: 25% lighter pigmentation or noticeably darker pigmentation compared to the patient's normal skin pigmentation.<br>3*<br><br>4 – Moderate: 50% lighter pigmentation or twice as dark pigmentation compared to the patient's normal skin pigmentation.<br>5*<br><br>6 – Severe: 75% lighter pigmentation or three times as dark pigmentation compared to the patient's normal skin pigmentation.<br>7*<br><br>8 – Very severe: Nearly complete absence of pigmentation or nearly as dark a pigmentation as could be observed compared to the patient's normal skin pigmentation. |
| **INDEX LESION AREA** | 0 – 0 $cm^2$ (no measurable area)<br>1 - > 0 and ≤ 4 $cm^2$<br><br>2 - > 4 and ≤ 10 $cm^2$<br><br>3 - >10 and ≤ 16 $cm^2$<br><br>4 - >16 and ≤ 25 $cm^2$<br><br>5 - >25 and ≤ 35 $cm^2$<br><br>6 - >35 and ≤ 45 $cm^2$<br><br>7 - >45 and ≤ 55 $cm^2$<br><br>8 - > 55 and ≤ 70 $cm^2$<br><br>9 - >70 and ≤ 90 $cm^2$<br><br>10 - >90 and ≤ 110 $cm^2$<br><br>11 - >110 and ≤ 130 $cm^2$<br><br>12 - >130 and ≤ 155 $cm^2$<br><br>13 - >155 and ≤ 180 $cm^2$ |

| | |
|---|---|
| | 14 - >180 and ≤ 210 $cm^2$ |
| | 15 - >210 and ≤ 240 $cm^2$ |
| | 16 - >240 and ≤ 270 $cm^2$ |
| | 17 - >270 and ≤ 300 $cm^2$ |
| | 18 - >300 $cm^2$ |

* Intermediate intervals 1,3,5 and 7 are to serve as mid-points between the defined grades 0,2,4,6 and 8.

TABLE. Grading Scale for Index Lesion PRURITUS

| | |
|---|---|
| **PRURITUS** | 0 – No complaint of itching on lesion |
| | 1* |
| | 2 – Mild: Occasional transient itch on lesion |
| | 3* |
| | 4 – Moderate: Frequent itch, every 1-3 hours; reflex scratching |
| | 5* |
| | 6 – Severe: Compelling itch; interrupts daily activities; must be scratched |
| | 7* |
| | 8 – Very severe: Unrelieved itch; prevents routine activities; awakens patient from sleep |

* Intermediate intervals 1,3,5 and 7 are to serve as mid-points between the defined grades 0,2,4,6 and 8.

Physician's Global Assessment of Clinical Condition: a Response Criteria

The Physician's Global Assessment (PGA) was an assessment of the overall extent of improvement/worsening of the patient's overall disease attributable to topical targretin therapy as compared to the cutaneous condition at entry (at baseline). This assessment considered all lesions treated from baseline (index and non-index cutaneous lesions).

TABLE Physician's Global Assessment of Clinical Condition

| | |
|---|---|
| 0 | **Completely clear:** No evidence of disease; 100% improvement |
| 1 | **Almost clear:** Very significant clearance (≥90% to <100%); only traces of disease remain |
| 2 | **Marked improvement:** Significant improvement (≥75% to <90%); some evidence of disease remains |
| 3 | **Moderate Improvement:** Intermediate between slight and marked improvement; (≥ 50% to <75%) |
| 4 | **Slight Improvement:** |

Some improvement (≥25% to <50%); however, significant evidence of disease remains

5 **No change:**

Disease has not changed from baseline condition (± <25%)

6 **Worse:**

Disease is worse than at baseline evaluation by ≥25% or more

Determination of Percentage Involvement of Total Body Surface Area

To make this determination, the area of the patient's palm was be defined as 1% of that patient's total body surface area. The extent of involvement of disease should be determined as multiples of the patient's palm area and expressed as a percentage of that patient's total body surface area at baseline (Day 1), every four weeks thereafter during treatment and at the follow-up visit.

Lymph Node and Other Tumor Assessments

Patients who have Stage IIA CTCL have clinically abnormal lymph nodes (≥1cm diameter) that will be evaluated at baseline (Day 1), every four weeks during treatment and again at follow-up. Clinically abnormal lymph nodes were to be assessed to the extent possible with regard to the number of discrete nodes and their anatomic location. The two largest perpendicular diameters of each discrete lymph node will be recorded. A representative biopsy(s) of clinically abnormal lymph nodes that were 2 cm or greater in diameter should would be obtained at screening whenever feasible in order to accurately stage each patient and to assure eligibility for this protocol.

Cutaneous tumors which appeared during the study would be counted, identified by their location and measured for their two largest perpendicular diameters and height from normal skin surface. In order to be considered a cutaneous tumor for the purpose of this protocol, a CTCL cutaneous lesion must have minimum bidimensional skin surface diameters of 10 mm by 10 mm and a height above the surrounding skin surface of at least 5 mm.

To the extent possible, visceral tumors/involvement which were detected during the study were to be counted and identified by location and the size of each tumor/involvement would be determined from the product of the two largest perpendicular diameters of the tumor image.

