CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
21-056

ADMINISTRATIVE DOCUMENTS

13. PATENT INFORMATION ON ANY PATENT WHICH CLAIMS THE DRUG IN ACCORDANCE WITH 21 U.S.C. §355(b)

Owner	Patent No.	Expiration Date	Type
Ligand Pharmaceuticals Inc.	5,780,676	July 14, 2015	Drug Product Method of Use
Ligand Pharmaceuticals Inc.	5,962,731	Oct. 5, 2016	Drug Product Method of Use
SRI International The Burnham Institute (Exclusively Licensed to Ligand Pharmaceuticals Inc.)	5,466,861	Nov. 14, 2012	Drug Drug Product

APPEARS THIS WAY
ON ORIGINAL

14. PATENT CERTIFICATION WITH RESPECT TO ANY PATENT WHICH CLAIMS THE DRUG

14. PATENT CERTIFICATION WITH RESPECT TO ANY PATENT WHICH CLAIMS THE DRUG IN ACCORDANCE WITH 21 U.S.C. §355(b)(2) OR §355(j)(2)(A)

No certificaton is necessary because this application is for a drug for which investigations described in 21 U.S. C. §355(b)(1)(A) and relied upon by the applicant for approval of this application ***were*** conducted by or for the applicant, and this application is not an abbreviated application for a new drug.

EXCLUSIVITY SUMMARY FOR NDA # 21-054 SUPPL #_____

Trade Name Targretin (bexarotene) gel 1% Generic Name _____

Applicant Name Ligand Pharmaceuticals HFD # 150

Approval Date If Known [redacted]

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /X/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /X/

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /X/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /___/ NO /X/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

no

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /___/ NO /X/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /X/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /X/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21-055 Targretin capsules

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /__/ NO / _ /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /X/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /X/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /X/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /X/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

L 1069T-25

_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /X/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /X/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

L1069T-25 _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !

IND ( ) YES /X/ ! NO /___/ Explain: _____

!

! _____

Investigation #2 !

!

IND # _____ YES /___/ ! NO /___/ Explain: _____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !

!

YES /___/ Explain _____ ! NO /___/ Explain _____

!

_____ ! _____

!

_____ ! _____

!

!

Investigation #2 !

!

YES /___/ Explain _____ ! NO /___/ Explain _____

!

_____ ! _____

!

_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /__/ NO /X/

If yes, explain: _____

_____

/S/ 6-1-00

Signature Date

Title: CSO

/S/ 6/26/00

Signature of Office/ Date

Division Director

cc: Original NDA Division File HFD-93 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	21056	**Trade Name:**	TARGRETIN (BEXAROTENE) GEL 1%
Supplement Number:		**Generic Name:**	BEXAROTENE
Supplement Type:		**Dosage Form:**	GEL
Regulatory Action:	AP	**Proposed Indication:**	Targretin (bexarotene) gel 1% is indicated for the topical treatment of cutaneous lesions in patients with CTCL (Stage Ia and IB) who have refractory or persistent disease after other therapies or who have not tolerated other therapies.

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No waiver and no pediatric data

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)

____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy Does Not Apply

Formulation Status

Studies Needed

Study Status

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

Orphan Drug Designation

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, AMY CHAPMAN

Signature 1ST, CSO

6-26-00

Date

DEBARMENT CERTIFICATION

NDA 21-056 - TARGRETIN® GEL

In compliance with the Generic Drug Enforcement Act of 1992, Section 306(k)(1) of the act (21 U.S.C. 335a(k)(1)), we, Ligand Pharmaceuticals Inc., state the following with respect to this new drug application:

> Ligand Pharmaceuticals Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Howard T. Holden

Howard T. Holden, Ph.D.
Vice President
Regulatory Affairs and Compliance
Ligand Pharmaceuticals Inc.
San Diego, California

NOV 9, 1995
Date

FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
5600 Fishers Lane, Rockville, MD 20857

To: Ray Lubecki/Ligand Pharm.	**From:** Amy Baird, CSO
Fax: 858-550-1827	**Fax:** (301) 594-0498
Phone: 858-550-7889	**Phone:** (301) 594-5771
Pages, including cover sheet: 3	**Date:** 5-23-00

Re: NDA 21-056 Targretin (bexarotene) gel 1%.

COMMENTS:

See the attached clinical comments. Please do not hesitate to call should you have any questions.

Thank you,

/S/

Amy Baird

CC: Orig. NDA 21-056
HFD-150 / Div. File
HFD-150 / Baird

1. For the patients listed, please provide the dates for the following indicated qualifying prior therapies and/or 1st histopathological diagnosis consistent with CTCL.

