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LIGAND PHARMACEUTICALS INC.

STN 103767

**ONTAK[®]
(denileukin diftitox)**

Volume I of I

BACKGROUND INFORMATION PACKAGE

**ONCOLOGIC DRUGS
ADVISORY COMMITTEE MEETING**

Information Regarding Phase IV Clinical Commitment to Fulfill the Requirements of Accelerated Approval

Executive Summary:

Seragen, a wholly owned subsidiary of Ligand Pharmaceuticals received accelerated approval on February 5, 1999, for the “treatment of patients with persistent or recurrent cutaneous T-cell lymphoma whose malignant cells express the CD25 component of the IL-2 receptor”. The clinical study commitment to fulfill the requirements of accelerated approval is completion of a Phase IV, double-blind, placebo-controlled, three arm study of ONTAK[®] in patients with Stage Ia-III, persistent, refractory CTCL who have received ≤ 3 prior therapies (Study L4389-11).

As of September 2005, this study has enrolled 135 patients. This represents the largest number of patients ever enrolled in a prospective, randomized, blinded, placebo-controlled trial in this type of tumor, which has an annual incidence of 4 per million in the U.S., with approximately 1,100 new cases reported this year. The largest previous study of a prospective nature in this disease, conducted by the NCI, enrolled 103 patients over 8 years and compared two active arms. Note also that the NCI study was able to enroll all patients that meet CTCL inclusion criteria, while the L4389-11 study is only able to accrue patients whose biopsies express CD25 (60-64%).

The 135 patient accrual number for Study L4389-11 was reached despite considerable difficulties that conspire to produce a low annual accrual rate. In order to compensate for slow patient enrollment, Ligand has expanded clinical trials to many hospitals in countries across three continents (North America, Europe, and Australia) where ONTAK[®] is currently unlicensed and/or where commercial access to multiple other CTCL therapies is limited. The last 62 patients enrolled have come from outside the U.S., reflecting efforts on the part of Ligand to improve accrual in this trial as access to potential study subjects in the U.S. has declined.

ONTAK[®] Clinical Study L4389-14, the companion study to L4389-11, has accrued 90 patients, and has completed its target enrollment. The study remains open, however, to provide a therapeutic option for L4389-11 study patients that were given placebo or whose biopsies were CD25 negative.

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I. ONTAK[®] (denileukin diftitox; DAB₃₈₉IL-2) Product Characteristics:

ONTAK[®] is a recombinant fusion protein composed of the catalytic and membrane translocation domains of diphtheria toxin (Met₁-Thr₃₈₇)-His linked to the full amino acid sequence for Interleukin-2 (IL-2; Ala₁-Thr₃₈₇):

- produced in an *E. coli* expression system; molecular mass = 58 kDa,
- designed to direct the cytotoxic activity of diphtheria toxin to cells that express the IL-2 receptor (IL-2R).

IL-2R exists in 4 different forms with varying affinity for IL-2, each a complex of one or more of three protein receptor subunits:

- The low-affinity IL-2 receptor is composed solely of the CD25 molecule (α chain)
- The intermediate-affinity receptor is formed by a complex of CD122 (β chain) and CD132 (γ chain) molecules
- The pseudo high-affinity receptor is composed of the CD25 and CD122 subunits
- The high-affinity IL-2 receptor is a complex of all three: CD25, CD122 and CD132 subunits
- Cells expressing the high-affinity receptor are most sensitive to ONTAK[®]-mediated cytotoxicity
- Cells with high expression of the CD122-CD132 intermediate receptor can have similar levels of sensitivity, hence the presence of CD25 is not essential for sensitivity to ONTAK-mediated cytotoxicity
- Internalization of denileukin diftitox into cells is mediated by binding to the intermediate and high affinity isoforms (1).

IL-2R is expressed on the following cell types:

- Activated T cells, activated B cells and macrophages,
- One or more subunits are constitutively expressed on certain leukemic and lymphoma cells of T and B-cell origin, including cutaneous T cell lymphoma (CTCL).

