LIGAND PHARMACEUTICALS

FACSIMILE TRANSMISSION

DATE:	February 12, 2003
TO:	Michael Harlow
COMPANY:	Food and Drug Administration Center for Biologics Evaluation and Research
PHONE: FAX:	(301) 827-4358 (301) 827-5397
FROM:	James L'Italien, Ph.D. Senior Vice President, Regulatory Affairs and Compliance
PHONE: FAX:	(858) 550-7600 (858) 550-1827
Pages including cover:	18

Please call Mary Szuch at (858) 550-7591 if this transmission is unclear or incomplete

RE: BLA 97-1325/STN 103767, ONTAK® (denileukin diftitox)
ODAC Background Information Package

Dear Mr. Harlow,

Please find attached the ODAC Background Information Package. This package will also be sent via Federal Express to the attention of Karen M. Templeton-Somers, Ph.D. of the Advisors and Consultants Staff, CDER.

Sincerely,

James L'Italien, Ph.D.

James L'Italien, Ph.D.
Senior Vice President
Regulatory Affairs and Compliance

RAV/jkc

LIGAND
PHARMACEUTICALS

Regulatory Affairs and Compliance

February 12, 2003

RE: BLA 97-1325/STN 103767
ONTAK® (denileukin diftitox)

General Correspondence:
ODAC Background Information Package – Available for public disclosure without redaction.

Karen M. Templeton-Somers, Ph.D.
Advisors and Consultants Staff
FDA, CDER, ORM
HFD-21, Room 1093
5630 Fishers Lane
Rockville, Maryland 20852-1734

Dear Dr. Templeton-Somers:

Reference is made to BLA 97-1325 (STN: BL 103767) for ONTAK® (denileukin diftitox), which was approved 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.

Reference is also made to the Agency letter dated January 7, 2003 inviting Seragen, Inc., a wholly owned subsidiary of Ligand Pharmaceuticals Inc., to attend and present to the Oncologic Drugs Advisory Committee (ODAC) an update on our Phase IV clinical commitments.

We discussed the upcoming ODAC meeting at a teleconference with FDA on February 3, 2003 and are submitting the background information package per the timing discussed at the teleconference. The contents of this submission are available for public disclosure without redaction. Ligand is submitting two copies to the document room, one desk copy to your attention, two CD's and 40 copies per your fax correspondence.

We will shortly provide a list of former ODAC members, Special Government Employees or other Federal Employees who will be attend the meeting with us.

DOCS #69371

The two CD's provided in this submission, each contain the cover letter and submission documents in MS Word and PDF format. The PDF format maintains pagination identical to the submitted hard copy when printed. The CD's were scanned with virus detection software (McAfee VirusScan, version: 4.5.1, virus definition updated on February 5, 2003). There are no viruses present.

If there are any questions regarding this submission, please contact the undersigned at 858-550-7600 (fax 858-550-1827).

Sincerely,

James L'Italien, Ph.D.

James L'Italien, Ph.D.
Senior Vice President
Regulatory Affairs and Compliance

RAV/jkc

LIGAND PHARMACEUTICALS INC., 10275 Science Center Drive, San Diego, CA 92121-1117 (858) 550-7600 fax (858) 550-1827

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Seragen, Inc. a wholly owned subsidiary of Ligand Pharmaceuticals Inc.	2/12/03
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
(858) 550-7600	(858) 550-1827
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* 10275 Science Center Drive San Diego, California 92121-1117	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE Not applicable

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 97-1325/ STN 103767

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
denileukin diftitox	ONTAK®

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*: $DAB_{389}IL\text{-}2$

CODE NAME *(If any)*: N/A

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Liquid frozen	150 µg/mL	Intravenous

(PROPOSED) INDICATION(S) FOR USE:
Cutaneous T-cell lymphoma

APPLICATION INFORMATION

APPLICATION TYPE *(check one)*
☐ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☒ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug: Not applicable Holder of Approved Application: _____

TYPE OF SUBMISSION *(check one)*
☐ ORIGINAL APPLICATION ☐ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
ODAC Background Information Package