Patient Quality of Life Questionnaires

Each patient was to be administered a concise, five item, validated quality of life questionnaire designed to assess the relative benefits and risks of various treatments for serious illness at baseline (Day 1), every four (4) weeks for as long as the patient remained on treatment, and again at the follow-up visit (49). In addition, a patient quality

of life questionnaire designed to collect subjective information, including the patient's own assessment of CTCL lesion signs and symptoms, interference with work, social and physical activities, and response to study medication were to be completed at baseline (Day 1), every four (4) weeks for as long as the patient remains on treatment, and again at the follow-up visit (see Appendix 5). These questionnaires were intended for interviewer-supervised, patient self-administration.

Photographs of Lesions

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

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

Efficacy Endpoints

Tumor Response

Response assessments of index lesion clinical signs and symptoms of CTCL were made at baseline (Day 1) and at every subsequent scheduled visit during treatment and again at the follow-up visit. A determination of the percentage involvement of total body surface area, patient quality of life questionnaires and, if present, assessment of clinically abnormal lymph nodes (≥1 cm diameter), were completed at baseline (Day 1) and every four weeks throughout the study and at follow-up. The Physician's Global Assessment of Clinical Condition was completed at Week 4 and every four weeks throughout the study and at follow-up.

Up to five index lesions representative of the overall extent of cutaneous disease were assessed at baseline and throughout the study.

Patients were evaluated pretreatment (within 14 days of initiation of therapy), baseline (Day 1), every two weeks until Week 4 and every four weeks thereafter for the duration of treatment. A follow-up evaluation was performed approximately four weeks after discontinuation of therapy.

Data from patients who reinitiated treatment after discontinuing treatment and/or withdrawing from the study were included in the safety analysis, but such patients were included only once in the primary efficacy analysis. Such patients were allowed an assessment of whether or not patients who respond to initial treatment with targretin topical gel would also respond to reinitiation of targretin topical gel.

The primary efficacy endpoints were the tumor responses (CCR + PR) determined by the Composite Assessment of Index Lesion Disease Severity and by the Physician's Global Assessment of Clinical Condition following up to sixteen (16) weeks of treatment and beyond if treatment is continued.

In addition to the Composite Assessment of Index Lesion Disease Severity grade and the Physician's Global Assessment of Clinical Condition, the overall extent of cutaneous disease (index and non-index lesions treated from baseline) were to be determined as a percentage involvement of total body surface and, if present, clinically abnormal lymph nodes were to be assessed.

Secondary efficacy endpoints included the response (CCR + PR) to treatment of the overall extent of cutaneous disease (index and non-index lesions treated from baseline) determined as a percentage involvement of total body surface area; the response to treatment of clinically abnormal lymph nodes, if present; the index lesion erythema, plaque elevation, scaling, pruritus, hypopigmentation or hyperpigmentation, and area responses to treatment; the time to response; the response duration; the time to disease progression; and the responses to the patient quality of life questionnaires, including both the validated five-item index and the CTCL-specific questionnaire (a reliability and validity study of the CTCL-specific questionnaire was to be conducted and the results of these analyses were to be correlated with those of the five-item index). Survival information was to be collected and analyzed.

Cutaneous T-cell lymphoma index lesion photographs, global photographs and histologic analyses of any CTCL lesion biopsies obtained were be considered as supporting data to the above evaluations.

Below are the methods used to determine a response to therapy using the CA or the PGA.

**Clinical Complete Response (CCR):**
Ratio of Composite Assessment of Index Lesion Disease Severity grades of 0 at two or more consecutive timepoints persisting over at least four (4) weeks, **OR**

Physician's Global Assessment of Clinical Condition grade of 0 at two or more consecutive timepoints persisting over at least four (4) weeks.

Complete Response (CR):

Ratio of Composite Assessment of Index Lesion Disease Severity grades of 0 at two or more consecutive timepoints persisting over at least four (4) weeks and a cutaneous biopsy documenting absence of histologic signs of CTCL from a cleared lesion, **OR**

Physician's Global Assessment of Clinical Condition grade of 0 at two or more consecutive timepoints persisting over at least four (4) weeks and a cutaneous biopsy documenting absence of histologic signs of CTCL from a cleared lesion.

**Partial Response (PR):**
Ratio of Composite Assessment of Index Lesion Disease Severity grades of 0.5 or less (≤50%) at two or more consecutive timepoints persisting over at least four (4) weeks, **OR**

Physician's Global Assessment of Clinical Condition grade of 1, 2 or 3 at two or more consecutive timepoints persisting over at least four (4) weeks.

**Stable Disease (SD):**
Ratio of Composite Assessment of Index Lesion Disease Severity grades and Physician's Global Assessment of Clinical Condition do not meet the response assessment criteria for CR, CCR, PR or PD.

**Progressive Disease (PD):**
Ratio of Composite Assessment of Index Lesion Disease Severity grades of 1.25 or more (≥125%) at two or more consecutive timepoints persisting over at least four (4) weeks; **OR**

Physician's Global Assessment of Clinical Condition grade of 6 at two or more consecutive timepoints persisting over at least four (4) weeks.