Study –25 **Patient #**		**Dates**
601	PUVA	
631	Nitrogen Mustard PUVA	
632	First histopathological diagnosis consistent with CTCL	
692	First histopathological diagnosis consistent with CTCL	
693	BCNU Nitrogen Mustard Interferon	
695	First histopathological diagnosis consistent with CTCL	
742	First histopathological diagnosis consistent with CTCL	
743	First histopathological diagnosis consistent with CTCL	
802	UVB	
803	Photopheresis PUVA First histopathological diagnosis consistent with CTCL	
811	PUVA PUVA with oxsarlen	
831	First histopathological diagnosis consistent with CTCL	
832	Nitrogen Mustard	
851	Nitrogen Mustard	
1622	Interferon CHOP COP PUVA Therapy	

	PUVA Therapy Soriatane	
1661	Nitrogen Mustard PUVA	
1662	PUVA	
1761	First histopathological diagnosis Consistent with CTCL	
1781	PUVA Interferon Interferon PUVA	

APPEARS THIS WAY
ON ORIGINAL

LIGAND PHARMACEUTICALS

FACSIMILE TRANSMISSION

DATE:	June 5, 2000
TO:	Amy Baird Project Manager, CSO
COMPANY:	Food and Drug Administration Division of Oncology Drug Products, HFD-150
PHONE: FAX:	(301) 594-5771 (301) 827-4590
FROM:	Ray Lubecki, R.Ph. Associate Director, Regulatory Affairs and Compliance
PHONE: FAX:	(858) 550-7600 (858) 550-1827
Pages including cover:	15

Please call Elizabeth Borst at (858) 550-7765 if this transmission is unclear or incomplete.

Subject: NDA 21-056 for Targretin® (bexarotene) gel 1%
Follow-up Response to FDA Request for Financial Disclosure Information of 1/18/00

Regarding the above subject, attached please find Ligand's response.

Should you have any questions concerning this submission or NDA 21-056, please contact the undersigned or Howard T. Holden, Ph.D., at 858-550-7600 (facsimile 858-550-1827).

Sincerely,

Ray Lubecki, R.Ph.

/emb

LIGAND PHARMACEUTICALS

Regulatory Affairs and Compliance

June 5, 2000

RE: NDA 21-056
Targretin® (bexarotene) gel 1%

General Correspondence:
Follow-up Response to FDA Request for
Financial Disclosure Information of 1/18/00

Richard Pazdur, M.D.
Food and Drug Administration
CDER/Oncology HFD-150
Attention: Document Control Room
1451 Rockville Pike
Rockville, Maryland 20852

Dear Dr. Pazdur:

Reference is made to NDA 21-056 for Targretin® gel 1% (submitted on December 8, 1999), to the request for financial disclosure information in the January 18, 2000 facsimile received from the Agency (See Comment 6, Appendix 1), and to Ligand's response submitted on January 24, 2000, which provided the requested information for the majority of investigators participating in covered studies.

Enclosed please find the financial disclosure information for the few remaining investigators participating in the covered studies (Appendix 2).

In addition, supplemental financial disclosure information requested by Ms. Amy Baird on June 5, 2000, is provided in Appendix 3.

We trust that this information will meet the Agency's immediate needs. Please contact the undersigned or Howard T. Holden, Ph.D., at 858-550-7600 (facsimile 858-550-1827) in the event you have any questions concerning the enclosed information.

Sincerely,

Ray Lubecki

Ray Lubecki, R.P.h.
Associate Director
Regulatory Affairs and Compliance

Enclosures

REL/emb

TABLE OF CONTENTS

APPENDIX 1

FDA 1/18/00 Request for Clinical Information

FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
5600 Fishers Lane, Rockville, MD 20857

To: Howard Holden, Ligand Pharm	**From:** Amy Chapman, CSO
Fax: 858-550-1827	**Fax:** (301) 594-0498
Phone: 858-550-7600	**Phone:** (301) 594-5771
Pages, including cover sheet: 2	**Date:** 1-18-00

Re: NDA 21-056 Targretin (bexarotene) gel 1%.

COMMENTS:

See the attached requests for clinical information. Please do not hesitate to call should you have any questions.

Thank you,

/s/

Amy Chapman

1. From Study 25, the following appear to be missing from the ACCESS database:

   CENTLABR: PID and visit columns
   LNBR: no data
   SAE_CASE: no data
   SAECASE: no data

2. From Study 04, the following appear to be missing from the ACCESS database:

   HISTORY: no data

3. From Study 11, the following appear to be missing from the ACCESS database:

   No data in: ADDIT, CD, CONTIN, DEATHS, DEO, KARNOFSK, KSHAGENT, KSHDIS, LOCATION, MEASUR, RANDOM, RESP, TERM, UNSCHED

4. From Study 12, the following appear to be missing from the ACCESS database:

   No data in: DEATH, SERAE, T6912

5. Where is the annotated CRF's for Study 04 (both electronically and hard copy)?

6. Where is the financial disclosure documentation for Studies 04, 11, and 12?

7. At the advisory committee open hearing, prior to the Targretin Capsules presentation, Ms. Nancy Borcherding made a presentation. Please provide her patient identification numbers from the targretin gel and targretin capsules studies she participated in.