II. Brief Development History:

Key development milestones for denileukin diftitox include the following:

- Received Orphan Drug Designation by the Office of Orphan Products Development, FDA (August, 1996).
- A biologics license application was submitted in December 1997; the product was designated for accelerated review under 21 CFR Part 601, Subpart E.
- Denileukin diftitox was granted accelerated approval for “the treatment of patients with persistent or recurrent cutaneous T-cell lymphoma whose malignant cells express the CD25 component of the IL-2 receptor” (February, 1999).
- Following re-initiation of enrollment (November, 1999), Ligand projected completion of the study L4389-11 in 2006.

Clinical studies of DAB₃₈₉IL-2 were initiated in 1992 after “proof of concept” was established for a precursor molecule, DAB₄₈₆IL-2 (2):

- DAB₃₈₉IL-2 demonstrated approximately 100-fold greater binding avidity for IL-2R vs. DAB₄₈₆IL-2.

Clinical data supporting the accelerated approval of denileukin diftitox is derived primarily from two clinical studies involving a total of 144 lymphoma patients:

- A Phase I/II, open-label, dose-escalation study (92-04-01) involving 73 lymphoma patients (35 with CTCL, 21 with Hodgkin’s Disease and 17 with non-Hodgkin’s lymphoma) whose tumors expressed either the CD25 or CD122 component of IL-2R (3), and
- A Phase III dose-comparison study (93-04-10) of 71 CTCL patients expressing CD25 comparing the safety and efficacy of 9 vs. 18µg/kg/day for 5 consecutive days in a 21-day cycle (4).

Key design elements and outcomes of the Phase I/II study were as follows:

- Safety, efficacy and pharmacokinetics of denileukin diftitox were evaluated at doses ranging from 3 to 31 µg/kg/day for 5 consecutive days in a 21 day treatment cycle (3).
- Pharmacokinetic results:

The product displays two-compartment behavior with a β elimination phase of 70-80 minutes.

The disposition of the drug was variable but dose proportional across all doses tested.

Its clearance rate was approximately 1.5 to 2.0 mL/kg/min; its volume of distribution was 60-80 mL/kg.

No accumulation of drug was evident between the first and fifth administrations during the first course of therapy (3).

- Safety results:
27µg/kg/day was established as the maximum tolerated dose based on the occurrence of moderate-to-severe nausea, vomiting, fever, chills and/or persistent asthenia at the 31µg/kg/day dose level (3).
- Efficacy results:
An objective response (≥50% reduction in tumor burden) was recorded in 13 of 35 CTCL patients treated at dose levels varying from 6 to 27µg/kg/day, for a response rate of 37% (95% CI: 21-53%) (3).

Key design elements and outcomes of the Phase III dose-comparison study (93-04-10) in CTCL were as follows:

- Safety and efficacy comparison of 9 vs. 18 µg/kg/day for 5 consecutive days in a 21 day cycle,
- Eligibility:
Patients with persistent/refractory Stages Ib to III CTCL after ≥ 4 prior therapies, whose tumors expressed CD25 on ≥20% of malignant lymphocytes, and
Patients with persistent/refractory Stage IVa disease and ≥ 1 prior therapy (4).
- Efficacy results:
Overall response rate was 30% (95% CI: 18-41%) for all treated patients.
A 36% response rate (95% CI: 21-54%) was recorded for patients receiving 18µg/kg/day of ONTAK[®], while those receiving 9µg/kg/day had a response rate of 23% (95% CI: 10-40%).
Difference in response rates between the two treatment arms was not statistically significant.
There was a trend suggesting a dose response effect for those patients with more advanced stage disease (i.e. ≥ Stage IIb) (4).

For both of the aforementioned clinical trials, the key study drug-related toxicities consisted of the following:

- Constitutional symptoms (fever, chills, nausea, vomiting, myalgias, asthenia),
- Hypersensitivity manifestations (rash, dyspnea, hypotension, vasodilation, back and muscle aches, chest tightness, laryngismus, dysphagia, syncope),
- Transient elevations of serum transaminase levels,
- Hypoalbuminemia, and
- A vascular leak syndrome consisting of hypoalbuminemia in the presence of peripheral edema and/or hypotension (3,4).