Time to Response

The time to response for a given patient was defined as the time interval from the first day of targretin topical gel treatment to the time of the first observation when the patient meets criteria for CR, CCR or PR.

Response Duration

The response duration for a given patient was 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.

Time to Progression

The time to progression for a given patient was defined as the time interval from the first day of targretin topical gel treatment to the time of the first observation when the patient meets criteria for PD.

Statistical Analysis

Baseline variables including demographics, laboratory measurements, health/disease status and symptoms were to be summarized.

Confidence intervals were to be constructed about the observed response rate. These confidence intervals were to be utilized to quantify the treatment effect.

The study would be successful if the observed response rate (CCR + PR) was at least 20% and the lower bound of the 95% confidence interval (centered around the observed response rate) excluded the theoretical maximal spontaneous response rate of 5%.

No spontaneous remission was expected for patients with CTCL. However, allowing for variations in CTCL disease assessments, the statistical analysis in this study allowed for up to a 5% spontaneous response as a historical control. Assuming a spontaneous response rate of no more than 5% for CTCL patients, an observed additive response rate (CCR + PR) of 15% (observed response rate of 20%) for 60 patients treated with targretin topical gel would yield 95% confidence interval for the true response rates of 11% to 32%. The study was to be deemed successful as a pivotal trial if the observed response rate (CCR + PR) is at least 20% and the lower bound of the 95% confidence interval (centered around the observed response rate) excluded the theoretical maximal spontaneous response rate of 5%.

Patients meeting entry criteria on the basis of intolerance to prior therapy were to be analyzed as a separate subpopulation in addition to being analyzed in the entire study patient population. The entire study patient population was the database that was to be used for the primary efficacy endpoints.

Safety Analysis

All patients enrolled and receiving at least one dose of TARGRETIN topical gel were evaluable for safety and toxicity. All adverse events, toxicities and laboratory abnormalities were to be recorded on the appropriate Case Report Forms and were to be summarized.

**Results reported by the Sponsor for Study -25**

All 50 patients were enrolled in the study through 12 October 1998. The study cut-off was February 15, 1999.

The Study population

Demographics and Baseline Characteristics

Demographics

| Demographics | | Targretin® gel 1%<br>N = 50<br>n (%) |
|---|---|---|
| | | |
| Age (Years) | N | 50 |
| | Mean (SE) | 62.1 (2.0) |
| | Median | 64 |
| | Range | 13 – 85 |
| | | |
| Gender (M/F) | M (%) | 23 (46) |
| | F (%) | 27 (54) |
| | | |
| Race | | |
| | White | 40 (80) |
| | Black | 10 (20) |

Fifty patients were accrued to the study. Eighty percent of the patients were white. The median age for the entire study population was 64 years.

All enrolled patients satisfied the protocol-required Karnofsky performance score of at least 60. The median score for the study population was 90, with scores ranging from 60 to 100. The majority (92%) of the patients had baseline Karnofsky performance scores of 80 to 100.

Baseline Patient Characteristics: Stage of CTCL

| Stage of CTCL | Targretin® gel 1% N = 50 n (%) |
|---|---|
| IA | 25 (50) |
| IB | 22 (44) |
| IIA | 2 ( 4) |
| IIB[3] | 1 ( 2) |

Ninety-four percent of the patients were Stage I; two patients were Stage IIA; one patient was Stage IIB in violation of the protocol.

Baseline Patient Characteristics: Duration of CTCL

| Duration of Disease | Targretin® gel 1% N = 50 n (%) |
|---|---|
| Time (Months) Since First Clinical Manifestation of CTCL: | |
| N | 50 (100) |
| Mean | 177.8 |
| SE | 19.3 |
| Median | 138.0 |
| Range | 15.2 – 644.7 |
| Time (Months) Since First Clinical Diagnosis of CTCL: | |
| N | 50 (100) |
| Mean | 95.6 |
| SE | 10.5 |
| Median | 73.1 |
| Range | 2.0 – 278.5 |
| Time (Months) Since First Histopathologic Determination Consistent with CTCL: | |
| N | 49 (98) |
| Mean | 87.0 |
| SE | 9.6 |
| Median | 69.7 |
| Range | 1.8 – 254.4 |

[3] This patient was considered to be a protocol violator.

Most patients in the study had signs of CTCL for more than 10 years. The median time since first clinical manifestation of CTCL was 11.5 years (range of 1.3 to 53.7 years); this was longer than the median time since first clinical diagnosis of CTCL, 6.1 years (range 2 months to 23.2 years) or the median time since first histopathological determination consistent with CTCL which was 5.8 years (range 1.8 months to 21.2 years). There were two patients (Patients 303/1661 and 204/721) who were diagnosed with CTCL just prior to study entry. Although these patients were clinically diagnosed with CTCL and had their first histopathologic determination consistent with CTCL in ≤3 months before starting treatment with targretin® gel, the first clinical manifestation of the disease for both patients had occurred at least five years prior to study entry. In addition, both patients had the requisite two prior therapies that qualified them for entry into the study (Patient 303/1661, topical nitrogen mustard and PUVA; Patient 204/721 UVB and methotrexate).