APPENDIX 2

Financial Disclosure Information

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☐ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	See Attachment for the follow-up status of investigators in studies:	
	L1069-94-04T and L1069T-11	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Paul Maier	Senior Vice President Chief Financial Officer
FIRM/ORGANIZATION Ligand Pharmaceuticals Inc.	
SIGNATURE	DATE
P Maier	June 5, 2000

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

Certification: Financial Interests and Arrangements of Clinical Investigators
Significant Equity Interest Certification
Investigators Certification List

Follow-up status

The Investigators listed who enrolled patients in the covered clinical studies L1069-94-04T and L1069T-11 (as defined in 21 CFR 54.2 (e)) have certified that neither they, nor their spouses nor dependent children, had an equity interest as defined in 21 CFR54.2(b) (i.e., stock ownership) in Ligand Pharmaceuticals Inc. that exceeds $50,000 based on current market value.

Protocol No.: L1069-94-04T

Protocol Title: "Phase 1-2 Evaluation of Topical LGD1069 in Patients with Cutaneous T-Cell Lymphoma (Mycosis Fungoides)"

Hannah, R.N., Kathleen

Protocol No.: L1069T-11

Protocol Title: "Phase 1-2 Evaluation of Topical LGD1069 in Patients with Cutaneous T-Cell Lymphoma (Mycosis Fungoides)"

Gadenne, M.D., Anne-Sophie

Paul V. Maier
Sr. Vice President, Finance

Certification: Financial Interests and Arrangements of Clinical Investigators
Significant Equity Interest Certification
Due Diligence: Information Not Obtained

Follow-up status

The Investigator listed who enrolled patients in the covered clinical study L1069-94-04T (as defined in 21 CFR 54.2(e)) could not be certified with regard to the lack of a significant equity interest as defined in 21 CFR 54.2(b). I certify that I have acted with due diligence to obtain from the listed clinical Investigators this information but it was not possible to do so. The reason why this information could not be obtained is provided below.

Protocol No.: L1069-94-04T

Protocol Title: "Phase 1-2 Evaluation of Topical LGD1069 in Patients with Cutaneous T-Cell Lymphoma (Mycosis Fungoides)"

Investigator	Reason Information Not Obtained
	No longer at site, forwarding address unknown by site

Paul V. Maier
Sr. Vice President, Finance

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

TO BE COMPLETED BY APPLICANT

The following information concerning [ ], who participated as a clinical investigator in the submitted study [See Attachment], is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Name of clinical investigator *Name of clinical study*

Please mark the applicable checkboxes.

☐ any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

☐ any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

☐ any proprietary interest in the product tested in the covered study held by the clinical investigator;

☒ any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
Paul Maier	Senior Vice President Chief Financial Officer
FIRM/ORGANIZATION	
Ligand Pharmaceuticals Inc.	
SIGNATURE	DATE
P Maier	June 5, 2000

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

Attachment to Form FDA 3455

Disclosure: Financial Interests and Arrangements of Clinical Investigators

Significant Equity Interest as Defined in 21 CFR 54.2(b), Held by the Clinical Investigator in the Sponsor of the Covered Study

Investigator:

Protocol No.:

Protocol Title: Phase 1-2 Evaluation of Topical LGD1069 in Patients with Cutaneous T-Cell Lymphoma (Mycosis Fungoides)

Details of the Disclosable Financial Interests:

Ligand Pharmaceuticals Inc. stock ownership exceeding based on current market value.

certified that spouse owned stock. also certified that owns no stock in portfolio, and that and spouse have separate assets.

Steps Taken to Minimize Potential Bias:

The clinical database for Targretin® gel NDA 21-056 was locked on October 13, 1999. The Ligand stock was purchased on October 19,1999 and on November 8, 1999. At the time of the stock purchases, only 3 of the 13 patients enrolled at this center were ongoing in Study .

Ligand believes that would not have been able to make any decisions that would have affected the reliability of the results for Study as reported in NDA 21-056, based on the relative timing of the stock purchases to the closure of the NDA database.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning _____ (*Name of clinical investigator*), who participated as a clinical investigator in the submitted study See Attachment (*Name of clinical study*), is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

☐ any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

☐ any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

☐ any proprietary interest in the product tested in the covered study held by the clinical investigator;

☒ any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
Paul Maier	Senior Vice President Chief Financial Officer
FIRM/ORGANIZATION	
Ligand Pharmaceuticals Inc.	
SIGNATURE	DATE
P Maier	June 5, 2000

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

Attachment to Form FDA 3455

Disclosure: Financial Interests and Arrangements of Clinical Investigators

Significant Equity Interest as Defined in 21 CFR 54.2(b), Held by the Clinical Investigator in the Sponsor of the Covered Study

Investigator:

Protocol No.:

Protocol Title: Phase 3 Evaluation of Targretin™ Topical Gel in Patients with Refractory or Persistent Early Stage Cutaneous T-Cell Lymphoma

Details of the Disclosable Financial Interests:

Ligand Pharmaceuticals Inc. stock ownership exceeding based on current market value.

certified that spouse owned stock. also certified that owns no stock in portfolio, and that and spouse have separate assets.