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED: 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

ragen, Inc.: BB-IND 4679, BB-IND 4896, BB-IND 5222, BB-IND 4682, BB-IND 5198, and BB MF 4681
Lilly and Company: BB-MF 5919, BB-IND 6429, BB-MF 4700

This application contains the following items: *(Check all that apply)*	
☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
James L'Italien, Ph.D.	James L'Italien, Ph.D. Sr. Vice President, Regulatory Affairs and Compliance	2/12/03

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
10275 Science Center Drive, San Diego, California 92121-1117	(858) 550-7600

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Department of Health and Human Services
Food and Drug Administration
[illegible]R, HFD-99
[illegible]l Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

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AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

LIGAND PHARMACEUTICALS INC.

BLA 97-1325/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.

This study has accrued approximately one-half of the total required patient cohort and is on target to enable submission of the final study report in the first quarter of 2006.

I. ONTAK® (denileukin diftitox; DAB_{389}IL-2) Product Characteristics:

ONTAK is a recombinant fusion protein composed of the catalytic and membrane translocation domains of diphtheria toxin (Met_1-Thr_{387})-His linked to the full amino acid sequence for Interleukin-2 (IL-2; Ala_1-Thr_{387}):

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

IL-2R exists in three isoforms with varying affinity for IL-2:

- the low affinity receptor is composed of CD25 and CD132 subunits,
- the intermediate affinity receptor consists of the CD122 and CD132 subunits, and
- the high affinity receptor consists of CD25, CD122 and CD132.

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), and
- internalization of denileukin diftitox into cells is mediated by binding to the intermediate and high affinity isoforms (1).

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 is tracking progress of the study for anticipated completion to enable submission of a final study report in first Quarter of 2006.

Clinical studies of DAB_{389}IL-2 were initiated in 1992 after "proof of concept" was established for a precursor molecule, DAB_{486}IL-2 (2):

- DAB_{389}IL-2 demonstrated approximately 100-fold greater binding avidity for IL-2R vs. DAB_{486}IL-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 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:

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

  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:

  ≥50% reduction in tumor burden was noted in 13 (37%; 95% CI: 21-53%) of 35 CTCL patients treated at dose levels varying from 6 to 27µg/kg/day (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 at least 4 prior therapies, whose tumors expressed CD25 on ≥20% of malignant lymphocytes, and

  patients with persistent/refractory Stage IVa disease and at least 1 prior therapy (4).

- efficacy results:

  Overall response rate was 30% (95% CI: 18-41%).

  23% (95% CI: 10-40%) and 36% (95% CI: 21-54%) of patients showed a ≥ 50% reduction in tumor burden in the 9 and 18µg/kg/day treatment arms, respectively.

  Difference in response rates between the two treatment arms -- not statistically significant.

  There was a trend suggesting a dose-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 (DAB_{389}IL-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 5th 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 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 1:2:2 randomization that was "weighted" towards active drug treatment.

- 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 arms 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	1:1:1 (40:40:40)	1:2:2 (39:78:78)

Annual updates have been filed in the BLA Annual report for the calendar years 1999, 2000, 2001, and 2002 providing updates on accrual and progress as requested in the Agency approval letter.

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 for enrollment.

   The key inclusion/exclusion criteria are:

   - biopsy documented, recurrent or persistent CTCL expressing CD25 on ≥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 DAB_{389}IL-2 or DAB_{486}IL-2.

2. *Endpoints*

   Primary endpoint:

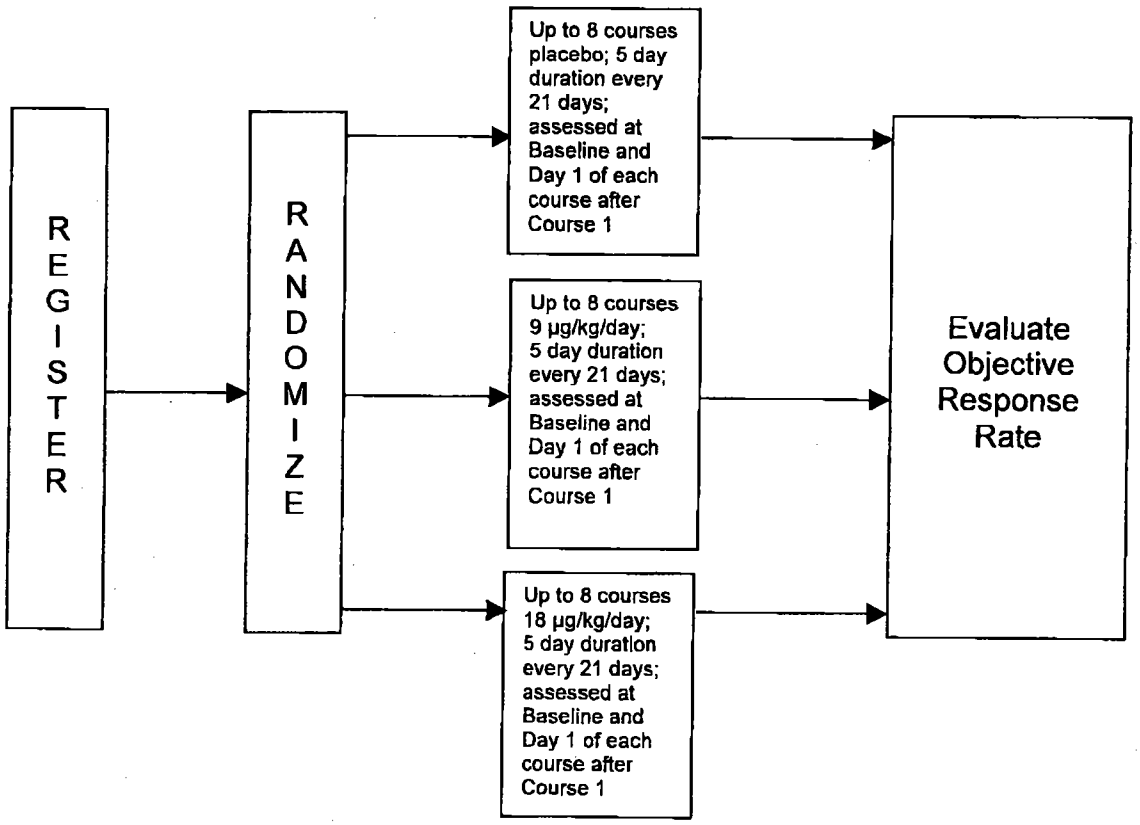
   - the objective rate of response, defined as the proportion of complete (CRs, CCRs) plus partial responders (PRs) in each arm of the study.

   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 includes:

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),

assessment of up to 5 target lesions in cm^2 is used for patients with ≤10% BSA involvement,

flow cytometry analysis is used for assessment of abnormal lymphocyte counts in blood.

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. An analysis of variance (ANOVA) for the three proportions (chi-square test) will be carried out. If significance at the level of 0.05 is found by ANOVA, then contrasts of 9 µg/kg/day versus placebo, 18 µg/kg/day versus placebo, and the combined groups (9 µg/kg/day and 18 µg/kg/day) versus placebo will be performed. 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 January 2003, study L4389-11 has accrued 98 of 195 patients as required by the protocol.

Estimated Timeline for Submission of Study Results to FDA:

First Quarter, 2006

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

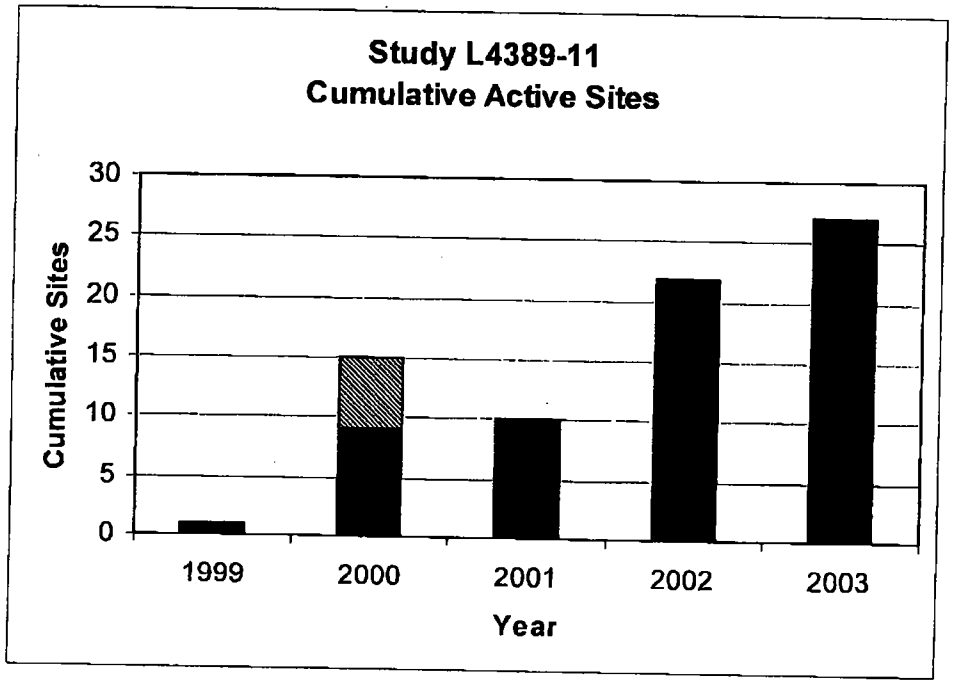
As of January 20, 2003, a total of 98 or one-half of the total required patient cohort have enrolled in study L4389-11. As noted above, enrollment was suspended for most of 1999 while significant protocol amendments were under discussion with FDA. A significant number of patients enrolled recently have 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 (see Section V).

TABLE 3: Summary of Study Sites (geography, number, initiation dates) for Protocol L4389-11 (formerly 93-04-11)

Study Sites (Listed by region)	Number of Study Sites Opened Per Region	Range of Site Initiation Dates
North America	6	11/4/99-present
Europe*	24	3/23/00-present
Australia	2	5/11/00-present
TOTAL	32	N/A