Number and Aggregate Area of Designated Index Lesions

There were 19 patients (38%) with at least 20 discrete cutaneous CTCL lesions. For the 31 patients (62%) with fewer than 20 discrete lesions, the median number of lesions was eight (range: 2 to 17).

The protocol specified that up to a maximum of five CTCL lesions were to be designated as index lesions for this study. These lesions were selected to be representative of the patient's overall cutaneous disease. Index lesions were preferably to be separate and distinct from other lesions in order to minimize the chance of lesion confluence.

Most patients had five designated index lesions and with the exception of three patients (Patients 348/632, 299/663, and 250/811) all index lesions were assessed at Baseline. Patient 348/632 did not have discrete individual lesions and as a result no lesion measurements were done at baseline according to the Additional Information Report (AIR) CRF for this patient. Patients 299/663 and 250/811 had designated five index lesions on the CTCL Lesion Location (LOC) CRF at Baseline. However, the measurements for lesion area on the CTCL Index Lesion Clinical Assessment Log (CTCLA) CRF for all five index lesions were recorded as "not applicable" for Patient 250/811 and as "not available" for Patient 299/663. Nine patients in the study had fewer than five total CTCL lesions at Baseline (Patients 179/731, 181/741, 246/801, and 184/851, four lesions; Patients 283/842 and 303/1661, three lesions; Patients 34/622, 283/841, and 310/1621, two lesions). All of these patients' lesions were designated as index lesions and with the exception of three patients (Patients 283/841, 283/842, and 184/851) all index lesions were assessed. Patient 283/841 had two index lesions designated on the LOC CRF at baseline, but the measurements for lesion area on the CTCLA CRF were recorded as "not applicable" for both lesions. Patient 283/842 had designated three index lesions at baseline on the LOC CRF but only two lesions were assessed on the CTCLA CRF. According to the LOC CRF for this patient, the index lesion designated as 3X was located in the patient's groin area and consequently may not have been accessible to measure. There were four lesions designated on the LOC CRF

for Patient 184/851 at baseline, but no data was entered on the CTCLA CRF for the index lesions designated 3X and 4X for this patient. There were two patients (Patients 348/631 and 349/1761) who had indicated the presence of more than five total CTCL lesions on the CTCL History (CLHX) CRF, but less than five were designated as index lesions at Baseline. Patient 348/631 had indicated ≥20 CTCL lesions on the CLHX CRF but only two lesions were designated as index lesions. According to the LOC CRF it appeared that the majority of this patient's lesions were confluent. In addition, the patient terminated from the study on Day 9 due to an adverse event (contact dermatitis). Patient 349/1761 had indicated seven discrete cutaneous lesions on the CLHX CRF. However, in the AIR CRF it was reported that the patient did not have five CTCL lesions and as a result only three lesions were designated as index lesions.

Body Surface Area CTCL-Involvement

CTCL-Involved Surface Area

| Patient Body Surface Area | Targretin® gel 1% N = 50 |
|---|---|
| of CTCL Patch Disease | |
| N | 47 |
| Percentile (percentage BSA in percentile) | |
| 0 – 25 pctl. (0 – 2) | 15 (32) |
| >25 – 50 pctl. (2.21 – 5) | 11 (23) |
| >50 – 75 pctl. (6 – 11) | 10 (21) |
| >75 – 100 pctl. (12 – 90) | 11 (23) |
| Min / 25 pctl. / Median / 75 pctl. / Max | 0/2/5/11/90 |
| | |
| Of CTCL Plaque Disease | |
| N | 49 |
| Percentile (percentage BSA in percentile) | |
| 0 – 50 (0 –1) | 26 (53) |
| >50 – 75 pctl. (1.5 – 6) | 11 (22) |
| >75 – 100 pctl. (8 – 42) | 12 (24) |
| Min / 25 pctl. / Median / 75 pctl. / Max | 0/0/1/6/42 |

Most patients had a relatively low percentage of their BSA involved with patch or plaque disease. There were three patients (Patients 299/663, 310/1621, and 317/1721) who had no BSA data recorded on the Involved Body Surface Area Assessment Log (BSA) CRF for patch disease at Baseline. Patient 299/663 also had no BSA data recorded at Baseline for plaque disease. Based on the 47 patients with BSA data for patch disease recorded at

Baseline, the median BSA involvement was 5% (range: 0% to 90%). The majority of patients (77%) had 11% or less BSA involved in patch disease. The percentage of patients in the >75$^{th}$ percentile for amount of BSA involvement by patch (12% to 90%) was 23%. Based on the 49 patients with BSA data for plaque disease recorded at Baseline, the median BSA involvement was 1% (range: 0% to 42%). The majority of patients (76%) had 6% or less BSA involved in plaque disease. The percentage of patients in the >75$^{th}$ percentile for amount of BSA involvement by plaque disease (8% to 42%) was 24%.

Prior Anti-CTCL Therapy

The next six tables are summarized in the two paragraphs that follow.