Steps Taken to Minimize Potential Bias:

The clinical database for Targretin® gel NDA 21-056 was locked on October 13, 1999. The Ligand stock was purchased on October 19,1999 and on November 8, 1999. At the time of the stock purchases, the one (1) patient enrolled at this center was <u>not</u> ongoing in the multi-center Study

Ligand believes that would not have been able to make any decisions that would have affected the reliability of the results for Study as reported in NDA 21-056, based on the relative timing of the stock purchases to the closure of the NDA database.

RE: NDA 21-056
Targretin® (bexarotene) gel 1%
June 5, 2000

APPENDIX 3

Supplemental Financial Disclosure Information

Requested by Ms. Amy Baird on June 5, 2000

In response to a telephone request from Ms. Amy Baird on June 5, 2000, the following supplemental information regarding the financial disclosure information (Form FDA 3455) in this submission for for studies and is provided below:

purchased a total of worth of Ligand stock during October and November 1999. This purchase was made independent of knowledge. When became aware that this could potentially be perceived as a conflict of interest sold the shares (February 2000).

19. OTHER (FINANCIAL DISCLOSURE/CERTIFICATION BY INVESTIGATORS)

19. OTHER (FINANCIAL DISCLOSURE/CERTIFICATION BY INVESTIGATORS)

In accordance with 21 CFR §314.50(k), this item contains financial certification by the applicant, Ligand, as required under 21 CFR § 54, for all clinical investigators (as defined in 21 CFR § 54.2 (d)) who have enrolled patients into the covered clinical studies identified below (as defined in 21 CFR 54.2(e)) in support of NDA 21-056 for Targretin® gel 1%, for use in patients with cutaneous T-cell lymphoma. No clinical investigator identified in this certification is a full-time or part-time employee of Ligand, the sponsor of each covered clinical study.

Covered Clinical Studies:

Protocol No. L1069T-25, entitled: "Phase 3 Evaluation of Targretin Topical Gel in Patients with Refractory or Persistent Early Stage Cutaneous T-Cell Lymphoma."

Certification Information:

Ligand certifies to the absence of financial interests and arrangements regarding *compensation affected by the outcome of clinical studies* (as defined in 21 CFR § 54.2(a)), *proprietary interest in the tested product* (as defined in 21 CFR § 54.2 (c)), and *significant payments of other sorts* (as defined in 21 CFR § 54.2(f)) for all clinical investigators who have enrolled patients into Protocol No. L1069T-25. A completed Form FDA 3454 for this certification (dated and signed by the Vice President, Senior Corporate Controller at Ligand) is provided.

Ligand certifies to the absence of financial interests and arrangements regarding *significant equity interest in the sponsor of a covered study* (as defined in 21 CFR § 54.2(b)) for all clinical investigators who have enrolled patients into Protocol No. L1069T-25, or certifies that it acted with due diligence to obtain information regarding significant equity interest in the sponsor of a covered study from all

investigators who have enrolled patients into Protocol No. L1069T-25, that it was not possible to do so, and provides the reasons why this information could not be obtained. This certification (dated and signed by the Vice President, Senior Corporate Controller at Ligand) for protocol L1069T-25, is provided in Attachment A.

Disclosure Statements:

Disclosure statements are not applicable to this NDA. (As the applicant, Ligand certifies to the absence of financial interests and arrangements for all clinical investigators who have enrolled patients into Protocol No. L1069T-25, or certifies that it acted with due diligence to obtain the information required under 21 CFR § 54 from all clinical investigators who have enrolled patients in Protocol No. L1069T-25, that it was not possible to do so, and provides the reasons why this information could not be obtained).

Attachment A

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	
See attached lists for study L1069T-25	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Gian Aliprandi	Vice President, Senior Corporate Controller
FIRM/ORGANIZATION	
Ligand Pharmaceuticals Inc.	
SIGNATURE	**DATE**
G. Aliprandi	10/12/99

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

FORM FDA 3454 (3/99)

Certification: Financial Interests and Arrangements of Clinical Investigators

The following is a list of Investigators who enrolled patients in the covered clinical study L1069T-25 as defined in 21 CFR 54.2 (e).