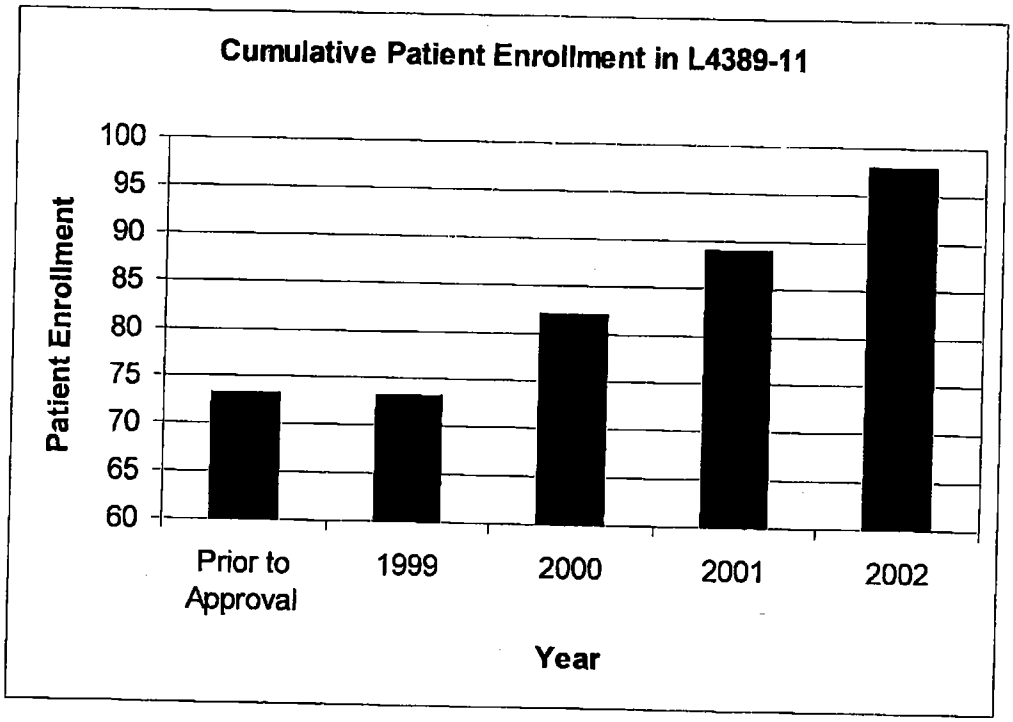
*including Russia and Poland

FIGURE 2: Cumulative Active Sites for Study L4389-11



- Includes an estimate of sites to be added in 2003. Four of the opened sites have been closed due to lack of patient enrollment.
- Diagonal area of Year 2000 bar signifies the addition of six study sites in France that could not be opened. See text for explanation.

FIGURE 3: Cumulative Patient Enrollment in L4389-11



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

Impact of Population Size

Ligand has encountered several 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 (5,6).
- The annual incidence rate is approximately 4 per 1,000,000 (5,6).
- It is estimated that approximately 1,100 new cases of CTCL are reported in the U.S. each year (5,6).

Practice Patterns for CTCL Favor Consideration of ONTAK Treatment in Late Stage Disease After Multiple Prior Therapies

In the context of the standard of care for CTCL in the U.S. and the eligibility criteria for study L4389-11, the candidate population for the study is quite restricted for the following reasons:

- Patients with Stage IV disease (i.e. lymph node or visceral involvement) are ineligible.
- Patients with earlier stage disease (i.e. < IIb) are not considered to be good candidates for ONTAK treatment because non-systemic (i.e. topical) therapies are preferred by both patients and clinicians (i.e. mostly dermatologists, who principally manage this disease in its earlier stages). The spectrum of therapies available to patients with early stage disease include topical mechlorethamine, psoralen/ultraviolet light, total skin electron beam radiation, interferon therapy and bexarotene gel/capsules.
- 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 (7).
- Patients with higher stage disease (i.e. ≥IIb) are often considered to be acceptable candidates for the study after they have received more than 3 prior therapies (an exclusion criterion for the study).

These perspectives have been corroborated through recent telephone interviews with a cross section of the L4389-11 study group from the U.S.

Impact of the Placebo Arm in Study L4389-11

Multiple investigators in the U.S. have repeatedly emphasized the use of a placebo arm as 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 patients

who exhibit progressive disease while receiving placebo can enroll in a companion, open-label study of ONTAK at the maximal dose, 18µg/kg/day x 5 days.

In an effort to increase enrollment in L4389-11, Ligand sought to recruit additional study sites outside of the U.S.:

- Investigators from six study sites in France agreed to participate in the L4389-11 study 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.
- 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 (8).
- This provision states that a placebo control should not be used in clinical studies of a disease for which other proven therapeutic modalities exist (8).

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.

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 of this is that candidates for the L4389-11 study are often ineligible by virtue of having had more than three prior therapies.

Ongoing Efforts

In an effort to compensate for these obstacles, Ligand has sought to increase the number of study sites that can enroll eligible patients in parts of the world where denileukin diftitox is currently unlicensed and/or commercial access to multiple other CTCL therapies is limited:

- Within the past 12 months, an additional 11 study sites, including 4 in Poland and 5 in Russia, that expressed interest in the L4389-11 trial have been activated to initiate enrollment.
- By the end of first quarter 2003, an additional 5 study sites will be activated, bringing the total to 28 study sites in North America, Europe, and Australia, for study L4389-11. (By comparison with Table 3, it is noted that 4 sites have closed for L4389-11).

We have attempted 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.

Our experience is that most study sites are excessively optimistic about their accrual rate prospects. The true accrual rate can only be determined empirically. For this reason, Ligand expects to monitor the rate of accrual for both new and old study sites for a period of approximately 6 months, commencing with the second quarter of 2003. Based on the information gathered during this period, Ligand will consider further adjusting the number of study sites in an effort to expedite completion of the study.

VI. References

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