The data show that the population of enrolled patients generally had prior therapies well in excess of the two required for entry in the protocol, with the majority having had either one or two prior therapies in any of the categories of systemic, topical/local and irradiation therapies. The number of prior therapies ranged from 2 to 7 with 28% of patients having received four or more prior therapies, 16% having received five or more, and 6% having received six or more prior therapies. The most common categories of prior anti-CTCL therapy were irradiation therapy and topical/local therapy, which had been used by 94% and 88% of patients, respectively. Despite the early stage disease status of these patients, 38% of all patients had received one or more systemic therapies for CTCL.

The most frequent systemic therapies used by patients prior to the study were interferon (18%) and methotrexate (14%). The most frequent topical/local therapies used prior to the study were nitrogen mustard (82%) and topical corticosteroids (30%). The most frequent irradiation therapies used by patients prior to the study were PUVA (66%), UVB (18%) and electron beam therapy (18%). There were four patients (8%) who had received photopheresis.

Prior Anti-CTCL Therapy

| Prior Anti-CTCL Therapies | Targretin® gel 1%<br>N = 50<br>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) |

Number of Prior Anti-CTCL Therapies

| Number of Prior Anti-CTCL Therapies (Systemic, Topical/Local, and Irradiation Combined)[1] | Targretin® gel 1% 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) |
| ≥8 Therapies | 0 |

[1] Multiple courses of the same therapy for a patient are counted only once.

Frequency of Prior Anti-CTCL Systemic Therapies

| Frequency of Prior Anti-CTCL Systemic Agents/Therapies[1] | Targretin® gel 1% N = 50 n (%) |
|---|---|
| Acitretin | 1 ( 2) |
| Cyclophosphamide | 1 ( 2) |
| Etretinate | 2 ( 4) |
| Interferon | 9 (18) |
| Isotretinoin | 2 ( 4) |
| Methotrexate | 7 (14) |
| Ontak | 1 ( 2) |
| Retinoids (NOS) | 1 ( 2) |
| Systemic Combination Chemotherapy | 1 ( 2) |
| Systemic Corticosteroid | 2 ( 4) |
| Targretin- Systemic | 1 ( 2) |

[1] Multiple courses of the same systemic agent/therapy for a patient are counted only once.

Frequency of Prior Anti-CTCL Topical/Local Therapies

| Frequency of Prior Anti-CTCL Topical/Local Therapies[1] | Targretin® gel 1% N = 50 n (%) |
|---|---|
| Nitrogen Mustard | 41 (82) |
| Topical Corticosteroid | 15 (30) |
| Topical BCNU | 7 (14) |

| | |
|---|---|
| Tretinoin Topical | 1 ( 2) |
| Vinblastine | 1 ( 2) |
| Peldesine[2] | 1 ( 2) |

[1] Multiple courses of the same topical/local therapy for a patient are counted only once.

[2] An investigational biological immunomodulator for the treatment of CTCL (also referred to as BCX-34).

Number of Prior Anti-CTCL Irradiation Therapies

| Number of Prior Anti-CTCL Irradiation Therapies[1] | Targretin® gel 1%<br>N = 50<br>n (%) |
|---|---|
| None | 3 ( 6) |
| 1 Therapy | 36 (72) |
| 2 Therapies | 9 (18) |
| 3 Therapies | 2 ( 4) |
| ≥ 4 Therapies | 0 |

[1] Multiple courses of the same irradiation therapy for a patient are counted only once.

Frequency of Prior Anti-CTCL Irradiation Therapies

| Frequency of Prior Anti-CTCL Irradiation Therapies[1] | Targretin® gel 1%<br>N = 50<br>n (%) |
|---|---|
| Electron Beam Therapy | 9 (18) |
| Photopheresis | 4 ( 8) |
| PUVA | 33 (66) |
| Radiation Therapy | 4 ( 8) |
| UVA + UVB | 1 ( 2) |
| UVB | 9 (18) |

[1] Multiple courses of the same irradiation therapy for a patient are counted only once.

Sixty-three percent of the patients who received systemic therapy had an objective response; 83% of the responders relapsed; 58% of responders had a response plateau of at least 6 months; 47% of the recipients of systemic therapy were unresponsive to at least one therapy; 42% were intolerant of at least therapy. The table is below.

Response to Prior Anti-CTCL Systemic Agents/Therapies

| Prior Anti-CTCL Systemic Agents/Therapies[1] | Targretin® gel 1% n (%) |
|---|---|
| If Systemic Therapy Given, at Least One Response (CR or PR)? | 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 (SD or PD) 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 |

[1] All courses of the same systemic agent/therapy for a patient are counted.

Fifty-one percent of patients who received prior topical therapy for CTCL had at least one objective response; 77% of the responders had a relapse while still on therapy; 36% of the responders had at least a six month plateau. Sixty-five percent of patients who received prior topical therapy for CTCL had at least SD or PD; 44% of patients who were given topical therapy were intolerant.