Protocol No.: L1069T-25

Protocol Title: "Phase 3 Evaluation of Targretin® Topical Gel in Patients with Refractory or Persistent Early Stage Cutaneous T-Cell Lymphoma"

Aeling, M.D., John
Aguilar, M.D., A. Robledo
Boh, M.D., Erin
Bran, M.D., E. Lopez
Breneman, M.D., Debra
Breneman, M.D., John
Bridges, D.O., Alina
Burg, M.D., Gunter
Caillouet, RN, MPH, Brenda
Charif, M.D., Maria
Cherry, R.N., Lisa
Chivhevsky, M.D., Vladislav
Chmielowska, Pd. D., Ewa
Christensen, RN, Inger R.
Clay-Cather, M.D., Jennifer
Clemens, PA-C, Anne E.
Cook, Linda
DeKoven, M.D., Joel G.
DiGiovanna, M.D., John J.
Douglass, M.D., Margaret
Dummer, M.D., Reinhard
Duncan, M.D., Karynne

el-Azhary, M. D., Rokea
Elmets, M.D., Craig
Fivenson, M.D., David
Friedman-Kien, M.D., Alvin
Fyock, RN, Carole J.
Gaspari, M.D., Anthony
Grivers-Cambra, RN, Joanna
Gupta-Burt, M.D., Shalina
Gutierrez, M.D., Elsa D.
Hannegan, M.D., Sandra
Heald, M.D., Peter
Heffernan, M.D., Michael P.
Hitchens, M.D., Lisa
Hofbauer, M.D., Gunther
Hohsfield, RN, Robin
Hymes, M.D., Kenneth
Iorio, M.D., Susan
Janakiraman, M.D., Nalini
Jochen, M.D., Timothy
Joly, Professor, Pascal
Juszkiewicz-Borowiec, Ph.D., Maria
Kashani-Sabet, M.D., Mohammed
Kleinhans, M.D., Martin
Korman, M.D., Neil
Krol, M.D., Alfons
Krueger, M.D., Gerald
Kukulska, M.D., Monika
Lamore, R.N., Connie
Lecewicz-Torun, Professor Barbara
Lee, M.D., Ha Rin
Lens, M.D., Raquel Novo
Lester, M.D., Robert S.
Lowe, M.D., Nicholas
Malecka, Ph.D., Elzbieta
Martin, M.D., Ann G.
McCormack, M.D., Chris
McDonald, M.D., Charles J.
McEvoy, M.D., Marian
Mehlmauer, M.D., Marilyn
Mehta, M.D., Jessica N.
Mendoza, MA, Margaret
Meyer, RN, Carol J.
Millikan, M.D., Larry E.
Millward, M.D., Michael
Muglia, M.D., Jennie J.
Nowlakha, M.D., Prem
Olsen, M.D., Elise
Pentland, M.D., Alice
Persaud, M.D., Andrea
Persky, RN, Martha S.
Phillips, M.D., Rhea
Pittelkow, M.D., Mark R.
Pluzanska, Professor, Anna
Prince, M.D., Miles
Rallis, M.D., Tena M.
Ramsey, M.D., David
Raphael, M.D., Bruce
Richard, M.D., Christine
Rizk, M.D., Dali
Robison, PA, Beverly
Rothstein, M.D., H.
Salopek, M.D., T.G.
Sauder, M.D., Daniel
Scoggins, RN, Kim
Shamban, M.D., Ava
Shear, M.D., Neil
Shroff-Mehta, M.D., Viraj
Shupack, M.D., Jerome
Sinha, M.D., Animesh A.
Smith, Jennifer
Stempczynska, Ph.D., Joanna
Talpur, M.D., Rakhshandra
Tharp, M.D., Michael D.
Tristani-Firouzi, M.D., Payam
Turner, M.D., Robert
Venugopal, M.D., Parameswaran
Vittorio, M.D., Carmella C.
Washenik, M.D., Kenneth
Whaley, M.D., Kevin
Wojnowska, M.D., Dorota
Wolf, M.D., Max
Wood, M.D., Gary
Young, M.D., Paul
Zackheim, M.D., Herschel
Zone, M.D., John

G. Aliprandi

Gian Aliprandi
Vice President & Senior Corporate Controller

Certification: Financial Interests and Arrangements of Clinical Investigators

No investigator included in this list received compensation that could be affected by the outcome of the study as defined in 21 CFR 54.2(a), had a proprietary interest in this product as defined in 21 CFR 54.2(c), or received significant payments of other sorts as defined in 21 CFR 54.2(f).

With respect to the certification regarding significant equity as defined in 21 CFR 54.2(b), please refer to Attachment A.

Gian Aliprandi
Vice President & Senior Corporate Controller

Certification: Financial Interests and Arrangements of Clinical Investigators
Significant Equity Interest Certification
Investigators Certification List

The following list of Investigators who enrolled patients in the covered clinical study L1069T-25 (as defined in 21 CFR 54.2 (e) have certified that neither they, nor their spouses nor dependent children, had an equity interest as defined in 21 CFR54.2(b) (i.e., stock ownership) in Ligand Pharmaceuticals, Inc. that exceeds $50,000 based on current market value.