III. Description of Phase IV, Post-approval, Clinical Commitment as a Condition for Final Approval of ONTAK[®]

Final approval of ONTAK[®] is contingent upon:

- Completion of the study entitled “A Multicenter Phase III Randomized Double-Blind Placebo-Controlled Study to Evaluate the Efficacy of Two Dose Levels of Denileukin Diftitox (DAB₃₈₉IL-2 [9 and 18 mcg/kg/day]) in Cutaneous T-cell Lymphoma (CTCL) Patients with Stage Ia-III Disease Who, Following ≤3 Previous Therapies, Have Recurrent or Persistent Disease that has been Biopsy Documented to Express CD25” (Protocol L4389-11, formerly 93-04-11),
- Verification that clinical benefit is associated with efficacy of the product in the aforementioned study, as measured by the objective rate of response.

Following accelerated approval, enrollment in the study was temporarily suspended for most of 1999 pending the submission and review of protocol amendments by the Agency. Table 1 outlines key developments that took place during this time period:

TABLE 1: Key Events in Study L4389-11

Event	Time Frame
Amended study protocol submitted to FDA	March 5, 1999
Additional amendments submitted to the Agency in response to comments stemming from March 5 th submission	July 19, 1999
Discussions between FDA and Ligand regarding additional modifications to L4389-11 study protocol	July – November, 1999
Study re-opened to patient entry	November, 1999
Anticipated submission of final study report	First Quarter, 2006

When the 93-04-11 study was originally conceived, it called for a study population of 120 subjects who would be equally distributed among the three study arms (placebo, 9 or 18 µg/kg/day x 5 days every 21 days). Anticipating difficulties in enrolling patients into a placebo-controlled study post-approval, Ligand, in consultation with the FDA, amended the 93-04-11 protocol (designated L4389-11 at the time of amendment) in order to make the study more appealing to prospective study subjects and investigators:

- The design was modified to incorporate a 1:4:4 randomization that was “weighted” towards active drug treatment. At study completion, the distribution was to be 1:2:2.
- To insure adequate power to detect a response rate difference from 0.10 in the placebo arm to 0.30 in best response rate, the modified randomization retained the provision for a total of 39 patients in the placebo arm.

- The total number of patients in each active treatment arm increased from 40 to 78.
- This had the effect of increasing the overall number of study subjects from 120 to 195 (see Table 2).

TABLE 2: Randomization Scheme for Protocol L4389-11

	Prior to Approval	Post Approval
Protocol Designation	93-04-11	L4389-11
Total number of study subject required	120	195
Final randomization distribution	1:1:1 (40:40:40)	1:2:2 (39:78:78)

Annual updates on progress and accrual have been filed in the BLA Annual report for the calendar years 1999, 2000, and 2001. Progress and accrual updates were filed in Postmarketing Study Status Reports in 2002, 2003, and 2004.

Key elements of the study design are described in the sections below:

1. *Patient Population (Inclusion/Exclusion criteria)*

As noted, a total of 195 patients (39 placebo patients and 78 patients in each of the two active treatment arms) are planned at completion of enrollment.

The key inclusion/exclusion criteria are:

- Biopsy documented, recurrent or persistent CTCL expressing CD25 on $\geq 20\%$ of tumor cells,
- Subjects must have Stage Ia to III CTCL with a history of ≤ 3 previous therapies,
- No systemic infection,
- ECOG performance status 0 or 1,
- Uncompromised and stable major organ function and no other active malignancy, and
- Subjects must not have received prior treatment with DAB₃₈₉IL-2 or DAB₄₈₆IL-2.

2. *Endpoints*

Primary endpoint:

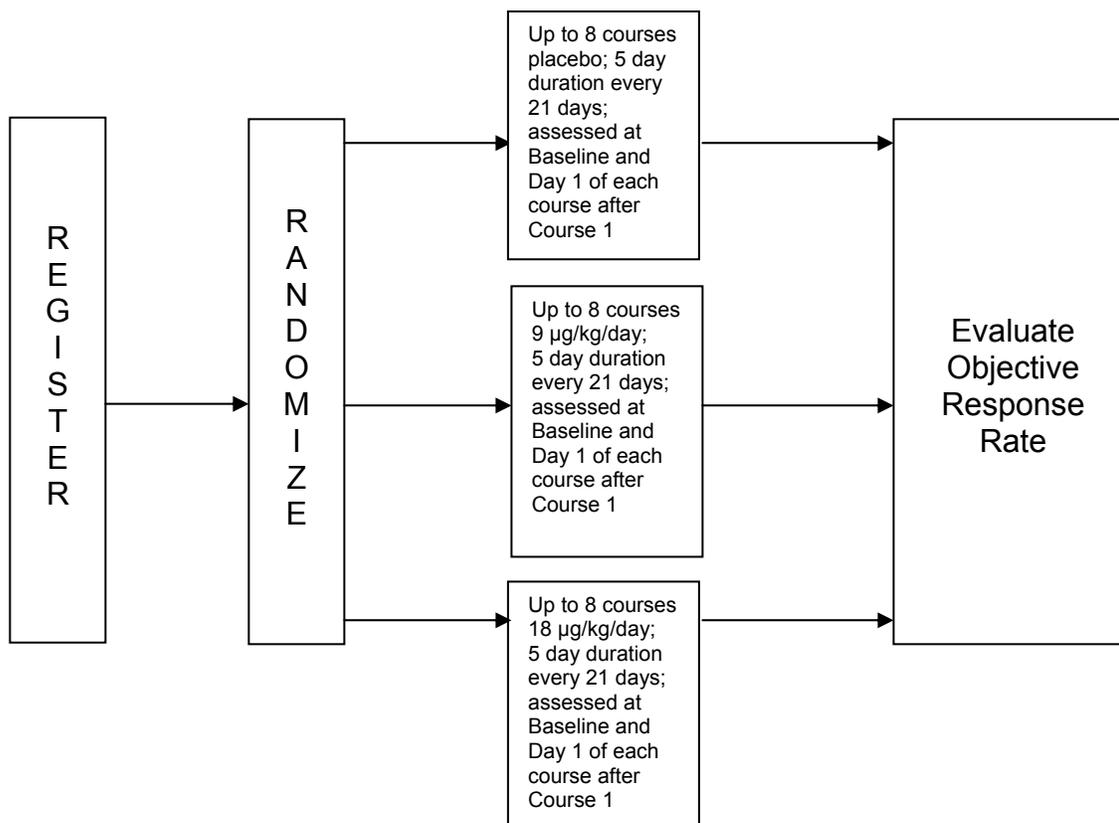
- The objective rate of response, defined as the proportion of complete (CRs, CCRs) plus partial responders (PRs) in each arm of the study.

Secondary efficacy endpoints:

- Time to treatment failure, time to progression and duration of response.

3. Treatment Schema

FIGURE 1: L4389-11 Treatment Schema



4. Efficacy and Safety Monitoring

Efficacy

Disease and symptom assessments (see below) are performed at Baseline and Day 1 of each course after Course 1. Lymph node biopsy is performed at the time of progressive disease (PD) or relapse if nodal involvement defines the PD or relapse.

The primary efficacy assessment is percent change in tumor burden as determined by calculation of the average change in skin disease (patch, plaque, tumor, and erythroderma). For patients with >10% body surface area (BSA) involvement, tumor burden is quantitated using a Weighted Skin/Erythroderma - Extent Severity Index (Weighted Extent Index). For patients with ≤10% BSA involvement, assessment of up to 5 target lesions in cm² is used. In addition, abnormal lymphocyte counts are assessed using flow cytometry. An assessment of LN involvement is also performed.

Additional efficacy assessments include:

- Physician's Erythroderma Severity Assessment based on a five-point severity scale,
- Physician's Global CTCL Severity Assessment by visual analog scale,
- Patient Global Assessment based on a seven-point scale,
- Pruritus Assessment by visual analog scale,
- Need for symptom relief medication, and
- Quality of Life (QOL) assessment using a multidimensional concept tool (FACT-G).

Safety assessments include:

- Baseline and weekly hematology and clinical chemistry profiles, urinalysis,
- Physical exam findings, and
- Data on the occurrence of adverse experiences, serious adverse experiences.

Statistical Design

The primary efficacy endpoint is the overall response rate calculated from the number of responders (CRs, CCRs, and PRs) divided by the number of patients at each randomized dose level. The data cut-off for analysis of the primary and supportive endpoints is when all subjects have received the maximum allowable (8) courses of therapy and two-thirds have been followed for six months after their last dose of ONTAK[®], or have withdrawn from the study due to treatment failure, death or toxicity.

Secondary efficacy analyses will examine:

- Time-to-Treatment Failure and Time-to-Progression, using Kaplan-Meier methods, and
- Predictors of response using a multiple logistic regression model.