Baseline Patient Characteristics: Response to Prior Anti-CTCL Topical/Local Therapies

| Prior Anti-CTCL Topical/Local Therapies[1] | Targretin® gel 1% n (%)[2] |
|---|---|
| If Topical Therapy Given, at Least One Response (CR or PR)? | 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 (SD or PD) 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) |

[1] All courses of the same Topical/Local Therapy for a patient are counted.
[2] Percent based on number of patients with the condition. A total of 44 patients were treated with topical/local prior therapies. However, no data for response to prior topical/local therapy were recorded for one patient (303-1662).

Sixty-eight percent of patients who received irradiation therapy had at least one objective response; 84% of responders to irradiation therapy had a relapse while on therapy; 28% of responders had a response plateau of at least six months. Forty-three percent of patients who received irradiation were unresponsive; thirty-two percent of patients who received irradiation therapy were intolerant of at least one therapy.

Baseline Patient Characteristics: Response to Prior Anti-CTCL Irradiation Therapies

| Prior Anti-CTCL Irradiation Therapies[1] | Targretin® gel 1% n (%) |
|---|---|
| If Irradiation Therapy Given, at Least One Response (CR or PR)? | 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 (SD or PD) 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) |

[1] All courses of the same Irradiation Therapy for a patient are counted.

In summary, with regard to qualifying prior therapies (table below), forty-eight of the 50 patients enrolled in the study satisfied the specific protocol inclusion criteria for refractory or persistent CTCL following at least two prior qualifying therapies. The categories of qualifying therapies included patients who were refractory to at least two prior therapies (26%), patients who were refractory to one therapy and intolerant to at least one prior therapy (32%), and patients who were refractory to one prior therapy and had reached a response plateau on at least one prior therapy (10%). Other patients qualified by being intolerant to one therapy and having reached a response plateau on at least one prior therapy (16%), or because they were intolerant to at least two therapies (6%), or reached a response plateau on at least two therapies (6%). The majority of patients (68%) satisfied the entry criteria by being refractory to one or more prior therapies. Patients 317/1721 and 34/621 had insufficient prior qualifying therapy at the time of enrollment into the study which resulted in a protocol deviation.

Basis of Qualification by Prior Anti-CTCL Therapies

| Basis of Qualification[1,2] | Targretin® gel 1%<br>N = 50<br>n (%) |
|---|---|
| Refractory to ≥2 Therapies | 13 (26) |
| Refractory to 1 Therapy and Intolerant to ≥1 Therapy | 16 (32) |
| Refractory to 1 Therapy and Response Plateau on ≥1 Therapy | 5 (10) |
| Intolerant to ≥2 Therapies | 3 ( 6) |
| Intolerant to 1 Therapy and Response Plateau on ≥1 Therapy | 8 (16) |
| Response Plateau on ≥2 Therapies | 3 ( 6) |

[1] Patients were only assigned to one category as the basis of qualification. If a patient met the criteria for more than one category, he/she was assigned to the highest listed category.

[2] Two patients had insufficient qualifying prior therapy.

Primary Efficacy Endpoints

The Response Criteria

The protocol specified two primary efficacy endpoints: the Physician's Global Assessment of Clinical Condition, or PGA and the Composite Assessment of Index Lesion Disease Severity, or CA. Ligand did not submit global photographs as specified in the protocol. Only the CA response will be accepted by the FDA. However, for this discussion, PGA and PEC will be included.

The protocol also specified that a patient would be considered a responder if that patient met the response criteria for either the PGA or the CA, designated as the Primary Endpoint Classification (PEC) for the study in this report. Therefore, as presented in the Ligand's analysis plan, the highest Primary Endpoint Classification hierarchy between the PGA and the CA for each patient was used for response calculation, except for the condition described below:

When a patient had a confirmed progressive disease (PD) classification from one primary endpoint assessment (e.g., PGA) and a higher hierarchy classification (i.e., CCR or PR) from the other assessment (e.g., CA), the final classification between these two assessments was determined by the confirmation time of the PD classification. If the

onset of confirmed PD occurred on or before the confirmation date of other assessment classification confirmation, the patient was classified as PD. If the onset of the confirmed PD occurred later than the other assessment confirmation date, the patient was classified according to the confirmed classification of the other assessment.

Evaluable Patients

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

A total of 34 (68%) patients from the ITT population did not satisfy all of the above protocol-specified evaluable patient criteria, and so the evaluable Patient Population was comprised of the remaining 16 patients.

**MEDICAL OFFICER NOTE: This is different than what the FDA believed they would receive in the NDA—i.e., 50 evaluable patients out of 60 – 70 intent-to-treat patients.**

The reasons patients were not evaluable were: receiving prohibited medication (25 patients), skin biopsy early or late (18 patients), did not meet other inclusion/exclusion criteria (3 patients), had not been treated for at least 8 weeks (2 patients), insufficient pathological confirmation (1 patient), and insufficient qualifying therapy (1 patient). Many patients were excluded for more than one reason.

The Refractory/Persistent CTCL Patient Population

The Refractory/Persistent CTCL Patient Population was defined as those patients enrolled and dispensed at least one dose of study drug who satisfied each of the following three criteria: skin biopsy histology evaluable (at least two dermatopathologist readings at least consistent with CTCL); qualifying prior CTCL therapy per protocol; and TNM stage within the range specified by the protocol (i.e., IA-IIA).

Ligand did not consider the timing of the skin biopsy in the first criterion above. Any biopsy, no matter how long before or after entry into the study was considered, even if it was not collected during the protocol-specified 30 days prior to entry.

A total of 92% (46/50) of the ITT population patients met all of the above. Two patients (317/1721 and 34/621) were excluded because of insufficient prior CTCL therapy. One patient (247/832) was excluded because of insufficient pathologic confirmation, and one patient (179/732) was excluded because the patient's TNM stage was IIB. The confirmed response status for these patients according to the PGA and the CA was as follows: Patient 317/1721, stable disease (PGA and CA); Patient 34/621, progressive disease (PGA and CA); Patient 179/732, stable disease (PGA and CA); and Patient 246/803, stable disease (PGA and CA). No responders, by PGA or CA criteria, were excluded.

Efficacy: Response Rates

Patients were classified according to their highest confirmed (two observations over at least four study weeks) response status for PGA, CA, and the Primary Endpoint Classification for the study based on efficacy observations following up to 16 weeks of treatment and beyond if treatment was continued. For the PGA, CA, and the Primary Endpoint Classification for the study, the response rate was defined as the sum of the number of patients with classification of CR, CCR, or PR divided by the total number of patients in the ITT population. Point estimates of response rate were provided for all categories of "response," including CCR+PR, CCR alone, PR alone, SD, and PD, and exact 95% confidence intervals were provided for the overall response rate (CCR+PR).

The response rate (CCR + PR) by the PGA was 38% (table below).

Physician's Global Assessment Response Rate[1]

| Response | Targretin® gel 1% (N=50) n (%) |
|---|---|
| CCR + PR[2] 95% CI [3] | 19 (38) (25, 53) |
| CCR | 1 ( 2) |
| PR[2] | 18 (36) |
| SD[4] | 20 (40) |
| PD[5] | 8 (16) |
| Unknown | 3 ( 6) |

(1) Required confirmation over at least 4 study weeks.

(2) Includes almost cleared, marked response, and moderate response.

(3) Ninety-five percent confidence interval was obtained using Exact method.

(4) Includes the patients without any confirmed response or progressive disease.

(5) Includes condition worsened.

The response rate (CCR + PR) by the CA was 36% (table below).

Composite Assessment Response Rate[1]

| Response | Targretin® gel 1% (N=50) n (%) |
|---|---|
| CCR + PR[2] 95% CI[3] | 18 (36) (23, 51) |
| CCR | 4 ( 8) |
| PR[2] | 14 (28) |
| SD[4] | 26 (52) |
| PD[5] | 5 (10) |
| Unknown | 1 ( 2) |

(1) Required confirmation over at least 4 study weeks.

(2) If CA ratio is ≤0.5.

(3) Ninety-five percent confidence interval was obtained using Exact method.

(4) If none of the other response classifications accurately described the disease state.

(5) If the CA ratio is ≥1.25.

The response rate by either PGA or CA was 44% (table below)

Primary Endpoint Classification Response Rate

| Response | Targretin® gel 1% (N=50) n (%) |
|---|---|
| CCR + PR 95% CI | 22 (44) (30, 59) |
| CCR | 4 ( 8) |
| PR | 18 (36) |
| SD | 20 (40) |
| PD | 7 (14) |
| Unknown | 1 ( 2) |

According to Ligand, the Refractory/Persistent CTCL patient population was not substantially different from the ITT population. No formal analyses were performed for the patients in this population. The response rate is higher for the Refractory/ Persistent CTCL Patient population than for the ITT population for both PGA [41% (19/46) vs. 38% (19/50)] and CA [39% (18/46) vs. 36% (18/50)].

Analysis of the PGA, CA, and Primary Endpoint Classification for the study response rates for the 12 "Intolerant" patients is summarized in the table below. The response rate by PGA, CA, or PEC was 25% in the intolerant patients.

Response Rates for the "Intolerant" Patient Analysis

| Response | Targretin® gel 1% n (%) |
|---|---|
| Response Rate According to the Physician's Global Assessment (N=12) | |
| CCR + PR<br>95% CI | 3 (25)<br>(5, 57) |
| CCR | 0 |
| PR | 3 (25) |
| SD | 7 (58) |
| PD | 2 (17) |
| Response Rate[1] According to the Composite Assessment (N=12) | |
| CCR + PR<br>95% CI | 3 (25)<br>(5, 57) |
| CCR | 2 (17) |
| PR | 1 ( 8) |
| SD | 7 (58) |
| PD | 2 (17) |
| Response Rate According to the Primary Endpoint Classification (N=12)[9] | |
| CCR + PR<br>95% CI | 3 (25)<br>(5, 57) |
| CCR | 2 (17) |
| PR | 1 ( 8) |
| SD | 6 (50) |
| PD | 3 (25) |