Protocol No.: L1069T-25

Protocol Title: "Phase 3 Evaluation of Targretin® Topical Gel in Patients with Refractory or Persistent Early Stage Cutaneous T-Cell Lymphoma"

Aeling, M.D., John
Aguilar, M.D., A. Robledo
Boh, M.D., Erin
Bran, M.D., E. Lopez
Breneman, M.D., Debra
Breneman, M.D., John
Bridges, D.O., Alina
Burg, M.D., Gunter
Caillouet, RN, MPH, Brenda
Chmielowska, Pd. D., Ewa
Christensen, RN, Inger R.
Clay-Cather, M.D., Jennifer
Cook, Linda
DeKoven, M.D., Joel G.
DiGiovanna, M.D., John J.
Douglass, M.D., Margaret
Dummer, M.D., Reinhard
Duncan, M.D., Karynne

el-Azhary, M. D., Rokea
Elmets, M.D., Craig
Fivenson, M.D., David
Friedman-Kien, M.D., Alvin
Fyock, RN, Carole J.
Gaspari, M.D., Anthony
Grivers-Cambra, RN, Joanna
Gupta-Burt, M.D., Shalina
Gutierrez, M.D., Elsa D.
Hannegan, M.D., Sandra
Heald, M.D., Peter
Heffernan, M.D., Michael P.
Hitchens, M.D., Lisa

Hofbauer, M.D., Gunther
Hohsfield, RN, Robin
Hymes, M.D., Kenneth
Iorio, M.D., Susan
Janakiraman, M.D., Nalini
Jochen, M.D., Timothy
Juszkiewicz-Borowiec, Ph.D., Maria
Kashani-Sabet, M.D., Mohammed
Kleinhans, M.D., Martin
Korman, M.D., Neil
Krol, M.D., Alfons
Krueger, M.D., Gerald
Lamore, R.N., Connie
Lecewicz-Torun, Professor Barbara
Lens, M.D., Raquel Novo
Lester, M.D., Robert S.
Lowe, M.D., Nicholas
Malecka, Ph.D., Elzbieta
Martin, M.D., Ann G.
McCormack, M.D., Chris
McDonald, M.D., Charles J.
McEvoy, M.D., Marian
Mehlmaner, M.D., Marilyn
Mehta, M.D., Jessica N.
Mendoza, MA, Margaret
Meyer, RN, Carol J.
Millikan, M.D., Larry E.
Millward, M.D., Michael
Muglia, M.D., Jennie J.
Olsen, M.D., Elise
Pentland, M.D., Alice
Persaud, M.D., Andrea

Persky, RN, Martha S.
Phillips, M.D., Rhea
Pittelkow, M.D., Mark R.
Pluzanska, Professor, Anna
Prince, M.D., Miles
Rallis, M.D., Tena M.
Ramsey, M.D., David
Raphael, M.D., Bruce
Rizk, M.D., Dali
Robison, P.A. Beverly
Rothstein, M.D., H.
Salopek, M.D., T.G.
Sauder, M.D., Daniel
Scoggins, RN, Kim
Shamban, M.D., Ava
Shear, M.D., Neil
Shroff-Mehta, M.D., Viraj
Shupack, M.D., Jerome
Stempczynska, Ph.D., Joanna
Talpur, M.D., Rakhshandra
Tharp, M.D., Michael D.
Tristani-Firouzi, M.D., Payam
Turner, M.D., Robert
Venugopal, M.D., Parameswaran
Vittorio, M.D., Carmella C.
Washenik, M.D., Kenneth
Whaley, M.D., Kevin
Wojnowska, M.D., Dorota
Wolf, M.D., Max
Wood, M.D., Gary
Zackheim, M.D., Herschel
Zone, M.D., John

Gian Aliprandi
Vice President & Senior Corporate Controller

Certification: Financial Interests and Arrangements of Clinical Investigators
Significant Equity Interest Certification
Due Diligence: Information Not Obtained

The attached list of Investigators who enrolled patients in the covered clinical study L1069T-25 (as defined in 21 CFR 54.2(e)) could not be certified with regard to the lack of a significant equity interest as defined in 21 CFR 54.2(b). I certify that I have acted with due diligence to obtain from the listed clinical Investigators this information but it was not possible to do so. Due diligence efforts taken and the reasons why this information could not be obtained are provided below.

Protocol No.: L1069T-25

Protocol Title: "Phase 3 Evaluation of Targretin® Topical Gel in Patients with Refractory or Persistent Early Stage Cutaneous T-Cell Lymphoma"

Due diligence was shown by Ligand Pharmaceuticals Inc. by sending each Principal Investigator and Subinvestigator who entered patients in Protocol L1069T-25, an explanatory letter and Financial Disclosure Form. For North American sites where no response was received from an Investigator or Subinvestigator, or there was receipt of an incomplete response, or there was an indication of where an Investigator may have relocated, multiple follow-up attempts were made by both facsimile and telephone communications to obtain the disclosure information. For European Investigators, follow-up was carried out through a Contract Research Organization.

Listed are the Investigators and/or Subinvestigators who participated in Protocol L1069T-25 and from whom complete financial disclosure information was not obtained. The reasons for information not being obtained are shown in three categories: 1) No response by the Investigator or site to initial and follow-up inquiries; 2) Incomplete response where a reply was received but the information requested was only partially completed; and 3) No longer at Institution. A (P) preceding the name indicates "Principal Investigator", and an (S) a "Subinvestigator".