Adverse experiences with associated incidence rates and severities will be tabulated by treatment group. The incidence and severity of clinically significant laboratory abnormalities at baseline and through the end of each course will be presented.

Study Status:

Ongoing

Current Status:

As of September 2005, this study has enrolled 135 patients. This represents the largest number of patients ever enrolled in a prospective, randomized, blinded, placebo-controlled trial in this type of tumor, which has an annual incidence of 4 per million in the U.S., with approximately 1,100 new cases reported this year. The largest previous study of a prospective nature in this disease, conducted by the NCI, enrolled 103 patients over 8 years and compared two active arms (7). Note also that the NCI study was able to enroll all patients that meet CTCL inclusion criteria, while the L4389-11 study is only able to accrue patients whose biopsies express CD25 (60-64%).

The 135 patient accrual number for Study L4389-11 was reached despite considerable difficulties that conspire to produce a low annual accrual rate. Key accrual issues are outlined below.

In order to compensate for slow patient enrollment, Ligand has expanded clinical trials to many hospitals in countries across three continents (North America, Europe, and Australia) where ONTAK[®] is currently unlicensed and/or where commercial access to multiple other CTCL therapies is limited.

Patient enrollment has been evaluated continuously, and additional sites have been sought on a continuous basis. Specifically in 2003, four new study sites were activated in Europe and Canada. Nine additional sites in Europe and Australia were evaluated, and the feasibility of adding sites in South America was being pursued that year. Ligand endeavored to engage centers with high referral rates for CTCL patients that are staffed by investigators with an established track record for delivering high quality care and accrual for clinical trials.

In 2004, additional sites in, Europe and Australia were actively pursued as potential study participants. Out of a total of five sites in Europe and Australia that moved along the selection process, two European sites and one Australian site were initiated.

A major initiative was undertaken in Latin America during 2004 and 2005 that was projected to add an estimated 40 to 50 patients to the L4389-11 study. Ligand contracted with a CRO in order to evaluate and recruit a large number of sites in Latin American cities with large patient populations. Fourteen study sites from Argentina and Brazil were selected and attended a multi-center investigator meeting in Bahia, Brazil on 22 and 23 November 2004. Twelve study sites received local ethics committee approvals to conduct the study after letters of justification for placebo use were provided by local opinion leaders. After initial rejection of the L4389-11 protocol by the Ministries of Health for Argentina (ANMAT) and Brazil (CONEP) due to the inclusion of a placebo arm, several attempts were made to support the placebo arm in the study both by providing further letters of support from experts in the field and additional assurances to further support study patients.

These further assurances for study patients included: assurance that placebo patients enrolled in the study would have treatment options available to them such as the ability to switch to study L4389-14 and a commitment by Ligand to provide those placebo patients as well as any other patients enrolled in either L4389-11 or L4389-14 access to compassionate use of denileukin diftitox as long as the patient or their physician felt the patient was benefiting from the treatment. Ultimately, none of these Latin American sites were allowed to participate in the study. The protocol was rejected by the Ministries of Health in both countries because of an objection to the use of a placebo in oncology patients.

In 2005, Ligand has continued its search for new sites. The CRO currently under contract was engaged to conduct feasibility studies in several countries world-wide. Four additional sites were identified in Germany, and site qualification is ongoing. Three additional sites were identified in the UK, but all three ultimately declined participation.

Of the two Australian sites selected in 2004 that still remained to be initiated, one was initiated in 2005, and negotiations on protocol design and informed consent issues were recently completed at the second site. This last site is on schedule to be initiated in September 2005. Additionally, one site in Switzerland was finally opened after over two years of administrative paperwork.

Lastly, Ligand staff, including the Executive Medical Director in charge of the ONTAK[®] program, met with investigators during the June 2005 Lugano International Lymphoma Congress, and visited investigators world-wide to discuss enrollment issues and potential solutions, and to continue to emphasize to the investigators the importance of completing this study. The Sponsor has also continued intensive monitoring by CRAs in an effort to keep investigators interested and active.

Estimated Timeline for Submission of Study Results to FDA:

At the current rate of accrual, Ligand projects that the study will be completed and the results submitted to the FDA in three or four years.