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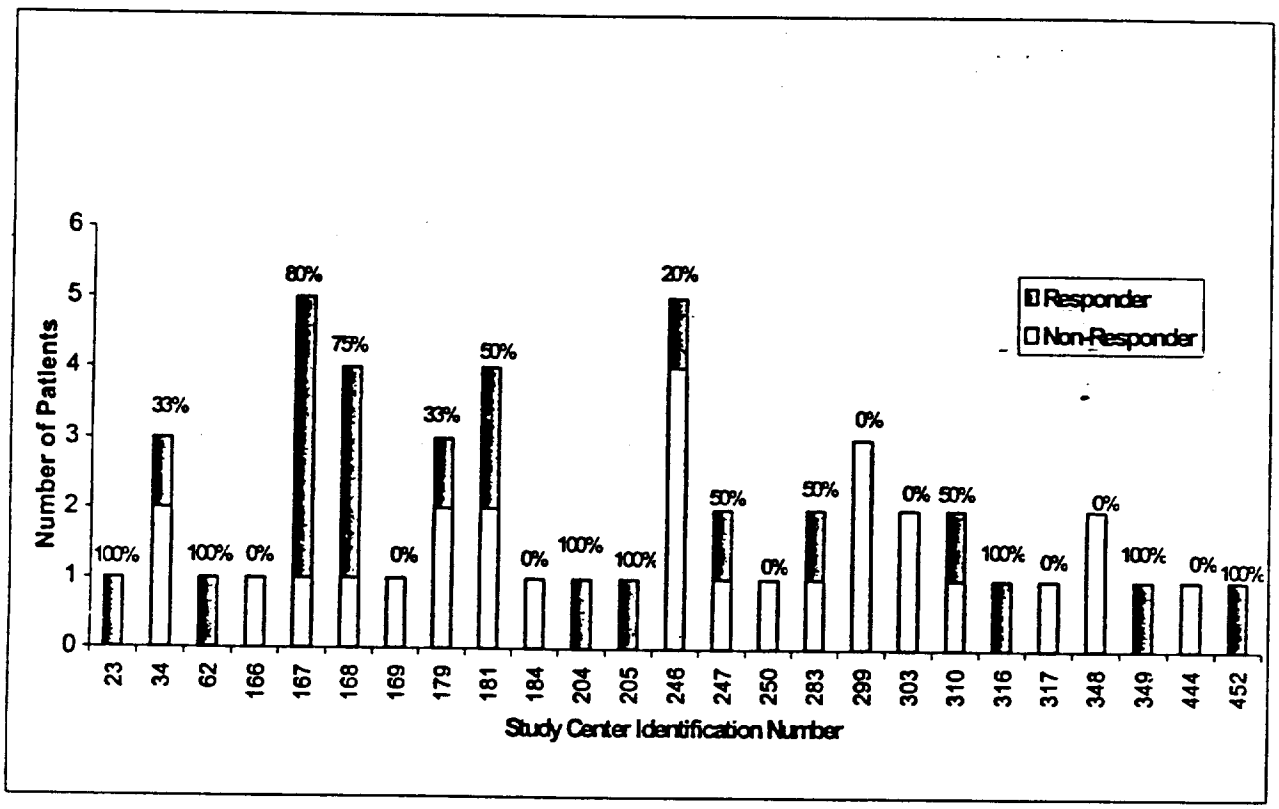
The figure below shows the distribution of response rates among the different centers.

Response Rate by Study Center According to Primary Endpoint Classification

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Efficacy: Time to Event

Time to Response

A table for time to first and best response is shown below. The medians for the respective response criteria have not been reached. The shortest time to first response for PEC, PGA, and CA was 28, 28, and 37 days, respectively. The longest recorded time to for first response for PEC, PGA, and CA was 124, 123, and 155 days, respectively.

Time to Onset of First and Best Response

| Response Category | Responding Patients | | Time to Response (Days) [1,2,3,4] | | | | |
|---|---|---|---|---|---|---|---|
| | N | % | Min | 25th pctl | Median | 75th pctl | Max |
| **Primary Endpoint Classification [5] (N=50)** | | | | | | | |
| First Response | 22 | 44.0 | 28 | 61 | NE | NE | 124 |
| Best Response | 22 | 44.0 | 28 | 84 | 337 | 435 | 435 |
| **Physician's Global Assessment (N=50)** | | | | | | | |
| First Response | 19 | 38.0 | 28 | 63 | NE | NE | 123 |
| Best Response | 19 | 38.0 | 28 | 63 | 337 | NE | 337 |
| **Composite Assessment (N=50)** | | | | | | | |
| First Response | 18 | 36.0 | 37 | 93 | NE | NE | 155 |
| Best Response | 18 | 36.0 | 37 | 113 | 435 | 463 | 463 |

(1) Time to response is defined as (Date of onset of response –Date of first dose of study drug + 1).

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

(3) NE = Not Estimable.

(4) Min and Max are calculated only from patients who responded and represents the minimum and maximum time to first or best response.

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

A table for duration of response is shown below. The medians for the respective response criteria have not been reached. The shortest duration of response for PEC, PGA, and CA was 57, 57, and 64 days, respectively. The longest recorded time to for first response for PEC, PGA, and CA was 204, 172, and 204 days, respectively.