Gian Aliprandi
Vice President & Senior Corporate Controller

Investigator	Reason Information Not Obtained
1) No Response	
US Investigators	
(S) Nowlakha, M.D., Prem	No response
European Investigators	
(P) Joly, Professor, Pascal	No response
(S) Kukulska, M.D., Monika	No response
(S) Richard, M.D., Christine	No response
(S) Young, M.D., Paul	No response
2) Incomplete Response	
US Investigators	
(S) Charif, M.D., Maria	Incomplete response, follow-up not received
3) No longer at Institution	
US Investigators	
(S) Chivhevsky, M.D., Vladislav	No longer employed at site
(S) Cherry, R.N., Lisa	No longer employed at site
(S) Clemens, PA-C, Anne E.	No longer at institution
(S) Lee, M.D., Ha Rin	No longer employed at site
(S) Sinha, M.D., Animesh A.	Relocated to new institution, cannot locate
(S) Smith, Jennifer	Site unable to locate; terminated employment

Gian Aliprandi
Vice President & Senior Corporate Controller

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville MD 20857

CLINICAL INSPECTION SUMMARY

DATE: May 26, 2000

TO: Amy Chapman, Regulatory Project Manager
Robert White, Jr., M.D., Clinical Reviewer
Division of Oncology, HFD-150

THROUGH: Antoine El-Hage, Ph.D., Chief
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

FROM: Gerald R. Hajarian

SUBJECT: Evaluation of Clinical Inspections and Sponsor Inspection

NDA: NDA 21-056

APPLICANT: Ligand Pharmaceuticals, Inc.

DRUG: Targretin® (bexarotene) 1% Gel

CHEMICAL CLASSIFICATION: Type 1

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATION: Topical treatment of cutaneous lesions in patients with CTCL (Stage IA, IB and IIA) who have not tolerated other therapies or who have refractory or persistent disease.

CONSULTATION REQUEST DATE: February 1, 2000

ACTION GOAL DATE: June 9, 2000

I. BACKGROUND:

Inspection assignments were issued on March 17, 2000 for three clinical investigators for protocols L1069T-11, L1069T-12 and L1069T-25 for the purpose of validating data in support of pending NDA 21-056. Inspection results for Dr. Kuzel are based on Form FDA 483 Inspectional Observations and the establishment inspection report (EIR) without exhibits. Inspection results for Drs. Breneman and Heald are based on Forms FDA 483 only.

An inspection assignment was also issued for the sponsor, Ligand Pharmaceuticals, Inc. The results of this inspection are based on telephone and e-mail communications.

II. RESULTS (by site):

DATE	CITY	STATE	ASSIGNED DATE	RECEIVED DATE	CLASSIFICATION
Breneman	Cincinnati	OH	3-17-2000	Pending	VAI
Heald	New Haven	CT	3-17-2000	Pending	VAI
Kuzel	Chicago	IL	3-17-2000	5-25-00 (EIR only)	VAI

A. Debra Breneman, M.D.

Protocol L1069T-11

Thirty three subjects were screened. All were enrolled. Thirteen subjects discontinued: 2 – adverse events (vasculitis, generalized itching); 10 – progressive disease; 1 – non-study related adverse event. Records of 7 subjects were audited.

The following protocol violations were noted:

1. Subject #633 was admitted to the study although she was on tamoxifen for breast cancer. The protocol indicates that subjects may not use prohibited medications during the study including anti-cancer drugs.

2. Subject #624 was admitted to the study having a Prothrombin Time (PT) of 13.4. The protocol indicates that the PT is to be within normal range (9.2-11.4).

3. Subject #604 was admitted to the study having an elevated bilirubin of 2.25. The protocol indicates that the bilirubin is to be <1.5X ULN (upper limit of normal). The subject's bilirubin of 2.25 was more than 1.5 times the normal upper limit of 1.1 mg/dL.

4. Subject #622 was admitted to the study having a PT of 27.5. The protocol indicates that the PT is to be within normal range (9.2-11.4).

5. Subject #608 was admitted to the study having an elevated SGOT liver function. The protocol indicates that the SGOT is to be <or= to 2X ULN. The subject had a SGOT (also known as AST) of 66 (where 10-30 IU/L is the normal range) which is greater than 2x ULN of 30.

Also, drug accountability records were inadequate and signatures on several documents purported to be those of Dr. Breneman appeared to have been made by someone else. The inspection assignment requested that the FDA investigator audit sponsor monitoring of the studies. However, the FDA investigator was unable to determine whether the sponsor's monitor compared CRFs to source documents at the study site to verify the accuracy of the CRFs.

Protocol L1069T-25
One subject was enrolled. No deficiencies were noted.

B. Peter Heald, M.D.

Protocol L1069T-25
Five subjects were screened. All were enrolled. Two subjects discontinued: #693 withdrew consent, #694 – partial response. Records of all 5 subjects were audited.