IV. Progress to Date in the Completion of Protocol L4389-11

As of September, 2005, a total of 135 of the total required patient cohort have enrolled in study L4389-11. As noted above, enrollment was suspended for most of 1999 while significant protocol amendments were under discussion with FDA. The last 62 patients enrolled have come from outside the U.S., reflecting efforts on the part of Ligand to improve accrual in this trial as access to potential study subjects in the U.S. has declined.

TABLE 3: Protocol L4389-11 Study Sites

Region	Total Number of Study Sites Opened
North America	24*
Western and Eastern Europe	31
Australia	5
TOTAL	60

* Twenty of these sites were opened prior to 1999

V. Challenges and Obstacles Encountered in the Accrual/Completion of L4389-11

1. Impact of Population Size

Ligand has encountered numerous obstacles in the recruitment of subjects for the L4389-11 study. First and foremost, CTCL is a relatively rare neoplasm. It accounts for only 2.2% of all cases of lymphoma in the U.S. The annual incidence rate is approximately 4 per 1,000,000, and it is estimated that approximately 1,100 new cases of CTCL are reported in the U.S. each year. The number of patients available is also restricted by the impact of practice patterns (Section 4 below) and the impact of prior therapies (Section 5 below). Lastly, the L4389-11 study is only able to accrue patients whose biopsies express CD25 (60-64%), which further reduces the recruitable patient population by 36-40%.

2. Impact of Logistical Difficulties Resulting From a Low Yearly Accrual

Generally, each site enrolls a maximum of one or two patients per year. This creates a site logistical issue, since a physician or nurse cannot be assigned full time to this study. The sites ultimately lose familiarity with the study, interest, and even incentive, and focus on projects targeting a larger patient population.

3. Impact of the Placebo Arm in Study L4389-11

Multiple investigators in the U.S. have repeatedly emphasized that the use of a placebo arm is a significant deterrent for patients to enroll in Study L4389-11 post-approval, despite the fact that the randomization was modified to favor active drug treatment and that patients who exhibit progressive disease while receiving placebo can enroll in a companion, open-label study of ONTAK[®] at the maximal dose, 18ug/kg/day x 5 days (Study L4389-14).

In an effort to increase enrollment in L4389-11, Ligand sought to recruit additional study sites outside of the U.S. For example, investigators from six study sites in France agreed to participate in both the L4389-11 and L4389-14 studies in November 1999. Local ethics committee approval for the study was obtained, and a clinical trials application was filed with the French Ministry of Health in order to obtain regulatory approval to proceed with the study.

However, the Ministry of Health refused to grant a clinical trials application for the study, invoking the October 2000 amended World Medical Association Declaration of Helsinki, provision 29, as the basis for its refusal. This provision states that a placebo control should not be used in clinical studies of a disease for which other proven therapeutic modalities exist. As a result of this decision on the part of the Ministry of Health, efforts to conduct this study in France could not be continued.

A major initiative was undertaken in Latin America during 2004 and 2005 that was projected to add an estimated 40 to 50 patients to the L4389-11 study. Fourteen study sites from Argentina and Brazil were selected and attended a multi-center investigator meeting in Bahia, Brazil on 22 and 23 November 2004. Twelve study

sites received local ethics committee approvals to conduct the study after letters of justification for placebo use were provided by local opinion leaders. After initial rejection of the L4389-11 protocol by the Ministries of Health for Argentina (ANMAT) and Brazil (CONEP) due to the inclusion of a placebo arm, several attempts were made to support the placebo arm in the study both by providing further letters of support from experts in the field and additional assurances to further support study patients. These further assurances for study patients included: assurance that placebo patients enrolled in the study would have treatment options available to them such as the ability to switch to Study L4389-14 and a commitment by Ligand to provide those placebo patients as well as any other patients enrolled in either L4389-11 or L4389-14 access to compassionate use of denileukin diftitox as long as the patient or their physician felt the patient was benefiting from the treatment. Ultimately, none of these Latin American sites were allowed to participate in the study. The protocol was rejected by the Ministries of Health in both countries because of an objection to the use of a placebo in oncology patients.

4. Impact of Prior Therapies on the Clinical Trial Population

Unlike in the Phase III dose comparison study in which all but Phase IVa patients must have had four or more prior therapies as a condition for enrollment, the L4389-11 study is endeavoring to enroll patients with ≤ 3 prior therapies. Topical (e.g., mechlorethamine, psoralen/ultra-violet light, total skin electron beam irradiation) and oral therapies (bexarotene) are generally favored by clinicians and patients as initial treatments for all but the most advanced stage disease. Parenteral therapies such as ONTAK[®] are generally reserved for patients with persistent/refractory disease after multiple prior treatments. The consequence is that candidates for the L4389-11 study are often ineligible by virtue of having had more than three prior therapies. This has been corroborated through recent telephone interviews with a cross section of the L4389-11 study group from the U.S.

5. Impact of Practice Patterns

Practice patterns for CTCL favor consideration of ONTAK[®] treatment in late stage disease following multiple prior therapies. Patients with earlier stage disease (i.e., $< \text{IIb}$) are not usually considered to be good candidates for ONTAK[®] treatment unless they have had multiple prior therapies, because non-systemic (i.e., topical) therapies are first used by clinicians (mostly dermatologists, who principally manage this disease in its earlier stages). Patients with higher stage disease (i.e., $> \text{IIb}$), are often considered by physicians to be better candidates for ONTAK[®] treatment. Unfortunately, these patients have often received more than three prior therapies, which excludes them from the study. Patients with Stage IV disease (i.e., lymph node or visceral involvement) are also ineligible for enrolling in the L4389-11 study. Thus the candidate population for the study is quite restricted by standard practice patterns.

A tangible illustration of the rarity of CTCL patients available for clinical trials of systemic therapies is derived from an NCI-sponsored study comparing combination therapy (total skin, electron-beam radiation plus CHOP) vs. sequential, topical

monotherapy as initial treatment. This study required 8 years to complete enrollment of 103 patients from 5 study sites.

VI. Description of Phase IV, Post-approval Commitment Companion Study L4389-14

Title:

A multicenter open-label study to evaluate the safety and efficacy of DAB₃₈₉IL-2 in cutaneous T-cell lymphoma (CTCL) patients following Protocol 93-04-10, Protocol 93-04-11 or Protocol 92-04-01 or who meet the requirements for Protocol 93-04-11 except have biopsy-documented CTCL that does not express CD25.

Objective:

To demonstrate the efficacy and safety of 18 µg/kg/day of denileukin diftitox in CTCL patients who received placebo, previously responded to denileukin diftitox and subsequently relapsed, or had biopsy-documented CTCL that does not express CD25 by immunohistochemistry; to assess changes in CTCL symptoms and functional status in association with denileukin diftitox; to further evaluate the safety, tolerability, and pharmacokinetic profile of denileukin diftitox for this dose and schedule.

Study Design:

This is an open-label study with denileukin diftitox at a single dose level with pharmacokinetic sampling. Up to 86 patients are intended to be treated for a maximum of 8 courses (~6 months), unless the patient meets the criteria for PD or withdraws for toxicity or administrative reasons. Patients with PD will discontinue treatment at the time PD is established. Patients will not be permitted to re-enroll into this study.

Summary of Study Sites:

Table 4. Protocol L4389-14 Study Sites

Region	Total Number of Study Sites Opened
North America	24*
Eastern and Western Europe	30
Australia	4
TOTAL	58

* Twenty of these sites were opened prior to 1999

Patient Selection Criteria:

Patients selected for enrollment in Protocol L4389-14 include those that were:

- Previously enrolled in Protocol L4389-11 and had PD during the Treatment Phase while on the placebo arm of the trial.

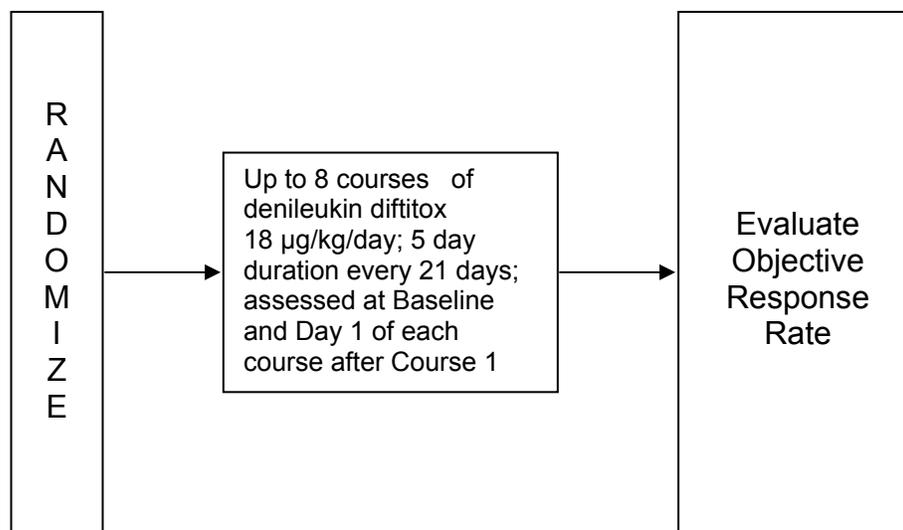
- Previously enrolled in Protocol L4389-11 and had SD at the completion of 8 courses while on the placebo arm of the trial.
- Met all eligibility criteria for Protocol L4389-11 except that the screening skin biopsy indicated CTCL that does not express CD25 by immunohistochemistry.
- Prior to 1999, patients previously enrolled in 92-04-01, 93-04-10, and 93-04-11 who experienced a response and subsequent relapse were allowed to be retreated in Protocol L4389-14.

Endpoints:

The primary efficacy endpoint is the total number of documented responses (CR, CCR, and PR). Each patient's best response will be used. Secondary efficacy endpoints include the time to treatment failure, the time to progression and the duration of the response.

Treatment Schema:

Figure 2. L4389-14 Treatment Schema



Patient Accrual:

Total enrollment to date for Protocol L4389-14 is 90 patients. This study has completed its targeted enrollment (of at least 86 patients) according to the timeline established in June 2002. In addition, the target of 29 patients whose tumors do not express CD25 was also met.

Current Status:

Ongoing.

As noted above, the study has completed its target enrollment but remains open to provide a therapeutic option for L4389-11 study patients that were given placebo or whose tumor biopsies do not express CD25.

The study will provide important data on three distinct subgroups of patients:

- a) CD25 negative patients (target of 29 patients exceeded),
- b) ONTAK[®] activity in patients that progressed while on placebo (>30 patients in this subgroup), and
- c) Impact of retreatment of patients that responded and later progressed while on ONTAK[®] in previous trials.

In addition, this study, as well as Study L4389-11, will also provide data on the response rates that are documented within the first 4 cycles of treatment versus those observed in the latter 4 cycles.

Estimated Timeline for Study Completion:

This study was originally projected to be completed with Protocol L4389-11 in the 3rd Quarter 2005, as presented to FDA in an amendment to Prior Approval Supplement (STN 103767/5018), submitted 11 June 2002. This study has met its target enrollment date, as projected.

VII. References

1. Foss FM. Interleukin-2 fusion toxin: Targeted therapy for cutaneous T-cell lymphoma. *Ann NY Acad Sci* 2001; 941:166-76.
2. LeMaistre CF, Meneghetti C, Rosenblum M, et al. Phase I trial of an interleukin-2 (IL-2) fusion toxin (DAB₄₈₆IL-2) in hematologic malignancies expressing the IL-2 receptor. *Blood* 1992; 79:2547-54.
3. LeMaistre CF, Saleh MN, Kuzel, TM, et al. Phase I trial of a ligand fusion-protein (DAB₃₈₉IL-2) in lymphomas expressing the receptor for interleukin-2. *Blood* 1998; 91:399-405.
4. Olsen E, Duvic M, Frankel A, et al. Pivotal phase III trial of two dose levels of denileukin diftitox for the treatment of cutaneous T-cell lymphoma. *J Clin Oncol* 2001; 19:376-88.
5. Weinstock MA et al. Twenty year trends in the reported incidence of mycosis fungoides and associated mortality. *Am J Pub Health* 1999; 89:1240.
6. Weinstock MA. Epidemiology of mycosis fungoides. *Sem Dermatol* 1994; 13:154.
7. Kaye FJ, Bunn PA, Steinberg SM, et al. A randomized trial comparing combination electron-beam radiation and chemotherapy with topical therapy in the initial treatment of mycosis fungoides. *N Engl J Med* 1989; 321:1784-90.
8. World Medical Association Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects (www.sar.co.uk/helsinki.htm).