The following deficiencies were noted:

1. Protocol L1069T-25 is a Phase 3 study in subjects with refractory or persistent early stage Cutaneous T-Cell Lymphoma (CTCL). The protocol required a maximum of 5 CTCL lesions to be designated as index lesions and the clinical signs and symptoms of the index lesions were to be graded at each visit. The 5 designated lesions were to be photographed at day 1 (baseline), every 4 weeks thereafter for the duration of treatment even if the lesion cleared, and again at follow-up.

Subject 694
Five index lesions were photographed and graded on day 1, and every 4 weeks through week 16. At week 28, 3 different index lesions were photographed and graded, and the original 5 lesions were no longer followed.

Subject 691
Five index lesions were photographed and graded on day 1, and every 4 weeks through week 24. At week 28, new lesions for index lesions #2 and #3 were selected for photographing and grading.

2. The protocol required that global photographs of each subject's CTCL disease be obtained on day 1, every 4 weeks during treatment, and again at follow-up. However, global photographs were not obtained for any of the subjects during the study.

3. Informed consent did not include (1) the expected duration of the subject's participation in the study; (2) a description of all procedures; and (3) a statement that refusal to participate would not involve a penalty or loss of benefits to which the subject would be entitled.

C. Timothy M. Kuzel, M.D.

Protocol L1069T-12

Fourteen subjects were screened and 13 were admitted to the study. All 13 subjects' records were audited. Eight subjects were discontinued (3 withdrew consent, 2 progressive disease, one had a negative biopsy, one was non-compliant and one because of an adverse event).

The following deficiencies were noted:

1. Protocol violations included:

a. For subject #601 - treatment with the study drug continued even though a Grade 2 toxicity (headache) was documented at week 10 of treatment. The protocol required that treatment be discontinued for at least one week following a Grade 2 or higher toxicity. There was no documentation that an unexpected adverse event (trigeminal neuralgia) was reported to the sponsor within 24 hours as required by the protocol. Subject #601 received prednisone, prohibited by the protocol, for an upper respiratory infection for approximately 9 days during the study.

b. For subject #604 - the dose of the study drug was incorrectly escalated from 0.5% to 1.0% twice a day. The required laboratory tests were not performed prior to dose escalation.

c. Photographs of Cutaneous T-Cell Lymphoma (CTCL) index lesions were not taken for subject #606 at week 16 and for subject #613 at week 8.

d. The following laboratory evaluations were not performed: for subject #601 - urinalysis at week 14; for subject #603 - pharmacokinetics at week 4; for subject#604 - hematology at week 2; for subject #608 - urinalysis at week 16; for subject #609 - chemistry at week 22; for subject #610 - pharmacokinetics at week 24 and for subject #613 - differential at week 8.

e. The final report of the study was not submitted to the sponsor within 90 days of the completion of the study, as required by the protocol. The last subject completed the study on 5/12/98, the IRB was notified 5/99, and the final report was dated 4/14/2000.

2. Prior CTCL systemic therapies were documented in the medical records for subjects #602, #606 and #608, but were not listed on the Previous CTCL Therapy Case Report Forms.

3. The biopsies of subjects #602, #603, #606, #608, #610 and #611, documenting a histological diagnosis of CTCL (an admission criterion), were performed prior to psoralen/UVA therapy for CTCL. The six subjects received psoralen/UVA therapy and were subsequently admitted to the study.

4. There were discrepancies in reporting adverse events to the IRB. For example, IND safety reports of cholestatic jaundice dated 10/15/97 and myocardial infarction dated 1/28/98 occurred during the study. Although both events were reported as serious, unexpected, and reasonably associated with the study drug, statements submitted to the IRB reported the events as expected, and listed on the consent form. However, the consent form did not list these as expected adverse events.

5. There was no documentation to account for the disposition of the study drug returned to the clinic by the subjects.

D. Ligand Pharmaceuticals, Inc.

This initial inspection of the sponsor revealed no deficiencies and no Form FDA 483 was issued. It was classified NAI.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Although there were deficiencies noted in the conduct of the studies by Drs. Breneman, Heald and Kuzel, which are outlined above, the data from all sites appear acceptable for use in support of pending NDA 21-056.

As noted above, this summary is based on a review and evaluation of Forms FDA 483 for Drs. Breneman and Heald, and Form FDA 483 and the EIR (no exhibits) for Dr. Kuzel. Should the EIRs for Drs. Breneman and Heald contain significant additional findings, you will so be notified.

Key to Classifications
NAI = No deviation from regulations. Data acceptable
VAI = Minor deviations(s) from regulations. Data acceptable
VAIr= Deviation(s) form regulations, response requested. Data acceptable
OAI = Significant deviations for regulations. Data unreliable
Pending = Inspection not completed

/S/

Gerald R. Hajarian
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

CONCURRENCE:

/S/

for Antoine El-Hage, Ph.D., Chief 05/26/11
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations