

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208794Orig1s000

PHARMACOLOGY REVIEW(S)

MEMORANDUM**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

FROM: David B. Joseph
Lead Pharmacologist

DATE: February 2, 2017

SUBJECT: NDA 208,794 (SD # 1 dated March 30, 2016)

Sponsor: Lexicon Pharmaceuticals, Inc.

Drug Product: XERMELO (telotristat ethyl) tablets, for oral use

Comments:

There are no nonclinical issues which preclude the approval of Xermelo. I concur with the recommendations related to approvability, stated in the Pharmacology/Toxicology review by Dr. Ke Zhang. The final revisions to nonclinical information in labeling subsections 8.1, 12.1, and 13.1 include minor changes from the recommended version in Dr. Zhang's review. The additional labeling revisions were developed through collaboration of the nonclinical team with other members of the review team.

The following paragraph appears on page 164 of Dr. Zhang's review:

"LX1606 (telotristat ethyl) is an inhibitor of L-tryptophan hydroxylase (TPH) which mediates serotonin synthesis in the mucosa of the gastrointestinal (GI) tract. LX1606 is rapidly converted in vivo to its active metabolite, LP778902 (telotristat). Both LX1606 and LP778902 inhibit TPH, thereby decreasing peripheral serotonin levels. However, the potency of telotristat exceeds that of telotristat ethyl by 29-fold and 38-fold for human TPH1 and TPH2, respectively. Furthermore, the systemic exposure to telotristat markedly exceeds that of the parent drug. Thus, the overall pharmacology and toxicology profile of telotristat ethyl should be attributed to the active metabolite, telotristat."

In both humans and animals, the plasma exposure (C_{max} and AUC) to telotristat, the active metabolite, markedly exceeds that of telotristat ethyl. The C_{max} for telotristat in the target patient population was 900 ng/mL (1645 nM), whereas the C_{max} for telotristat ethyl was only 7 ng/mL (12 nM), as stated in the labeling. These values were obtained with administration of 500 mg TID, however the approved dose is expected to be 250 mg TID. The extrapolated C_{max} (6 nM) for telotristat ethyl in humans at the recommended dose level of 250 mg TID is approximately 133 times lower than the IC_{50} determined from assays with purified recombinant human tryptophan hydroxylase, the

drug target. Thus, the final sentence in the above paragraph from Dr. Zhang's review, which attributes the overall pharmacology and toxicology profile to telotristat, is highly appropriate with respect to the systemically mediated effects.

The drug target (tryptophan hydroxylase) is an intracellular enzyme, with different isoforms expressed in enterochromaffin cells in the GI mucosa (TPH1) and in central and enteric neurons (TPH2) (Cote et al., Proc Natl Acad Sci USA 100:13525–30, 2003; Walther et al., Science 299:76, 2003). However, the critical site of action for the proposed indication, carcinoid syndrome diarrhea, is expected to be metastatic neuroendocrine tumors in the GI tract.

Although telotristat ethyl exhibited low potency when measured in assays with purified human tryptophan hydroxylase (see page 16 of Dr. Zhang's review), it is reasonable to expect that extremely high local concentrations of telotristat ethyl will be present immediately after ingestion of each dose. Based on an assumed volume of 250 mL water consumed with each dose of 250 mg, the initial local concentration in the GI tract is estimated to be 1740 μM , which markedly exceeds the reported IC_{50} values for purified human tryptophan hydroxylase type 1 ($\text{IC}_{50} = 0.8 \mu\text{M}$) and type 2 ($\text{IC}_{50} = 1.2 \mu\text{M}$). Therefore, it is possible that telotristat ethyl contributes to the pharmacological response (i.e. inhibition of serotonin production by metastatic neuroendocrine (carcinoid) tumors in the GI tract), prior to systemic absorption and conversion to its more potent metabolite, telotristat. However, since no information on the concentrations of telotristat ethyl and telotristat in the GI mucosa or in GI carcinoid tumors is available, it is impossible to evaluate the relative contributions of telotristat ethyl and telotristat to pharmacological activity in the GI tract. Telotristat alone appears to be the active mediator with respect to systemic circulation through the GI tract.

The recommended revisions in the Mechanism of Action subsection (12.1) of the labeling provide an accurate representation of the known difference in potency (in vitro) between the parent drug (telotristat ethyl) and its metabolite (telotristat), and the unknown relative contributions of the parent drug and metabolite to pharmacodynamic activity (in vivo).

David B. Joseph, PhD Lead Pharmacologist Division of Gastroenterology and Inborn Errors Products	Date
--	------

cc:
NDA 208,794
DGIEP
DGIEP/PM
DGIEP/D. Joseph
DGIEP/K. Zhang
OND IO/A. Jacobs

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/s/

DAVID B JOSEPH
02/02/2017

Comments on N208794 Xermelo

From: A. Jacobs 1/9/17

I concur that there are no outstanding pharm-tox issues for this NDA.

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/s/

ABIGAIL C JACOBS
01/09/2017

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 208,794
Supporting document/s: 1
Applicant's letter date: March 30, 2016
CDER stamp date: March 30, 2016
Product: Xermelo (telotristat ethyl) tablets, for oral use
Indication: Treatment of carcinoid syndrome diarrhea in patients with metastatic neuroendocrine tumors
Applicant: Lexicon Pharmaceuticals, Inc
The Woodlands, TX
Review Division: Gastroenterology and Inborn Errors Products
Reviewer: Ke Zhang, PhD
Supervisor/Team Leader: David B. Joseph, PhD
Division Director: Donna Griebel, MD
Project Manager: Brian K. Strongin

Template Version: September 1, 2010

Disclaimer

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1 Executive Summary

1.1 Introduction

Telotristat ethyl is an inhibitor of L-tryptophan hydroxylase which mediates serotonin synthesis in the mucosa of the gastrointestinal (GI) tract. Telotristat ethyl (LX1606) is rapidly converted in vivo to its active metabolite, telotristat (LP778902). The sponsor hypothesizes that by decreasing the peripheral serotonin level, LX1606 will be beneficial for patients with carcinoid syndrome, in which excessive production and release of serotonin from metastatic neuroendocrine tumors is a major contributing factor. The sponsor has developed telotristat ethyl for the treatment of diarrhea associated with carcinoid syndrome.

1.2 Brief Discussion of Nonclinical Findings

Telotristat ethyl hippurate was used in the nonclinical and clinical development programs, and will be used in the commercial product. Animal dose levels shown in this review indicate the dose of the hippurate salt.

The major finding in toxicology studies was degeneration/necrosis in the non-glandular and/or glandular regions of stomach and/or increased protein droplets in the glandular regions at doses of 200 mg/kg/day or higher in the 26-week oral toxicity study in rats. These changes were not seen in the 13-week and 39-week oral toxicity studies in dogs. Telotristat ethyl had no effects on embryo-fetal development in rats. Increased post-implantation loss was observed in a rabbit embryo-fetal development study, but this was associated with maternal toxicity. In a pre-/postnatal development study in rats, an increased incidence of pup mortality was observed during postnatal days 0-4 at 500 mg/kg/day (approximately 5 times the AUC for the active metabolite at the human dose). Neither the parent drug nor its active metabolite (telotristat) was genotoxic. Telotristat ethyl was not tumorigenic in the 26-week carcinogenicity study in Tg.rasH2 mice.

1.3 Recommendations

1.3.1 Approvability

From a nonclinical standpoint, there are no approvability issues.

1.3.2 Additional Nonclinical Recommendations

A 2-year carcinogenicity study in rats is in progress. The Agency agreed to allow this study to be submitted post-approval, given that the proposed indication is a serious condition with an unmet medical need (meeting with sponsor held on April 11, 2012). To assure that the final report is submitted within a reasonable time period, a Postmarketing Requirement should be conveyed to the sponsor.

1.3.3 Labeling

Established Pharmacologic Class (HIGHLIGHTS)

The EPC text phrase for telotristat ethyl in the Sponsor's proposed label is: "tryptophan hydroxylase inhibitor", which is consistent with its mechanism of action. The Sponsor provided data that demonstrates inhibition of tryptophan hydroxylase by the active metabolite, telotristat (LP778902). Thus, the proposed EPC text phrase is scientifically valid. In addition, the review team concurs that "tryptophan hydroxylase inhibitor" is a clinically meaningful term. Therefore, the proposed EPC text phrase for telotristat ethyl is acceptable.

Sponsor's Version:

8.1 Pregnancy

Risk Summary

(b) (4)

[Redacted text block]

(b) (4)

[Redacted text block]

Data

Animal data

(b) (4)

[Redacted text block]

(b) (4)

(b) (4)

(b) (4)

Evaluation: The following revised version was developed in collaboration with the Maternal Health team (Tamara Johnson and Christos Mastroyannis). The value of 5371 ng•hr/ml was used as the estimated $AUC_{0-24 \text{ hr}}$ for 250 mg TID in humans, for calculation of the animal/human exposure ratios as recommended by the clinical pharmacology reviewer, Dr. Insook Kim.

After the original submission of this NDA, the sponsor proposed (b) (4) "telotristat ethyl". This change is included in the recommended version below.

Recommended Version:

8.1. Pregnancy

Risk Summary

There are no human data with Xermelo use in pregnant women to inform a drug-associated risk. In animal reproduction studies, no effects on embryo-fetal development were observed with the administration of oral telotristat ethyl to rats during organogenesis at doses up to 750 mg/kg/day (approximately 9 times the exposure at the RHD [recommended human dose]). Treatment of pregnant rabbits with oral (b) (4)

(b) (4) In a pre-/postnatal development study, an increased incidence of mortality in rat offspring was observed during postnatal days 0-4 at the maternal oral dose of 500

mg/kg/day (approximately 5 times the exposure at the RHD), given during organogenesis through lactation [see *Data*].

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal data

An embryo-fetal development study performed in rats with oral telotristat ethyl at doses up to 750 mg/kg/day (approximately 9 times the AUC [area under the plasma concentration-time curve] for the active metabolite at the RHD) during organogenesis produced no harm to embryo-fetal development.

In pregnant rabbits treated orally with telotristat ethyl during organogenesis, an increased incidence of post-implantation loss at doses of 250 and 500 mg/kg/day (approximately 15 times the AUC for the active metabolite at the RHD) and a decrease in fetal weight at 500 mg/kg/day (approximately 33 times the AUC for the active metabolite at the RHD) was observed. The adverse effects on embryo-fetal development were associated with maternal toxicity (impaired weight gain and mortality) at 250 and 500 mg/kg/day. No adverse effects on embryo-fetal development were observed at 125 mg/kg/day (approximately 5 times the AUC for the active metabolite at the RHD).

A pre-/postnatal development study was conducted in rats using oral administration of 100, 200, and 500 mg/kg/day telotristat ethyl during organogenesis through lactation. An increased incidence of pup mortality was observed during postnatal days 0-4 at the maternal dose of 500 mg/kg/day (approximately 5 times the AUC for the active metabolite at the RHD). No developmental abnormalities or effects on growth, learning and memory, or reproductive performance were observed through maturation of offspring at maternal doses of up to 500 mg/kg/day in surviving offspring.

Sponsor's Version:

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

(b) (4)

The text "(b) (4)" is followed by four horizontal grey bars of varying lengths, indicating that the content of this section has been redacted.

(b) (4)

Evaluation: [REDACTED] (b) (4)

[REDACTED] This subsection should be revised as shown below.

After the original submission of this NDA, the sponsor proposed [REDACTED] (b) (4) [REDACTED] "telotristat ethyl". This change is included in the recommended version below.

Recommended Version:

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 26-week study in transgenic (Tg.rasH2) mice, telotristat ethyl was not tumorigenic at oral doses up to 300 mg/kg/day.

Telotristat ethyl was negative in the in vitro Ames test, the in vitro chromosomal aberration test using Chinese hamster ovary cells, and the *in vivo* rat micronucleus test.

Telotristat ethyl at oral doses up to 500 mg/kg/day (approximately 5 times the AUC for the active metabolite at the RHD) was found to have no effect on fertility and reproductive performance of male or female rats.

Sponsor's Version:

(b) (4)

Evaluation: This (b) (4) should be removed from the labeling.

2 Drug Information**2.1 Drug**

CAS Registry Number: 1137608-69-5

Generic Name: telotristat ethyl (telotristat ethyl hippurate is telotristat etiprate)

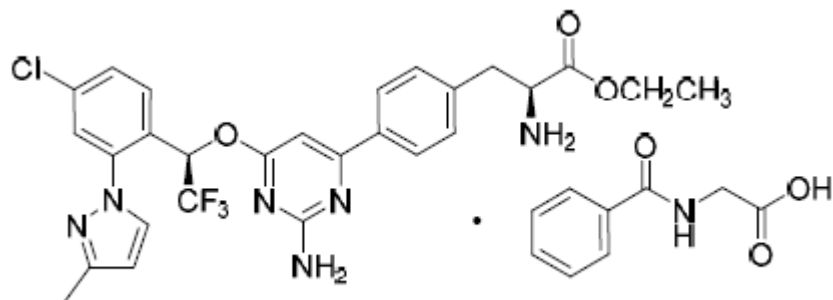
Code Name: LX1606 hippurate, LX1032 hippurate, LP-778914

LX1606 is telotristat ethyl (free base) / LP-778902 is telotristat (active metabolite)

Chemical Name: L-Phenylalanine, 4-[2-amino-6-[(1*R*)-1-[4-chloro-2-(3-methyl-1*H*-pyrazol-1-yl)phenyl]-2,2,2-trifluoroethoxy]-4-pyrimidinyl]-,ethyl ester, compound with *N*-benzoylglycine (1:1)

Molecular Formula/Molecular Weight: C₂₇H₂₆ClF₃N₆O₃ • C₉H₉NO₃ / 754.2

Structure or Biochemical Description:



Pharmacologic Class: tryptophan hydroxylase (TPH) inhibitor

2.2 Relevant INDs, NDAs, and DMFs: IND 78,749

2.3 Drug Formulation

Table 2.3.P-1 Composition of Telotristat Etiprate Coated Tablets, 250mg (as Free Base)

Component	Function	Reference to Standard	Amount per Tablet	Amount per Core Tablet	Amount per Coated Tablet
(b) (4)			mg	%	%
Telotristat etiprate ^a	Active Ingredient	In-house Standard	327.9 ^{a, b}	(b) (4)	54.31
(b) (4)					
Lactose Anhydrous	(b) (4)	NF, Ph. Eur., JP	(b) (4)	(b) (4)	(b) (4)
Hydroxypropyl Cellulose		NF, Ph. Eur., JP			
Croscarmellose Sodium		NF, Ph. Eur., JP			
Magnesium Stearate ^c		NF, Ph. Eur.			
(b) (4)					
Colloidal Silicon Dioxide	(b) (4)	NF, Ph. Eur., JP	(b) (4)	(b) (4)	(b) (4)
		NF, Ph. Eur., JP			
		NF, Ph. Eur., JP			
		NF, Ph. Eur.			
(b) (4)	--				
Coated Tablet					
Coating Components		(b) (4)			
(b) (4)					
Coated Tablet Total	--		603.7		100.0
(b) (4)					

^a 327.9 mg of telotristat etiprate is equivalent to 250.0 mg of free base (327.9 mg is rounded to 328 mg for labeling purposes).

(b) (4)

2.4 Comments on Novel Excipients:

The formulation contains no novel excipients. There is no safety concern for the daily dose of individual excipients at the human dose recommended for approval by the medical team (250 mg TID free base equivalent, or 3 tablets per day), since the daily intake will not exceed that from other FDA-approved drug products for oral administration.

2.5 Comments on Impurities/Degradants of Concern:

The drug product specifications are shown in the sponsor's table below.

Table 3.2.P.5.1-1 Specifications for Telotristat Etiprate Coated Tablets, 250 mg (as free base)

Test	Method	Acceptance Criteria at Release	Acceptance Criteria on Stability (Shelf Life)
Product Appearance (Visual)	QM0028	White to off-white coated oval tablet with "T-E" debossed on one side and "250" debossed on the other side.	White to off-white coated oval tablet with "T-E" debossed on one side and "250" debossed on the other side.
Identification I (HPLC Retention Time)	QM4976	The ratio of the retention time of the major peak in the sample is within (b) (4) of the standard retention time.	Not tested on stability
Identification II (HPLC Diode Array UV)	QM4977	The UV spectrum of the major peak in the sample is consistent with the standard spectrum.	Not tested on stability
Assay (HPLC)	QM4976	(b) (4) % of Label Claim	(b) (4) % of Label Claim
Degradation Products (HPLC)	QM4976	Specified: Report Results $\geq$ (b) (4) % (b) (4) NMT (b) (4) % (b) (4) NMT % (b) (4) NMT % (b) (4) NMT %	Specified: Report results $\geq$ (b) (4) % (b) (4) NMT (b) (4) % (b) (4) NMT % (b) (4) NMT % (b) (4) NMT %
		Unspecified: Report Results $\geq$ (b) (4) % Any Other Degradants: NMT (b) (4) %	Unspecified: Report results $\geq$ (b) (4) % Any Other Degradants: NMT (b) (4) %
Total Degradation Products (HPLC)	QM4976	NMT (b) (4) % (b) (4)	NMT (b) (4) % (b) (4)
Uniformity of Dosage Units	USP <905> and Ph. Eur. 2.9.40	Meets USP and Ph. Eur. requirements for Content Uniformity by Weight Variation	Not tested on stability
Dissolution	QM3830	$Q = \frac{(b) (4)}{(4)}\%$ released at (b) (4) minutes	$Q = \frac{(b) (4)}{(4)}\%$ released at (b) (4) minutes
(b) (4)			

Table 3.2.P.5.1–1 Specifications for Telotristat Etiprate Coated Tablets, 250 mg (as free base) (Continued)

Test	Method	Acceptance Criteria at Release	Acceptance Criteria on Stability (Shelf Life)
Total Aerobic Microbial Count (TAMC) ^a	QM4443 (Harmonized USP<61>, Ph.Eur. 2.6.12 and JP 4.05)	NMT (b) (4) cfu/g	NMT (b) (4) cfu/g
Total Yeast and Molds Count (TYMC) ^a	QM4443 (Harmonized USP<61>, Ph.Eur. 2.6.12 and JP 4.05)	NMT (b) (4) cfu/g	NMT (b) (4) cfu/g
Tests for Specified Microorganisms – <i>E coli</i> ^a	QM4443 (Harmonized USP <62>, Ph.Eur. 2.6.13 and JP 4.05)	Absent in 1 g	Absent in 1 g

NMT = Not more than; cfu = colony forming units

^aThis test is performed only at release and at yearly intervals, as specified in [Section 3.2.P.8.2](#).

(b) (4) (limit of $\leq$ (b) (4) %) is a (b) (4) and is therefore considered as qualified.

2.6 Proposed Clinical Population and Dosing Regimen

Xermelo is indicated for the (b) (4) treatment of carcinoid syndrome in patients with metastatic neuroendocrine tumors who are receiving somatostatin analogue therapy. The recommended starting dose is 250 mg three times daily (b) (4)

2.7 Regulatory Background

Xermelo (telotristat ethyl) was developed under IND 78,749 for the treatment of GI symptoms associated with carcinoid syndrome in patients that no longer respond to standard care with somatostatin analogues. This development program was designated as a Fast Track development program on May 19, 2008. LX1606 was designated as an orphan drug on March 9, 2012. A pre-NDA meeting was held February 24, 2015. All needed study reports are submitted to this NDA.

3 Studies Submitted

Pharmacology

Safety Pharmacology

Pharmacokinetics

Toxicology

Mice

28-Day oral toxicity study in CByB6F1 Mice

Rats

Single dose oral toxicity study in rats

5-Day oral toxicity studies in rats

2-Week oral toxicity study in rats

4-Week oral toxicity study in rats

13-Week oral toxicity study in rats

6-Month oral toxicity study in rats

Dogs

Single dose oral toxicity study in dogs

7-Day oral toxicity studies in dogs

4-Week oral toxicity study in dogs

13-Week oral toxicity study in dogs

9-Month oral toxicity study in dogs

Genotoxicity

Ames test

In vitro chromosomal aberration test in Chinese Hamster Ovary (CHO) cells

In vivo micronucleus test in rats

Ames tests with impurity (b) (4) (two Ames tests)

Carcinogenicity

26-Week Repeated Dose Oral Carcinogenicity Study in Tg.rasH2 Mice

Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development study with LP-778914 in Rats

Effects on Embryo-fetal Development of LP-778914 in Rats

Effects on Embryo-fetal Development of LP-778914 in Rabbits

Pre- and Postnatal Development study with LX1606 in Rats

3.1 Studies Reviewed

Pharmacology

Safety Pharmacology

Pharmacokinetics

Toxicology

Mice

28-Day oral toxicity study in CByB6F1 Mice

Rats

Single dose oral toxicity study in rats

5-Day oral toxicity studies in rats

2-Week oral toxicity study in rats

4-Week oral toxicity study in rats

13-Week oral toxicity study in rats

6-Month oral toxicity study in rats

Dogs

Single dose oral toxicity study in dogs

7-Day oral toxicity studies in dogs

4-Week oral toxicity study in dogs

13-Week oral toxicity study in dogs

9-Month oral toxicity study in dogs

Genotoxicity

Ames test

In vitro chromosomal aberration test in Chinese Hamster Ovary (CHO) cells

In vivo micronucleus test in rats

Ames tests with impurity (b) (4) (two Ames tests)

Carcinogenicity

26-Week Repeated Dose Oral Carcinogenicity Study in Tg.rasH2 Mice

Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development study with LP-778914 in Rats

Effects on Embryo-fetal Development of LP-778914 in Rats

Effects on Embryo-fetal Development of LP-778914 in Rabbits

Pre- and Postnatal Development study with LX1606 in Rats

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

Pharmacology/Toxicology reviews of IND 78,749 dated January 3, 2014, April 23, 2015, and May 21, 2015 were referenced in the current review.

4 Pharmacology

LX1606 is an inhibitor of L-tryptophan hydroxylase (TPH) which mediates serotonin synthesis in the mucosa of the gastrointestinal (GI) tract. LX1606 is rapidly converted in vivo to its active metabolite, LP778902. Both LX1606 and LP778902 inhibited TPH,

thereby decreasing the peripheral serotonin levels. Carcinoid tumors are mostly derived from enterochromaffin cells of the midgut, and often produce and release large amounts of 5-HT. By reducing the serotonin level, LX1606 would be beneficial for patients with carcinoid syndrome, which is caused by excessive production and release of serotonin from metastatic neuroendocrine tumors.

4.1 Primary Pharmacology

In Vitro Studies

Both telotristat ethyl and its active metabolite, LP-778902, inhibited purified human L-tryptophan hydroxylase (TPH1 and TPH2). The active metabolite, LP-778902, was a more potent inhibitor of purified human TPH1 and TPH2 compared to telotristat ethyl. The minor metabolite LP-951757 showed no inhibitory activity against TPH1. The results were summarized in the sponsor's table below.

Table 2.6.2-1 Summary of *in vitro* Inhibitory Activities of Telotristat Ethyl, LP-778902 and LP-951757

Target	IC ₅₀ (nM)		
	LP-778902	LX1606	LP-951757
Human Tryptophan Hydroxylase Type 1 (TPH1)	28 ± 3 (7)	800 ± 90 (4)	> 10,000 (2)
Human Tryptophan Hydroxylase Type 2 (TPH2)	32 ± 4 (2)	1210 ± 20 (2)	ND
RBL-2H3 (rat leukemia cell line)	6 ± 1 (7)	11 ± 4 (4)	ND
BON (human carcinoid cell line)	180 ± 40 (5)	100 ± 20 (3)	ND
Human Phenylalanine Hydroxylase (PAH)	> 10,000 (2)	> 10,000 (2)	ND
Human Tyrosine Hydroxylase (TH)	> 10,000 (2)	> 10,000 (2)	ND
ND = not determined			
Data expressed as Mean ± SEM (N)			
Data for LX1606 and LP-778902 from P103-002, Table 1 ; Data for LP-951757 from 160629			

In Vivo Studies

Oral administration of telotristat ethyl for 5 days significantly reduced 5-HT levels in the intestine in rats, with an ED₅₀ (daily dose causing 50% depletion of 5-HT) of approximately 50 and 100 mg/kg/day for jejunum and proximal colon, respectively (study # P103-002).

Reduction of 5-HT levels in the intestine was also seen following oral administration of telotristat ethyl in mice and dogs.

Telotristat ethyl also delayed GI transit and gastric emptying following two oral doses in rats (P103-002).

Telotristat ethyl had no effects on brain 5-HT levels at doses up to 300 mg/kg/day, 500 mg/kg/day, and 100 mg/kg/day in mice, rats, and dogs respectively.

4.2 Secondary Pharmacology

The binding of telotristat ethyl and the active metabolite LP-778902 to a variety of receptors, enzymes, and ion channels was assessed in vitro at a concentration of 10 μ M. Telotristat ethyl (LP-778914) showed binding activity at a number of these targets. The results are summarized in the sponsor's table below.

Assay (b)(4)	Compound I.D.	Client Compound I.D.	Test Concentration (M)	% Inhibition of Control Specific Binding
A ₁ (h)	939039-2	LP-778914-02-002	1.0E-05	61
A _{2A} (h)	939039-2	LP-778914-02-002	1.0E-05	-3
A ₃ (h)	939039-2	LP-778914-02-002	1.0E-05	99
α_1 (non-selective)	939039-2	LP-778914-02-002	1.0E-05	15
α_2 (non-selective)	939039-2	LP-778914-02-002	1.0E-05	11
β_1 (h)	939039-2	LP-778914-02-002	1.0E-05	41
β_2 (h)	939039-2	LP-778914-02-002	1.0E-05	8
AT ₁ (h)	939039-2	LP-778914-02-002	1.0E-05	81
AT ₂ (h)	939039-2	LP-778914-02-002	1.0E-05	27
BZD (central)	939039-2	LP-778914-02-002	1.0E-05	4
BZD (peripheral)	939039-2	LP-778914-02-002	1.0E-05	21
BB (non-selective)	939039-2	LP-778914-02-002	1.0E-05	-24
B ₂ (h)	939039-2	LP-778914-02-002	1.0E-05	28
CGRP (h)	939039-2	LP-778914-02-002	1.0E-05	-14
CB ₁ (h)	939039-2	LP-778914-02-002	1.0E-05	57
CCK _A (h) (CCK ₁)	939039-2	LP-778914-02-002	1.0E-05	94

Assay (b) (4)	Compound I.D.	Client Compound I.D.	Test Concentration (M)	% Inhibition of Control Specific Binding
CCK _B (<i>h</i>) (CCK ₂)				
939039-2		LP-778914-02-002	1.0E-05	-10
D ₁ (<i>h</i>)				
939039-2		LP-778914-02-002	1.0E-05	92
D _{2S} (<i>h</i>)				
939039-2		LP-778914-02-002	1.0E-05	84
D ₃ (<i>h</i>)				
939039-2		LP-778914-02-002	1.0E-05	72
D _{4.4} (<i>h</i>)				
939039-2		LP-778914-02-002	1.0E-05	4
D ₅ (<i>h</i>)				
939039-2		LP-778914-02-002	1.0E-05	69
ET _A (<i>h</i>)				
939039-2		LP-778914-02-002	1.0E-05	-10
ET _B (<i>h</i>)				
939039-2		LP-778914-02-002	1.0E-05	33
GABA (non-selective)				
939039-2		LP-778914-02-002	1.0E-05	-21
GAL1 (<i>h</i>)				
939039-2		LP-778914-02-002	1.0E-05	-4
GAL2 (<i>h</i>)				
939039-2		LP-778914-02-002	1.0E-05	0
PDGF				
939039-2		LP-778914-02-002	1.0E-05	12
CXCR2 (<i>h</i>) (IL-8B)				
939039-2		LP-778914-02-002	1.0E-05	52
TNF- α (<i>h</i>)				
939039-2		LP-778914-02-002	1.0E-05	8
CCR1 (<i>h</i>)				
939039-2		LP-778914-02-002	1.0E-05	2
H ₁ (<i>h</i>)				
939039-2		LP-778914-02-002	1.0E-05	16
H ₂ (<i>h</i>)				
939039-2		LP-778914-02-002	1.0E-05	61
MC ₄ (<i>h</i>)				
939039-2		LP-778914-02-002	1.0E-05	28
MT ₁ (<i>h</i>)				
939039-2		LP-778914-02-002	1.0E-05	52

Assay (b) (4)	Compound I.D.	Client Compound I.D.	Test Concentration (M)	% Inhibition of Control Specific Binding
M ₁ (h)	939039-2	LP-778914-02-002	1.0E-05	78
M ₂ (h)	939039-2	LP-778914-02-002	1.0E-05	32
M ₃ (h)	939039-2	LP-778914-02-002	1.0E-05	100
M ₄ (h)	939039-2	LP-778914-02-002	1.0E-05	54
M ₅ (h)	939039-2	LP-778914-02-002	1.0E-05	79
NK ₁ (h)	939039-2	LP-778914-02-002	1.0E-05	21
NK ₂ (h)	939039-2	LP-778914-02-002	1.0E-05	57
NK ₃ (h)	939039-2	LP-778914-02-002	1.0E-05	35
Y ₁ (h)	939039-2	LP-778914-02-002	1.0E-05	35
Y ₂ (h)	939039-2	LP-778914-02-002	1.0E-05	48
NT ₁ (h) (NTS1)	939039-2	LP-778914-02-002	1.0E-05	-83
δ ₂ (h) (DOP)	939039-2	LP-778914-02-002	1.0E-05	77
κ (KOP)	939039-2	LP-778914-02-002	1.0E-05	16
μ (h) (MOP) (agonist site)	939039-2	LP-778914-02-002	1.0E-05	57
ORL1 (h) (NOP)	939039-2	LP-778914-02-002	1.0E-05	43
PACAP (PAC ₁) (h)	939039-2	LP-778914-02-002	1.0E-05	-52
PCP	939039-2	LP-778914-02-002	1.0E-05	-8
TXA ₂ /PGH ₂ (h) (TP)	939039-2	LP-778914-02-002	1.0E-05	17
P2X	939039-2	LP-778914-02-002	1.0E-05	-7

Assay (b) (4)	Compound I.D.	Client Compound I.D.	Test Concentration (M)	% Inhibition of Control Specific Binding
P2Y				
939039-2		LP-778914-02-002	1.0E-05	7
5-HT _{1A} (h)				
939039-2		LP-778914-02-002	1.0E-05	37
5-HT _{1B}				
939039-2		LP-778914-02-002	1.0E-05	88
5-HT _{2A} (h)				
939039-2		LP-778914-02-002	1.0E-05	78
5-HT _{2C} (h)				
939039-2		LP-778914-02-002	1.0E-05	41
5-HT ₃ (h)				
939039-2		LP-778914-02-002	1.0E-05	43
5-HT _{5A} (h)				
939039-2		LP-778914-02-002	1.0E-05	93
5-HT ₆ (h)				
939039-2		LP-778914-02-002	1.0E-05	21
5-HT ₇ (h)				
939039-2		LP-778914-02-002	1.0E-05	21
σ (non-selective)				
939039-2		LP-778914-02-002	1.0E-05	55
sst (non-selective)				
939039-2		LP-778914-02-002	1.0E-05	21
VIP ₁ (h) (VPAC ₁)				
939039-2		LP-778914-02-002	1.0E-05	-13
V _{1a} (h)				
939039-2		LP-778914-02-002	1.0E-05	25
Ca ²⁺ channel (L, verapamil site) (phenylalkylamines)				
939039-2		LP-778914-02-002	1.0E-05	62
K ⁺ _v channel				
939039-2		LP-778914-02-002	1.0E-05	7
SK ⁺ _{Ca} channel				
939039-2		LP-778914-02-002	1.0E-05	4
Na ⁺ channel (site 2)				
939039-2		LP-778914-02-002	1.0E-05	93
Cl ⁻ channel				
939039-2		LP-778914-02-002	1.0E-05	49
NE transporter (h)				
939039-2		LP-778914-02-002	1.0E-05	90

Assay	Compound I.D.	Client Compound I.D.	Test Concentration (M)	% Inhibition of Control Specific Binding
Cerep				
DA transporter (h)				
939039-2		LP-778914-02-002	1.0E-05	101
5-HT transporter (h)				
939039-2		LP-778914-02-002	1.0E-05	73

LP-778902 had limited binding affinity for most of these targets. However, it showed significant binding to A₃, 5-HT_{1B}, and 5-HT_{2A} receptors (i.e. >50% inhibition of radioligand binding). The results are shown in the sponsor's table below.

Assay (b) (4)	Compound I.D.	Client Compound I.D.	Test Concentration (M)	% Inhibition of Control Specific Binding
A ₁ (h)	939038-1	LP-778902-01-001	1.0E-05	12
A _{2A} (h)	939038-1	LP-778902-01-001	1.0E-05	-10
A ₃ (h)	939038-1	LP-778902-01-001	1.0E-05	80
α ₁ (non-selective)	939038-1	LP-778902-01-001	1.0E-05	38
α ₂ (non-selective)	939038-1	LP-778902-01-001	1.0E-05	34
β ₁ (h)	939038-1	LP-778902-01-001	1.0E-05	16
β ₂ (h)	939038-1	LP-778902-01-001	1.0E-05	-5
AT ₁ (h)	939038-1	LP-778902-01-001	1.0E-05	7
AT ₂ (h)	939038-1	LP-778902-01-001	1.0E-05	-7
BZD (central)	939038-1	LP-778902-01-001	1.0E-05	4
BZD (peripheral)	939038-1	LP-778902-01-001	1.0E-05	8
BB (non-selective)	939038-1	LP-778902-01-001	1.0E-05	12
B ₂ (h)	939038-1	LP-778902-01-001	1.0E-05	6
CGRP (h)	939038-1	LP-778902-01-001	1.0E-05	-3
CB ₁ (h)	939038-1	LP-778902-01-001	1.0E-05	9
CCK _A (h) (CCK ₁)	939038-1	LP-778902-01-001	1.0E-05	-21

Assay (b) (4)	Compound I.D.	Client Compound I.D.	Test Concentration (M)	% Inhibition of Control Specific Binding
CCK _B (<i>h</i>) (CCK ₂)				
939038-1		LP-778902-01-001	1.0E-05	2
D ₁ (<i>h</i>)				
939038-1		LP-778902-01-001	1.0E-05	8
D _{2S} (<i>h</i>)				
939038-1		LP-778902-01-001	1.0E-05	-6
D ₃ (<i>h</i>)				
939038-1		LP-778902-01-001	1.0E-05	-10
D _{4.4} (<i>h</i>)				
939038-1		LP-778902-01-001	1.0E-05	11
D ₅ (<i>h</i>)				
939038-1		LP-778902-01-001	1.0E-05	-2
ET _A (<i>h</i>)				
939038-1		LP-778902-01-001	1.0E-05	18
ET _B (<i>h</i>)				
939038-1		LP-778902-01-001	1.0E-05	8
GABA (non-selective)				
939038-1		LP-778902-01-001	1.0E-05	14
GAL1 (<i>h</i>)				
939038-1		LP-778902-01-001	1.0E-05	-6
GAL2 (<i>h</i>)				
939038-1		LP-778902-01-001	1.0E-05	9
PDGF				
939038-1		LP-778902-01-001	1.0E-05	-5
CXCR2 (<i>h</i>) (IL-8B)				
939038-1		LP-778902-01-001	1.0E-05	-14
TNF- α (<i>h</i>)				
939038-1		LP-778902-01-001	1.0E-05	-3
CCR1 (<i>h</i>)				
939038-1		LP-778902-01-001	1.0E-05	6
H ₁ (<i>h</i>)				
939038-1		LP-778902-01-001	1.0E-05	11
H ₂ (<i>h</i>)				
939038-1		LP-778902-01-001	1.0E-05	-1
MC ₄ (<i>h</i>)				
939038-1		LP-778902-01-001	1.0E-05	17
MT ₁ (<i>h</i>)				
939038-1		LP-778902-01-001	1.0E-05	6

Assay (b) (4)	Compound I.D.	Client Compound I.D.	Test Concentration (M)	% Inhibition of Control Specific Binding
M ₁ (h)	939038-1	LP-778902-01-001	1.0E-05	43
M ₂ (h)	939038-1	LP-778902-01-001	1.0E-05	16
M ₃ (h)	939038-1	LP-778902-01-001	1.0E-05	4
M ₄ (h)	939038-1	LP-778902-01-001	1.0E-05	29
M ₅ (h)	939038-1	LP-778902-01-001	1.0E-05	-6
NK ₁ (h)	939038-1	LP-778902-01-001	1.0E-05	1
NK ₂ (h)	939038-1	LP-778902-01-001	1.0E-05	12
NK ₃ (h)	939038-1	LP-778902-01-001	1.0E-05	0
Y ₁ (h)	939038-1	LP-778902-01-001	1.0E-05	31
Y ₂ (h)	939038-1	LP-778902-01-001	1.0E-05	7
NT ₁ (h) (NTS1)	939038-1	LP-778902-01-001	1.0E-05	-66
δ ₂ (h) (DOP)	939038-1	LP-778902-01-001	1.0E-05	5
κ (KOP)	939038-1	LP-778902-01-001	1.0E-05	-31
μ (h) (MOP) (agonist site)	939038-1	LP-778902-01-001	1.0E-05	10
ORL1 (h) (NOP)	939038-1	LP-778902-01-001	1.0E-05	-16
PACAP (PAC ₁) (h)	939038-1	LP-778902-01-001	1.0E-05	-40
PCP	939038-1	LP-778902-01-001	1.0E-05	3
TXA ₂ /PGH ₂ (h) (TP)	939038-1	LP-778902-01-001	1.0E-05	-3
P2X	939038-1	LP-778902-01-001	1.0E-05	-3

Assay (b) (4)	Compound I.D.	Client Compound I.D.	Test Concentration (M)	% Inhibition of Control Specific Binding
P2Y				
939038-1		LP-778902-01-001	1.0E-05	7
5-HT _{1A} (h)				
939038-1		LP-778902-01-001	1.0E-05	4
5-HT _{1B}				
939038-1		LP-778902-01-001	1.0E-05	90
5-HT _{2A} (h)				
939038-1		LP-778902-01-001	1.0E-05	75
5-HT _{2C} (h)				
939038-1		LP-778902-01-001	1.0E-05	16
5-HT ₃ (h)				
939038-1		LP-778902-01-001	1.0E-05	21
5-HT _{5A} (h)				
939038-1		LP-778902-01-001	1.0E-05	5
5-HT ₆ (h)				
939038-1		LP-778902-01-001	1.0E-05	0
5-HT ₇ (h)				
939038-1		LP-778902-01-001	1.0E-05	-9
σ (non-selective)				
939038-1		LP-778902-01-001	1.0E-05	21
sst (non-selective)				
939038-1		LP-778902-01-001	1.0E-05	8
VIP ₁ (h) (VPAC ₁)				
939038-1		LP-778902-01-001	1.0E-05	-2
V _{1a} (h)				
939038-1		LP-778902-01-001	1.0E-05	23
Ca ²⁺ channel (L, verapamil site) (phenylalkylamines)				
939038-1		LP-778902-01-001	1.0E-05	13
K ⁺ _v channel				
939038-1		LP-778902-01-001	1.0E-05	5
SK ⁺ _{Ca} channel				
939038-1		LP-778902-01-001	1.0E-05	0
Na ⁺ channel (site 2)				
939038-1		LP-778902-01-001	1.0E-05	2
Cl ⁻ channel				
939038-1		LP-778902-01-001	1.0E-05	31
NE transporter (h)				
939038-1		LP-778902-01-001	1.0E-05	43

Assay (b) (4)	Compound I.D.	Client Compound I.D.	Test Concentration (M)	% Inhibition of Control Specific Binding
DA transporter (<i>h</i>)	939038-1	LP-778902-01-001	1.0E-05	48
5-HT transporter (<i>h</i>)	939038-1	LP-778902-01-001	1.0E-05	27

4.3 Safety Pharmacology

Neurological Effects: A single oral dose of telotristat ethyl at 0 (control), 100, 500, or 2000 mg/kg induced liquid or nonformed stools, and slightly decreased open field locomotor activity in rats (study # 7648-205).

Respiratory System: A single oral dose of telotristat ethyl at 0 (control), 100, 500, or 2000 mg/kg had no clear treatment-related effects in rats (study # 7648-204).

Cardiovascular Effects: A single oral dose of telotristat ethyl at 0 (control), 30, 100 and 200 mg/kg had no clear treatment-related effects on blood pressure, heart rate, or ECGs in conscious telemeterized dogs (study # 2572/016).

Telotristat ethyl inhibited hERG current with an IC_{50} of 0.3 μ M (~172 ng/ml), and its active metabolite, LP-778902, had an IC_{50} > 10 μ M in the hERG assay (study # 7648-208).

Renal System: A single oral dose of telotristat ethyl at 0 (control), 100, 500, or 2000 mg/kg was tested in rats. Treatment significantly decreased urine output, and increased K^+ excretion during the first 6 hours after dosing at 2000 mg/kg (study # 2572/013). The Na^+ , K^+ , and Cl^- excretion during 6-24 hours after dosing was significantly decreased.

Gastrointestinal (GI) System: A single oral dose of telotristat ethyl at 0 (control), 100, 500, or 2000 mg/kg was tested in rats. Telotristat ethyl significantly decreased GI transit and stomach emptying time at doses of 500 and 2000 mg/kg (study # 2572/012).

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Absorption:

The parent drug, telotristat ethyl, was rapidly converted to the active metabolite, LP-778902, following oral administration in animals. The pharmacokinetic properties of LP-778902 are presented in the following tables (taken from study reports).

Table 2.6.5.3–1 Pharmacokinetics of LP-778902 After a Single Dose of LP-778902 or Telotristat Ethyl in Mice

Species	Mouse	Mouse	Mouse
Number of animals	4	4	4
Gender	M	M	M
Feeding condition	NA	NA	NA
Compound administered	LP-778902	LP-778902	Telotristat ethyl
Method of administration	Intravenous	Intravenous	Oral gavage
Dose (mg/kg)	1	1	50
Samples	Plasma	Plasma	Plasma
Assay	LC-MS/MS	LC-MS/MS	LC-MS/MS
Pharmacokinetic Parameters of LP-778902			
T _{max} (hr)	NA	NA	0.4 ± 0.1
Est C ₀ (µg/mL)	3.31 ± 0.6	4.48 ± 0.5	NA
C _{max} (µg/mL)	NA	NA	6.1 ± 0.9
Bioavailability (%)	NA	NA	11.6 ± 3.9
AUC _{0-t} (hr*µg/mL)	2.10 ± 0.3 ¹	2.75 ± 0.4 ²	12.3 ± 4.2 ²
AUC _{0-inf} (hr*µg/mL)	2.14 ± 0.3	2.75 ± 0.4	12.4 ± 4.2
T _{1/2} (hr)	1.25 ± 0.2	2.83 ± 0.1	3.1 ± 0.3
V _{ss} (L/kg)	0.5 ± 0.1	0.5 ± 0.05	NA
CL (L/hr/kg)	0.47 ± 0.06	0.37 ± 0.05	NA
Study number	160603	103301	160607
Location in CTD	4.2.2.2	4.2.2.2	4.2.2.2
Source: 160603, 103301, 160607 1 – AUC _{0-6hr} 2 – AUC _{0-24hr} M = male LC-MS/MS = liquid chromatography-tandem mass spectrometry NA = not applicable Where appropriate, data expressed as mean ± standard deviation <u>Brief Results:</u> No significant differences were observed between the 2 studies analyzing the pharmacokinetic parameters of LP-778902 following a bolus intravenous injection of LP-778902 at 1 mg/kg in mice. Low oral bioavailability was observed in the mouse following administration of 50 mg/kg dose of telotristat ethyl.			

Oral bioavailability of LP-778902 was approximately 12% in mice following a single oral dose of telotristat ethyl at 50 mg/kg.

Table 2.6.5.3-2 Pharmacokinetics of Telotristat Ethyl and LP-778902 After a Single Dose of Telotristat Etiprate in Male and Female Rats

Species	Rat	Rat	Rat	Rat	Rat	Rat	Rat	Rat
Number of animals	6	6	6	6	6	6	6	6
Gender	M	F	M	F	M	F	M	F
Feeding condition	Fed	Fed	Fed	Fed	Fed	Fed	Fed	Fed
Method of administration	Oral gavage	Oral gavage	Oral gavage	Oral gavage	Oral gavage	Oral gavage	Oral gavage	Oral gavage
Dose (mg/kg)	100	100	500	500	1000	1000	2000	2000
Samples	Plasma	Plasma	Plasma	Plasma	Plasma	Plasma	Plasma	Plasma
Assay	HPLC-MS/MS	HPLC-MS/MS	HPLC-MS/MS	HPLC-MS/MS	HPLC-MS/MS	HPLC-MS/MS	HPLC-MS/MS	HPLC-MS/MS
Pharmacokinetic Parameters of Telotristat Ethyl								
T _{max} (hr)	1	1	8	8	8	8	24	24
C _{max} (µg/mL)	0.003	0.003	0.005	0.008	0.007	0.008	0.009	0.014
AUC _{0-24hr} (hr*µg/mL)	0.04	0.04	0.07	0.16	0.14	0.15	0.12	0.19
Pharmacokinetic Parameters of LP-778902								
T _{max} (hr)	1	1	1	1	2	2	24	24
C _{max} (µg/mL)	1.5	1.3	2.8	1.6	2.3	1.6	2.1	1.9
AUC _{0-24hr} (hr*µg/mL)	4.4	3.8	20.0	15.5	33.4	28.1	35.9	31.3
Study number	LX1606-N11	LX1606-N11	LX1606-N11	LX1606-N11	LX1606-N11	LX1606-N11	LX1606-N11	LX1606-N11
Location in CTD	4.2.2.2	4.2.2.2	4.2.2.2	4.2.2.2	4.2.2.2	4.2.2.2	4.2.2.2	4.2.2.2
Source: LX1606-N11 M = male F = female HPLC-MS/MS = High performance liquid chromatography - tandem mass spectrometry Mean values reported								

Species	Rat	Rat	Rat	Rat	Rat	Rat	Rat	Rat
Brief Results: Plasma levels of telotristat ethyl generally increased with increase in dose from 100 to 500 mg/kg in female rats and from 100 to 1000 mg/kg in male rats. Exposure of LP-778902 increased from 100 to 1000 mg/kg in both genders with no further appreciable increase in exposure to LP-778902 at doses above 1000 mg/kg.								

Table 2.6.5.3-3 Pharmacokinetics of LP-778902 After a Single Dose of Telotristat Ethyl in Rats

Species	Rat	Rat	Rat	Rat	Rat	Rat	Rat	Rat
Number of animals	5	5	5	5	5	5	5	5
Gender	M	M	M	M	M	M	M	M
Feeding condition	Fed	Fed	Fed	Fed	Fed	Fed	Fed	Fed
Method of administration	Oral gavage	Oral gavage	Oral gavage	Oral gavage	Oral gavage	Oral gavage	Oral gavage	Oral gavage
Dose (mg/kg/day)	10	30	50	150	250	400	1000	2000
Samples	Plasma	Plasma	Plasma	Plasma	Plasma	Plasma	Plasma	Plasma
Pharmacokinetic Parameters of LP-778902								
T _{max} (hr)	1.0 ± 0.0	1.0 ± 0.0	1.0 ± 0.0	1.0 ± 0.0	1.0 ± 0.0	1.0 ± 0.0	11.0 ± 11.9	15.6 ± 11.5
C _{max} (µg/mL)	0.2 ± 0.0	1.0 ± 0.1	3.2 ± 0.6	4.5 ± 1.2	6.5 ± 1.6	4.9 ± 0.9	3.6 ± 0.5	4.8 ± 0.7
AUC _{0-24hr} (hr*µg/mL)	0.4 ± 0.1	1.9 ± 0.4	5.0 ± 0.9	16.2 ± 2.5	23.2 ± 5.2	35.1 ± 5.4	58.8 ± 19.6	77.0 ± 15.7
Study number	IVT 06-021	IVT 06-021	IVT 06-019	IVT 06-025	IVT 06-019	IVT 06-025	IVT 06-019	IVT 06-019
Location in CTD	4.2.2.2	4.2.2.2	4.2.2.2	4.2.2.2	4.2.2.2	4.2.2.2	4.2.2.2	4.2.2.2
Source: IVT 06-019, IVT 06-021, IVT 06-025 M = male Data expressed as mean ± standard deviation Brief Results: Exposure to LP-778902 increased approximately linearly with increase in dose at the lower dose levels, but approached saturation at the higher doses levels.								

Table 2.6.5.3–4 Pharmacokinetics of Telotristat Ethyl, LP-778902 and LP-951757 After a Single Dose of Telotristat Etiprate in Male and Female Rats

Species	Rat	Rat	Rat	Rat	Rat	Rat
Number of animals	6	6	6	6	6	6
Gender	M	F	M	F	M	F
Feeding condition	Fed	Fed	Fed	Fed	Fed	Fed
Method of administration	Oral gavage	Oral gavage	Oral gavage	Oral gavage	Oral gavage	Oral gavage
Dose (mg/kg)	20	20	60	60	170	170
Samples	Plasma	Plasma	Plasma	Plasma	Plasma	Plasma
Assay	LC-MS/MS	LC-MS/MS	LC-MS/MS	LC-MS/MS	LC-MS/MS	LC-MS/MS
Pharmacokinetic Parameters of Telotristat ethyl						
C _{max} (ng/mL)	0.823	1.03	1.54	3.97	2.21	4.64
T _{max} (hr)	1.00	0.50	1.00	1.00	8.00	1.00
AUC _{0-24hr} (hr*ng/mL)	NR	NR	NR	NR	NR	33.8
Pharmacokinetic Parameters of LP-778902						
C _{max} (ng/mL)	243	487	611	1180	1430	2110
T _{max} (hr)	1.00	1.00	1.00	1.00	2.00	1.00
AUC _{0-24hr} (hr*ng/mL)	652	892	2780	3530	11600	12800
T _{1/2} (hr)	1.57	NC	3.08	3.58	3.06	3.34
Pharmacokinetic Parameters of LP-951757						
C _{max} (ng/mL)	20.2	23.1	51.5	73.2	112	197
T _{max} (hr)	4.00	4.00	4.00	4.00	4.00	8.00
AUC _{0-24hr} (hr*ng/mL)	142	311	436	962	1410	3160
Study number	LX1606-N60	LX1606-N60	LX1606-N60	LX1606-N60	LX1606-N60	LX1606-N60
Location in CTD	4.2.2.2	4.2.2.2	4.2.2.2	4.2.2.2	4.2.2.2	4.2.2.2
Source: LX1606-N60						
M = male						
F = female						

Species	Rat	Rat	Rat	Rat	Rat	Rat
LC-MS/MS = liquid chromatography-tandem mass spectrometry						
NR = not reported						
NC = not calculated						
<u>Brief Results:</u> Telotristat ethyl was rapidly absorbed and converted into LP-778902 and LP-951757. Exposures of telotristat ethyl, LP-778902 and LP-951757 increased with increase in dose. In general, females had higher C _{max} and AUC _{0-24hr} values when compared to males.						

Table 2.6.5.3–5 Pharmacokinetics of Telotristat Ethyl and LP-778902 After a Single Dose of Telotristat Etiprate in Pregnant Rabbits

Species	Rabbit	Rabbit	Rabbit	Rabbit	Rabbit	Rabbit	Rabbit	Rabbit	Rabbit
Number of animals	3	3	3	3	3	3	3	3	3
Gender	F	F	F	F	F	F	F	F	F
Feeding condition	Fed	Fed	Fed	Fed	Fed	Fed	Fed	Fed	Fed
Method of administration	Oral gavage	Oral gavage	Oral gavage	Oral gavage	Oral gavage	Oral gavage	Oral gavage	Oral gavage	Oral gavage
Dose (mg/kg)	10	30	100	125	250	300	500	1000	2000
Samples	Plasma	Plasma	Plasma	Plasma	Plasma	Plasma	Plasma	Plasma	Plasma
Assay	HPLC-MS/MS	HPLC-MS/MS	HPLC-MS/MS	HPLC-MS/MS	HPLC-MS/MS	HPLC-MS/MS	HPLC-MS/MS	HPLC-MS/MS	HPLC-MS/MS
Pharmacokinetic Parameters of Telotristat Ethyl									
T _{max} (hr)	BLQ	5.00 ± NA ¹	0.50 ± NA ²	0.50 ± NA ¹	0.50 ± 0.00	3.33 ± 1.15	3.00 ± 4.33	24.0 ± 0.00	24.0 ± 0.00
C _{max} (ng/mL)	BLQ	3.24 ± NA ¹	2.12 ± NA ²	2.30 ± NA ¹	6.88 ± 2.65	3.78 ± 0.92	3.98 ± 0.32	10.3 ± 2.00	8.52 ± 1.92
AUC ₀₋₄ (hr*ng/mL)	BLQ	NA	NA	NA	22.2 ± 2.9	24.1 ± 6.6	37.4 ± 25.9	194 ± 46	149 ± 37
AUC _{0-24hr} (hr*ng/mL)	BLQ	NA	NA	NA	41.4 ± 3.6	50.1 ± 12.9	54.9 ± 12.5	194 ± 46	149 ± 37
Pharmacokinetic Parameters of LP-778902									
T _{max} (hr)	0.50 ± 0.00	0.67 ± 0.29	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00	2.67 ± 1.15	3.33 ± 1.15	4.00 ± 0.00	10.7 ± 11.5
C _{max} (ng/mL)	124 ± 34	507 ± 129	968 ± 268	2293 ± 1115	4273 ± 1242	4307 ± 1031	10163 ± 2455	10160 ± 720	12373 ± 4633

Species	Rabbit	Rabbit	Rabbit	Rabbit	Rabbit	Rabbit	Rabbit	Rabbit	Rabbit
AUC ₀₋₄ (hr*ng/mL)	314 ± 154	1275 ± 326	4706 ± 3020	10126 ± 3415	32233 ± 6589	45035 ± 12634	132156 ± 51751	193008 ± 28311	228375 ± 99761
AUC _{0-24hr} (hr*ng/mL)	358 ± 175	1356 ± 254	4706 ± 3020	10126 ± 3415	32233 ± 6589	45035 ± 12634	132156 ± 51751	193008 ± 28311	228375 ± 99761
T _{1/2} (hr)	1.82 ± 0.15	2.2 ± 0.93	3.63 ± 0.6	2.97 ± 0.28	3.25 ± 0.20	3.58 ± NA	2.58 ± NA	NA	NA
Study number	LX1606-N25	LX1606-N25	LX1606-N25	LX1606-N30	LX1606-N30	LX1606-N25	LX1606-N30	LX1606-N25	LX1606-N25
Location in CTD	4.2.2.2	4.2.2.2	4.2.2.2	4.2.2.2	4.2.2.2	4.2.2.2	4.2.2.2	4.2.2.2	4.2.2.2
Source: LX1606-N25, LX1606-N30 1 – n = 2 instead of 3 2 – n = 1 instead of 3 F = female HPLC-MS/MS = high performance liquid chromatography - tandem mass spectrometry BLQ = below the limit of quantitation NA = not applicable Where appropriate, data expressed as mean ± standard deviation <u>Brief Results:</u> Telotristat etiprate was administered once daily by oral gavage to pregnant rabbits beginning on gestation day 7. Following administration of a single dose, telotristat ethyl was readily absorbed and converted to LP-778902. Exposure to LP-778902 increased with the increase in dose level from 10 to 2000 mg/kg.									

Table 2.6.5.3–6 Pharmacokinetics of Telotristat Ethyl and LP-778902 After a Single Dose of Telotristat Etiprate in Dogs

Species	Dog	Dog	Dog	Dog	Dog	Dog
Number of animals	3	3 ¹	3	3	3	3 ²
Gender	M	M	M	M	M	M
Feeding condition	Fasted	Fasted	Fasted	Fasted	Fed	Fed
Method of administration	Oral gavage	Oral gavage	Oral gavage	Oral gavage	Oral gavage	Oral gavage
Dose (mg/kg)	50	100	200	500	200	500

Species	Dog	Dog	Dog	Dog	Dog	Dog
Samples	Plasma	Plasma	Plasma	Plasma	Plasma	Plasma
Assay	LC-MS/MS	LC-MS/MS	LC-MS/MS	LC-MS/MS	LC-MS/MS	LC-MS/MS
Pharmacokinetic Parameters of Telotristat Ethyl						
C _{max} (µg/mL)	0.04 ± 0.0	0.02	0.05 ± 0.1	0.05 ± 0.0	0.10 ± 0.0	0.39
T _{max} (hr)	2.75 ± 3.0	3.00	2.33 ± 1.5	1.50 ± 1.3	5.00 ± 2.7	12.00
AUC ₀₋₄ (hr*µg/mL)	0.14 ± 0.1	0.09	0.33 ± 0.5	0.20 ± 0.2	0.61 ± 0.3	5.42
T _{1/2} (hr)	2.03 ³	1.56	2.56 ³	1.95 ± 0.5	2.89 ³	4.58
Pharmacokinetic Parameters of LP-778902						
C _{max} (µg/mL)	1.3 ± 0.3	1.2	2.2 ± 2.5	2.3 ± 0.6	3.9 ± 0.6	10.8
T _{max} (hr)	3.0 ± 1.0	2.5	3.0 ± 1.0	3.3 ± 0.6	5.0 ± 2.7	12.0
AUC ₀₋₄ (hr*µg/mL)	7.6 ± 2.4	5.5	15.9 ± 20.4	14.5 ± 4.4	30.2 ± 9.2	191.0
T _{1/2} (hr)	5.6 ± 0.6	5.3	5.5 ± 2.5	6.4 ± 1.0	8.5 ± 0.7	7.7
Study number	LX1606-N15	LX1606-N15	LX1606-N15	LX1606-N15	LX1606-N15	LX1606-N15
Location in CTD	4.2.2.2	4.2.2.2	4.2.2.2	4.2.2.2	4.2.2.2	4.2.2.2
Source: LX1606-N15 1 - One animal vomited between 15 and 30 minutes post-dose; pharmacokinetic values were not used in mean and standard deviation calculations 2 - One animal vomited 15 and 30 minutes post-dose, had additional emesis between 1 and 2 hours post-dose; pharmacokinetic values not used in mean and SD calculations 3 - T _{1/2} not calculated for 1 animal due to insufficient elimination phase data M = male LC-MS/MS = liquid chromatography-tandem mass spectrometry Where appropriate, data expressed as mean ± standard deviation <u>Brief Results:</u> Exposure of both telotristat ethyl and LP-778902 were increased in the presence of food. C _{max} and AUC ₀₋₄ for telotristat ethyl and LP-778902 showed an approximate 2-fold increase in the presence of food at 200 mg/kg. At 500 mg/kg, C _{max} and AUC ₀₋₄ of LP-778902 showed a 4.6- and 13.2-fold increase, respectively, in the presence of food.						

Table 2.6.5.3–7 Pharmacokinetics of LP-778902 After a Single Dose of Telotristat Ethyl in Male and Female Monkeys

Species	Monkey	Monkey
Number of animals	5	2
Gender	M	F
Feeding condition	Fasted	Fasted
Method of administration	Oral gavage	Oral gavage
Dose (mg/kg/day)	75	75
Samples	Plasma	Plasma
Assay	LC-MS/MS	LC-MS/MS
Pharmacokinetic Parameters of LP-778902		
C _{max} (µg/mL)	1.23 ± 0.9	0.59
T _{max} (hr)	2.20 ± 1.1	4.00
AUC _{0-24hr} (hr*µg/mL)	6.62 ± 4.3	3.42
T _{1/2} (hr)	4.16 ± 1.0	4.27
Study number	(b) (4) 7648-187 Appendix 2 (160602)	(b) (4) 7648-187 Appendix 2 (160602)
Location in CTD	4.2.2.2	4.2.2.2
Source: (b) (4) 7648-187 Appendix 2 (160602) M = male F = female LC-MS/MS = Liquid chromatography-tandem mass spectrometry Where appropriate, data expressed as mean ± standard deviation <u>Brief Results:</u> The rate of appearance of LP-778902 in the circulation following oral dosing with telotristat ethyl was slower in female monkeys when compared to males. Exposure of LP-778902 in male monkeys was approximately 2-fold higher than in females (caution should be used when interpreting this data as only 2 female monkeys were tested).		

In general, the plasma levels of the parent drug were much lower than the active metabolite LP-778902 in all species, and the exposure to LP-778902 increased with dose level. Similar findings were reported in human PK studies.

Distribution:

Tissue distribution studies with ¹⁴C-LX1606 in rats indicated that the radioactivity was mainly concentrated in the liver, GI tract, and kidney with no measurable radioactivity in the brain. The results were summarized in the following sponsor's table.

Table 2.6.5.5–1 Distribution of ¹⁴C-Telotristat Ethyl in Sprague-Dawley Rats

Species: Sprague-Dawley Rat			Test Article: ¹⁴ C-Telotristat ethyl hydrochloride	
Gender (M/F)/Number of Animals: 3M/time point			Study Number: LX1606-N16	
Feeding Condition: Fed			Location in CTD: 4.2.2.3	
Vehicle/Formulation: 0.25% methylcellulose				
Method of Administration: Oral gavage				
Dose (mg/kg): 30 and 100				
Radionuclide: ¹⁴ C-LX1606				
Specific Activity: 84.5 µCi/mg (free base)				
Sampling Time: 2 and 24 hr				
	ng Equivalents ¹⁴ C-Telotristat Ethyl/g			
Dose	30 mg/kg		100 mg/kg	
Tissues/organs	<u>2 Hours</u>	<u>24 Hours</u>	<u>2 Hours</u>	<u>24 Hours</u>
Brain	ND	ND	ND	ND
Blood	187 ± 62	BLQ	1040 ± 140	45 ± 40
Plasma	321 ± 103	27 ± 1	1580 ± 140	93 ± 25
Esophagus	27200 ¹	ND	76000 ± 31400	ND
Kidney	1590 ± 550	ND	6770 ± 2320	ND
Liver	5300 ± 1870	712 ± 102	28400 ± 10400	1130 ²
Source: LX1606-N16				
1: n = 2 instead of 3				
2: n = 1 instead of 3				
BLQ = below limit of quantitation				
ND = not detectable (sample shape not discernible from background)				
Blood and plasma were analyzed for total radioactivity by liquid scintillation counting (LSC). Distribution of ¹⁴ C-telotristat ethyl-derived radioactivity to tissues was determined by quantitative whole-body autoradiography (QWBA)				
<u>Brief Results:</u> Distribution of ¹⁴ C-telotristat ethyl-derived radioactivity was very limited with radioactivity detectable only in the tissues of the hepatic and renal systems and the tissues and contents of the gastrointestinal tract. No evidence of radioactivity in brain was apparent at any dose level or time point.				

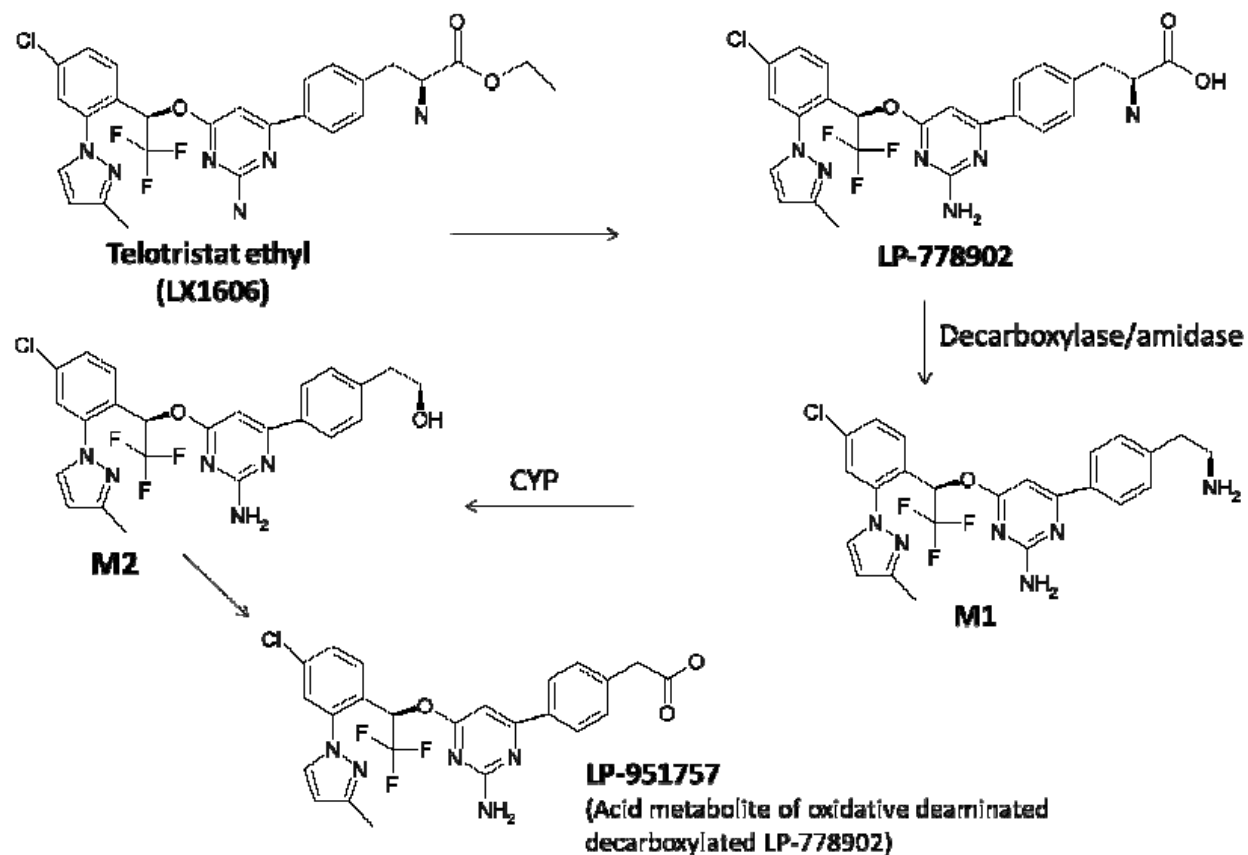
Both the parent drug and LP-778902 have high plasma protein binding (> 96% and > 98%, respectively) in all species tested (see sponsor's table below).

Table 2.6.5.6–1 Summary of Plasma Protein Binding Studies With Telotristat Ethyl and LP-778902

Study System: In vitro Target entity, Test System and Method: Plasma from mice, rats, dogs, monkeys and humans, Equilibrium dialysis		Test Article: Telotristat ethyl trihydrochloride, LP-778902 Study Number: 160618 Location in CTD: 4.2.2.3
Species	Telotristat Ethyl % Bound	LP-778902 % Bound
Mouse	ND	99.4
Rat	ND	98.8
Dog	99.8	99.8
Monkey	96.7	98.3
Human	99.8	99.8
Source: 160618 All values represent the mean of 2 observations ND = not determined, due to telotristat ethyl lability in rodent plasma (ref: 160619) <u>Brief Results:</u> Both compounds exhibited high plasma protein binding in all species tested.		

Metabolism:

Telotristat ethyl was rapidly hydrolyzed to its active metabolite, LP-778902, which was converted to an inactive metabolite LP-951757 (oxidative, decarboxylated, deaminated LP-778902). No unique human metabolites were found. The metabolic pathways are depicted in the sponsor's figure below.

Figure 2.6.5.11-1 Proposed Metabolic Pathway of Telotristat Ethyl

In rats, the plasma levels of LP-951757 were substantially lower than the active metabolite, LP-778902 (see sponsor's table below).

Table 2.6.5.4–1 Pharmacokinetics of LP-778902 and LP-951757 After Repeated Doses of Telotristat Etiprate in Rats

Species	Rat	Rat	Rat
Number of animals	5	5	5
Gender	M	M	M
Feeding condition	Fed	Fed	Fed
Method of administration	Oral gavage	Oral gavage	Oral gavage
Dose (mg/kg)	100	200	300
Dosing frequency and duration	Once daily, 5 days	Once daily, 5 days	Once daily, 5 days
Samples	Plasma	Plasma	Plasma
Assay	LC-MS/MS	LC-MS/MS	LC-MS/MS
Pharmacokinetic Parameters of LP-778902			
C _{max} (µg/mL)	0.45 ± 0.1	0.68 ± 0.1	1.22 ± 0.2
T _{max} (hr)	1.4 ± 0.9	7.2 ± 2.7	3.4 ± 3.4
AUC _{0-last} (hr*µg/mL)	2.49 ± 0.5	6.62 ± 1.1	13.25 ± 3.8
AUC _{0-inf} (hr*µg/mL)	2.57 ± 0.5 ¹	6.75 ± 1.2 ¹	11.40 ± 2.5 ²
T _{1/2} (hr)	3.6 ± 0.4 ¹	5.3 ± 3.6 ¹	3.4 ± 0.3 ²
Pharmacokinetic Parameters of LP-951757			
C _{max} (µg/mL)	0.14 ± 0.1	0.28 ± 0.0	0.43 ± 0.1
T _{max} (hr)	5.2 ± 2.2	9.2 ± 2.7	8 ± 0.0
AUC _{0-last} (hr*µg/mL)	1.68 ± 0.6	4.00 ± 0.9	6.03 ± 0.9
AUC _{0-inf} (hr*µg/mL)	1.94 ± 0.5 ¹	NA	NA
T _{1/2} (hr)	4.8 ± 1.1 ¹	NA	NA
Study number	LX1606-N53	LX1606-N53	LX1606-N53
Location in CTD	4.2.2.2	4.2.2.2	4.2.2.2
Source: LX1606-N53 1 – n = 4 instead of 5 2 – n = 3 instead of 5 M = male LC-MS/MS = liquid chromatography-tandem mass spectrometry NA = not available due to lack of terminal phase Where appropriate, data expressed as mean ± standard deviation <u>Brief Results:</u> Both LP-778902 and LP-951757 demonstrated an approximately linear increase in exposure with dose. Exposure was markedly higher for LP-778902 when compared to LP-951757 while the T _{max} of LP-951757 was noticeably longer than that of LP-778902.			

Excretion:

In rats, approximately 90% of the administered dose was excreted in feces by 24 hours after dosing, with <0.1% of the dose eliminated in urine (see the sponsor's table below).

Table 2.6.5.13–1 Excretion of ^{14}C -Telotristat Ethyl in Sprague-Dawley Rats

Species: Sprague-Dawley Rat		Test Article: ^{14}C -telotristat ethyl		
Gender (M/F)/Number of Animals: 3M/time point		Study Number: LX1606-N16		
Feeding Condition: Fed		Location in CTD: 4.2.2.5		
Vehicle/Formulation: 0.25% methylcellulose				
Method of Administration: Oral gavage				
Analyte: ^{14}C -LX1606				
Assay: LSC				
Dose (mg/kg)	Collection Interval (hr)	Urine (%)	Feces (%)	Cage Wash + Cage Wipe (%)
30	0-8	0.06 ± 0.01	0.00 ± 0.00	0.00 ± 0.00
	8-24	0.02 ± 0.01	88.1 ± 4.8	0.00 ± 0.00
	Subtotal	0.08 ± 0.00	88.1 ± 4.8	0.00 ± 0.00
100	0-8	0.06 ± 0.01	0.00 ± 0.00	0.00 ± 0.00
	8-24	0.03 ± 0.00	92.1 ± 12.8	0.00 ± 0.00
	Subtotal	0.09 ± 0.01	92.1 ± 12.8	0.00 ± 0.00
Source: LX1606-N16				
M = male				
LCS = liquid scintillation counting				
Data reported as percent of radioactive dose in urine, feces, cage wash, and cage wipe at specified intervals after a single oral administration of ^{14}C -telotristat ethyl				
Data expressed as mean ± standard deviation of 3 observations				
Brief Results: ^{14}C -Telotristat ethyl-derived radioactivity was rapidly excreted after oral administration to male Sprague-Dawley rats. Approximately 86% to 92% of the administered dose was excreted in feces by 24 hours post-dose. Elimination in urine accounted for less than 0.2% of the administered dose by 24 hours post-dose.				

Enzyme Induction/Inhibition:

The effects of telotristat ethyl and LP-778902 on P450 isoenzymes were studied in vitro using human liver microsomal samples. The results are presented in the sponsor's table below.

Table 2.6.5.12–1 Human Cytochrome P450 Inhibition by Telotristat Ethyl and LP-778902

Study System: In vitro Target entity, Test System and Method: Cytochrome P450 isozymes using specific fluorometric substrates or human liver microsomal samples with LC-MS/MS analysis		Test Article: Telotristat ethyl, LP-778902 Study Number: 160614, (b) (4) (b) (4) 15A010 Location in CTD: 4.2.2.4
P450 Isoenzyme	Telotristat Ethyl % Inhibition	LP-778902 % Inhibition
CYP1A2 ¹	0	0
CYP2C9 ¹	73	46
CYP2C19 ¹	11	28
CYP2D6 ¹	23	19
CYP3A4 ¹	79	18
CYP2C8 ²	15	0.6
CYP2E1 ²	-6	-4
1: Source: 160614 2: Source: (b) (4) 15A010 LC-MS/MS = liquid chromatography-tandem mass spectrometry Study 160614 was conducted using telotristat ethyl trihydrochloride and study (b) (4) 15A010 was conducted using telotristat etiprate % inhibition determined at 1 µM concentration following 30 minute incubation Brief Results: Telotristat ethyl showed > 50% inhibition of both CYP2C9 and CYP3A4, whereas LP-778902 showed reduced potential for inhibition of any P450 isoenzymes tested.		

Telotristat ethyl (1 µM) inhibited CYP2C9 and CYP3A4 by over 70%, and LP-778902 inhibited a number of P450 isoenzymes ranging from 18% for CYP3A4 to 46% for CYP2C9.

Telotristat ethyl was not a substrate for P-glycoprotein (P-gp) or Breast Cancer Resistance Protein (BCRP). LP-778902 had some substrate activity with P-gp, but not for BCRP (see the sponsor's table below).

Table 2.6.5.15-1 Efflux Ratio of Telotristat Ethyl and LP-778902 in Caco-2 Cells

Study System: In vitro				Test Article: Telotristat ethyl trihydrochloride, LP-778902	
Target entity, Test System and Method: Efflux transporters (P-gp and BCRP), Caco-2 cells, LC-MS/MS				Study Number:: 160631, 103312	
Location in CTD: 4.2.2.6					
Test Compound	P _{ab} (nm/sec)	P _{ba} (nm/sec)	Efflux ratio	% Inhibition in Presence of Inhibitor	Comment
Telotristat ethyl ¹	1.2	0.34	0.29	NA	Telotristat ethyl is not a P-gp or BCRP substrate
LP-778902 ²	4.0	46.7	11.6	NA	LP-778902 has some P-gp substrate activity
LP-778902 + P-gp inhibitor ²	8.0	34.3	4.3	63%	
LP-778902 ²	7.5	40.9	5.4	NA	LP-778902 is not a BCRP substrate
LP-778902 + BCRP inhibitor ²	8.7	28.5	3.3	39%	
P-gp inhibitor was 10 µM ketoconazole and BCRP inhibitor was 10 µM KO143					
1: Source: 160631					
2: Source: 103312					
LC-MS/MS = liquid chromatography-tandem mass spectrometry					
NA = not applicable					
Brief Results: Telotristat ethyl was not a P-gp or BCRP substrate in human Caco-2 cells while LP-778902 was shown to have some substrate activity against P-gp but not for BCRP					

5.2 Toxicokinetics

TK data were included in the reviews of the toxicity studies.

6 General Toxicology

6.1 Single-Dose Toxicity

LX1606 was tested at single oral doses up to 2000 mg/kg in rats (study 7648-199). There were no deaths in this study. Non-formed or liquid feces were noted in high dose animals.

LX1606 was tested at 1 mg/kg IV and oral doses up to 500 mg/kg in dogs (study 7648-211). No treatment-related changes were noted in the IV dose group. A dose-dependent emetic response was noted following oral administration. Vomiting became severe at doses of 200 mg/kg and higher.

Repeat-Dose Toxicity

Note: The following study review was presented in the Pharmacology/Toxicology review of IND 78,749 dated January 3, 2014.

28-Day Repeated Dose Oral Toxicity and Toxicokinetic Study with LX1606 hippurate in CByB6F1 Mice**Study No:** AD58ET.2G3R (b) (4)**Conducting Laboratory and Location:**
(b) (4)**Date of study initiation:** September 14, 2012**Report date:** June 27, 2013**GLP compliance:** This study was conducted in accordance with Good Laboratory Practice Regulations of the United States Food and Drug Administration (21 CFR Part 58).**QA-Report** Yes (x) No ().**Animals:** CByB6F1 mice, 7-8 weeks old**Weight:** males: 22.5 to 27.2 grams

females: 18.5 to 21.6 grams

Drug lot#: L0304653**Key Study Findings:**

LX1606 hippurate was given by oral gavage at 0, 300, 750, and 1500 mg/kg/day to males and 0, 300, 750, 2000, and 3000 mg/kg/day to females, for 28 days. The doses of 2000 and 3000 mg/kg/day produced deaths in all female mice. Nasal cavity inflammation and/or serocellular exudates were observed in 6/10 females treated with 750 mg/kg/day. Two male mice given 750 mg/kg/day in the main toxicity study were sacrificed due to moribund condition, resulting from necrotizing inflammation in the nasal cavity. Also, one male at 750 mg/kg/day and four males at 1500 mg/kg/day in the TK study were sacrificed due to moribund condition.

The nasal cavity lesions were dose dependent and did not occur in the control group. One male had acute inflammation and two females had serocellular exudates at 300 mg/kg/day. The incidence of these changes was higher at 750 mg/kg/day. The dose of 300 mg/kg/day was tolerated in this study with limited toxicity, and is considered to be the MTD.

Methods: LX1606 hippurate was given by oral gavage at 0, 300, 750, 1500, 2000, and 3000 mg/kg/day for 28 days. The study design is summarized in the sponsor's table below.

Group	Dose Levels (mg/kg/day)	Number of Animals			
		Main Cohort		TK Cohort*	
		Male	Female	Male	Female
Group 1 (Vehicle control)	0	10	10	5	5
Group 2	300	10	10	20	20
Group 3	750	10	10	20	20
Group 4	1500	10	-	20	-
Group 5	2000	-	10	-	20
Group 6	3000	-	10	-	20
Total		40	50	65	85

*Extra TK animals (2/sex/group) were used to ensure adequate animals for TK bleeding.

The dose selection was based on the results of the 14-day oral dose ranging study in CByB6F1 mice. In that study, the dose of 2000 mg/kg/day was lethal to males. Decreased motor activity and hunched posture in two males and one female were observed at 2000 mg/kg/day. Therefore, the sponsor selected a high dose of 1500 mg/kg/day for males and 3000 mg/kg/day for females in the 28-day dose ranging study.

The parameters observed in the current study are summarized below.

Observations and times:

- **Clinical signs:** Clinical signs of toxicity were observed daily.
- **Body weights:** Body weights were determined weekly.
- **Food consumption:** Food consumption was determined weekly.
- **Hematology:** at termination
- **Clinical chemistry:** at termination.
- **Gross pathology:** Animals were necropsied at termination.
- **Organs weights:** Organs were weighed at termination.
- **Histopathology:** The following organs or tissues were examined microscopically from all early deaths (except females in groups 5 and 6), control animals, and from all animals in the high-dose groups. Additionally, the nasal cavity (both sexes), stomach (males only) and testes were evaluated microscopically in all test article treated groups.

Note: the 14-day dose ranging study in CByB6F1 mice is study # IVT 07-006.

Tissues/Organs	
Adrenal glands	Pancreas
Aorta	Parathyroid glands
Bone (femur and sternum)	Pituitary gland
Bone marrow (femur and sternum)	Prostate gland
Brain	Salivary gland
Epididymides	Sciatic nerve
Esophagus	Seminal vesicles
Eyes	Skeletal muscle (thigh)
Gall bladder	Small intestine (duodenum, jejunum, and ileum)
Gross lesions	Spinal cord (cervical, thoracic, and lumbar)
Harderian gland	Spleen
Heart	Stomach
Kidneys	Testes
Large intestine (cecum, colon, rectum)	Thymus
Liver	Thyroid glands
Lungs and bronchi	Trachea
Lymph nodes (mesenteric and mandibular)	Urinary bladder
Skin from mammary area (male and female mice)	Uterus
Mammary gland (females only)	Vagina
Nasal Cavity	Ovaries

- **Toxicokinetics:** Toxicokinetic parameters were determined before dosing and at 1, 2, 4, 8, and 24 hours after dosing on day 27.

Results:

Clinical Signs: Decreased motor activity, ruffled fur, and thin appearance were noted in one mid- and one high-dose male. Decreased motor activity and/or ruffled fur were noted in most females in the 2000 and 3000 mg/kg/day groups. Tremors were also noted in one high dose female (3000 mg/kg/day). One high dose female had hunched posture.

Mortality: Two mid-dose males (750 mg/kg/day) were sacrificed due to moribund condition. Nasal cavity necrotizing inflammation was the cause of death. One male at 750 mg/kg/day and four males at 1500 mg/kg/day in the TK study were also sacrificed due to moribund condition. All females in the two high dose groups (2000 and 3000 mg/kg/day) died or were sacrificed in a moribund condition during the first two weeks of the study.

Body Weights: The initial and final body weights in the control group were 23.78 and 25.96 g for males and 19.41 and 21.66 g for females. The terminal body weight gain was 2.18 g and 1.1 g in the control and high dose males (1500 mg/kg/day), respectively. The terminal body weight gain in the high dose males was significantly decreased (50%) as compared to the control. There were no clearly treatment-related changes in females.

Food Consumption: The food consumption was not clearly affected by the treatment.

Hematology: There were no clear treatment-related changes.

Clinical Chemistry: There were no clear treatment-related changes.

Organ Weights: Decrease in the absolute and relative weights of the spleen and testes were noted in the high dose males.

Gross Pathology: Small testes was noted in one mid-dose male. This change was correlated with testicular atrophy in the histopathological exam.

Histopathology: Nasal cavity inflammation and/or serocellular exudates were noted in drug-treated males and females. These findings are summarized in the sponsor's table below.

	Male				Female		
Group	1	2	3	4	1	2	3
Dose (mg/kg/day)	0	300	750	1500	0	300	750
Number per Group	10	10	10	10	10	10	10
Microscopic Observation							
Within Normal Limits	10	9	4	5	10	8	4
Inflammation, Acute	0	1	2	4	0	0	1
Exudate, Serocellular	0	0	3	5	0	2	6
Inflammation, Necrotizing, Moderate	0	0	2	0	0	0	0

The nasal cavity lesions were likely due to the local irritation following oral gavage.

Focal inflammation and/or hyperplasia in the squamous portion of stomach (forestomach) were also noted. These lesions may have been due to local irritation of the test article following oral gavage. Testicular atrophy was found in one male each in the mid- and high-dose groups.

Toxicokinetics: The TK results were presented in the following sponsor's table.

Group	LX1606 Dose Level (mg/kg/day)	Sex	C _{max} (ng/mL)	T _{max} (hr)	AUC ₀₋₂₄ (ng·hr/mL)
2	300	M	6520	0.500	59200
		F	8130	1.00	71700
3	750	M	8200	1.00	69100
		F	9390	2.00	90300
4	1500	M	19400	1.00	197000

In summary, LX1606 hippurate was given by oral gavage at 0, 300, 750, and 1500 mg/kg/day to males and 0, 300, 750, 2000, and 3000 mg/kg/day to females, for 28 days. The doses of 2000 mg/kg/day or higher were lethal to female mice. Histopathological changes including nasal cavity inflammation and/or serocellular exudates were observed in 6/10 females treated with 750 mg/kg/day.

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Two male mice given 750 mg/kg/day in the main toxicity study were sacrificed due to moribund condition. Nasal cavity necrotizing inflammation was the cause of death. Also, one male at 750 mg/kg/day and four males at 1500 mg/kg/day in the TK study were sacrificed due to moribund condition.

The nasal cavity lesions were dose dependent and did not occur in the control group. One male had acute inflammation and two females had serocellular exudates at 300 mg/kg/day. The incidence of these changes was higher at 750 mg/kg/day. The dose of 300 mg/kg/day was tolerated in this study with limited toxicity.

Study title: 4-Week Oral Gavage Toxicity and Toxicokinetic Study with LP-778914 in Rats with a 2-Week Recovery Period

Study no.: 7648-201
 Study report location: N/A
 Conducting laboratory and location: (b) (4)
 Date of study initiation: July 13, 2007
 GLP compliance: Yes
 QA statement: Yes
 Drug, lot #, and % purity: See table below

Test Article	Lot No.	Storage	Purity	Stability ^a	Reserve (Archive) Sample
LP-778914 (also known as LX1606)	AA-020763-Batch-01-2007	In a tightly sealed container protected from light in a refrigerator, set to maintain 2 to 8°C, with desiccant	95.87%	See footnote a	Collected

a The sponsor established 3 month accelerated stability from the time of manufacturing (18 June 2007). As the study terminated prior to the end of this 3 month period, the test article was deemed stable during the time frame of dose administration on this study.

Key Study Findings

In the 4-week oral toxicity study in rats, LX1606 was tested by oral gavage at 0, 100, 500, and 1000 mg/kg/day. One male and 4 females in the high dose group were sacrificed on Day 12 and the remaining animals in this group were sacrificed on Day 13 due to clinical signs of toxicity, weight loss, and reduced food consumption. The clinical signs of toxicity noted in this group included hunched posture, thin appearance, liquid feces, rough or discolored haircoat, and piloerection.

The following clinical signs of toxicity were observed in the mid-dose group: audible respirations (1 male), few feces (1 female), and clear oral discharge (1 female).

Distended or enlarged segments of the stomach, duodenum, jejunum, ileum, and/or cecum were noted in the high-dose group. The histopathological evaluation revealed submucosal edema localized to the limiting ridge of the nonglandular portion of the stomach in the high-dose group and enterocyte hypertrophy/hyperplasia in the duodenum and jejunum in the mid- and high-dose groups. GI tract was the target organ of toxicity. The dose of 100 mg/kg/day is considered as the NOAEL.

Methods

Doses: 100, 500, and 1000 mg/kg/day
 Frequency of dosing: daily
 Route of administration: oral gavage
 Dose volume: 5 mL/kg
 Formulation/Vehicle: 0.25% (w/v) methylcellulose
 Species/Strain: Crl:CD (SD) rats
 Number/Sex/Group: See Sponsor's table below
 Age: 6 to 7 weeks old at initiation
 Weight: 228 to 302 g for males
 163 to 227 g for females
 Satellite groups: See Sponsor's table below
 Unique study design: None
 Deviation from study protocol: There were no deviations that affected the outcome of this study.

Group	No. of Animals ^a		Dose Level (mg/kg/day)	Dose Concentration ^b (mg/mL)
	Male	Female		
Toxicity Animals				
1 (Control) ^c	15	15	0	0
2 (Low)	10	10	100	10
3 (Mid)	15	15	500	50
4 (High)	15	15	1000	100
Toxicokinetic Animals				
5 (Control) ^c	3	3	0	0
6 (Low)	6	6	100	10
7 (Mid)	6	6	500	50
8 (High)	6	6	1000	100

a Toxicity animals designated for recovery phase sacrifice (five animals/sex in Groups 1 and 3, dependent on survival) underwent 2 weeks of recovery following dose administration.

b All dose concentrations were corrected for salt content (correction factor = 1.312).

c Groups 1 and 5 received control article only.

The basis of dose selection was not clearly stated in the study report. However, there were 5-day (studies #IVT 06-019, #IVT 06-021, #IVT 06-025, #IVT 07-020) and 2-week (study #IVT 06-029) oral toxicity studies in rats. In the 2-week oral toxicity study, doses of LX1606 were tested up to 400 mg/kg/day. Glandular hyperplasia in the small intestine occurred in the 400 mg/kg/day group.

Observations and Results

Mortality: One male and four females in the high dose group were sacrificed on Day 12, and the remaining animals in this group were sacrificed on Day 13 due to clinical signs of toxicity, weight loss, and reduced food consumption. The clinical signs of toxicity in this group included hunched posture, thin appearance, liquid feces, rough or discolored haircoat, and piloerection.

Clinical Signs: The following clinical signs of toxicity were observed in the mid-dose group: audible respirations (1 male), few feces (1 female), and clear oral discharge (1 female).

Body Weights: The initial and final body weights in the control group were 267 g and 422 g in males and 190 g and 263 g in females, respectively. All high-dose animals were sacrificed on day 13. The terminal body weight gain in the high-dose group during first week (days 1-8) was 31 g in males (-34%) and 18 g in females (-25%). In contrast, the body weight gain in the control group during first week (days 1-8) was 47 g in males and 24 g in females. Body weights were not affected in the mid- and low-dose groups.

Feed Consumption: Decreased food consumption was noted in the high-dose group during the first 7 days. The high-dose males consumed 167 g/animal/period (~23% decrease), and high-dose females consumed 127 g/animal/period (~11% decrease), as compared to 216 g/animal/period in control males and 143 g/animal/period in control females.

Ophthalmoscopy: There were no treatment-related changes.

Hematology: There were no treatment-related changes.

Clinical Chemistry: There were no treatment-related changes.

Urinalysis: There were no treatment-related changes.

Gross Pathology: There were no treatment-related changes.

Organ Weights: There were no treatment-related changes.

Histopathology: The tissues listed in the table below from the study report were examined in all control and high-dose animals, and in animals that died or were sacrificed prematurely. Macroscopic lesions, stomach, ileum, jejunum, duodenum, colon, and rectum were also examined microscopically from each animal in the low- and mid-dose groups.

adrenal (2)	optic nerve (2) ^a
aorta	ovary (2)
brain	pancreas
cecum	pituitary gland
cervix	prostate
colon	rectum
duodenum	salivary gland [mandibular (2)]
epididymis (2) ^a	sciatic nerve
esophagus	seminal vesicle
eye (2) ^a	skeletal muscle (thigh)
femur with bone marrow (articular surface of the distal end)	skin/subcutis
Harderian gland ^a	spinal cord (cervical, thoracic, and lumbar)
heart	spleen
ileum	sternum with bone marrow
jejunum	stomach
kidney (2)	testis (2) ^a
lesions	thymus
liver	thyroid (2 lobes) with parathyroid
lung with large bronchi	tongue
lymph node (mandibular)	trachea
lymph node (mesenteric)	urinary bladder
mammary gland (females)	uterus
	vagina

^a Preserved in modified Davidson's fixative.

Distended or enlarged segments of the stomach, duodenum, jejunum, ileum, and/or cecum were noted in the high-dose group. Histopathological evaluation revealed submucosal edema localized to the limiting ridge of the nonglandular portion of the stomach in the high-dose group, and enterocyte hypertrophy/hyperplasia in the duodenum and jejunum in the mid- and high-dose groups. The results are summarized in the sponsor's tables below.

Text Table 1. Distribution, Incidence, Number Examined, and Mean Severity of Test Article-related Edema of the Gastric Limiting Ridge

Sex		Male				Female			
Group	1	2	3	4	1	2	3	4	
Gastric Limiting	0/15	0/10	0/15	9/15	0/15	0/10	0/15	7/15	
Ridge	(0.0)	(0.0)	(0.0)	(1.0)	(0.0)	(0.0)	(0.0)	(0.7)	

Text Table 2. Distribution, Incidence, Number Examined, and Mean Severity of Test Article-related Enterocyte Hypertrophy/Hyperplasia

Sex Group	Male				Female			
	1	2	3	4	1	2	3	4
Duodenum	0/15 (0.0)	0/10 (0.0)	1/15 (0.1)	11/15 (1.1)	0/15 (0.0)	0/10 (0.0)	5/15 (0.4)	4/15 (0.3)
Jejunum	0/15 (0.0)	0/10 (0.0)	0/15 (0.0)	9/15 (0.8)	0/15 (0.0)	0/10 (0.0)	1/15 (0.1)	4/15 (0.3)

Toxicokinetics: LX1606 was quickly converted to LP-778902, its active metabolite. LX1606 concentrations were close to or below the lower limit of quantitation (< 2.00 ng/mL). The TK data for LP-778902 were presented in the following sponsor's table.

Toxicokinetic Parameters of LP-778902 in Rat Plasma

Dose Group	LP-778914 Dose Level (mg/kg/day)	Sex	C _{max} (ng/mL)	DN C _{max} (ng/mL)/(mg/kg/day)	T _{max} (hr)	AUC ₀₋₂₄ (ng·hr/mL)	DN AUC ₀₋₂₄ (ng·hr/mL)/(mg/kg/day)	AUC ₀₋₄ (ng·hr/mL)	AUC _{0-∞} (ng·hr/mL)	t _{1/2} (hr)
Day 1										
6	100	M	1460	14.6	1.00	4781	47.8	4781	4793	2.79
		F	1370	13.7	1.00	4718	47.2	4718	4726	2.62
7	500	M	2477	4.95	2.00	16917	33.8	16917	17688	5.48
		F	2267	4.53	1.00	16655	33.3	16655	16976	4.31
8	1000	M	2030	2.03	2.00	36002	36.0	36002	NC	NC
		F	2557	2.56	2.00	34705	34.7	34705	NC	NC
Day 12										
8	1000	M	3137	3.14	1.00	35481	35.5	35481	NA	NC
		F	3627	3.63	2.00	59963	60.0	59963	NA	NC
Week 4										
6	100	M	1053	10.5	1.00	4954	49.5	4954	NA	2.91
		F	1066	10.7	1.00	4301	43.0	4301	NA	2.62
7	500	M	2273	4.55	1.00	17774	35.5	17774	NA	4.40
		F	2087	4.17	1.00	20988	42.0	20988	NA	NC

Dosing Solution Analysis

The analysis of drug concentrations in samples of dosing formulations from each dose-group was in agreement with target concentrations (between 96% and 101%).

Study title: 3-Month Toxicity and Toxicokinetic Study in Rats Administered LP-778914 with a 1-Month Recovery

Study no.: 7648-250
 Study report location: N/A
 Conducting laboratory and location: (b) (4)
 Date of study initiation: April 7, 2008
 GLP compliance: Yes
 QA statement: Yes
 Drug, lot #, and % purity: See sponsor's table below

Test Article	Lot No.	Storage	Purity	Expiration Date	Reserve (Archive) Sample
LP-778914 (also known as LX1606 and LX1032)	AA-020763-Batch-01-2008	Stored protected from light in a refrigerator, set to maintain 2 to 8°C, with desiccant	98.0%	14 Nov 2008	Collected ^a

^a See [Protocol Deviations](#).

Key Study Findings

LP-778914 (LX1606) was tested at dosages of 50, 200, and 500 mg/kg/day by oral gavage in rats for 3 months. Treatment with 500 mg/kg/day produced a decrease in body weight gain. Based on the decreased body weight gain in the high dose group, the NOAEL was identified at 200 mg/kg/day, and the high dose was close to the MTD.

Methods

Doses: 50, 200, and 500 mg/kg/day (see table below)
 Frequency of dosing: daily
 Route of administration: oral gavage
 Dose volume: 5 mL/kg
 Formulation/Vehicle: 0.25% (w/v) methylcellulose
 Species/Strain: Crl:CD (SD) rats
 Number/Sex/Group: 16/sex/group
 3 or 6/sex/group
 Age: 6 to 7 weeks old at initiation
 Weight: Males: 189-276 g
 Females: 151-209 g
 Satellite groups: 8 or 16/sex/group
 Unique study design: None
 Deviation from study protocol: There were no deviations that affected the outcome of this study.

Group	No. of Animals ^a		Dose Level (mg/kg/day)	Dose Concentration ^b (mg/mL)
	Male	Female		
1 (Control) ^c	16	16	0	0
2 (Low)	16	16	50	10
3 (Mid)	16	16	200	40
4 (High)	16	16	500	100

a Animals designated for recovery phase sacrifice (six animals/sex in Groups 1, 2, 3, and 4) underwent 1 month of recovery following dose administration.

b All dose concentrations were corrected for salt content (correction factor = 1.312).

c Group 1 received vehicle control article only.

The basis of dose selection was not clearly stated in the study report. However, a 4-week oral toxicity studies was conducted in rats. The high dose of 1000 mg/kg in this study was lethal.

Observations and Results

Clinical Signs: There were no treatment-related changes.

Body Weights: The initial and final body weights in the control group were 227 g and 554 g in males and 176 g and 299 g in females, respectively. High-dose males had significantly decreased terminal body weight gain (~12%) as compared to controls.

Feed Consumption: There were no treatment-related changes.

Ophthalmoscopy: There were no treatment-related changes.

Hematology: There were no treatment-related changes.

Clinical Chemistry: There were no treatment-related changes.

Urinalysis: There were no treatment-related changes.

Gross Pathology: There were no treatment-related changes.

Organ Weights: There were no treatment-related changes.

Histopathology: The tissues listed in the table below from the study report were examined in all control and high-dose animals, and in animals that died or were sacrificed prematurely. Macroscopic lesions, stomach, ileum, jejunum, duodenum, colon, and rectum were also examined microscopically from each animal in the low- and mid-dose groups. There were no treatment-related changes.

adrenal (2)	optic nerve (2) ^a
aorta	ovary (2)
brain	pancreas
cecum	pituitary gland
cervix	prostate
colon	rectum
duodenum	salivary gland [mandibular (2)]
epididymis (2) ^a	sciatic nerve
esophagus	seminal vesicle
eye (2) ^a	skeletal muscle (thigh)
femur with bone marrow (articular surface of the distal end)	skin/subcutis
Harderian gland ^a	spinal cord (cervical, thoracic, and lumbar)
heart	spleen
ileum	sternum with bone marrow
jejunum	stomach
kidney (2)	testis (2) ^a
lesions	thymus
liver	thyroid (2 lobes) with parathyroid
lung with large bronchi	tongue
lymph node (mandibular)	trachea
lymph node (mesenteric)	urinary bladder
mammary gland (females)	uterus
	vagina

a Preserved in modified Davidson's fixative.

Toxicokinetics: The results are shown in the tables below (taken from the study report).

Table 1. Toxicokinetic Parameters for LX1606 in Rat Plasma

Dose Group	Dose Level (mg/kg/day)	Sex	C _{max} (ng/mL)	DN C _{max} (ng/mL)/(mg/kg/day)	T _{max} (hr)	AUC ₀₋₁ (ng•hr/mL)	AUC ₀₋₂₄ (ng•hr/mL)	DN AUC ₀₋₂₄ (ng•hr/mL)/(mg/kg/day)	AUC _{0-∞} (ng•hr/mL)	t _{1/2} (hr)
Day 1										
2 ^a	50	M	1.23	0.0245	2.00	NA	NA	NA	NA	NA
		F	0.831	0.0166	2.00	NA	NA	NA	NA	NA
3	200	M	2.51	0.0126	4.00	14.3	30.9	0.154	NC	NC
		F	3.84	0.0192	4.00	18.8	37.6	0.188	NC	NC
4	500	M	4.22	0.00845	4.00	59.4	59.4	0.119	NC	NC
		F	5.30	0.0106	8.00	82.9	82.9	0.166	NC	NC
Week 13										
2	50	M	12.2	0.244	1.00	36.2	36.2	0.725	NA	NC
		F	21.4	0.428	8.00	228	228	4.55	NA	NC
3	200	M	7.97	0.0399	2.00	80.3	80.3	0.402	NA	NC
		F	28.8	0.144	8.00	78.4	309	1.54	NA	NC
4	500	M	7.14	0.0143	1.00	73.6	73.6	0.147	NA	NC
		F	9.26	0.0185	1.00	117	117	0.235	NA	NC

a Due to limited concentration data, only C_{max}, DN C_{max}, and T_{max} are reported for Group 2 on Day 1.

It appears that some concentration values for LX1606 were close to or below the lower limit of quantitation (< 2.00 ng/mL). LX1606 was quickly converted to LP-778902, its active metabolite. The TK data for LP-778902 were presented in the following sponsor's table.

Table 3. Toxicokinetic Parameters for LP-778902 in Rat Plasma

LX1606										
Dose Group	Dose Level (mg/kg/day)	Sex	C _{max} (ng/mL)	DN C _{max} (ng/mL)/(mg/kg/day)	T _{max} (hr)	AUC _{0-t} (ng•hr/mL)	AUC ₀₋₂₄ (ng•hr/mL)	DN AUC ₀₋₂₄ (ng•hr/mL)/(mg/kg/day)	AUC _{0-∞} (ng•hr/mL)	t _{1/2} (hr)
Day 1										
2	50	M	599	12.0	1.00	1867	1988	39.8	1893	1.18
		F	497	9.94	1.00	1378	1457	29.1	1395	1.22
3	200	M	1463	7.31	2.00	9000	9000	45.0	9035	3.02
		F	1274	6.37	1.00	8119	8119	40.6	8142	2.86
4	500	M	1624	3.25	1.00	17955	17955	35.9	19513	6.70
		F	1303	2.61	1.00	14774	14774	29.5	16770	8.27
Week 13										
2	50	M	725	14.5	0.500	2333	2333	46.7	NA	3.77
		F	770	15.4	1.00	2356	2356	47.1	NA	2.68
3	200	M	1046	5.23	1.00	6885	6885	34.4	NA	6.72
		F	1232	6.16	2.00	8635	8635	43.2	NA	7.70
4	500	M	1603	3.21	1.00	12655	12655	25.3	NA	NC
		F	2114	4.23	1.00	18948	18948	37.9	NA	8.62

The analysis of drug concentrations in samples of dosing formulations from each dose-group was in agreement with target concentrations (between 96% and 101%).

Study title: 26-Week Oral Gavage Chronic Toxicity and Toxicokinetic Study with LP-778914 in Rats with a 4-Week Recovery Phase

Study no.: 7648-289
 Study report location: N/A
 Conducting laboratory and location: (b) (4)
 Date of study initiation: October 6, 2008
 GLP compliance: Yes
 QA statement: Yes
 Drug, lot #, and % purity: See Sponsor's table below

The test article, LP-778914 (also known as LX1606 or LX1032), was supplied by the sponsor as follows.

Test Article ^a	Lot No.	Storage ^b	Purity	Retest Date	Reserve (Archive) Sample
LP-778914	AA-020763-B-5-48 (b) (4)	Protected from light in a refrigerator, set to maintain 2 to 8°C, with desiccant.	98.08%	01 Jul 2010	Collected
LP-778914	AA-020763-B-5-54 (b) (4)	Protected from light in a refrigerator, set to maintain 2 to 8°C, with desiccant.	98.35%	01 Oct 2010	Collected ^b

a See [Certificates of Analysis](#). Information on synthesis methods, composition, or other characteristics that define the test article is on file with the sponsor.

b See [Protocol Deviations](#).

Key Study Findings

LP-778914 (LX1606) was tested at doses of 50, 200, and 500 mg/kg/day by oral gavage in rats for 26 weeks. Two high-dose males were sacrificed due to moribund condition, including clinical signs of toxicity, decreased body weight and weight gain, and decreased food consumption. The major treatment-related changes were degeneration/necrosis in the nonglandular and/or glandular portions of the stomach and/or increased protein droplets in the glandular portion of stomach in the mid- and high-dose animals. The NOAEL was identified at 50 mg/kg/day.

Methods

Doses: 50, 200, and 500 mg/kg/day
 Frequency of dosing: daily
 Route of administration: oral gavage
 Dose volume: 5 mL/kg
 Formulation/Vehicle: 0.25% (w/v) methylcellulose
 Species/Strain: Crl:CD (SD) rats
 Number/Sex/Group: 10 or 15/sex/group
 Age: 6.4 to 7.3 weeks old at initiation
 Weight: Males: 210-288 g
 Females: 168-207 g
 Satellite groups: 3 or 6/sex/group (see Sponsor's table below)
 Unique study design: None
 Deviation from study protocol: There were no deviations that affected the outcome of this study.

Group	No. of Animals ^a		Dose Level (mg/kg/day)	Dose Concentration ^b (mg/mL)
	Male	Female		
Toxicity Animals				
1 (Control) ^c	15	15	0	0
2 (Low)	10	10	50	10
3 (Mid)	15	15	200	40
4 (High)	15	15	500	100
Toxicokinetic Animals				
5 (Control) ^c	3	3	0	0
6 (Low)	6	6	50	10
7 (Mid)	6	6	200	40
8 (High)	6	6	500	100

a Toxicity animals designated for recovery phase sacrifice (up to five animals/sex in Groups 1, 3, and 4, dependent on survival) underwent 4 weeks of recovery following dose administration.

b All dose concentrations were corrected for salt content (correction factor = 1.312).

c Groups 1 and 5 received vehicle control article only.

The basis of dose selection was not clearly stated in the study report. However, 4-week and 3-month oral toxicity studies were conducted in rats. The high dose of 1000 mg/kg/day in the 4-week study was lethal, and the high dose of 500 mg/kg/day LX1606 in the 3-month study was close to the MTD.

Observations and Results

Mortality: Two high-dose males (Days 92 and 150 of the dosing phase) and one TK female (Day 120 of the dosing phase) were sacrificed due to moribund condition. These animals had few feces, rough or red haircoat, general debilitation and/or thin body condition, decreased body weight (12.4% and 29.1%, respectively, as compared to their peak body weight) and food consumption.

Clinical Signs: Rough haircoat was noted in 3/15 high-dose females. Few feces, rough or red haircoat, general debilitation and/or thin body condition were observed in the sacrificed animals.

Body Weights: The initial and final body weights in the control group were 250 g and 724 g in males and 184 g and 358 g in females, respectively. High-dose males had significantly decreased terminal body weight gain (25.7%) as compared to controls.

Feed Consumption: For the duration of the dosing phase (Days 1 through 182), mean food consumption in males given 500 mg/kg/day was decreased by 8.5% relative to controls.

Ophthalmoscopy: There were no treatment-related changes.

Hematology: Decreased absolute reticulocyte counts were noted in the high-dose males mainly due to the two sacrificed animals. The results are presented in the sponsor's table below.

Test Article		Control		LP-778914					
Group		1		2		3		4	
Level		(mg/kg/day)		50		200		500	
Group/ Sex		DSNG 9	RETI DSNG 87	E3/uL DSNG 184	RECO 30	DSNG 9	PRET % DSNG 87	DSNG 184	RECO 30
1M	Mean	382.7	230.7	203.1	178.6	5.4	2.6	2.2	1.9
	SD	36.11	30.35	21.45	25.59	0.59	0.36	0.24	0.23
	N	15	15	14	5	15	15	14	5
2M	Mean	373.4	227.5	198.4	.	5.1	2.5	2.1	.
	SD	61.40	29.28	32.60	.	0.84	0.29	0.34	.
	N	9	10	10	0	9	10	10	0
3M	Mean	411.5	228.3	204.4	171.0	5.7	2.5	2.2	1.8
	SD	45.59	32.03	33.97	27.50	0.54	0.37	0.39	0.26
	N	15	15	15	5	15	15	15	5
4M	Mean	405.4	180.5*	162.2*	126.7*	5.6	2.0*	1.7*	1.3*
	SD	32.95	53.71	41.90	18.68	0.46	0.59	0.43	0.16
	N	15	15	13	4	15	15	13	4
Statistics		P	P	P	P	P	P	P	P
* P< or =0.05									
P = ANOVA (and Dunnett's, if applicable)									

Clinical Chemistry: A mild decrease in globulin concentration occurred in the 500 mg/kg/day males. The results are summarized in the sponsor's table below.

Table 13
Mean Clinical Chemistry Data

Test Article		Control				LP-778914			
Group		1				2 3 4			
Level		(mg/kg/day)				50 200 500			
Group/ Sex		DSNG 9	ALB g/dL DSNG 87	DSNG 184	RECO 30	DSNG 9	GLOB g/dL DSNG 87	DSNG 184	RECO 30
1M	Mean	4.1	4.1	4.3	4.5	1.7	3.0	3.0	3.2
	SD	0.12	0.15	0.17	0.22	0.15	0.20	0.13	0.05
	N	15	15	15	5	15	15	15	5
2M	Mean	4.1	4.3	4.4	.	1.7	2.9	2.9	.
	SD	0.11	0.43	0.23	.	0.08	0.25	0.20	.
	N	9	10	10	0	9	10	10	0
3M	Mean	4.1	4.2	4.3	4.3	1.7	3.0	2.9	2.9
	SD	0.15	0.44	0.26	0.13	0.16	0.33	0.30	0.52
	N	15	15	15	5	15	15	15	5
4M	Mean	4.1	4.1	4.4	4.6	1.6	2.5*	2.4*	2.6
	SD	0.17	0.20	0.23	0.26	0.17	0.46	0.47	0.37
	N	15	15	13	4	15	15	13	4
Statistics		P	P	P	P	P	P	PK	PK

* P< or =0.05

K = rank-transformed data
P = ANOVA (and Dunnett's, if applicable)

Minimal decrease in total protein concentration with a subsequent increase in albumin-to-globulin ratio (AGR) was also noted.

Urinalysis: There were no treatment-related changes.

Gross Pathology: There were no treatment-related changes.

Organ Weights: The kidney/body weight ratio and kidney/brain weight ratio were significantly increased by approximately 8.5% and 13%, respectively, in the high-dose females as compared to the control.

Histopathology: The tissues listed in the table below from the study report were examined in all control and high-dose animals, and in animals that died or were sacrificed prematurely. Macroscopic lesions, stomach, ileum, jejunum, duodenum, colon, rectum, and ovary were also examined microscopically from each animal in the low- and mid-dose groups.

adrenal (2)	optic nerve (2) ^a
aorta	ovary (2)
brain	pancreas
cecum	pituitary gland
cervix	prostate
colon	rectum
duodenum	salivary gland [mandibular (2)]
epididymis (2) ^a	sciatic nerve
esophagus	seminal vesicle
eye (2) ^a	skeletal muscle (thigh)
femur with bone marrow (articular surface of the distal end)	skin/subcutis
Harderian gland ^a	spinal cord (cervical, thoracic, and lumbar)
heart	spleen
ileum	sternum with bone marrow
	stomach
jejunum	testis (2) ^a
kidney (2)	thymus
lesions	thyroid (2 lobes) with parathyroid
liver	tongue
lung with large bronchi	trachea
lymph node (mandibular)	urinary bladder
lymph node (mesenteric)	uterus
mammary gland (females)	vagina

^a Preserved in modified Davidson's fixative.

Test article-related microscopic findings in the main study groups consisted of degeneration/necrosis in the nonglandular and/or glandular portions of the stomach and/or increased protein droplets in the glandular portion of stomach in some animals given 200 or 500 mg/kg. This finding was absent after the 4-week recovery phase. The results are summarized in the sponsor's table below.

Text Table 1
Incidence and Severity^{a, b} of Test Article-Related Stomach Findings - Dosing Phase^{c, d}

Sex		Male				Female			
Group		1	2	3	4	1	2	3	4
mg of LP-778914/kg/day		0	50	200	500	0	50	200	500
Number Examined		10	10	10	11	10	10	10	10
Non-Glandular Stomach									
Degeneration/Necrosis (Limiting Ridge)									
Unremarkable		10	10	9	11	10	10	8	7
Minimal		0	0	1	0	0	0	1	0
Slight		0	0	0	0	0	0	1	2
Moderate		0	0	0	0	0	0	0	1
Mean Severity Grade		0	0	1.0	0	0	0	1.5	2.3
Glandular Stomach									
Increased Protein Droplets (Foveolar Cells)									
Unremarkable		10	10	9	8	10	10	9	6
Minimal		0	0	0	1	0	0	1	2
Slight		0	0	1	2	0	0	0	1
Moderate		0	0	0	0	0	0	0	1
Mean Severity Grade		0	0	2.0	1.7	0	0	1.0	1.8
Epithelial Necrosis (Pyloric Region)									
Unremarkable		10	10	9	10	10	10	10	9
Minimal		0	0	1	1	0	0	0	0
Slight		0	0	0	0	0	0	0	1
Mean Severity Grade		0	0	1.0	1.0	0	0	0	2.0

a Average severity of animals with finding.

b Severity grades- minimal- 1, slight- 2, moderate- 3.

c Unscheduled sacrifice animals were combined with dosing phase terminal sacrifice animals.

d Findings were absent after 4-week recovery phase.

Toxicokinetics: The results are shown in the tables below (taken from the study report).

Table 1. Toxicokinetic Parameters for LX1606 in Rat Plasma

Dose Group	Dose Level (mg/kg/day)	Sex	C _{max} (ng/mL)	DN C _{max} [(ng/mL)/(mg/kg/day)]	T _{max} (hr)	AUC _{0-t} (ng·hr/mL)	AUC ₀₋₂₄ (ng·hr/mL)	DN AUC ₀₋₂₄ [(ng·hr/mL)/(mg/kg/day)]
Day 1								
7	200	M	4.11	0.0206	4.00	23.2	49.7	0.249
		F	15.3	0.0765	8.00	51.1	173	0.865
8	500	M	6.13	0.0123	8.00	81.2	81.2	0.162
		F	5.90	0.0118	8.00	97.5	97.5	0.195
Week 13								
7	200	M	1.92	0.00960	2.00	11.9	25.7	0.129
		F	1.55	0.00775	0.500	9.77	16.0	0.0800
8	500	M	2.52	0.00504	24.0	52.7	52.7	0.105
		F	4.23	0.00846	8.00	62.4	62.4	0.125
Week 26								
7	200	M	0.877	0.00439	2.00	3.05	4.65	0.0233
		F	5.88	0.0294	0.500	24.1	34.3	0.172
8	500	M	2.71	0.00542	8.00	53.5	53.5	0.107
		F	8.35	0.0167	4.00	102	102	0.204

Note: Due to limited data for LX1606, Dose Group 6 was excluded from toxicokinetic analysis.

It appears that some concentration values of LX1606 were close or below to the lower limit of quantitation (< 2.00 ng/mL). LX1606 was quickly converted to LP-778902, its active metabolite. The TK data for LP-778902 are presented in the following table (taken from the study report).

Table 3. Toxicokinetic Parameters for LP-778902 in Rat Plasma

LX1606										
Dose	Dose Level		C _{max}	DN C _{max}	T _{max}	AUC _{0-t}	AUC ₀₋₂₄	DN AUC ₀₋₂₄	AUC _{0-∞}	t _{1/2}
Group (mg/kg/day)	Sex		(ng/mL)	[(ng/mL)/ (mg/kg/day)]	(hr)	(ng·hr/mL)	(ng·hr/mL)	[(ng·hr/mL)/ (mg/kg/day)]	(ng·hr/mL)	(hr)
<u>Day 1</u>										
6	50	M	708	14.2	1.00	2042	2042	40.8	2046	2.60
		F	520	10.4	1.00	1322	1405	28.1	1340	1.23
7	200	M	1467	7.33	2.00	11694	11694	58.5	11722	2.70
		F	1313	6.57	1.00	11100	11100	55.5	11124	2.83
8	500	M	1980	3.96	2.00	21902	21902	43.8	NC	NC
		F	1330	2.66	1.00	15721	15721	31.4	19928	10.9
<u>Week 13</u>										
6	50	M	610	12.2	0.500	2148	2148	43.0	NA	3.33
		F	628	12.6	0.500	2471	2471	49.4	NA	2.99
7	200	M	900	4.50	1.00	8940	8940	44.7	NA	5.61
		F	1194	5.97	1.00	6327	6327	31.6	NA	4.22
8	500	M	1261	2.52	2.00	18427	18427	36.9	NA	NC
		F	2007	4.01	1.00	26632	26632	53.3	NA	6.20
<u>Week 26</u>										
6	50	M	924	18.5	1.00	2726	2726	54.5	NA	3.90
		F	978	19.6	0.500	2729	2729	54.6	NA	2.91
7	200	M	1096	5.48	2.00	9276	9276	46.4	NA	NC
		F	1720	8.60	1.00	8421	8421	42.1	NA	4.16
8	500	M	1447	2.89	2.00	19439	19439	38.9	NA	NC
		F	2210	4.42	4.00	29974	29974	59.9	NA	NC

NA Not applicable.

NC Not calculated.

The analysis of drug concentrations in samples of dosing formulations from each dose-group was in agreement with target concentrations (between 96% and 101%).

Study title: 4-Week Oral Gavage Toxicity and Toxicokinetic Study with LP-778914 in Dogs with a 2-Week Recovery Period

Study no.: 7648-202
 Study report location: N/A
 Conducting laboratory and location: (b) (4)
 Date of study initiation: June 28, 2007
 GLP compliance: Yes
 QA statement: Yes
 Drug, lot #, and % purity: See sponsor's table below

Test Article	Lot No.	Storage	Purity	Stability ^a	Reserve (Archive) Sample
LP-778914 (also known as LX1606)	AA-020763-Batch-01-2007	In a tightly sealed container protected from light in a refrigerator, set to maintain 2 to 8°C, with desiccant	95.87%	See footnote a	Collected ^b

a The sponsor established 3 month accelerated stability from the time of manufacturing (18 June 2007). As the study terminated prior to the end of this 3 month period, the test article was deemed stable during the time frame of dose administration on this study.

b See Protocol Deviations for exception regarding storage conditions.

Key Study Findings

LP-778914 (LX1606) was tested at dosages of 30, 100, and 500/200 mg/kg/day by oral gavage in dogs for 4 weeks. There were no deaths. Treatment at 500 mg/kg/day induced toxicities including clinical signs (dehydration, hypoactivity, thin appearance, and excessive struggling or vocalizing) and body weight loss. The dose of 500 mg/kg/day was reduced to 200 mg/kg/day on day 16. Vomitus and liquid and mucoid feces were noted in the animals treated at 100 and 200/500 mg/kg/day. The NOAEL was identified at 30 mg/kg/day.

Methods

Doses: 30, 100, and 500/200 mg/kg/day (see table below)
 Frequency of dosing: daily
 Route of administration: oral gavage
 Dose volume: 5 mL/kg
 Formulation/Vehicle: 0.25% (w/v) methylcellulose
 Species/Strain: beagle dogs
 Number/Sex/Group: 4 or 5/sex/group
 Age: 5.5 - 6.5 months old at initiation
 Weight: Males: 9.1 - 10.9 kg
 Females: 7.2 - 9.0 kg
 Satellite groups: No
 Unique study design: None
 Deviation from study protocol: There were no deviations that affected the outcome of this study.

Group	No. of Animals ^a		Dose Level (mg/kg/day)	Dose Concentration ^b (mg/mL)
	Male	Female		
1 (Control) ^c	5	5	0	0
2 (Low)	3	3	30	6
3 (Mid)	3	3	100	20
4 (High)	5	5	500/200 ^d	100/40 ^d

a Animals in Groups 1 and 4 (two animals/sex/group) went through a 2 week recovery phase following dose administration.

b All dose concentrations were corrected for salt content (correction factor = 1.312).

c Control animals received control article only.

d Group 4 animals received 500 mg/kg/day (100 mg/mL) on Days 1 through 15 and 200 mg/kg/day (40 mg/mL) on Days 16 through 29.

The basis of dose selection was not clearly stated in the study report. However, the sponsor conducted 7-day dose ranging studies in dogs (# 7648-200, 7648-227, and 7648-228). The doses tested were up to 500 mg/kg/day and the major toxicity was increased incidence of liquid feces and vomiting in these studies.

Observations and Results

Mortality: None.

Clinical Signs: Clinical signs of toxicity including dehydration, hypoactivity, thin appearance, and excessive struggling or vocalizing in the 500 mg/kg/day group. The animals in this group lost weight between days 1 and 15. The dose of 500 mg/kg/day was reduced to 200 mg/kg/day on day 16. Vomitus and liquid/mucoid feces were noted in the animals treated with 100 and 200/500 mg/kg/day.

Body Weights: The initial and final body weights in the control group were 9.9 kg and 10.4 kg in males and 8.3 kg and 8.6 kg in females, respectively. Loss of body weight was noted in the high-dose group (500 mg/kg/ day) between days 1 and 15.

Feed Consumption: Lower food consumption was noted in the animals treated with 500 mg/kg/day.

Ophthalmoscopy: There were no treatment-related changes.

ECG: There were no treatment-related changes.

Hematology: Slight decreases in red blood cell count, hemoglobin, and hematocrit were noted in the high-dose animals.

Clinical Chemistry: There were no treatment-related changes.

Urinalysis: There were no treatment-related changes.

Gross Pathology: There were no treatment-related changes.

Organ Weights: There were no treatment-related changes.

Histopathology: The following tissues or organs were examined microscopically in all animals. There were no clear treatment-related changes.

adrenal (2)	optic nerve (2) ^a
aorta	ovary (2)
brain	pancreas
cecum	pituitary gland
cervix	prostate
colon	rectum
duodenum	salivary gland [mandibular (2)]
epididymis (2)	sciatic nerve
esophagus	skeletal muscle (thigh)
eye (2) ^a	skin/subcutis
femur with bone marrow (articular surface of the distal end)	spinal cord (cervical, thoracic, and lumbar)
gallbladder	spleen
heart	sternum with bone marrow
ileum	stomach
jejunum	testis (2) ^a
kidney (2)	thymus
lacrimal gland	thyroid (2 lobes) with parathyroid
lesions	tongue
liver	trachea
lung with large bronchi	urinary bladder
lymph node (mandibular)	uterus
lymph node (mesenteric)	vagina
mammary gland (females)	

Toxicokinetics: The plasma levels of the active metabolite, LP-778902, were determined on study day 1, day 13, and week 4. The results are summarized in the following tables (taken from study report).

Summary of Mean Toxicokinetic Parameters of LP-778902 in Dog Plasma: Day 1

Dose Group	LP-778914 Dose Level (mg/kg/day)	Sex		C _{max} (ng/mL)	DN C _{max} (ng/mL)/(mg/kg/day)	T _{max} (hr)	AUC ₀₋₂₄ (ng·hr/mL)	DN AUC ₀₋₂₄ (ng·hr/mL)/(mg/kg/day)	AUC ₀₋₄ (ng·hr/mL)	AUC _{0-∞} (ng·hr/mL)	t _{1/2} (hr)
2	30	M	Mean	3003	100	1.00	15956	532	15956	16232	4.64
			SD	673	NA	0	4268	NA	4268	4325	0.06
			N	3	NA	3	3	NA	3	3	3
		F	Mean	3067	102	2.33	19973	666	19973	20482	4.71
			SD	755	NA	1.53	5610	NA	5610	5946	0.10
			N	3	NA	3	3	NA	3	3	3
3	100	M	Mean	3803	38.0	3.00	37100	371	37100	39340	6.21
			SD	2997	NA	1.73	42682	NA	42682	44376	2.09
			N	3	NA	3	3	NA	3	3	3
		F	Mean	2291	22.9	4.67	24014	240	24014	4712	4.72
			SD	2609	NA	3.06	33585	NA	33585	NA	NA
			N	3	NA	3	3	NA	3	2	2
4	500	M	Mean	7774	15.5	7.40	98692	197	98692	30389	5.22
			SD	5478	NA	4.88	79838	NA	79838	NA	NA
			N	5	NA	5	5	NA	5	2	2
		F	Mean	5402	10.8	5.60	64726	129	64726	17635	4.80
			SD	2906	NA	3.29	49160	NA	49160	NA	NA
			N	5	NA	5	5	NA	5	2	2

Summary of Mean Toxicokinetic Parameters of LP-778902 in Dog Plasma: Day 13

Dose Group	LP-778914 Dose Level (mg/kg/day)	Sex		C _{max} (ng/mL)	DN C _{max} (ng/mL)/(mg/kg/day)	T _{max} (hr)	AUC ₀₋₂₄ (ng·hr/mL)	DN AUC ₀₋₂₄ (ng·hr/mL)/(mg/kg/day)	AUC ₀₋₄ (ng·hr/mL)	t _{1/2} (hr)
2	30	M	Mean	4117	137	1.33	21181	706	21181	5.90
			SD	862	NA	0.58	2190	NA	2190	0.35
			N	3	NA	3	3	NA	3	3
		F	Mean	2853	95.1	1.33	17613	587	17613	5.73
			SD	325	NA	0.58	4055	NA	4055	0.30
			N	3	NA	3	3	NA	3	3
3	100	M	Mean	5523	55.2	2.67	40778	408	40778	7.55
			SD	1612	NA	1.15	19568	NA	19568	0.18
			N	3	NA	3	3	NA	3	3
		F	Mean	4820	48.2	3.33	39177	392	39177	7.90
			SD	2215	NA	1.15	24749	NA	24749	2.58
			N	3	NA	3	3	NA	3	3
4	500	M	Mean	16504	33.0	8.00	212060	424	212060	6.46
			SD	7171	NA	2.83	96807	NA	96807	NA
			N	5	NA	5	5	NA	5	1
		F	Mean	23780	47.6	6.40	311524	623	311524	5.07
			SD	13790	NA	2.19	198574	NA	198574	NA
			N	5	NA	5	5	NA	5	1

Summary of Mean Toxicokinetic Parameters of LP-778902 in Dog Plasma: Week 4

Dose Group	LP-778914 Dose Level (mg/kg/day)	Sex		C _{max} (ng/mL)	DN C _{max} (ng/mL)/(mg/kg/day)	T _{max} (hr)	AUC ₀₋₂₄ (ng·hr/mL)	DN AUC ₀₋₂₄ (ng·hr/mL)/(mg/kg/day)	AUC ₀₋₄ (ng·hr/mL)	t _{1/2} (hr)
2	30	M	Mean	2423	80.8	1.33	15036	501	15036	4.55
			SD	365	NA	0.58	2141	NA	2141	0.82
			N	3	NA	3	3	NA	3	3
		F	Mean	2607	86.9	1.33	15187	506	15187	5.27
			SD	124	NA	0.58	2083	NA	2083	0.53
			N	3	NA	3	3	NA	3	3
3	100	M	Mean	8377	83.8	3.33	73479	735	73479	5.57
			SD	3316	NA	1.15	31569	NA	31569	0.25
			N	3	NA	3	3	NA	3	3
		F	Mean	6763	67.6	3.33	55050	551	55050	6.78
			SD	1000	NA	1.15	8372	NA	8372	0.93
			N	3	NA	3	3	NA	3	3
4	200	M	Mean	11630	58.2	3.60	120118	601	120118	5.87
			SD	4548	NA	0.89	47241	NA	47241	0.84
			N	5	NA	5	5	NA	5	4
		F	Mean	13000	65.0	4.80	134021	670	134021	5.51
			SD	3362	NA	1.79	30461	NA	30461	0.64
			N	5	NA	5	5	NA	5	4

The analysis of drug concentrations in samples of dosing formulations from each dose-group was in agreement with target concentrations (between 96% and 101%).

Study title: 3-Month Toxicity and Toxicokinetic Study in Dogs Administered LP-778914 with a 1-Month Recovery Phase

Study no.: 7648-251
Study report location: N/A
Conducting laboratory and location: (b) (4)
Date of study initiation: March 10, 2008
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: See Sponsor's table below

Test Article	Lot No.	Storage	Purity	Expiration Date	Reserve (Archive) Sample
LP-778914-03 (also known as LX1606 and LX1032)	AA-020763-Batch-01-2008	Stored protected from light in a refrigerator, set to maintain 2 to 8°C, with desiccant ^a	98.0%	14 Nov 2008	Collected

^a See [Protocol Deviations](#).

Key Study Findings

LP-778914 (LX1606) was tested at doses of 30, 100, and 200 mg/kg/day by oral gavage in dogs for 13 weeks. There were no deaths. The major treatment-related

changes were clinical signs of toxicity including liquid feces in the mid- and high-dose groups. These are not considered as adverse effects. Hypospermatogenesis in testis was noted mainly in the low-dose group; therefore the clinical significance is uncertain. NOAEL was identified at 200 mg/kg/day.

Methods

Doses:	30, 100, and 200 mg/kg/day (see table below)
Frequency of dosing:	Daily
Route of administration:	oral gavage
Dose volume:	5 mL/kg
Formulation/Vehicle:	0.25% (w/v) methylcellulose
Species/Strain:	beagle dogs
Number/Sex/Group:	4 or 6/sex/group
Age:	23 to 27 weeks old at initiation
Weight:	Males: 8.6-10.3 kg Females: 6.2-7.8 kg
Satellite groups:	None
Unique study design:	None
Deviation from study protocol:	There were no deviations that affected the outcome of this study.

Group ^c	No. of Animals ^a		Dose Level (mg/kg/day)	Dose Concentration ^b (mg/mL)
	Male	Female		
1 (Control)	5	5	0	0
2 (Low)	3	3	30	6
3 (Mid)	5	5	100	20
4 (High)	5	5	200	40

- a Animals designated for recovery sacrifice (2 animals/sex in Groups 1, 3, and 4, dependent on survival) underwent 1 month of recovery following dose administration.
- b All dose concentrations were corrected for salt content (correction factor = 1.312).
- c Group 1 received vehicle control article only.

The basis of dose selection was not clearly stated in the study report. However, the Sponsor conducted a 4-week oral toxicity study in dogs. The high dose of 500 mg/kg in the 4-week study was above MTD.

Observations and Results

Mortality: One control female was sacrificed in a moribund condition during the recovery phase.

Clinical Signs: Liquid feces was noted in the mid- and high-dose groups.

Body Weights: The initial and final body weights in the control group were 9.5 kg and 11.4 kg in males and 7.2 kg and 8.9 kg in females, respectively. There were no treatment-related changes.

Feed Consumption: There were no treatment-related changes.

Ophthalmoscopy: There were no treatment-related changes.

ECG: There were no treatment-related changes.

Hematology: There were no treatment-related changes.

Clinical Chemistry: There were no treatment-related changes.

Urinalysis: There were no treatment-related changes.

Gross Pathology: There were no treatment-related changes.

Organ Weights: There were no treatment-related changes.

Histopathology: The following tissues or organs were examined microscopically in all animals.

adrenal (2)	optic nerve (2) ^a
aorta	ovary (2)
brain	pancreas
cecum	pituitary gland
cervix	prostate
colon	rectum
duodenum	salivary gland [mandibular (2)]
epididymis (2)	sciatic nerve
esophagus	skeletal muscle (thigh)
eye (2) ^a	skin/subcutis
femur with bone marrow (articular surface of the distal end)	spinal cord (cervical, thoracic, and lumbar)
gallbladder	spleen
heart	sternum with bone marrow
ileum	stomach
jejunum	testis (2) ^a
kidney (2)	thymus
lacrimal gland	thyroid (2 lobes) with parathyroid
lesions	tongue
liver	trachea
lung with large bronchi	urinary bladder
lymph node (mandibular)	uterus
lymph node (mesenteric)	vagina
mammary gland (females)	

In the main study groups, minimal to moderate hypospermatogenesis in testis was noted in all males in the low-dose group and minimal or slight hypospermatogenesis was also observed in two high-dose males. At the end of the recovery phase, one high-dose male had moderate hypospermatogenesis and minimal degeneration, and one mid-dose male had slight hypospermatogenesis, slight degeneration, and minimal chronic inflammation. These alterations were not clearly dose dependent and the clinical significance is uncertain.

Toxicokinetics: The plasma levels of the parent compound and its active metabolite were determined on study day 1, week 7, and week 13. The TK parameters for the parent compound are shown in the tables below (taken from the study report).

Table 1. Summary of the Mean Toxicokinetic Parameters for LX1606 in Dog Plasma: Day 1

LX1606														
Dose	Dose Level			C _{max}	DN C _{max}	T _{max}	AUC _{0-t}	AUC ₀₋₂₄	DN AUC ₀₋₂₄	AUC _{0-∞}	t _{1/2}			
Group	(mg/kg/day)	Gender		(ng/mL)	(ng/mL)/(mg/kg/day)	(hr)	(ng•hr/mL)	(ng•hr/mL)	(ng•hr/mL)/(mg/kg/day)	(ng•hr/mL)	(hr)			
2	30	M	Mean	86.0	2.87	1.50	111	139	4.62	150	0.733			
			SD	104.2	NA	0.87	40	41	NA	NA	NA			
			N	3	NA	3	3	3	NA	1	1			
		F	Mean	143	4.77	0.833	288	339	11.3	410	2.31			
			SD	65	NA	0.289	132	162	NA	NA	NA			
			N	3	NA	3	3	3	NA	1	1			
		3	100	M	Mean	187	1.87	1.20	660	941	9.41	283	3.44	
					SD	127	NA	1.57	662	940	NA	NA	2.12	
					N	5	NA	5	5	5	NA	2	3	
F	Mean			150	1.50	1.10	528	647	6.47	350	1.13			
	SD			91	NA	0.82	478	538	NA	NA	NA			
	N			5	NA	5	5	5	NA	2	2			
4	200	M	Mean	174	0.868	2.30	1299	1489	7.45	1987	4.07			
			SD	44	NA	3.25	1071	912	NA	NA	NA			
			N	5	NA	5	5	5	NA	1	1			
		F	Mean	200	1.00	0.500	512	877	4.39	310	1.68			
			SD	75	NA	0	481	1115	NA	68	0.54			
			N	5	NA	5	5	5	NA	3	3			

Table 2. Summary of the Mean Toxicokinetic Parameters for LX1606 in Dog Plasma: Week 7

LX1606													
Dose Group	Dose Level (mg/kg/day)	Gender		C _{max} (ng/mL)	DN C _{max} (ng/mL)/(mg/kg/day)	T _{max} (hr)	AUC _{0-t} (ng•hr/mL)	AUC ₀₋₂₄ (ng•hr/mL)	DN AUC ₀₋₂₄ (ng•hr/mL)/(mg/kg/day)	t _{1/2} (hr)			
2	30	M	Mean	154	5.13	0.667	493	581	19.4	1.76			
			SD	65	NA	0.289	93	81	NA	NA			
			N	3	NA	3	3	3	NA	2			
		F	Mean	175	5.83	0.833	495	595	19.8	2.12			
			SD	57	NA	0.289	79	35	NA	0.70			
			N	3	NA	3	3	3	NA	3			
3	100	M	Mean	345	3.45	2.60	2282	2282	22.8	3.37			
			SD	66	NA	1.34	587	587	NA	0.11			
			N	5	NA	5	5	5	NA	3			
		F	Mean	324	3.24	2.40	1962	1962	19.6	3.65			
			SD	85	NA	0.89	779	779	NA	0.45			
			N	5	NA	5	5	5	NA	4			
4	200	M	Mean	621	3.11	3.00	5451	5451	27.3	3.61			
			SD	186	NA	1.41	1243	1243	NA	NA			
			N	5	NA	5	5	5	NA	2			
		F	Mean	585	2.92	1.70	4842	4842	24.2	3.32			
			SD	120	NA	0.67	1471	1471	NA	0.21			
			N	5	NA	5	5	5	NA	4			

Table 3. Summary of the Mean Toxicokinetic Parameters for LX1606 in Dog Plasma: Week 13

LX1606										
Dose Group	Dose Level (mg/kg/day)	Gender		C _{max} (ng/mL)	DN C _{max} (ng/mL)/(mg/kg/day)	T _{max} (hr)	AUC _{0-t} (ng•hr/mL)	AUC ₀₋₂₄ (ng•hr/mL)	DN AUC ₀₋₂₄ (ng•hr/mL)/(mg/kg/day)	t _{1/2} (hr)
2	30	M	Mean	183	6.09	0.667	528	595	19.8	1.37
			SD	57	NA	0.289	102	75	NA	NA
			N	3	NA	3	3	3	NA	2
		F	Mean	197	6.57	0.667	543	590	19.7	1.42
			SD	45	NA	0.289	164	156	NA	0.27
			N	3	NA	3	3	3	NA	3
3	100	M	Mean	389	3.89	1.80	1723	2075	20.8	2.59
			SD	46	NA	0.45	518	435	NA	NA
			N	5	NA	5	5	5	NA	2
		F	Mean	381	3.81	1.80	1683	1949	19.5	3.56
			SD	104	NA	0.45	509	519	NA	NA
			N	5	NA	5	5	5	NA	1
4	200	M	Mean	574	2.87	2.80	5531	5531	27.7	2.99
			SD	164	NA	1.10	1974	1974	NA	0.16
			N	5	NA	5	5	5	NA	3
		F	Mean	506	2.53	2.80	4011	4011	20.1	2.92
			SD	65	NA	1.10	1016	1016	NA	0.08
			N	5	NA	5	5	5	NA	3

The TK parameters for LP-778902, the active metabolite, are summarized in the following table (taken from the study report).

Table 5. Summary of the Mean Toxicokinetic Parameters for LP-778902 in Dog Plasma: Day 1

LX1606											
Dose Group	Dose Level (mg/kg/day)	Gender		C _{max} (ng/mL)	DN C _{max} (ng/mL)/(mg/kg/day)	T _{max} (hr)	AUC ₀₋₁ (ng•hr/mL)	AUC ₀₋₂₄ (ng•hr/mL)	DN AUC ₀₋₂₄ (ng•hr/mL)/(mg/kg/day)	AUC _{0-∞} (ng•hr/mL)	t _{1/2} (hr)
2	30	M	Mean	1502	50.1	1.50	5121	5121	171	5170	3.94
			SD	861	NA	0.87	1574	1574	NA	1577	0.14
			N	3	NA	3	3	3	NA	3	3
		F	Mean	2307	76.9	1.33	11844	11844	395	12057	4.25
			SD	959	NA	0.58	6512	6512	NA	6664	0.13
			N	3	NA	3	3	3	NA	3	3
3	100	M	Mean	3646	36.5	2.40	23390	23390	234	16564	4.60
			SD	2217	NA	1.52	17185	17185	NA	6852	0.54
			N	5	NA	5	5	5	NA	3	3
		F	Mean	3674	36.7	2.00	23053	23053	231	16595	4.49
			SD	1457	NA	1.22	15789	15789	NA	4497	0.56
			N	5	NA	5	5	5	NA	4	4
4	200	M	Mean	3834	19.2	2.80	40855	40855	204	38121	5.34
			SD	1394	NA	1.64	16332	16332	NA	NA	NA
			N	5	NA	5	5	5	NA	1	1
		F	Mean	3114	15.6	1.10	19751	19751	98.8	20182	4.37
			SD	823	NA	0.55	15413	15413	NA	15942	0.34
			N	5	NA	5	5	5	NA	5	5

Table 6. Summary of the Mean Toxicokinetic Parameters for LP-778902 in Dog Plasma: Week 7

LX1606											
Dose Group	Dose Level (mg/kg/day)	Gender		C _{max} (ng/mL)	DN C _{max} (ng/mL)/(mg/kg/day)	T _{max} (hr)	AUC ₀₋₁ (ng•hr/mL)	AUC ₀₋₂₄ (ng•hr/mL)	DN AUC ₀₋₂₄ (ng•hr/mL)/(mg/kg/day)		t _{1/2} (hr)
2	30	M	Mean	1749	58.3	1.00	10145	10145	338		4.70
			SD	887	NA	0	2483	2483	NA		0.04
			N	3	NA	3	3	3	NA		3
		F	Mean	2113	70.4	1.67	14466	14466	482		4.57
			SD	400	NA	0.58	3249	3249	NA		0.61
			N	3	NA	3	3	3	NA		3
3	100	M	Mean	6672	66.7	3.20	59233	59233	592		5.92
			SD	1711	NA	1.10	22643	22643	NA		NA
			N	5	NA	5	5	5	NA		2
		F	Mean	7120	71.2	3.20	62414	62414	624		5.79
			SD	3059	NA	1.10	28462	28462	NA		NA
			N	5	NA	5	5	5	NA		2
4	200	M	Mean	12124	60.6	4.00	127137	127137	636		NA
			SD	3233	NA	0	24467	24467	NA		NA
			N	5	NA	5	5	5	NA		0
		F	Mean	10134	50.7	4.00	105423	105423	527		NA
			SD	1256	NA	0	26591	26591	NA		NA
			N	5	NA	5	5	5	NA		0

Table 7. Summary of the Mean Toxicokinetic Parameters for LP-778902 in Dog Plasma: Week 13

LX1606										
Dose Group	Dose Level (mg/kg/day)	Gender		C _{max} (ng/mL)	DN C _{max} (ng/mL)/(mg/kg/day)	T _{max} (hr)	AUC _{0-t} (ng•hr/mL)	AUC ₀₋₂₄ (ng•hr/mL)	DN AUC ₀₋₂₄ (ng•hr/mL)/(mg/kg/day)	t _{1/2} (hr)
2	30	M	Mean	1887	62.9	1.33	11050	11050	368	4.95
			SD	431	NA	0.58	2799	2799	NA	0.26
			N	3	NA	3	3	3	NA	3
		F	Mean	3170	106	1.33	19341	19341	645	5.00
			SD	1406	NA	0.58	9374	9374	NA	0.68
			N	3	NA	3	3	3	NA	3
3	100	M	Mean	6752	67.5	2.80	59948	59948	599	5.84
			SD	1084	NA	1.10	15028	15028	NA	0.42
			N	5	NA	5	5	5	NA	3
		F	Mean	7664	76.6	2.80	65096	65096	651	5.87
			SD	2253	NA	1.10	19945	19945	NA	NA
			N	5	NA	5	5	5	NA	2
4	200	M	Mean	14058	70.3	4.00	162764	162764	814	NA
			SD	4359	NA	0	43970	43970	NA	NA
			N	5	NA	5	5	5	NA	0
		F	Mean	10978	54.9	4.00	109845	109845	549	NA
			SD	1505	NA	0	18797	18797	NA	NA
			N	5	NA	5	5	5	NA	0

The analysis of drug concentrations in samples of dosing formulations from each dose-group was in agreement with target concentrations (between 96% and 101%).

Study title: 39-Week Oral Gavage Chronic Toxicity and Toxicokinetic Study with LP-778914 in Dogs with a 4-Week Recovery Period

Study no.: 7648-288
 Study report location: N/A
 Conducting laboratory and location: (b) (4)
 Date of study initiation: August 18, 2008
 GLP compliance: Yes
 QA statement: Yes
 Drug, lot #, and % purity: See Sponsor's table below

Test Article ^a	Lot No.	Storage	Purity	Retest Date	Reserve (Archive) Sample
LP-778914	AA-020763-B-5-48 (b) (4)	Protected from light in a refrigerator, set to maintain 2 to 8°C, with desiccant ^b	98.08%	01 Jul 2010	Collected
LP-778914	AA-020763-B-5-54 (b) (4)	Protected from light in a refrigerator, set to maintain 2 to 8°C, with desiccant	98.35%	01 Oct 2010	Collected ^b

a See [Certificates of Analysis](#). Information on synthesis methods, composition, or other characteristics that define the test article is on file with the sponsor.

b See [Protocol Deviations](#).

Key Study Findings

LP-778914 (LX1606) was tested at doses of 75, 150, and 300 mg/kg/day by oral gavage in dogs for 39 weeks. There were no deaths. The major treatment related changes were clinical signs of toxicity including liquid feces in the mid and high dose group. These are not considered as adverse effects. The NOAEL was identified at 300 mg/kg/day.

Methods:

Doses: 75, 150, and 300 mg/kg/day (see table below)
 Frequency of dosing: daily
 Route of administration: oral gavage
 Dose volume: 5 mL/kg
 Formulation/Vehicle: 0.25% (w/v) methylcellulose
 Species/Strain: beagle dogs
 Number/Sex/Group: 4 or 6/sex/group
 Age: 4.8 to 5.8 months
 Weight: Males: 7.1-9.7 kg
 Females: 6.1-8.3 kg
 Satellite groups: None
 Unique study design: None
 Deviation from study protocol: There were no deviations that affected the outcome of this study.

Group ^a	No. of Animals ^b		Dose Level (mg/kg/day)	Dose Concentration ^c (mg/mL)
	Male	Female		
1 (Control)	6	6	0	0
2 (Low)	4	4	75	15
3 (Mid)	6	6	150	30
4 (High)	6	6	300	60

a Group 1 received vehicle control article only.

b Animals designated for recovery sacrifice (two animals/sex in Groups 1, 3, and 4) underwent 4 weeks of recovery following dose administration.

c All dose concentrations were corrected for salt content (correction factor = 1.312).

The basis of dose selection was not clearly stated in the study report. However, the Sponsor conducted 4-week and 3-month oral toxicity studies in dogs. The high dose of 500 mg/kg/day in the 4-week study was above MTD, and the high dose of 200 mg/kg/day in the 3-month study was NOAEL.

Observations and Results

Mortality: None

Clinical Signs: Increased incidence of liquid feces was noted in the 150 and 300 mg/kg/day groups. The results are summarized in the sponsor's table below.

Text Table 1
Dosing Phase - Incidence of Liquid Feces

Dose Level (mg/kg/day)	0	75	150	300
Number of Animals/Sex/Group	6	4	6	6
Male	3 ^a 2 ^b (0-5) ^c	4 ^a 12 ^b (5-22) ^c	6 ^a 39 ^b (7-65) ^c	6 ^a 64 ^b (18-92) ^c
Female	6 ^a 3 ^b (1-8) ^c	3 ^a 13 ^b (0-29) ^c	6 ^a 46 ^b (5-84) ^c	6 ^a 53 ^b (26-101) ^c

a Number of animals noted with liquid feces during the dosing phase.

b Mean number of days liquid feces was noted during 275 days of observation, rounded to nearest whole number.

c Frequency (range of number of days) liquid feces was noted for individual animals during 275 days of observation.

Body Weights: The initial and final body weights in control group were 8.3 kg and 11.6 kg in males and 7.1 kg and 9.7 kg in females. There were no-treatment related changes.

Feed Consumption: There were no treatment-related changes.

Ophthalmoscopy: There were no treatment-related changes.

ECG: There were no treatment-related changes.

Hematology: There were no treatment-related changes.

Clinical Chemistry: There were no treatment-related changes.

Urinalysis: There were no treatment related changes.

Gross Pathology: There were no treatment-related changes.

Organ Weights: There were no treatment-related changes.

Histopathology: The following tissues or organs were examined microscopically in all animals.

adrenal (2)	optic nerve (2) ^a
aorta	ovary (2)
brain	pancreas
cecum	pituitary gland
cervix	prostate
colon	rectum
duodenum	salivary gland [mandibular (2)]
epididymis (2)	sciatic nerve
esophagus	skeletal muscle (thigh)
eye (2) ^a	skin/subcutis
femur with bone marrow (articular surface of the distal end)	spinal cord (cervical, thoracic, and lumbar)
gallbladder	spleen
heart	sternum with bone marrow
ileum	stomach
jejunum	testis (2) ^a
kidney (2)	thymus
lacrimal gland	thyroid (2 lobes) with parathyroid
lesions	tongue
liver	trachea
lung with large bronchi	urinary bladder
lymph node (mandibular)	uterus
lymph node (mesenteric)	vagina
mammary gland (females)	

a Preserved in modified Davidson's fixative.

There were no treatment-related changes. Although hypospermatogenesis in testis occurred in the 13-week oral toxicity study in dogs, this finding was not observed in the present study, which used higher doses.

Toxicokinetics: The plasma levels of the parent compound and its active metabolite were determined on study day 1, week 13, and week 39. The TK parameters for the parent compound are shown in the tables below (taken from the study report).

Table 1. Summary of the Mean Toxicokinetic Parameters for LX1606 in Dog Plasma: Day 1

Dose Group	Dose Level (mg/kg/day)	Sex		C _{max} (ng/mL)	DN C _{max} [(ng/mL)/(mg/kg/day)]	T _{max} (hr)	AUC ₀₋₄ (ng·hr/mL)	AUC ₀₋₂₄ (ng·hr/mL)	DN AUC ₀₋₂₄ [(ng·hr/mL)/(mg/kg/day)]	AUC _{0-∞} (ng·hr/mL)	t _{1/2} (hr)
2	75	M	Mean	200	2.66	1.00	679	1004	13.4	125	0.762
			SD	49		0.71	371	606		NA	NA
			N	4		4	4	4		1	1
		F	Mean	196	2.61	0.875	637	999	13.3	1009	3.36
			SD	65		0.750	237	160		NA	NA
			N	4		4	4	4		2	2
3	150	M	Mean	232	1.54	3.17	1754	2009	13.4	433	2.66
			SD	94		2.84	1450	1276		NA	NA
			N	6		6	6	6		1	1
		F	Mean	165	1.10	0.583	422	553	3.69	500	1.79
			SD	34		0.204	163	219		174	0.35
			N	6		6	6	6		3	3
4	300	M	Mean	243	0.81	3.33	1940	2154	7.18	771	5.07
			SD	138		3.66	2125	1977		NA	NA
			N	6		6	6	6		1	1
		F	Mean	241	0.80	3.17	2010	2183	7.28	1818	2.69
			SD	70		2.84	1659	1520		NA	NA
			N	6		6	6	6		2	2

Table 2. Summary of the Mean Toxicokinetic Parameters for LX1606 in Dog Plasma: Week 13

Dose Group	Dose Level (mg/kg/day)	Sex		C _{max} (ng/mL)	DN C _{max} [(ng/mL)/(mg/kg/day)]	T _{max} (hr)	AUC ₀₋₄ (ng·hr/mL)	AUC ₀₋₂₄ (ng·hr/mL)	DN AUC ₀₋₂₄ [(ng·hr/mL)/(mg/kg/day)]	t _{1/2} (hr)
2	75	M	Mean	190	2.53	1.63	715	904	12.1	2.56
			SD	57		0.75	222	269		NA
			N	4		4	4	4		1
		F	Mean	378	5.04	2.00	1266	1453	19.4	NA
			SD	117		0	321	338		NA
			N	4		4	4	4		0
3	150	M	Mean	433	2.89	2.67	2760	2885	19.2	3.21
			SD	122		1.03	790	781		0.63
			N	6		6	6	6		3
		F	Mean	462	3.08	3.00	2334	2596	17.3	2.99
			SD	204		1.10	1031	965		NA
			N	6		6	6	6		1
4	300	M	Mean	672	2.24	5.33	7251	7251	24.2	NA
			SD	153		2.07	1370	1370		NA
			N	6		6	6	6		0
		F	Mean	730	2.43	4.33	7075	7075	23.6	2.97
			SD	169		1.97	1737	1737		NA
			N	6		6	6	6		1

Table 3. Summary of the Mean Toxicokinetic Parameters for LX1606 in Dog Plasma: Week 39

Dose Group	Dose Level (mg/kg/day)	Sex		C _{max} (ng/mL)	DN C _{max} [(ng/mL)/(mg/kg/day)]	T _{max} (hr)	AUC ₀₋₁ (ng·hr/mL)	AUC ₀₋₂₄ (ng·hr/mL)	DN AUC ₀₋₂₄ [(ng·hr/mL)/(mg/kg/day)]	t _{1/2} (hr)
2	75	M	Mean	208	2.77	2.00	1137	1289	17.2	3.57
			SD	71		0	329	368		NA
			N	4		4	4	4		2
		F	Mean	367	4.90	2.00	1781	1932	25.8	3.37
			SD	105		0	418	481		0.09
			N	4		4	4	4		3
3	150	M	Mean	427	2.85	1.83	3454	3454	23.0	3.71
			SD	76		1.17	922	922		0.57
			N	6		6	6	6		5
		F	Mean	494	3.29	3.00	3148	3148	21.0	3.96
			SD	179		1.10	754	754		0.63
			N	6		6	6	6		3
4	300	M	Mean	456	1.52	3.83	4698	4698	15.7	3.69
			SD	108		2.40	966	966		NA
			N	6		6	6	6		2
		F	Mean	577	1.92	4.33	5946	5946	19.8	4.12
			SD	177		1.97	2453	2453		NA
			N	6		6	6	6		1

The TK parameters for LP-778902, the active metabolite, are summarized in the following table (taken from the study report).

Table 5. Summary of the Mean Toxicokinetic Parameters for LP-778902 in Dog Plasma: Day 1

Dose Group	LX1606 Dose Level (mg/kg/day)	Sex		C _{max} (ng/mL)	DN C _{max} [(ng/mL)/(mg/kg/day)]	T _{max} (hr)	AUC ₀₋₁ (ng·hr/mL)	AUC ₀₋₂₄ (ng·hr/mL)	DN AUC ₀₋₂₄ [(ng·hr/mL)/(mg/kg/day)]	AUC _{0-∞} (ng·hr/mL)	t _{1/2} (hr)
2	75	M	Mean	3345	44.6	1.38	26464	26464	353	27364	4.67
			SD	1097		0.75	15597	15597		16235	0.54
			N	4		4	4	4		4	4
		F	Mean	2945	39.3	2.77	29444	29444	393	40273	5.46
			SD	376		1.47	6783	6783		NA	NA
			N	4		4	4	4		1	1
3	150	M	Mean	4463	29.8	5.00	48277	48277	322	17051	3.68
			SD	1791		2.45	22141	22141		NA	NA
			N	6		6	6	6		1	1
		F	Mean	3037	20.2	1.25	17917	17917	119	18263	4.27
			SD	967		0.61	8051	8051		8272	0.42
			N	6		6	6	6		6	6
4	300	M	Mean	5985	20.0	4.58	70172	70172	234	19309	4.46
			SD	3979		3.77	57699	57699		NA	NA
			N	6		6	6	6		2	2
		F	Mean	4862	16.2	5.17	56493	56493	188	30123	4.37
			SD	1205		3.25	27593	27593		NA	NA
			N	6		6	6	6		2	2

Table 6. Summary of the Mean Toxicokinetic Parameters for LP-778902 in Dog Plasma: Week 13

Dose Group	LX1606 Dose Level (mg/kg/day)	Sex		C _{max} (ng/mL)	DN C _{max} [(ng/mL)/(mg/kg/day)]	T _{max} (hr)	AUC ₀₋₄ (ng·hr/mL)	AUC ₀₋₂₄ (ng·hr/mL)	DN AUC ₀₋₂₄ [(ng·hr/mL)/(mg/kg/day)]	t _{1/2} (hr)
2	75	M	Mean	3618	48.2	2.50	27686	27686	369	5.66
			SD	1794		1.00	11646	11646		0.30
			N	4		4	4	4		3
		F	Mean	4785	63.8	2.50	37579	37579	501	5.57
			SD	1530		1.00	9229	9229		0.28
			N	4		4	4	4		3
3	150	M	Mean	7092	47.3	3.67	70395	70395	469	4.99
			SD	1039		0.82	13069	13069		NA
			N	6		6	6	6		1
		F	Mean	6523	43.5	4.00	56760	56760	378	NA
			SD	3279		0	20676	20676		NA
			N	6		6	6	6		0
4	300	M	Mean	14628	48.8	6.67	199269	199269	664	NA
			SD	5390		2.07	73379	73379		NA
			N	6		6	6	6		0
		F	Mean	13990	46.6	4.67	162450	162450	542	NA
			SD	3541		1.63	44913	44913		NA
			N	6		6	6	6		0

Table 7. Summary of the Mean Toxicokinetic Parameters for LP-778902 in Dog Plasma: Week 39

Dose Group	LX1606 Dose Level (mg/kg/day)	Sex		C _{max} (ng/mL)	DN C _{max} [(ng/mL)/(mg/kg/day)]	T _{max} (hr)	AUC ₀₋₄ (ng·hr/mL)	AUC ₀₋₂₄ (ng·hr/mL)	DN AUC ₀₋₂₄ [(ng·hr/mL)/(mg/kg/day)]	t _{1/2} (hr)
2	75	M	Mean	3780	50.4	2.50	34221	34221	456	5.59
			SD	664		1.00	10025	10025		0.44
			N	4		4	4	4		3
		F	Mean	4920	65.6	2.50	44139	44139	589	5.92
			SD	233		1.00	5251	5251		0.14
			N	4		4	4	4		3
3	150	M	Mean	7307	48.7	4.00	77835	77835	519	NA
			SD	1328		0	22913	22913		NA
			N	6		6	6	6		0
		F	Mean	8773	58.5	4.00	74435	74435	496	NA
			SD	3034		0	18030	18030		NA
			N	6		6	6	6		0
4	300	M	Mean	11593	38.6	4.67	132949	132949	443	NA
			SD	5748		1.63	49250	49250		NA
			N	6		6	6	6		0
		F	Mean	11362	37.9	4.67	128720	128720	429	NA
			SD	2193		1.63	38611	38611		NA
			N	6		6	6	6		0

The analysis of drug concentrations in samples of dosing formulations from each dose-group was in agreement with target concentrations (between 96% and 101%).

7 Genetic Toxicology

LX1606 was negative in the Ames test, the in vitro chromosome aberration test, and the in vivo rat micronucleus test.

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study title: *Salmonella-Escherichia coli*/Mammalian-Microsome Reverse Mutation Assay with a Confirmatory Assay

Study no.: 7648-191
Study report location: N/A
Conducting laboratory and location: (b) (4)
Date of study initiation: April 16, 2007
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: See table below

Test Article	Batch No.	Description	Storage	Purity	Expiration Date
LP-778914 (also known as LX1606)	03-005	White powder	Refrigerated, 2 to 8°C, with desiccant	97.96%	01 May 2008
LP-778902	02-004	Light-yellow powder	Refrigerated, 2 to 8°C, with desiccant	97.5%	18 Sep 2008

Key Study Findings

LP-778914 and the active metabolite, LP-778902, were tested at concentrations of 3.33, 10.0, 33.3, 100, 333, 1000, and 5000 µg per plate using the plate incorporation method. The results indicate that both LP-778914 and LP-778902 were not mutagenic under the study conditions.

Methods

Strains: TA98, TA100, TA1535 and TA1537 and *Escherichia coli* WP2 *uvrA*

Concentrations in definitive study: 3.33, 10.0, 33.3, 100, 333, 1000, and 5000 µg per plate

Basis of concentration selection: the maximum dose of 5000 µg per plate was tested

Negative control: dimethyl sulfoxide (DMSO)

Positive control: See table below

Formulation/Vehicle: DMSO

Incubation & sampling time: 52 +/- 4 hours at 37°C using the plate incorporation method

Table I. Positive Controls

Tester Strain	S9 Mix	Positive Control	Dose (µg/plate)
TA98	+	benzo[a]pyrene	2.5
TA98	-	2-nitrofluorene	1.0
TA100	+	2-aminoanthracene	2.5
TA100	-	sodium azide	2.0
TA1535	+	2-aminoanthracene	2.5
TA1535	-	sodium azide	2.0
TA1537	+	2-aminoanthracene	2.5
TA1537	-	ICR-191	2.0
WP2 <i>uvrA</i>	+	2-aminoanthracene	25.0
WP2 <i>uvrA</i>	-	4-nitroquinoline-N-oxide	1.0

Study Validity

The positive controls significantly increased the number of revertant colonies compared to the solvent controls.

Results

The results are summarized in the sponsor's tables below.

Table 4 : Mutagenicity Assay Results – Summary—LP-778914

Test Article ID: LP-778914

Assay No.: 29093-0-409OECD

Trial No.: B1

Date Plated: 27-Jun-07

Vehicle: DMSO

Date Counted: 03-Jul-07, 05-Jul-07

Plating Aliquot: 50 µL

Mean Revertants Per Plate with Standard Deviation												Back-ground Lawn ^a
Dose/Plate		TA98		TA100		TA1535		TA1537		WP2uvrA		
		Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	
Microsomes: Rat Liver												
Vehicle Control		26	6	85	9	10	4	22	5	17	5	N
Test Article	3.33 µg	29	3	96	12	8	2	22	5	NT	--	N
	10.0 µg	32	2	84	3	8	2	25	7	17	4	N
	33.3 µg	25	3	80	11	10	2	27	2	13	3	N
	100 µg	24	6	83	7	10	5	19	3	16	2	N
	333 µg	27	6	78	8	12	3	23	4	14	4	N
	1000 µg	20	2	21	6	9	1	7	3	17	7	N/NP ^d
	2500 µg	NT	--	NT	--	NT	--	NT	--	11	3	NP
5000 µg	16	1	1	1	4	2	0	1	12	3	NP/RP ^e	
Positive Control ^b		283	48	688	123	140	14	149	28	410	85	N
Microsomes: None												
Vehicle Control		10	2	72	7	9	1	12	5	8	3	N
Test Article	0.333 µg	11	6	60	9	8	5	10	1	NT	--	N
	1.00 µg	11	2	74	4	10	2	14	7	NT	--	N
	3.33 µg	13	6	71	14	10	2	10	0	NT	--	N
	10.0 µg	7	3	75	10	10	3	11	6	14	6	N
	33.3 µg	19	2	55	12	7	1	8	3	10	4	N/R ^f
	100 µg	12	2	10	2	3	1	0	1	11	4	N/R ^f
	333 µg	0	0	0	0	1	2	0	0	11	4	N/R ^f
	1000 µg	NT	--	NT	--	NT	--	NT	--	4	4	N
	2500 µg	NT	--	NT	--	NT	--	NT	--	2	1	NP
5000 µg	NT	--	NT	--	NT	--	NT	--	1	1	RP	
Positive Control ^c		333	47	1090	100	667	73	709	107	281	108	N

^a Background Lawn Evaluation Codes:

N = normal R = reduced O = obscured A = absent P = precipitate

^b TA98	benzo[a]pyrene	2.5 µg/plate	^c TA98	2-nitrofluorene	1.0 µg/plate
TA100	2-aminoanthracene	2.5 µg/plate	TA100	sodium azide	2.0 µg/plate
TA1535	2-aminoanthracene	2.5 µg/plate	TA1535	sodium azide	2.0 µg/plate
TA1537	2-aminoanthracene	2.5 µg/plate	TA1537	ICR-191	2.0 µg/plate
WP2uvrA	2-aminoanthracene	25.0 µg/plate	WP2uvrA	4-nitroquinoline-N-oxide	1.0 µg/plate

NT = dose not tested.

^d The first entry is the lawn evaluation for tester strains TA98, TA100, and WP2uvrA.

The second entry is the lawn evaluation for tester strains TA1535 and TA1537.

^e The first entry is the lawn evaluation for tester strains TA98, TA1535, and WP2uvrA.

The second entry is the lawn evaluation for tester strains TA100 and TA1537.

^f The first entry is the lawn evaluation for tester strain WP2uvrA.

The second entry is the lawn evaluation for tester strains TA98, TA100, TA1535, and TA1537.

Table 6 : Mutagenicity Assay Results – Summary—LP-778902

Test Article ID: LP-778902

Assay No.: 29093-0-409OECD

Trial No.: B2

Date Plated: 27-Jun-07

Vehicle: DMSO

Date Counted: 03-Jul-07

Plating Aliquot: 50 µL

		Mean Revertants Per Plate with Standard Deviation										Back-ground Lawn ^a
Dose/Plate		TA98		TA100		TA1535		TA1537		WP2 ^{uvrA}		
		Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	
Microsomes: Rat Liver												
Vehicle Control		33	9	85	9	11	3	23	6	19	1	N
Test Article	33.3 µg	33	3	102	13	11	1	27	8	19	5	N
	100 µg	34	6	91	26	14	2	28	7	14	3	N
	333 µg	29	6	80	5	13	2	19	4	17	6	N
	1000 µg	36	14	66	3	8	1	19	7	19	1	N
	2500 µg	28	5	45	14	7	1	13	7	13	2	NP
	5000 µg	14	1	32	2	3	2	8	1	4	2	NP
Positive Control ^b		392	29	823	103	213	18	160	8	612	70	N
Microsomes: None												
Vehicle Control		19	5	78	7	15	3	21	8	14	4	N
Test Article	33.3 µg	23	4	85	18	9	4	23	6	18	4	N
	100 µg	22	5	86	2	12	4	21	6	11	4	N
	333 µg	21	7	81	5	12	3	26	8	12	4	N
	1000 µg	18	3	74	1	11	2	17	10	17	3	N
	2500 µg	12	3	53	2	13	1	14	5	14	4	NP
	5000 µg	5	2	46	13	5	1	12	4	5	4	NP
Positive Control ^c		339	23	1157	109	843	27	711	48	269	30	N

^a Background Lawn Evaluation Codes:

N = normal

R = reduced

O = obscured

A = absent

P = precipitate

^b TA98	benzo[a]pyrene	2.5 µg/plate	^c TA98	2-nitrofluorene	1.0 µg/plate
TA100	2-aminoanthracene	2.5 µg/plate	TA100	sodium azide	2.0 µg/plate
TA1535	2-aminoanthracene	2.5 µg/plate	TA1535	sodium azide	2.0 µg/plate
TA1537	2-aminoanthracene	2.5 µg/plate	TA1537	ICR-191	2.0 µg/plate
WP2 ^{uvr} A	2-aminoanthracene	25.0 µg/plate	WP2 ^{uvr} A	4-nitroquinoline-N-oxide	1.0 µg/plate

The results suggest that LP-778914 and LP-778902 were not mutagenic in this test system.

In Vitro Assays in Mammalian Cells**Study title: In Vitro Chromosomal Aberrations in Chinese Hamster Ovary (CHO) Cells**

Study no.: 7648-192
Study report location: N/A
Conducting laboratory and location: (b) (4)
Date of study initiation: April 12, 2007
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: LP-778914, lot # AA-020763 and LP-778914-03-005; 91.7-109%
LP-778902, lot # LP-778902-02-004; 96.9-103%

Key Study Findings

The results indicated that both LP-778914 and LP-778902 were not clastogenic in this test system.

Methods

Cell line: Chinese hamster ovary (CHO) cells
Concentrations in definitive study: See table below
Basis of concentration selection: cell growth inhibition
Negative control: DMSO
Positive control: Mitomycin C 0.2 or 0.75 µg/ml and Cyclophosphamide 12.5 µg/ml
Formulation/Vehicle: DMSO
Incubation & sampling time: Cells were treated for 3 or 18-20 hours
Cells were harvested 20 hours after treatment

Study Validity

The positive and solvent controls fulfilled the requirements for a valid test.

Results

The results are summarized in the following sponsor's table.

Table 3: Chromosomal Aberrations in Chinese Hamster Ovary Cells - Without Metabolic Activation - 3-Hour Treatment, ~20-Hour Harvest

Assay No.: 29093-0-437OECD Trial No.: B1 Date: 06/12/07 Lab No.: CY061407 Test Article: LP-778914

				# Cells Scored for pp and er	# of pp Cells	# of er Cells	Judge- ment (+/-) ^b	Numbers and Percentages of Cells Showing Structural Chromosome Aberrations							Judge- ment (+/-) ^d	
													Totals ^c			
								gaps	simple breaks	chte	chre	mab	-g	+g		
Controls																
Negative:	McCoy's 5a		A 100	100	3	0		1						0	1	
			B 100	100	4	0							1	1		
			Total 200	200				1					1	2		
			Average %	--	3.5	0.0		0.5			0.5		0.5	1.0		
Vehicle:	DMSO	10.0 μL/mL	A 100	100	5	4		2						0	2	
			B 100	100	6	4								0	0	
			Total 200	200				2						0	2	
			Average %	0	5.5	4.0		1.0					0.0	1.0		
Positive:	MMC	0.750 μg/mL	A 50	100	4	0		3	10	17		1	23	25		
			B 51	100	5	0		2	10	11		4	22	22		
			Total 101	200				5	20	28		5	45	47		
			Average %	--	4.5	0.0	-	5.0	19.8	27.7		5.0	44.6	46.5		+
Test Article		3.88 μg/mL	A 100	100	6	0								0	0	
			B 100	100	5	0		2						0	2	
			Total 200	200				2						0	2	
			Average %	5	5.5	0.0	-	1.0					0.0	1.0		-
		5.54 μg/mL	A 100	100	8	3		4						0	4	
			B 100	100	6	5		1	1				1	2		
			Total 200	200				5	1				1	6		
			Average %	38	7.0	4.0	-	2.5	0.5				0.5	3.0		-
		7.91 μg/mL	A 100	100	5	6		6		2				2	8	
			B 100	100	6	5		7						0	7	
			Total 200	200				13		2				2	15	
			Average %	58	5.5	5.5	-	6.5		1.0			1.0	7.5		-

chte: chromatid exchange chre: chromosome exchange mab: multiple aberrations, greater than 4 aberrations pp: polyploidy er: endoreduplication

^a% Mitotic index reduction as compared to the vehicle control.^bSignificantly greater in % polyploidy and % endoreduplication than the vehicle control, $p \leq 0.01$.^c-g = # or % of cells with chromosome aberrations; +g = # or % of cells with chromosome aberrations + # or % of cells with gaps.^dSignificantly greater in -g than the vehicle control, $p \leq 0.01$. McCoy's 5a = culture medium DMSO = dimethylsulfoxide MMC = Mitomycin C**Table 9: Chromosomal Aberrations in Chinese Hamster Ovary Cells - With Metabolic Activation - 3-Hour Treatment, ~20-Hour Harvest**

Assay No.: 29093-0-437OECD Trial No.: B1 Date: 06/12/07 Lab No.: CY061407 Test Article: LP-778914

				# Cells Scored for Aberrations	% Mitotic Index Reduction ^a	# Cells Scored for pp and er	# of pp Cells	# of er Cells	Judge- ment (+/-) ^b	Numbers and Percentages of Cells Showing Structural Chromosome Aberrations							Judge- ment (+/-) ^d
										gaps simple chte chre mab					Totals ^c		
															-g	+g	
Controls																	
Negative:	McCoy's 5a			A 100		100	4	1							0	0	
				B 100		100	5	1		2			1		1	3	
				Total 200		200				2			1		1	3	
				Average %	--		4.5	1.0		1.0			0.5		0.5	1.5	
Vehicle:	DMSO	10.0	µL/mL	A 100		100	6	2					1		1	1	
				B 100		100	6	2							0	0	
				Total 200		200							1		1	1	
				Average %	0		6.0	2.0					0.5		0.5	0.5	
Positive:	CP	12.5	µg/mL	A 50		100	6	0		6	10	21		9	34	35	
				B 50		100	4	0		2	8	21	1	14	35	35	
				Total 100		200				8	18	42	1	23	69	70	
				Average %	--		5.0	0.0	-	8.0	18.0	42.0	1.0	23.0	69.0	70.0	+
Test Article		47.1	µg/mL	A 100		100	6	0		1			3		3	4	
				B 100		100	5	0		2					0	2	
				Total 200		200				3			3		3	6	
				Average %	1		5.5	0.0	-	1.5			1.5		1.5	3.0	-
		67.2	µg/mL	A 100		100	4	0		1					0	1	
				B 100		100	4	2				2			2	2	
				Total 200		200				1		2			2	3	
				Average %	35		4.0	1.0	-	0.5		1.0			1.0	1.5	-
		96.0	µg/mL	A 100		100	5	0		1			1		1	2	
				B 100		100	4	2		4			1		1	5	
				Total 200		200				5			2		2	7	
				Average %	58		4.5	1.0	-	2.5			1.0		1.0	3.5	-

chte: chromatid exchange chre: chromosome exchange mab: multiple aberrations, greater than 4 aberrations pp: polyploidy er: endoreduplication

^a% Mitotic index reduction as compared to the vehicle control.^bSignificantly greater in % polyploidy and % endoreduplication than the vehicle control, $p \leq 0.01$.^c-g = # or % of cells with chromosome aberrations; +g = # or % of cells with chromosome aberrations + # or % of cells with gaps.^dSignificantly greater in -g than the vehicle control, $p \leq 0.01$. McCoy's 5a = culture medium DMSO = dimethylsulfoxide CP = Cyclophosphamide

Table 15: Chromosomal Aberrations in Chinese Hamster Ovary Cells - Without Metabolic Activation - ~20-Hour Treatment, ~20-Hour Harvest

Assay No.: 29093-0-437OECD Trial No.: C1 Date: 07/19/07 Lab No.: CY072007A Test Article: LP-778914

										Numbers and Percentages of Cells Showing Structural Chromosome Aberrations							Judge- ment (+/-) ^d
		# Cells Scored for Aberrations	% Mitotic Index Reduction ^a	# Cells Scored for pp and er	# of pp Cells	# of er Cells	Judge- ment (+/-) ^b						Totals ^c				
								gaps	breaks	chte	chre	mab	-g	+g			
Controls																	
Negative:	McCoy's 5a		A	100		100	10	0							0	0	
			B	100		100	12	0		2					0	2	
			Total	200		200				2					0	2	
			Average	%	--		11.0	0.0		1.0					0.0	1.0	
Vehicle:	DMSO	10.0	μL/mL	A	100		100	7	0		1				0	1	
			B	100		100	10	0						0	0		
			Total	200		200				1				0	1		
			Average	%	0		8.5	0.0		0.5				0.0	0.5		
Positive:	MMC	0.200	μg/mL	A	50		100	3	0		2	12	9		2	21	23
			B	50		100	4	0				10	14		1	23	23
			Total	100		200				2	22	23		3	44	46	
			Average	%	--		3.5	0.0	-	2.0	22.0	23.0		3.0	44.0	46.0	+
Test Article	3.75	μg/mL	A	100		100	7	0							0	0	
			B	100		100	5	0		3					0	3	
			Total	200		200				3					0	3	
			Average	%	0		6.0	0.0	-	1.5					0.0	1.5	-
	5.00	μg/mL	A	100		100	6	0							0	0	
			B	100		100	4	0		1		1			1	2	
			Total	200		200				1	1	1		1	2		
			Average	%	29		5.0	0.0	-	0.5	0.5	0.5		0.5	1.0	-	
	6.50	μg/mL	A	100		100	4	0						1	1	1	
			B	100		100	2	0		2					0	2	
			Total	200		200				2			1		1	3	
			Average	%	50		3.0	0.0	-	1.0			0.5		0.5	1.5	-

chte: chromatid exchange chre: chromosome exchange mab: multiple aberrations, greater than 4 aberrations pp: polyploidy er: endoreduplication

^a% Mitotic index reduction as compared to the vehicle control.^bSignificantly greater in % polyploidy and % endoreduplication than the vehicle control, $p \leq 0.01$.^c-g = # or % of cells with chromosome aberrations; +g = # or % of cells with chromosome aberrations + # or % of cells with gaps.^dSignificantly greater in -g than the vehicle control, $p \leq 0.01$. McCoy's 5a = culture medium DMSO = dimethylsulfoxide MMC = Mitomycin C**Table 12: Chromosomal Aberrations in Chinese Hamster Ovary Cells - With Metabolic Activation - 3-Hour Treatment, ~20-Hour Harvest**

Assay No.: 29093-0-437OECD Trial No.: B1 Date: 06/12/07 Lab No.: CY061407 Test Article: LP-778902

				# Cells Scored for Aberrations	% Mitotic Index Reduction ^a	# Cells Scored for pp and er	# of pp Cells	# of er Cells	Judge- ment (+/-) ^b	Numbers and Percentages of Cells Showing Structural Chromosome Aberrations							Judge- ment (+/-) ^d
										gaps breaks chte chre mab					Totals ^c		
															-g	+g	
Controls																	
Negative:	McCoy's 5a			A 100		100	6	3		1					0	1	
				B 100		100	7	3							0	0	
				Total 200		200				1					0	1	
				Average %	--		6.5	3.0		0.5					0.0	0.5	
Vehicle:	DMSO	10.0	µL/mL	A 100		100	5	0							0	0	
				B 100		100	8	0							0	0	
				Total 200		200									0	0	
				Average %	0		6.5	0.0							0.0	0.0	
Positive:	CP	12.5	µg/mL	A 50		100	6	0		6	10	21		9	34	35	
				B 50		100	4	0		2	8	21	1	14	35	35	
				Total 100		200				8	18	42	1	23	69	70	
				Average %	--		5.0	0.0	-	8.0	18.0	42.0	1.0	23.0	69.0	70.0	+
Test Article		96.0	µg/mL	A 100		100	5	1		1			2		2	3	
				B 100		100	4	1		2	1				1	3	
				Total 200		200				3	1		2		3	6	
				Average %	0		4.5	1.0	-	1.5	0.5		1.0		1.5	3.0	-
		137	µg/mL	A 100		100	6	1		1					0	1	
				B 100		100	6	3		3			1		1	4	
				Total 200		200				4			1		1	5	
				Average %	0		6.0	2.0	-	2.0			0.5		0.5	2.5	-
		196	µg/mL	A 100		100	6	0		1			1		1	2	
				B 100		100	5	0		2	1				1	3	
				Total 200		200				3	1		1		2	5	
				Average %	6		5.5	0.0	-	1.5	0.5		0.5		1.0	2.5	-

chte: chromatid exchange chre: chromosome exchange mab: multiple aberrations, greater than 4 aberrations pp: polyploidy er: endoreduplication

^a% Mitotic index reduction as compared to the vehicle control.^bSignificantly greater in % polyploidy and % endoreduplication than the vehicle control, $p \leq 0.01$.^c-g = # or % of cells with chromosome aberrations; +g = # or % of cells with chromosome aberrations + # or % of cells with gaps.^dSignificantly greater in -g than the vehicle control, $p \leq 0.01$. McCoy's 5a = culture medium DMSO = dimethylsulfoxide CP = Cyclophosphamide

Table 18: Chromosomal Aberrations in Chinese Hamster Ovary Cells - Without Metabolic Activation - ~18-Hour Treatment, ~20-Hour Harvest

Assay No.: 29093-0-437OECD Trial No.: C1 Date: 07/19/07 Lab No.: CY072007A Test Article: LP-778902

				# Cells Scored for Aberrations	% Mitotic Index Reduction ^a	# Cells Scored for pp and er	# of pp Cells	# of er Cells	Judge- ment (+/-) ^b	Numbers and Percentages of Cells Showing Structural Chromosome Aberrations							Judge- ment (+/-) ^d
										gaps simple chre chre mab					Totals ^c		
															-g	+g	
Controls Negative:	McCoy's 5a			A	100	100	9	0		3					0	3	
				B	100	100	7	0						0	0		
				Total	200	200				3				0	3		
				Average	%	--	8.0	0.0		1.5				0.0	1.5		
Vehicle:	DMSO	10.0	μL/mL	A	100	100	7	0						0	0		
				B	100	100	4	0		2				0	2		
				Total	200	200				2				0	2		
				Average	%	0	5.5	0.0		1.0				0.0	1.0		
Positive:	MMC	0.200	μg/mL	A	50	100	3	0		2	12	9		2	21	23	
				B	50	100	4	0			10	14		1	23	23	
				Total	100	200				2	22	23		3	44	46	
				Average	%	--	3.5	0.0	-	2.0	22.0	23.0		3.0	44.0	46.0	+
Test Article	3.13	μg/mL	A	100	100	100	7	0		3					0	3	
			B	100	100	7	0		1			1		1	2		
			Total	200	200				4			1		1	5		
			Average	%	17	7.0	0.0	-	2.0			0.5		0.5	2.5	-	
	6.25	μg/mL	A	100	100	100	4	0							0	0	
			B	100	100	2	0		3					0	3		
			Total	200	200				3					0	3		
			Average	%	29	3.0	0.0	-	1.5					0.0	1.5	-	
	12.5	μg/mL	A	100	100	100	3	0		3			1	1	2	5	
			B	100	100	1	0		1					0	1		
			Total	200	200				4			1	1	2	6		
			Average	%	55	2.0	0.0	-	2.0			0.5	0.5	1.0	3.0	-	

chte: chromatid exchange chre: chromosome exchange mab: multiple aberrations, greater than 4 aberrations pp: polyploidy er: endoreduplication

^a % Mitotic index reduction as compared to the vehicle control.^b Significantly greater in % polyploidy and % endoreduplication than the vehicle control, $p \leq 0.01$.^c -g = # or % of cells with chromosome aberrations; +g = # or % of cells with chromosome aberrations + # or % of cells with gaps.^d Significantly greater in -g than the vehicle control, $p \leq 0.01$. McCoy's 5a = culture medium DMSO = dimethylsulfoxide MMC = Mitomycin C

HISTORICAL CONTROL DATA

Chromosome Aberrations In Chinese Hamster Ovary Cells
~20 Hour Harvest - 1/2005 through 12/2005

	Activation		% -g	% +g	% Poly- ploid Cells	% Endore- duplicated Cells	% Mitotic Index
Negative Control	Without	MIN	0.0	0.0	0.0	0.0	8.4
3-4 Hour Treatment		MAX	5.0	7.0	7.0	2.5	25.8
		AVG	0.7	1.9	2.7	0.5	15.8
		SD (±)	1.13	1.91	2.16	0.63	3.74
		N	38	38	38	38	36
Vehicle Control (Pooled)	Without	MIN	0.0	0.0	0.0	0.0	10.0
3-4 Hour Treatment		MAX	3.0	6.0	8.0	3.5	26.3
		AVG	0.9	2.2	2.8	0.5	16.1
		SD (±)	0.93	1.50	2.37	0.87	3.30
		N	39	39	39	39	37
Positive Control - MMC	Without	MIN	42.5	42.5	0.0	0.0	-
3-4 Hour Treatment		MAX	97.3	97.3	11.0	2.5	-
		AVG	78.4	80.4	3.3	0.4	-
		SD (±)	13.73	13.53	2.66	0.65	-
		N	39	39	39	39	-
Negative Control	Without	MIN	0.0	0.0	0.0	0.0	7.4
Continuous Treatment		MAX	4.5	7.5	10.0	1.5	24.2
		AVG	1.1	2.4	2.6	0.2	14.0
		SD (±)	1.06	1.71	2.48	0.36	3.53
		N	38	38	38	38	36
Vehicle Control (Pooled)	Without	MIN	0.0	0.0	0.0	0.0	6.7
Continuous Treatment		MAX	2.5	6.5	11.5	3.0	22.6
		AVG	0.7	2.3	2.5	0.2	13.8
		SD (±)	0.65	1.56	2.56	0.55	3.82
		N	39	39	39	39	37
Positive Control - MMC	Without	MIN	35.2	36.3	0.0	0.0	-
Continuous Treatment		MAX	91.0	93.0	11.5	3.0	-
		AVG	66.3	68.7	2.6	0.2	-
		SD (±)	12.32	12.20	2.81	0.57	-
		N	39	39	39	39	-
Negative Control	With	MIN	0.0	0.0	0.0	0.0	7.4
3-4 Hour Treatment		MAX	4.0	7.0	12.0	6.5	25.1
		AVG	0.8	2.1	3.1	1.1	15.4
		SD (±)	0.91	1.57	2.79	1.54	3.67
		N	63	63	63	63	59
Vehicle Control (Pooled)	With	MIN	0.0	0.0	0.0	0.0	9.2
3-4 Hour Treatment		MAX	3.5	6.0	12.0	8.5	26.6
		AVG	1.0	2.4	3.1	1.1	16.1
		SD (±)	1.01	1.47	2.66	1.61	3.76
		N	65	65	65	65	61
Positive Control - CP	With	MIN	18.0	22.0	0.0	0.0	-
3-4 Hour Treatment		MAX	85.0	89.0	16.0	6.0	-
		AVG	53.3	56.6	3.4	0.5	-
		SD (±)	14.46	14.25	3.14	1.01	-
		N	65	65	65	65	-

N = Number of trials

MMC = Mitomycin C

CP = Cyclophosphamide

-g = % of cells with chromosome aberrations

+g = % of cells with chromosome aberrations + % of cells with gaps

The results indicated that both LP-778914 and LP-778902 were not clastogenic in this test system.

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title: In Vivo Rat Bone Marrow Micronucleus Assay

Study no: 7648-193
 Study report location: N/A
 Conducting laboratory and location: (b) (4)
 Date of study initiation: July 5, 2007
 GLP compliance: Yes
 QA statement: Yes
 Drug, lot #, and % purity: See table below

Test Article	Lot No.	Description	Storage	Purity	Expiration Date
LP-778914 (also known as LX1606)	03-005	White powder	Refrigerated, 2 to 8°C, with desiccant	97.96%	01 May 2008

Key Study Findings: Treatment with LP-778914 did not significantly increase the frequency of micronucleated polychromatic erythrocytes.

Methods:

Doses in definitive study: 100, 500 and 2000 mg/kg
 Frequency of dosing: daily for two days
 Route of administration: oral gavage
 Dose volume: 10 or 20 ml/kg
 Formulation/Vehicle: 0.25% methylcellulose
 Species/Strain: CD®(SD)IGS BR rats
 Number/Sex/Group: 5 males/group
 Satellite groups: none
 Basis of dose selection: high dose produced clinical signs of toxicity
 Negative control: 0.25% methylcellulose
 Positive control: cyclophosphamide monohydrate

At least 2000 polychromatic cells were evaluated per animal.

Study Validity: The study is valid based on the positive response in the positive control group.

Results:

Treatment at 2000 mg/kg/day induced clinical signs of toxicity including anal discharge (yellow/brown/green), unformed feces, red nasal discharge, red hair coat on the front legs, hunched posture, squinted eyes, irregular respiration, and/or hypoactivity.

Treatment with LP-778914 did not significantly increase the frequency of micronucleated polychromatic erythrocytes. However, the positive control compound (cyclophosphamide) produced the expected increase. The results are summarized in the sponsor's table below.

Table 2: Micronucleus Assay – Summary Table

Assay No.: 29093-0-454OECD

Test Article: LP-778914

Initiation of Dosing: 11 July 2007

Treatment	Dose	Harvest Time	% Micronucleated PCEs Mean of 2000 per Animal $\pm$ S.E. Males	Ratio PCE:NCE Mean $\pm$ S.E. Males
Controls				
Vehicle	VC 20 mL/kg/day	24 hr	0.10 $\pm$ 0.02	0.69 $\pm$ 0.06
Positive	CP 60 mg/kg	24 hr	1.56 $\pm$ 0.14*	0.75 $\pm$ 0.02
Test Article	100 mg/kg/day	24 hr	0.02 $\pm$ 0.01**	0.77 $\pm$ 0.04
	500 mg/kg/day	24 hr	0.03 $\pm$ 0.01**	0.65 $\pm$ 0.07
	2000 mg/kg/day	24 hr	0.08 $\pm$ 0.01	0.69 $\pm$ 0.07

* Significantly greater than the corresponding vehicle control, $p \leq 0.01$.

** Significantly less than the corresponding vehicle control, $p \leq 0.05$.

CP = Cyclophosphamide

PCE = Polychromatic erythrocyte

NCE = Normochromatic erythrocyte

VC = 0.25% Methylcellulose in reverse osmosis (RO) water

The results indicate LP-778914 was not clastogenic in this test system.

7.4 Other Genetic Toxicity Studies

Genetic Toxicity Studies with Impurities

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)**Study title:** (b) (4) **Bacterial Reverse Mutation Assay**

Study no.: 8310730

Study report location: N/A

Conducting laboratory and location: (b) (4)

Date of study initiation: October 29, 2014

GLP compliance: Yes

QA statement: Yes

Drug, lot #, and % purity: see sponsor's table below

Test Article	Batch No.	Storage	Purity	Re-test Date
(b) (4)	21094589	Refrigerated (2-8°C)	98.2 (HPLC area %)	04 September 2016
	P04574-025	Refrigerated (2-8°C)	99.1 (HPLC area %)	28 April 2016

Key Study Findings

The impurity (b) (4) was tested in the Ames test at concentrations of 1.60, 5.00, 16.0, 50.0, 160, 500, 1600, and 5000 µg/plate with and without S9 using the plate incorporation method. The results suggest that the test article was positive with batch # 21094589, but negative with batch # P04574-025 in this test system. Batch # P04574-025 had higher purity than batch # 21094589, which suggests that the positive finding observed with batch # 21094589 was due to a mutagenic impurity.

Methods

Strains: TA98, TA100, TA1535 and TA1537 and *Escherichia coli* WP2 *uvrA*

Concentrations in definitive study: 1.6, 5.0, 16.0, 50.0, 160, 500, 1600, and 5000 µg/plate

Basis of concentration selection: the maximum dose of 5000 µg per plate was tested.

Negative control: dimethyl sulfoxide (DMSO)

Positive control: See table below

Formulation/Vehicle: DMSO

Incubation & sampling time: 52 +/- 4 hours at 37 ° C using the plate incorporation method

Positive Control Articles					
Tester Strain(s)	S9	Positive Control	Dose (µg/plate)	CAS No.	Lot No.
TA98	–	2-nitrofluorene	1.0	607-57-8	S43858V
TA100, TA1535	–	sodium azide	2.0	26628-22-8	MKBQ4465V
TA1537	–	ICR-191	2.0	17070-45-0	SLBH1792V
WP2 <i>uvrA</i>	–	4-nitroquinoline-N-oxide	1.0	56-57-5	A0305157
TA98	+	benzo[a]pyrene	2.5	50-32-8	SLBF4553V
TA100, TA1535, TA1537	+	2-aminoanthracene	2.5	613-13-8	STBD3302V
WP2 <i>uvrA</i>	+	2-aminoanthracene	25.0	613-13-8	STBD3302V

Study Validity

The positive controls significantly increased the colonies compared to the solvent controls.

Results

The results are summarized in the sponsor's tables below.

Table 14.1: Initial Mutagenicity Assay Results with S9

Study Number: 8310730				Batch # 21094589		
Experiment Number: 8310730 Initial				Date Plated: 18-Nov-2014		
Assay Conditions: Plate incorporation assay				Date Counted: 20-Nov-2014 to 25-Nov-2014		
Strain	Compound	Conc. Level (µg/plate)	Mean	Standard Deviation	Fold Increase	Revertant Numbers Per Plate
TA98	Dimethyl Sulfoxide	-	21.0	7.5	-	14 M N, 29 M N, 20 M N
	(b) (4)	5000	33.0	7.9	1.6	42 M P O, 30 M P O, 27 M P O
		1600	24.3	5.1	1.2	23 M P O, 20 M P O, 30 M P O
		500	18.7	6.4	0.9	15 N, 26 N, 15 N
		160	18.0	2.6	0.9	19 N, 20 N, 15 N
		50.0	17.3	2.1	0.8	15 N, 18 N, 19 N
		16.0	19.3	6.4	0.9	23 N, 12 N, 23 N
		5.00	19.7	9.5	0.9	29 N, 10 N, 20 N
		1.60	16.3	9.1	0.8	8 N, 26 N, 15 N
	BP	2.5	496.7	46.9	23.7	486 N, 548 N, 456 N
TA100	Dimethyl Sulfoxide	-	136.0	24.3	-	124 N, 164 N, 120 N
	(b) (4)	5000	312.7	7.0	2.3	306 M P O, 320 P O, 312 M P O
		1600	212.0	16.4	1.6	226 P O, 216 P O, 194 P O
		500	158.0	16.1	1.2	143 N, 175 N, 156 N
		160	135.0	7.2	1.0	133 N, 143 N, 129 N
		50.0	124.0	8.5	0.9	115 N, 125 N, 132 N
		16.0	128.7	8.0	0.9	121 N, 128 N, 137 N
		5.00	133.7	15.3	1.0	116 N, 143 N, 142 N
		1.60	119.7	8.1	0.9	116 N, 129 N, 114 N
	2AA	2.5	1131.0	72.1	8.3	1095 N, 1214 N, 1084 N
TA1535	Dimethyl Sulfoxide	-	11.0	2.6	-	9 N, 10 N, 14 N
	(b) (4)	5000	7.0	0.0	0.6	7 M P O, 7 M P O, 7 M P O
		1600	5.3	2.3	0.5	4 M P O, 8 M P O, 4 M P O
		500	13.3	5.0	1.2	8 N, 18 M N, 14 M N
		160	8.3	2.1	0.8	6 N, 9 N, 10 N
		50.0	6.7	5.8	0.6	0 N, 10 N, 10 N
		16.0	9.7	3.5	0.9	13 N, 6 N, 10 N
		5.00	11.7	4.7	1.1	8 N, 10 N, 17 N
		1.60	14.0	3.6	1.3	10 N, 17 N, 15 N
	2AA	2.5	143.7	7.4	13.1	152 M N, 141 M N, 138 M N
Positive controls				Postfixes		
2AA	2-aminoanthracene			M	Plate counted manually	
BP	Benzo{a}pyrene			N	Normal background bacterial lawn	
				O	Obscured background bacterial lawn	
				P	Precipitation of test article observed	

Table 14.1 (Continued): Initial Mutagenicity Assay Results with S9

Study Number: 8310730				Batch # 21094589		
Experiment Number: 8310730 Initial				Date Plated: 18-Nov-2014		
Assay Conditions: Plate incorporation assay				Date Counted: 20-Nov-2014 to 25-Nov-2014		
Strain	Compound	Conc. Level (µg/plate)	Mean	Standard Deviation	Fold Increase	Revertant Numbers Per Plate
TA1537	Dimethyl Sulfoxide	-	5.7	4.0	-	2 M N, 5 N, 10 N
	(b) (4)	5000	3.7	2.1	0.6	2 M P O, 6 M P O, 3 M P O
		1600	7.0	5.2	1.2	10 M P O, 1 M P O, 10 M P O
		500	4.3	0.6	0.8	4 N, 4 N, 5 N
		160	4.7	1.5	0.8	5 N, 6 N, 3 N
		50.0	9.3	4.6	1.6	4 N, 12 N, 12 M N
		16.0	7.3	2.1	1.3	8 N, 5 N, 9 N
		5.00	7.3	1.2	1.3	8 N, 8 N, 6 N
		1.60	5.7	2.1	1.0	8 N, 4 N, 5 N
	2AA	2.5	102.0	7.0	18.0	105 M N, 94 M N, 107 M N
WP2uvrA	Dimethyl Sulfoxide	-	13.0	1.0	-	14 N, 13 N, 12 N
	(b) (4)	5000	12.0	2.0	0.9	14 M P O, 12 M P O, 10 M P O
		1600	11.0	2.0	0.8	13 M P O, 11 M P O, 9 M P O
		500	10.0	4.0	0.8	6 N, 10 N, 14 N
		160	13.3	6.1	1.0	12 N, 8 N, 20 N
		50.0	11.7	2.9	0.9	10 N, 10 N, 15 N
		16.0	12.3	5.9	0.9	19 N, 10 N, 8 N
		5.00	10.7	3.8	0.8	15 N, 8 N, 9 N
		1.60	10.3	2.5	0.8	13 N, 10 N, 8 N
	2AA	25.0	262.0	17.1	20.2	281 M N, 257 M N, 248 M N
Positive controls				Postfixes		
2AA	2-aminoanthracene			M	Plate counted manually	
BP	Benzo{a}pyrene			N	Normal background bacterial lawn	
				O	Obscured background bacterial lawn	
				P	Precipitation of test article observed	

Table 14.2: Initial Mutagenicity Assay Results without S9

Study Number: 8310730				Batch # 21094589		
Experiment Number: 8310730 Initial				Date Plated: 18-Nov-2014		
Assay Conditions: Plate incorporation assay				Date Counted: 20-Nov-2014 to 25-Nov-2014		
Strain	Compound	Conc. Level (µg/plate)	Mean	Standard Deviation	Fold Increase	Revertant Numbers Per Plate
TA98	Dimethyl Sulfoxide	-	15.7	3.2	-	12 N, 18 N, 17 N
	(b) (4)	5000	0.0	0.0	0.0	0 M R, 0 M R, 0 M R
		1600	9.3	3.1	0.6	12 M R, 10 M R, 6 M R
		500	14.3	5.5	0.9	8 N, 18 N, 17 N
		160	15.0	1.7	1.0	14 N, 17 N, 14 N
		50.0	13.0	1.7	0.8	12 N, 15 M N, 12 N
		16.0	12.3	3.1	0.8	13 N, 15 N, 9 N
		5.00	13.0	4.6	0.8	8 N, 17 N, 14 N
		1.60	16.7	2.9	1.1	15 N, 15 N, 20 N
	2NF	1.0	223.7	19.7	14.3	236 N, 201 N, 234 M N
TA100	Dimethyl Sulfoxide	-	102.3	17.0	-	86 N, 120 N, 101 N
	(b) (4)	5000	0.0	0.0	0.0	0 M R, 0 M R, 0 M R
		1600	68.0	2.6	0.7	69 R, 65 R, 70 R
		500	106.3	2.5	1.0	106 N, 104 N, 109 N
		160	105.3	4.0	1.0	109 N, 101 N, 106 N
		50.0	95.3	10.3	0.9	104 N, 98 N, 84 N
		16.0	100.0	9.2	1.0	92 N, 110 N, 98 N
		5.00	104.3	3.8	1.0	107 N, 106 N, 100 N
		1.60	94.7	1.5	0.9	95 N, 96 N, 93 N
	SA	2.0	820.0	64.4	8.0	863 N, 851 N, 746 N
TA1535	Dimethyl Sulfoxide	-	13.0	3.5	-	9 N, 15 N, 15 N
	(b) (4)	5000	0.0	0.0	0.0	0 M R, 0 M R, 0 M R
		1600	5.7	2.9	0.4	4 R, 4 R, 9 R
		500	7.0	3.6	0.5	10 N, 8 N, 3 N
		160	10.7	4.9	0.8	5 M N, 14 N, 13 N
		50.0	12.7	1.2	1.0	12 N, 12 N, 14 N
		16.0	7.3	2.9	0.6	4 N, 9 N, 9 N
		5.00	12.3	0.6	0.9	13 N, 12 N, 12 N
		1.60	15.0	10.4	1.2	9 N, 27 N, 9 N
	SA	2.0	593.7	39.3	45.7	639 N, 573 N, 569 N
Positive controls				Postfixes		
SA	sodium azide			M	Plate counted manually	
ICR	ICR-191			N	Normal background bacterial lawn	
2NF	2-nitrofluorene			R	Reduced background bacterial lawn	
4NQO	4-nitroquinoline-N-oxide					

Table 14.2 (Continued): Initial Mutagenicity Assay Results without S9

Study Number: 8310730				Batch # 21094589		
Experiment Number: 8310730 Initial				Date Plated: 18-Nov-2014		
Assay Conditions: Plate incorporation assay				Date Counted: 20-Nov-2014 to 25-Nov-2014		
Strain	Compound	Conc. Level (µg/plate)	Mean	Standard Deviation	Fold Increase	Revertant Numbers Per Plate
TA1537	Dimethyl Sulfoxide	-	6.0	3.6	-	5 N, 10 N, 3 N
	(b) (4)	5000	0.0	0.0	0.0	0 M R, 0 M R, 0 M R
		1600	4.3	0.6	0.7	5 M R, 4 M R, 4 M R
		500	12.0	3.6	2.0	13 N, 8 N, 15 N
		160	4.3	1.5	0.7	4 N, 3 N, 6 N
		50.0	5.3	2.5	0.9	5 N, 8 N, 3 N
		16.0	4.7	1.2	0.8	4 N, 4 N, 6 N
		5.00	4.3	1.5	0.7	4 N, 3 M N, 6 N
		1.60	4.7	1.5	0.8	6 N, 5 M N, 3 N
	ICR	2.0	80.7	2.3	13.4	82 N, 78 N, 82 N
WP2uvrA	Dimethyl Sulfoxide	-	14.0	3.5	-	12 M N, 12 N, 18 N
	(b) (4)	5000	0.0	0.0	0.0	0 M R, 0 M R, 0 M R
		1600	4.7	1.5	0.3	5 N, 3 N, 6 N
		500	10.7	6.0	0.8	5 N, 10 N, 17 N
		160	9.3	5.1	0.7	8 N, 15 N, 5 N
		50.0	6.3	1.5	0.5	6 N, 8 N, 5 N
		16.0	9.3	4.2	0.7	6 N, 8 N, 14 N
		5.00	15.3	6.4	1.1	19 N, 8 N, 19 N
		1.60	11.3	1.2	0.8	10 N, 12 N, 12 N
	4NQO	1.0	177.0	11.1	12.6	175 M N, 189 M N, 167 M N
Positive controls				Postfixes		
SA	sodium azide			M	Plate counted manually	
ICR	ICR-191			N	Normal background bacterial lawn	
2NF	2-nitrofluorene			R	Reduced background bacterial lawn	
4NQO	4-nitroquinoline-N-oxide					

Table 14.3: Confirmatory (1) Mutagenicity Assay Results with S9

Study Number: 8310730				Batch # 21094589		
Experiment Number: 8310730 Confirm				Date Plated: 17-Dec-2014		
Assay Conditions: Plate incorporation assay				Date Counted: 19-Dec-2014 to 22-Dec-2014		
Strain	Compound	Conc. Level (µg/plate)	Mean	Standard Deviation	Fold Increase	Revertant Numbers Per Plate
TA98	Dimethyl Sulfoxide	-	15.7	3.8	-	13 N, 14 N, 20 M N
	(b) (4)	5000	30.0	8.9	1.9	23 M P O, 40 M P O, 27 M P O
		1600	19.7	5.9	1.3	22 M P O, 24 M P O, 13 M P O
		500	20.0	3.0	1.3	20 N, 23 N, 17 N
		160	14.7	2.1	0.9	14 N, 13 N, 17 N
		50.0	16.0	7.5	1.0	8 N, 23 N, 17 N
		16.0	18.0	3.5	1.1	20 N, 14 N, 20 N
		5.00	18.0	2.6	1.1	19 N, 15 N, 20 N
		1.60	18.0	3.6	1.1	22 N, 15 N, 17 N
	BP	2.5	421.0	30.5	26.9	420 N, 452 N, 391 N
TA100	Dimethyl Sulfoxide	-	107.0	16.4	-	89 N, 121 N, 111 N
	(b) (4)	5000	280.0	39.1	2.6	325 P O, 254 P O, 261 P O
		1600	196.7	40.0	1.8	198 P O, 156 P O, 236 P O
		500	136.0	21.2	1.3	120 N, 160 N, 128 N
		160	118.7	4.5	1.1	114 N, 123 N, 119 N
		50.0	100.7	4.0	0.9	100 N, 105 N, 97 N
		16.0	93.0	7.0	0.9	100 N, 86 N, 93 N
		5.00	117.3	12.1	1.1	106 N, 130 N, 116 N
		1.60	121.0	8.2	1.1	114 N, 130 N, 119 N
	2AA	2.5	1174.3	45.7	11.0	1139 N, 1226 N, 1158 N
TA1535	Dimethyl Sulfoxide	-	14.7	1.5	-	16 M N, 15 N, 13 N
	(b) (4)	5000	9.3	2.5	0.6	12 M P O, 7 M P O, 9 M P O
		1600	10.0	2.6	0.7	7 M P O, 12 M P O, 11 M P O
		500	11.3	2.1	0.8	9 N, 12 M N, 13 N
		160	8.7	0.6	0.6	9 N, 8 N, 9 N
		50.0	9.7	7.0	0.7	9 N, 17 N, 3 N
		16.0	13.7	0.6	0.9	13 N, 14 N, 14 M N
		5.00	9.3	5.1	0.6	5 N, 8 N, 15 N
		1.60	9.0	1.0	0.6	10 N, 8 N, 9 N
	2AA	2.5	154.7	20.2	10.5	142 N, 178 N, 144 N
Positive controls				Postfixes		
2AA	2-aminoanthracene			M	Plate counted manually	
BP	Benzo{a}pyrene			N	Normal background bacterial lawn	
				O	Obscured background bacterial lawn	
				P	Precipitation of test article observed	

Table 14.3 (Continued): Confirmatory (1) Mutagenicity Assay Results with S9

Study Number: 8310730				Batch # 21094589		
Experiment Number: 8310730 Confirm				Date Plated: 17-Dec-2014		
Assay Conditions: Plate incorporation assay				Date Counted: 19-Dec-2014 to 22-Dec-2014		
Strain	Compound	Conc. Level (µg/plate)	Mean	Standard Deviation	Fold Increase	Revertant Numbers Per Plate
TA1537	Dimethyl Sulfoxide	-	6.0	2.0	-	6 N, 8 N, 4 N
	(b) (4)	5000	7.7	2.3	1.3	9 M P O, 9 M P O, 5 M P O
		1600	4.7	3.5	0.8	8 M P O, 5 M P O, 1 M P O
		500	6.7	3.2	1.1	9 N, 8 N, 3 N
		160	6.3	1.5	1.1	8 N, 6 N, 5 N
		50.0	5.0	0.0	0.8	5 N, 5 N, 5 N
		16.0	4.3	0.6	0.7	4 N, 5 N, 4 N
		5.00	6.0	2.0	1.0	8 N, 6 N, 4 N
		1.60	5.0	1.0	0.8	6 N, 4 N, 5 N
	2AA	2.5	128.0	20.5	21.3	148 N, 129 N, 107 N
WP2uvr A	Dimethyl Sulfoxide	-	13.0	2.0	-	13 M N, 15 M N, 11 M N
	(b) (4)	5000	17.0	6.1	1.3	10 M P O, 21 M P O, 20 M P O
		1600	13.3	4.5	1.0	9 M P O, 18 M P O, 13 M P O
		500	9.3	3.2	0.7	8 M N, 7 M N, 13 N
		160	11.7	6.7	0.9	19 N, 10 N, 6 N
		50.0	13.3	7.6	1.0	22 N, 8 N, 10 N
		16.0	11.0	2.6	0.8	12 N, 8 M N, 13 N
		5.00	9.0	1.0	0.7	10 N, 9 N, 8 N
		1.60	10.0	6.6	0.8	9 N, 4 N, 17 N
	2AA	25.0	161.7	28.0	12.4	193 N, 139 N, 153 N
Positive controls				Postfixes		
2AA	2-aminoanthracene			M	Plate counted manually	
BP	Benzo{a}pyrene			N	Normal background bacterial lawn	
				O	Obscured background bacterial lawn	
				P	Precipitation of test article observed	

Table 14.4: Confirmatory (2) Mutagenicity Assay Results with S9

Study Number: 8310730			Batch # P04574-025			
Experiment Number: 8310730 Confirm 2			Date Plated: 09-Feb-2015			
Assay Conditions:			Date Counted: 11-Feb-2015			
Strain	Compound	Conc. Level (µg/plate)	Mean	Standard Deviation	Fold Increase	Revertant Numbers Per Plate
TA98	Dimethyl Sulfoxide	-	25.0	6.1	-	18 M N, 28 M N, 29 M N
	(b) (4)	5000	20.7	2.1	0.8	19 M P N, 20 M P N, 23 M P N
		3300	22.7	7.1	0.9	15 M P N, 24 M P N, 29 M P N
		1600	23.0	8.7	0.9	27 M P N, 29 M P N, 13 M P N
		1200	14.7	4.0	0.6	19 M P N, 14 M P N, 11 M P N
		800	21.3	5.5	0.9	24 M P N, 15 M P N, 25 M P N
		500	13.7	6.0	0.5	8 M P N, 13 M P N, 20 M P N
		160	24.0	2.6	1.0	27 M N, 22 M N, 23 M N
		50.0	22.0	1.7	0.9	23 M N, 20 M N, 23 M N
	BP	2.5	381.7	33.2	15.3	353 N, 374 N, 418 N
TA100	Dimethyl Sulfoxide	-	120.7	11.0	-	128 M N, 108 M N, 126 M N
	(b) (4)	5000	127.3	16.2	1.1	119 M P N, 146 M P N, 117 M P N
		3300	124.0	4.6	1.0	128 M P N, 119 M P N, 125 M P N
		1600	127.3	6.5	1.1	127 M P N, 134 M P N, 121 M P N
		1200	124.7	8.6	1.0	117 M P N, 123 M P N, 134 M P N
		800	134.3	8.1	1.1	125 M P N, 139 M P N, 139 M P N
		500	108.3	15.3	0.9	125 M P N, 105 M P N, 95 M P N
		160	115.3	11.0	1.0	103 M N, 124 M N, 119 M N
		50.0	118.7	7.5	1.0	110 M N, 123 M N, 123 M N
	2AA	2.5	1458.3	66.8	12.1	1466 N, 1521 N, 1388 N
Positive controls			Postfixes			
BP	Benzo{a}pyrene		M	Plate counted manually		
2AA	2-aminoanthracene		N	Normal background bacterial lawn		
			P	Precipitation of test article observed		

In the presence of S9, (b) (4) (batch # 21094589) induced a two-fold increase in revertant counts in strain TA100 at highest concentration tested (5000 ug/plate), as compared to the vehicle control in the initial test (table 14.1). There were dose dependent increases in the revertant counts in strain TA100 at lower concentrations, but the increases were less than two fold as compared to the vehicle control. This was also observed in the confirmatory test with batch # 21094589 (table 14.3). However, the increase in revertant count in strain TA100 (with S9) was not seen with batch # P04574-025, which was 99.1% pure as compared to 98.2% purity for batch # 21094589. The results suggest that the positive finding observed with batch # 21094589 was due to a mutagenic impurity.

Study title: (b) (4) **Second Bacterial Reverse Mutation Assay**

Study no.: 8321394
Study report location: N/A
Conducting laboratory and location: (b) (4)
Date of study initiation: March 18, 2015
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: See table below

Test Article	Batch No.	Storage	Purity	Re-test Date
(b) (4)	21094589	Refrigerated (2-8°C)	98.2 (HPLC area %)	04 September 2016
	P04574-025	Refrigerated (2-8°C)	99.1 (HPLC area %)	28 April 2016

Key Study Findings

The sponsor repeated the Ames test with impurity, (b) (4) at concentrations of 1.6, 5.0, 16.0, 50.0, 160, 500, 1600, and 5000 µg/plate with and without S9 using the plate incorporation method. The results indicated that the test article, (b) (4) was positive with batch # 21094589, and negative with batch # P04574-025 in this test system. Batch # P04574-025 had higher purity than batch # 21094589, which suggests that the positive finding observed with batch # 21094589 was due to a mutagenic impurity.

Methods

Strains: TA98, TA100, TA1535 and TA1537 and *Escherichia coli* WP2 *uvrA*

Concentrations in definitive study: 1.6, 5.0, 16.0, 50.0, 160, 500, 1600, and 5000 µg/plate

Basis of concentration selection: the maximum dose of 5000 µg per plate was tested

Negative control: dimethyl sulfoxide (DMSO)

Positive control: see table below

Formulation/Vehicle: DMSO

Incubation & sampling time: 52 +/- 4 hours at 37°C using the plate incorporation method

Positive Control Articles					
Tester Strain(s)	S9	Positive Control	Dose (µg/plate)	CAS No.	Lot No.
TA98	–	2-nitrofluorene	1.0	607-57-8	S43858V
TA100, TA1535	–	sodium azide	2.0	26628-22-8	MKBQ4465V
TA1537	–	ICR-191	2.0	17070-45-0	SLBH1792V
WP2 <i>uvrA</i>	–	4-nitroquinoline-N-oxide	1.0	56-57-5	A0305157
TA98	+	benzo[a]pyrene	2.5	50-32-8	SLBF4553V
TA100, TA1535, TA1537	+	2-aminoanthracene	2.5	613-13-8	STBD3302V
WP2 <i>uvrA</i>	+	2-aminoanthracene	25.0	613-13-8	STBD3302V

Study Validity

The positive controls significantly increased the revertant colonies compared to the solvent controls.

Results

The results are summarized in the sponsor's tables below.

Table 14.1: Mutagenicity Assay Results with S9 for (b) (4)

Study Number: 8321394			Batch # 21094589			
Experiment Number: 8321394 Initial (b) (4)			Date Plated: 31-Mar-2015			
Assay Conditions: Plate incorporation assay			Date Counted: 02-Apr-2015 to 03-Apr-2015			
Strain	Compound	Conc. Level (µg/plate)	Mean	Standard Deviation	Fold Increase	Revertant Numbers Per Plate
TA98	Dimethyl Sulfoxide	-	31.3	7.2	-	35 N, 23 N, 36 N
	(b) (4)	5000	36.7	6.5	1.2	37 M P O, 30 M P O, 43 M P O
		1600	31.7	5.8	1.0	25 M P O, 35 M P O, 35 M P O
		500	31.0	4.4	1.0	28 N, 29 N, 36 N
		160	37.0	8.0	1.2	45 N, 37 N, 29 N
		50.0	26.0	6.1	0.8	23 N, 33 N, 22 N
		16.0	24.3	4.7	0.8	28 N, 19 N, 26 N
		5.00	33.7	4.2	1.1	37 N, 35 N, 29 N
		1.60	24.7	6.7	0.8	32 N, 19 N, 23 N
	BP	2.5	386.7	35.2	12.3	362 N, 371 N, 427 N
TA100	Dimethyl Sulfoxide	-	111.7	4.9	-	115 N, 114 N, 106 N
	(b) (4)	5000	275.7	32.5	2.5	309 M P O, 244 M P O, 274 M P O
		1600	170.7	2.9	1.5	174 M P O, 169 M P O, 169 M P O
		500	140.0	2.6	1.3	141 N, 142 N, 137 N
		160	123.3	11.5	1.1	130 N, 130 N, 110 N
		50.0	117.3	15.0	1.1	102 N, 132 N, 118 N
		16.0	107.7	18.2	1.0	124 N, 111 N, 88 N
		5.00	110.0	12.5	1.0	123 N, 98 N, 109 N
		1.60	116.0	10.5	1.0	106 N, 127 N, 115 N
	2AA	2.5	1210.0	185.5	10.8	1387 N, 1017 N, 1226 N
TA1535	Dimethyl Sulfoxide	-	14.0	3.5	-	12 N, 12 N, 18 N
	(b) (4)	5000	11.7	2.9	0.8	10 M P O, 15 M P O, 10 M P O
		1600	12.0	3.6	0.9	11 M P O, 9 M P O, 16 M P O
		500	13.0	3.5	0.9	15 N, 9 N, 15 N
		160	13.7	0.6	1.0	14 N, 13 N, 14 N
		50.0	11.3	2.9	0.8	13 N, 13 N, 8 N
		16.0	13.7	5.1	1.0	8 N, 15 N, 18 N
		5.00	11.7	3.5	0.8	8 N, 15 N, 12 N
		1.60	15.3	2.3	1.1	18 N, 14 N, 14 N
	2AA	2.5	171.3	16.9	12.2	157 N, 167 N, 190 N
Positive controls			Postfixes			
2AA	2-aminoanthracene		M	Plate counted manually		
BP	Benzo{a}pyrene		N	Normal background bacterial lawn		
			O	Obscured background bacterial lawn		
			P	Precipitation of test article observed		

Table 14.1 (Continued): Mutagenicity Assay Results with S9 for (b) (4)

Study Number: 8321394			Batch # 21094589			
Experiment Number: 8321394 Initial (b) (4)			Date Plated: 31-Mar-2015			
Assay Conditions: Plate incorporation assay			Date Counted: 02-Apr-2015 to 03-Apr-2015			
Strain	Compound	Conc. Level (µg/plate)	Mean	Standard Deviation	Fold Increase	Revertant Numbers Per Plate
TA1537	Dimethyl Sulfoxide	-	18.3	4.5	-	18 M N, 14 M N, 23 N
	(b) (4)	5000	11.0	3.0	0.6	14 M P O, 11 M P O, 8 M P O
		1600	12.7	5.1	0.7	17 M P O, 14 M P O, 7 M P O
		500	9.0	4.6	0.5	5 N, 14 N, 8 N
		160	9.7	2.1	0.5	8 N, 12 N, 9 N
		50.0	13.3	6.7	0.7	9 N, 21 M N, 10 N
		16.0	11.7	2.3	0.6	13 N, 9 N, 13 N
		5.00	12.7	4.5	0.7	17 N, 13 N, 8 N
		1.60	11.0	4.4	0.6	14 N, 13 N, 6 M N
	2AA	2.5	143.7	17.4	7.8	124 N, 150 N, 157 N
WP2uvr A	Dimethyl Sulfoxide	-	27.0	4.6	-	31 N, 28 N, 22 N
	(b) (4)	5000	28.0	5.2	1.0	25 M P O, 34 M P O, 25 M P O
		1600	29.0	1.0	1.1	30 M P O, 29 M P O, 28 M P O
		500	24.0	2.0	0.9	24 N, 26 N, 22 N
		160	22.0	2.0	0.8	20 N, 24 M N, 22 M N
		50.0	24.0	4.6	0.9	23 N, 20 N, 29 M N
		16.0	22.7	3.1	0.8	22 M N, 20 N, 26 N
		5.00	24.3	3.8	0.9	20 M N, 26 N, 27 N
		1.60	29.7	6.1	1.1	35 N, 23 N, 31 N
	2AA	25.0	268.7	53.6	10.0	207 N, 295 N, 304 N
Positive controls			Postfixes			
2AA	2-aminoanthracene		M	Plate counted manually		
BP	Benzo {a} pyrene		N	Normal background bacterial lawn		
			O	Obscured background bacterial lawn		
			P	Precipitation of test article observed		

Table 14.2: Mutagenicity Assay Results without S9 for (b) (4)

Study Number: 8321394			Batch # 21094589			
Experiment Number: 8321394 Initial (b) (4)			Date Plated: 31-Mar-2015			
Assay Conditions: Plate incorporation assay			Date Counted: 02-Apr-2015 to 03-Apr-2015			
Strain	Compound	Conc. Level (µg/plate)	Mean	Standard Deviation	Fold Increase	Revertant Numbers Per Plate
TA98	Dimethyl Sulfoxide	-	30.3	13.6	-	43 N, 32 M N, 16 M N
	(b) (4)	5000	10.0	2.6	0.3	13 R, 9 R, 8 R
		1600	21.7	3.2	0.7	18 R, 24 R, 23 R
		500	33.3	8.1	1.1	38 N, 38 N, 24 N
		160	30.3	6.7	1.0	32 N, 36 N, 23 N
		50.0	27.7	9.0	0.9	27 N, 37 N, 19 N
		16.0	30.3	7.0	1.0	37 N, 31 N, 23 N
		5.00	27.0	1.0	0.9	28 N, 26 N, 27 N
		1.60	28.0	9.5	0.9	18 N, 29 N, 37 N
	2NF	1.0	166.7	10.7	5.5	176 N, 169 N, 155 N
TA100	Dimethyl Sulfoxide	-	89.3	13.7	-	87 N, 104 N, 77 N
	(b) (4)	5000	4.3	4.5	0.0	9 M R, 0 R, 4 M R
		1600	26.3	9.5	0.3	37 R, 23 R, 19 R
		500	82.3	0.6	0.9	83 N, 82 N, 82 N
		160	93.0	13.9	1.0	86 N, 109 N, 84 N
		50.0	90.0	2.6	1.0	91 N, 87 N, 92 N
		16.0	94.0	6.1	1.1	87 N, 98 N, 97 N
		5.00	85.0	3.6	1.0	89 N, 82 N, 84 N
		1.60	84.0	28.5	0.9	59 N, 78 N, 115 N
	SA	2.0	1156.3	47.1	12.9	1102 N, 1181 N, 1186 N
TA1535	Dimethyl Sulfoxide	-	10.0	3.5	-	12 N, 12 N, 6 N
	(b) (4)	5000	6.3	3.5	0.6	3 R, 6 R, 10 R
		1600	4.3	1.5	0.4	6 R, 3 R, 4 R
		500	9.7	4.9	1.0	4 N, 12 N, 13 N
		160	9.3	0.6	0.9	10 N, 9 N, 9 N
		50.0	12.3	3.8	1.2	8 N, 14 N, 15 N
		16.0	9.7	2.1	1.0	9 N, 8 N, 12 N
		5.00	11.0	5.6	1.1	17 N, 6 N, 10 N
		1.60	7.7	1.5	0.8	6 N, 8 N, 9 N
	SA	2.0	749.7	50.0	75.0	749 N, 800 N, 700 N
Positive controls			Postfixes			
SA	sodium azide		A	Absence of background bacterial lawn		
ICR	ICR-191		M	Plate counted manually		
2NF	2-nitrofluorene		N	Normal background bacterial lawn		
4NQO	4-nitroquinoline-N-oxide		R	Reduced background bacterial lawn		

Table 14.2 (Continued): Mutagenicity Assay Results without S9 for (b) (4)

Study Number: 8321394			Batch # 21094589			
Experiment Number: 8321394 Initial (b) (4)			Date Plated: 31-Mar-2015			
Assay Conditions: Plate incorporation assay			Date Counted: 02-Apr-2015 to 03-Apr-2015			
Strain	Compound	Conc. Level (µg/plate)	Mean	Standard Deviation	Fold Increase	Revertant Numbers Per Plate
TA1537	Dimethyl Sulfoxide	-	14.3	4.0	-	10 N, 15 M N, 18 N
	(b) (4)	5000	0.0	0.0	0.0	0 A, 0 A, 0 A
		1600	4.0	1.7	0.3	2 M R, 5 M R, 5 M R
		500	9.0	3.6	0.6	6 N, 8 N, 13 N
		160	10.7	2.1	0.7	13 N, 10 N, 9 N
		50.0	16.0	3.6	1.1	19 N, 12 N, 17 N
		16.0	11.0	1.7	0.8	10 N, 13 N, 10 N
		5.00	14.3	3.2	1.0	18 N, 13 N, 12 N
		1.60	12.7	4.0	0.9	9 N, 12 N, 17 N
	ICR	2.0	651.0	77.3	45.4	739 N, 620 N, 594 N
WP2uvr A	Dimethyl Sulfoxide	-	22.3	5.5	-	17 M N, 28 N, 22 N
	(b) (4)	5000	20.0	1.7	0.9	19 M N, 19 M N, 22 M N
		1600	14.3	1.5	0.6	16 M N, 13 M N, 14 N
		500	16.3	3.1	0.7	13 M N, 19 N, 17 N
		160	16.0	3.6	0.7	17 N, 19 N, 12 M N
		50.0	17.7	9.0	0.8	13 N, 12 N, 28 N
		16.0	20.0	2.0	0.9	18 N, 22 N, 20 N
		5.00	27.3	3.5	1.2	27 N, 24 N, 31 N
		1.60	19.7	7.4	0.9	17 N, 14 N, 28 N
	4NQO	1.0	620.0	39.0	27.8	575 N, 643 N, 642 N
Positive controls			Postfixes			
SA	sodium azide		A	Absence of background bacterial lawn		
ICR	ICR-191		M	Plate counted manually		
2NF	2-nitrofluorene		N	Normal background bacterial lawn		
4NQO	4-nitroquinoline-N-oxide		R	Reduced background bacterial lawn		

Table 14.3: Mutagenicity Assay Results with S9 for (b) (4) (Pure)

Study Number: 8321394

Batch # P04574-025

Experiment Number: 8321394 Initial (Pure) (b) (4)

Date Plated: 31-Mar-2015

(b) (4)

Assay Conditions: Plate incorporation assay

Date Counted: 03-Apr-2015

Strain	Compound	Conc. Level (µg/plate)	Mean	Standard Deviation	Fold Increase	Revertant Numbers Per Plate
TA98	Dimethyl Sulfoxide	-	26.7	3.2	-	23 N, 29 N, 28 N
	(Pure) (b) (4)	5000	28.3	6.7	1.1	24 M P N, 25 M P N, 36 M P N
	(b) (4)	1600	29.3	5.1	1.1	28 M P N, 35 M P N, 25 M P N
		500	32.0	3.0	1.2	32 N, 29 N, 35 N
		160	29.3	6.8	1.1	27 N, 24 N, 37 N
		50.0	36.7	4.2	1.4	38 N, 32 N, 40 N
		16.0	31.7	8.5	1.2	35 N, 22 N, 38 N
		5.00	28.0	8.5	1.1	27 N, 37 N, 20 N
		1.60	30.7	4.0	1.2	33 N, 33 N, 26 N
	BP	2.5	417.3	46.2	15.7	466 N, 374 N, 412 N
TA100	Dimethyl Sulfoxide	-	101.3	12.7	-	87 N, 106 N, 111 N
	(Pure) (b) (4)	5000	109.7	10.0	1.1	109 M P N, 120 M P N, 100 M P N
	(b) (4)	1600	108.0	5.2	1.1	111 M P N, 102 M P N, 111 M P N
		500	111.7	11.5	1.1	125 N, 105 N, 105 N
		160	111.3	10.3	1.1	114 N, 120 N, 100 N
		50.0	107.7	11.6	1.1	106 N, 97 N, 120 N
		16.0	116.3	19.1	1.1	109 N, 102 N, 138 N
		5.00	115.3	16.3	1.1	112 N, 133 N, 101 N
		1.60	117.7	6.8	1.2	110 N, 120 N, 123 N
	2AA	2.5	1278.3	75.9	12.6	1365 N, 1224 N, 1246 N
TA1535	Dimethyl Sulfoxide	-	8.3	4.9	-	14 N, 6 N, 5 N
	(Pure) (b) (4)	5000	8.0	4.0	1.0	12 M P N, 8 M P N, 4 M P N
	(b) (4)	1600	7.7	3.8	0.9	6 M P N, 5 M P N, 12 M P N
		500	9.7	2.1	1.2	9 N, 12 N, 8 N
		160	11.0	4.6	1.3	12 N, 6 N, 15 N
		50.0	13.7	7.5	1.6	18 N, 5 N, 18 N
		16.0	10.7	2.9	1.3	14 N, 9 N, 9 N
		5.00	13.3	4.7	1.6	15 N, 17 N, 8 N
		1.60	12.0	6.2	1.4	14 N, 17 N, 5 N
	2AA	2.5	154.7	17.6	18.6	169 N, 135 N, 160 N
Positive controls			Postfixes			
2AA	2-aminoanthracene		M	Plate counted manually		
BP	Benzo{a}pyrene		N	Normal background bacterial lawn		
			P	Precipitation of test article observed		

Table 14.3 (Continued): Mutagenicity Assay Results with S9 for
(Pure)

Study Number: 8321394

Batch # P04574-025

Experiment Number: 8321394 Initial (Pure)

Date Plated: 31-Mar-2015

Assay Conditions: Plate incorporation assay

Date Counted: 03-Apr-2015

Strain	Compound	Conc. Level (µg/plate)	Mean	Standard Deviation	Fold Increase	Revertant Numbers Per Plate
TA1537	Dimethyl Sulfoxide (Pure)	-	16.0	5.3	-	20 N, 18 N, 10 M N
		5000	9.7	3.1	0.6	7 M P N, 9 M P N, 13 M P N
		1600	8.0	3.6	0.5	5 M P N, 12 M P N, 7 M P N
		500	12.3	2.1	0.8	10 N, 13 N, 14 N
		160	14.7	4.5	0.9	15 N, 10 N, 19 N
		50.0	12.7	6.1	0.8	14 N, 6 N, 18 N
		16.0	11.7	2.5	0.7	14 N, 9 N, 12 N
		5.00	15.7	2.1	1.0	18 N, 15 N, 14 N
		1.60	12.3	4.9	0.8	9 N, 10 N, 18 M N
	2AA	2.5	151.0	13.7	9.4	166 N, 139 N, 148 N
WP2uvr A	Dimethyl Sulfoxide (Pure)	-	21.3	4.9	-	18 M N, 19 N, 27 N
		5000	14.0	4.4	0.7	12 M P N, 11 M P N, 19 M P N
		1600	18.7	1.5	0.9	19 M P N, 20 M P N, 17 M P N
		500	28.0	9.5	1.3	27 N, 38 N, 19 N
		160	19.7	2.1	0.9	19 N, 22 N, 18 M N
		50.0	27.7	0.6	1.3	28 N, 28 N, 27 N
		16.0	23.0	5.2	1.1	29 N, 20 N, 20 N
		5.00	26.3	2.5	1.2	24 N, 29 N, 26 M N
		1.60	20.0	3.0	0.9	23 N, 20 N, 17 N
	2AA	25.0	288.0	40.9	13.5	268 N, 335 N, 261 N
Positive controls			Postfixes			
2AA	2-aminoanthracene		M	Plate counted manually		
BP	Benzo {a} pyrene		N	Normal background bacterial lawn		
			P	Precipitation of test article observed		

Table 14.4: Mutagenicity Assay Results without S9 for (b) (4) (Pure)

Study Number: 8321394				Batch # P04574-025		
Experiment Number: 8321394 Initial (Pure (b) (4))				Date Plated: 31-Mar-2015		
Assay Conditions: Plate incorporation assay				Date Counted: 03-Apr-2015		
Strain	Compound	Conc. Level (µg/plate)	Mean	Standard Deviation	Fold Increase	Revertant Numbers Per Plate
TA98	Dimethyl Sulfoxide	-	28.7	8.7	-	19 N, 31 N, 36 N
	(Pure) (b) (4)	5000	10.7	2.1	0.4	13 R, 9 R, 10 R
		1600	24.7	5.7	0.9	20 R, 23 R, 31 R
		500	25.0	7.5	0.9	32 N, 17 N, 26 N
		160	27.3	6.7	1.0	24 N, 23 N, 35 N
		50.0	26.0	5.3	0.9	24 N, 32 N, 22 N
		16.0	25.0	9.6	0.9	14 N, 29 N, 32 N
		5.00	36.3	3.5	1.3	36 N, 40 N, 33 N
		1.60	26.3	2.5	0.9	26 N, 24 N, 29 N
	2NF	1.0	168.3	11.2	5.9	181 N, 160 N, 164 N
TA100	Dimethyl Sulfoxide	-	102.7	9.9	-	96 N, 114 N, 98 N
	(Pure) (b) (4)	5000	0.0	0.0	0.0	0 R, 0 R, 0 R
		1600	61.3	13.1	0.6	75 R, 60 R, 49 R
		500	102.3	4.5	1.0	102 N, 98 N, 107 N
		160	88.0	23.3	0.9	69 N, 114 N, 81 N
		50.0	102.7	8.7	1.0	105 N, 110 N, 93 N
		16.0	91.7	11.9	0.9	78 N, 100 N, 97 N
		5.00	98.3	12.5	1.0	84 N, 107 N, 104 N
		1.60	91.7	15.0	0.9	84 N, 82 N, 109 N
	SA	2.0	1078.3	86.8	10.5	1010 N, 1049 N, 1176 N
TA1535	Dimethyl Sulfoxide	-	16.3	3.8	-	19 N, 18 M N, 12 N
	(Pure) (b) (4)	5000	4.7	1.5	0.3	5 R, 3 R, 6 R
		1600	8.3	5.0	0.5	3 R, 9 R, 13 R
		500	11.3	6.7	0.7	4 N, 13 N, 17 N
		160	10.3	5.5	0.6	4 N, 13 N, 14 N
		50.0	11.7	5.5	0.7	12 N, 17 N, 6 N
		16.0	10.0	4.4	0.6	12 N, 13 N, 5 N
		5.00	10.3	8.1	0.6	9 N, 3 M N, 19 N
		1.60	14.3	1.2	0.9	13 N, 15 N, 15 N
	SA	2.0	894.0	14.8	54.7	884 N, 911 N, 887 N
Positive controls				Postfixes		
SA	sodium azide		M	Plate counted manually		
ICR	ICR-191		N	Normal background bacterial lawn		
2NF	2-nitrofluorene		R	Reduced background bacterial lawn		
4NQO	4-nitroquinoline-N-oxide					

Table 14.4 (Continued): Mutagenicity Assay Results without S9 for (b) (4) (Pure)

Study Number: 8321394				Batch # P04574-025		
Experiment Number: 8321394 Initial (Pure (b) (4))				Date Plated: 31-Mar-2015		
Assay Conditions: Plate incorporation assay				Date Counted: 03-Apr-2015		
Strain	Compound	Conc. Level (µg/plate)	Mean	Standard Deviation	Fold Increase	Revertant Numbers Per Plate
TA1537	Dimethyl Sulfoxide (Pure (b) (4))	-	8.0	2.0	-	10 N, 6 N, 8 N
	(b) (4)	5000	0.0	0.0	0.0	0 M R, 0 R, 0 R
		1600	0.0	0.0	0.0	0 R, 0 R, 0 R
		500	11.7	1.5	1.5	13 M N, 10 N, 12 N
		160	16.3	6.0	2.0	17 N, 22 N, 10 M N
		50.0	14.0	3.0	1.8	17 N, 14 N, 11 M N
		16.0	14.7	3.1	1.8	18 N, 12 N, 14 N
		5.00	15.3	3.2	1.9	19 N, 14 N, 13 N
		1.60	13.3	2.9	1.7	10 N, 15 N, 15 N
	ICR	2.0	300.0	98.1	37.5	188 N, 341 N, 371 N
WP2uvr A	Dimethyl Sulfoxide (Pure (b) (4))	-	17.7	1.2	-	17 N, 17 N, 19 N
	(b) (4)	5000	15.7	6.4	0.9	12 N, 12 M N, 23 N
		1600	14.0	5.2	0.8	17 N, 17 N, 8 N
		500	15.3	2.5	0.9	15 N, 18 N, 13 M N
		160	16.0	2.6	0.9	14 N, 19 N, 15 N
		50.0	20.3	4.9	1.2	26 N, 17 N, 18 N
		16.0	21.7	8.3	1.2	31 N, 15 N, 19 N
		5.00	19.0	5.0	1.1	19 N, 14 N, 24 N
		1.60	19.0	4.0	1.1	15 N, 23 N, 19 N
	4NQO	1.0	317.0	42.9	17.9	286 N, 366 N, 299 N
Positive controls			Postfixes			
SA	sodium azide		M	Plate counted manually		
ICR	ICR-191		N	Normal background bacterial lawn		
2NF	2-nitrofluorene		R	Reduced background bacterial lawn		
4NQO	4-nitroquinoline-N-oxide					

In the presence of S9, (b) (4) (batch # 21094589) induced a 2.5-fold increase in revertant counts in strain TA100 at the highest concentration tested (5000 µg/plate), as compared to the vehicle control in the initial test (table 14.1). There were dose dependent increases in the revertant counts in test strain TA 100 at lower concentrations, but the increases were less than two fold. However, the increase in revertant count in strain TA100 (with S9) was not seen with batch # P04574-025, which was 99.1% pure as compared to 98.2% purity for batch # 21094589. The results

suggest that the positive finding observed with batch # 21094589 was due to a mutagenic impurity.

Impurity (b) (4)

Impurity (b) (4) telotristat ethyl in vivo. The sponsor conducted (Q)SAR analysis for (b) (4) with Leadscape expert rule based methodology and Statistical QSAR methodology (Study #LX1606-N63). No alerts or concerns were identified.

7 Carcinogenicity

MOUSE:

Study title: LX1606 hippurate: 26-Week Repeated Dose Oral Carcinogenicity Study in Tg.rasH2 Mice

Study no.:	AD58ET.7G8R. (b) (4) (LX1606-N52)
Study report location:	N/A
Conducting laboratory and location:	(b) (4)
Date of study initiation:	February 10, 2014 (report dated April 30, 2015)
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	LX1606 hippurate / PT-C10052511-C13002 / 98.4%
CAC concurrence:	Yes (see meeting minutes in Appendix 1)

Key Study Findings

Treatment with LX1606 hippurate at doses of 30, 100, and 300 mg/kg/day for 26 weeks did not increase the incidence of neoplastic lesions in hemizygous Tg.rasH2 mice. Treatment-related non-neoplastic lesions included hyperplasia of non-glandular stomach in the high dose group and exudative inflammation of the nasal cavity mainly in mid- and high-dose groups. These lesions could be due to direct local irritation of the test article.

The FDA statistical review concluded that treatment with LX1606 hippurate did not produce any significant increase in tumor incidence.

C_{max} for LP-778902 (active metabolite) in males and females was 8990 and 15,600 ng/ml, respectively, and AUC₀₋₂₄ in males and females was 64,100 or 101,000 ng•hr/ml, respectively, following administration of 300 mg/kg/day on study day 177.

Adequacy of Carcinogenicity Study

The carcinogenicity study was conducted appropriately.

Appropriateness of Test Models

The test model was appropriate.

Evaluation of Tumor Findings

The tumor incidences were within the historical control ranges from the testing laboratory. No statistically significant increase in tumors was observed in groups treated with LX1606. Treatment with urethane (positive control) produced a high incidence of lung tumors and splenic hemangiosarcomas.

Methods

Doses:	0 (vehicle control), 30, 100, and 300 mg/kg/day; 1000 mg/kg/day Urethane in 0.9% sterile saline (positive control)
Frequency of dosing:	daily
Dose volume:	10 ml/kg
Route of administration:	oral
Formulation/Vehicle:	0.25% (w/v) methylcellulose
Basis of dose selection:	MTD (see Executive CAC minutes from December 5, 2013 in the Appendix 1)
Species/Strain:	Tg.rasH2 mice [CByB6F1-Tg(HRAS)2Jic (+/- hemizygous c-Ha-ras)]
	Males: 20.0 - 24.4 g
	Females: 15.3 - 19.2 g
Number/Sex/Group:	25
Age:	7 weeks
Animal housing:	individually
Paradigm for dietary restriction:	None
Dual control employed:	No
Interim sacrifice:	No
Satellite groups:	20/sex/group (5/sex/group for control)
Deviation from study protocol:	Deviations did not have a significant impact on the study outcome.

Mice were treated with LX1606 at dose levels of 30, 100, and 300 mg/kg/day via oral gavage for 26 weeks. These dose levels were recommended by the Executive Carcinogenicity Assessment Committee, based on toxicity and mortality due to nasal cavity irritation. The positive control animals received urethane at 1000 mg/kg via intraperitoneal injection on Days 1, 3 and 5. The toxicokinetic evaluation (exposure study) was conducted in hybrid CByB6F1 (nontransgenic) mice (5 or 20

mice/sex/group). The study design is summarized in Text Table 2 from the study report (shown below).

Text Table 2: Study Design

Group	Dose Levels (mg/kg/day)	Number of Animals			
		Main Cohort (Tg.rasH2)		TK Cohort** (CByB6F1)	
		Male	Female	Male	Female
Group 1	0	25	25	5	5
Group 2	30	25	25	20	20
Group 3	100	25	25	20	20
Group 4	300	25	25	20	20
Group 5*	1000 (urethane)	10	10	-	-
Total		110	110	65	65

*The positive control animals were administered a total of 3 intraperitoneal (i.p.) injections, one each day on Days 1, 3, and 5.

**Extra TK animals (2/sex) were used to ensure adequate animals for TK bleeding.

Clinical signs of toxicity and mortality were observed daily. Body weights and food consumption were determined. All animals were necropsied at termination. Complete histopathological examination was performed on all treated animals in all main study groups. The tumor data were analyzed using the Peto prevalence method, Peto death rate method, and Peto combined analysis (incidental and fatal tumors).

Observations and Results

Mortality: There were no treatment-related deaths. The mortality data was summarized in the following table (taken from the study report).

TABLE 1A - SUMMARY OF MORTALITY, MAIN COHORT**MALES**

	Group:	1	2	3	4	5
Day 80	Scheduled Sacrifice	-	-	-	-	10
Day 106	Natural Death	-	-	-	1	-
Day 109	Natural Death	-	1	-	-	-
Day 112	Natural Death	-	-	-	1	-
Day 123	Moribund Sacrifice	-	1	-	-	-
Day 148	Moribund Sacrifice	-	-	1	-	-
Day 183	Terminal Sacrifice	25	-	-	23	-
Day 184	Terminal Sacrifice	-	23	24	-	-
Total Unscheduled Deaths		0/25	2/25	1/25	2/25	0/10

FEMALES

	Group:	1	2	3	4	5
Day 56	Natural Death	-	-	-	-	1
Day 68	Natural Death	1	-	-	-	-
Day 78	Scheduled Sacrifice	-	-	-	-	9
Day 115	Moribund Sacrifice	-	-	-	1	-
Day 125	Moribund Sacrifice	-	1	-	-	-
Day 162	Moribund Sacrifice	1	-	-	-	-
Day 163	Natural Death	1	-	-	-	-
Day 168	Moribund Sacrifice	1	-	-	-	-
Day 177	Moribund Sacrifice	-	1	-	-	-
Day 183	Terminal Sacrifice	21	-	-	24	-
Day 184	Terminal Sacrifice	-	23	25	-	-
Total Unscheduled Deaths		4/25	2/25	0/25	1/25	1/10

Note: Represents the number of animals affected / the number of animals started on the study.

- = Not Applicable

Natural Death = Found Dead

Nominal Dose:

Group 1 - 0 mg/kg/day (Vehicle Control)

Group 3 - 100 mg/kg/day

Group 5 - 1000 mg/kg/day (Positive Control)

Group 2 - 30 mg/kg/day

Group 4 - 300 mg/kg/day

TABLE 1B - SUMMARY OF MORTALITY, TK COHORT

MALES

	Group:	1	2	3	4
Day 177	Scheduled Sacrifice	3	15	15	15
Day 178	Scheduled Sacrifice	2	5	5	5
Total Unscheduled Deaths		0/5	0/20	0/20	0/20

FEMALES

	Group:	1	2	3	4
Day 86	Moribund Sacrifice	-	-	-	1
Day 177	Scheduled Sacrifice	3	15	15	15
Day 178	Scheduled Sacrifice	2	5	5	4
Total Unscheduled Deaths		0/5	0/20	0/20	1/20

Note: Represents the number of animals affected / the number of animals started on the study.

- = Not Applicable

Nominal Dose:

Group 1 - 0 mg/kg/day (Vehicle Control)

Group 3 - 100 mg/kg/day

Group 2 - 30 mg/kg/day

Group 4 - 300 mg/kg/day

Clinical Signs: There were no clear treatment-related changes.

Body Weight: The initial and final body weights for the control animals were 22.01 and 29.74 g for males and 17.44 and 23.4 g for females, respectively. The terminal body weight gains were 7.73, 9.03, 7.8, and 8.29 g in vehicle control, low-, mid-, and high-dose males, and 6.02, 6.03, 6.20, and 6.14 g in vehicle control, low-, mid-, and high-dose females, respectively. Treatment with LX1606 did not affect body weight or body weight gain. The body weights and body weight gains are summarized in the sponsor's tables below.

TABLE 4A – SUMMARY OF BODY WEIGHTS - GROUP 1 VS. GROUPS 2-4

RTA054-05/01

Provantis (v.8.2.0.8)

Date: 09/29/2014 11:07

Bodyweights - Intergroup Comparison of Bodyweights

AD58ET.7G8R.BTL:LX1606 hippurate: 26-Week Repeated Dose Oral Carcinogenicity Study in Tg.rasH2 Mice

		Bodyweight (Grams)										
		Day numbers relative to Start Date										
Group	Sex		1	8	15	22	29	36	43	50	57	64
1	m	Mean	22.01	22.45	23.32	23.91	24.46	24.98	25.36	25.71	26.23	26.84
		S.D.	0.93	1.00	1.22	1.53	1.86	1.59	1.66	1.80	1.94	2.23
		N	25	25	25	25	25	25	25	25	25	25
2	m	Mean	22.02	22.20	23.34	24.12	24.80	25.32	25.59	26.14	26.60	26.88
		S.D.	1.05	1.34	1.30	1.32	1.43	1.59	1.68	1.99	2.10	2.41
		N	25	25	25	25	25	25	25	25	25	25
3	m	Mean	21.85	22.06	23.21	23.88	24.50	24.98	25.78	26.22	26.49	27.08
		S.D.	1.03	0.96	1.25	1.18	1.48	1.95	1.60	1.86	1.81	2.21
		N	25	25	25	25	25	25	25	25	25	25
4	m	Mean	21.93	22.48	23.69	24.45	25.02	25.62	26.18	26.52	26.84	27.30
		S.D.	1.07	1.10	1.14	1.36	1.67	1.78	1.51	1.51	1.62	1.95
		N	25	25	25	25	25	25	25	25	25	25

Statistical analysis (Dunnett's Test) did not reveal any significant differences when the test-article treated groups were compared to the vehicle control (Group 1).

Arithmetic Mean Values Presented.

Group 1 - 0 mg/kg/day

Group 2 - 30 mg/kg/day

Group 3 - 100 mg/kg/day

Group 4 - 300 mg/kg/day

TABLE 4A – SUMMARY OF BODY WEIGHTS – GROUP 1 vs. GROUPS 2-4 (CONTINUED)

RTA054-05/01

Provantis (v.8.2.0.8)

Date: 09/29/2014 11:07

Bodyweights - Intergroup Comparison of Bodyweights

AD58ET.7G8R.BTL:LX1606 hippurate: 26-Week Repeated Dose Oral Carcinogenicity Study in Tg.rasH2 Mice

		Bodyweight (Grams)						
		Day numbers relative to Start Date						
Group	Sex		71	78	85	99	113	127
1	m	Mean	27.08	27.54	27.62	28.04	28.21	28.60
		S.D.	2.14	2.37	2.55	2.66	2.78	3.16
		N	25	25	25	25	25	25
2	m	Mean	26.82	27.72	27.81	28.01	28.50	29.49
		S.D.	2.69	2.65	2.47	2.99	3.05	2.98
		N	25	25	25	25	24	23
3	m	Mean	27.32	27.85	27.97	28.63	28.33	29.26
		S.D.	2.56	2.35	2.27	2.33	2.51	2.84
		N	25	25	25	25	25	25
4	m	Mean	27.83	28.13	28.36	28.60	28.29	28.96
		S.D.	2.19	2.04	2.30	2.43	2.31	2.91
		N	25	25	25	25	23	23

Statistical analysis (Dunnett's Test) did not reveal any significant differences when the test-article treated groups were compared to the vehicle control (Group 1).

Arithmetic Mean Values Presented.

Group 1 - 0 mg/kg/day

Group 2 - 30 mg/kg/day

Group 3 - 100 mg/kg/day

Group 4 - 300 mg/kg/day

TABLE 4A – SUMMARY OF BODY WEIGHTS – GROUP 1 vs. GROUPS 2-4 (CONTINUED)

RTA054-05/01

Provantis (v.8.2.0.8)

Date: 09/29/2014 11:07

Bodyweights - Intergroup Comparison of Bodyweights

AD58ET.7G8R.BTL:LX1606 hippurate: 26-Week Repeated Dose Oral Carcinogenicity Study in Tg.rasH2 Mice

			Bodyweight (Grams)				
			Day numbers relative to Start Date				
Group	Sex		141	155	169	183	184
1	m	Mean	28.94	29.33	29.37	29.74	.
		S.D.	3.41	3.54	3.89	3.75	.
		N	25	25	25	25	0
2	m	Mean	29.98	30.37	30.60	31.12	31.19n
		S.D.	3.10	3.32	3.54	4.05	4.00
		N	23	23	23	23	23
3	m	Mean	29.26	29.24	29.41	29.61	29.55n
		S.D.	2.55	2.55	3.00	3.31	3.16
		N	25	24	24	24	24
4	m	Mean	29.46	29.80	30.28	30.17	.
		S.D.	3.00	2.92	3.20	3.12	.
		N	23	23	23	23	0

Statistical analysis (Dunnett's Test) did not reveal any significant differences when the test-article treated groups were compared to the vehicle control (Group 1).

n - Data not appropriate for statistical analysis.

Arithmetic Mean Values Presented.

Group 1 - 0 mg/kg/day

Group 2 - 30 mg/kg/day

Group 3 - 100 mg/kg/day

Group 4 - 300 mg/kg/day

TABLE 4A – SUMMARY OF BODY WEIGHTS – GROUP 1 vs. GROUPS 2-4 (CONTINUED)

RTA054-05/01

Provantis (v.8.2.0.8)

Date: 09/29/2014 11:07

Bodyweights - Intergroup Comparison of Bodyweights

AD58ET.7G8R.BTL:LX1606 hippurate: 26-Week Repeated Dose Oral Carcinogenicity Study in Tg.rasH2 Mice

			Bodyweight (Grams)									
			Day numbers relative to Start Date									
Group	Sex		1	8	15	22	29	36	43	50	57	64
1	f	Mean	17.44	17.85	18.61	19.21	19.42	19.98	20.43	20.56	20.88	21.30
		S.D.	0.85	0.82	0.77	0.89	0.96	0.78	0.97	0.83	0.91	0.90
		N	25	25	25	25	25	25	25	25	25	25
2	f	Mean	17.44	17.97	18.79	19.20	19.65	20.29	20.81	20.98	21.14	21.44
		S.D.	0.67	0.68	0.89	0.79	1.19	1.36	1.02	1.06	1.08	0.92
		N	25	25	25	25	25	25	25	25	25	25
3	f	Mean	17.35	17.84	18.46	19.17	19.79	19.73	20.28	20.34	21.05	21.09
		S.D.	0.82	1.11	0.96	0.89	0.92	1.14	0.80	1.21	0.96	1.05
		N	25	25	25	25	25	25	25	25	25	25
4	f	Mean	17.09	17.76	18.85	19.14	19.58	19.87	20.52	20.55	20.79	21.37
		S.D.	0.82	0.87	0.94	0.78	1.10	1.04	0.84	0.84	0.85	1.08
		N	25	25	25	25	25	25	25	25	25	25

Statistical analysis (Dunnett's Test) did not reveal any significant differences when the test-article treated groups were compared to the vehicle control (Group 1).

Arithmetic Mean Values Presented.

Group 1 - 0 mg/kg/day

Group 2 - 30 mg/kg/day

Group 3 - 100 mg/kg/day

Group 4 - 300 mg/kg/day

TABLE 4A – SUMMARY OF BODY WEIGHTS – GROUP 1 vs. GROUPS 2-4 (CONTINUED)

RTA054-05/01

Provantis (v.8.2.0.8)

Date: 09/29/2014 11:07

Bodyweights - Intergroup Comparison of Bodyweights

AD58ET.7G8R.BTL:LX1606 hippurate: 26-Week Repeated Dose Oral Carcinogenicity Study in Tg.rasH2 Mice

			Bodyweight (Grams)					
			Day numbers relative to Start Date					
Group	Sex		71	78	85	99	113	127
1	f	Mean	21.25	21.48	21.50	21.82	22.00	22.10
		S.D.	0.95	1.10	1.50	1.55	1.05	1.14
		N	24	24	24	24	24	24
2	f	Mean	21.73	21.62	21.86	22.18	21.76	22.13
		S.D.	1.16	1.17	0.90	1.07	1.13	0.98
		N	25	25	25	25	25	24
3	f	Mean	21.21	21.52	21.46	21.84	21.48	21.72
		S.D.	1.08	1.21	1.02	0.77	0.78	0.88
		N	25	25	25	25	25	25
4	f	Mean	21.30	21.39	21.51	21.91	21.36	21.73
		S.D.	1.10	1.30	1.22	1.52	1.68	1.42
		N	25	25	25	25	25	24

Statistical analysis (Dunnett's Test) did not reveal any significant differences when the test-article treated groups were compared to the vehicle control (Group 1).

Arithmetic Mean Values Presented.

Group 1 - 0 mg/kg/day

Group 2 - 30 mg/kg/day

Group 3 - 100 mg/kg/day

Group 4 - 300 mg/kg/day

TABLE 4A – SUMMARY OF BODY WEIGHTS – GROUP 1 vs. GROUPS 2-4 (CONTINUED)

RTA054-05/01

Provantis (v.8.2.0.8)

Date: 09/29/2014 11:07

Bodyweights - Intergroup Comparison of Bodyweights

AD58ET.7G8R.BTL:LX1606 hippurate: 26-Week Repeated Dose Oral Carcinogenicity Study in Tg.rasH2 Mice

			Bodyweight (Grams)				
			Day numbers relative to Start Date				
Group	Sex		141	155	169	183	184
1	f	Mean	23.28	22.68	23.32	23.40	.
		S.D.	1.66	2.22	1.79	1.68	.
		N	24	24	21	21	0
2	f	Mean	23.20	22.30	23.41	23.46	23.52n
		S.D.	1.00	1.53	1.38	1.11	1.07
		N	24	24	24	23	23
3	f	Mean	22.90	22.67	23.01	23.55	23.48n
		S.D.	1.27	0.93	1.29	1.32	1.17
		N	25	25	25	25	25
4	f	Mean	22.73	22.65	23.10	23.20	.
		S.D.	1.56	1.55	1.60	1.44	.
		N	24	24	24	24	0

Statistical analysis (Dunnett's Test) did not reveal any significant differences when the test-article treated groups were compared to the vehicle control (Group 1).

n - Data not appropriate for statistical analysis.

Arithmetic Mean Values Presented.

Group 1 - 0 mg/kg/day

Group 2 - 30 mg/kg/day

Group 3 - 100 mg/kg/day

Group 4 - 300 mg/kg/day

TABLE 5A – SUMMARY OF BODY WEIGHT GAINS – GROUP 1 vs. GROUPS 2-4 (CONTINUED)

RTA023-04/02

Provantis (v.8.2.0.8)

Date: 09/29/2014 11:06

Bodyweights - Intergroup Comparison of Bodyweight Gains

AD58ET.7G8R.BTL:LX1606 hippurate: 26-Week Repeated Dose Oral Carcinogenicity Study in Tg.rasH2 Mice

		Body Weight Gain (Grams)									
Day numbers relative to Start Date											
Group	Sex	Base	From:	113	127	141	155	169	Abs	%	
		Weight							Day	To:	1
		1		127	141	155	169	183	183	183	
1	m	22.01	Mean	0.39	0.33	0.40	0.04	0.36	7.73	34.96	
		0.93	S.D.	0.91	0.62	0.52	0.85	0.89	3.33	14.44	
		25	N	25	25	25	25	25	25	25	
----	----	----	----	----	----	----	----	----	----	----	
2	m	22.02	Mean	0.87	0.50	0.39	0.23	0.53	9.03	40.71	
		1.05	S.D.	0.85	1.07	0.60	0.66	0.86	3.52	15.03	
		25	N	23	23	23	23	23	23	23	
----	----	----	----	----	----	----	----	----	----	----	
3	m	21.85	Mean	0.94	-0.00	0.07	0.17	0.20	7.80	35.67	
		1.03	S.D.	0.86	0.85	0.68	1.11	0.98	2.89	13.06	
		25	N	25	25	24	24	24	24	24	
----	----	----	----	----	----	----	----	----	----	----	
4	m	21.93	Mean	0.67	0.50	0.34	0.48	-0.11	8.29	37.84	
		1.07	S.D.	1.05	0.75	0.65	0.65	0.72	2.75	12.36	
		25	N	23	23	23	23	23	23	23	
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Statistical analysis (Dunnett's Test) did not reveal any significant differences when the test-article treated groups were compared to the vehicle control (Group 1).

Abs Gain = absolute bodyweight gain between base period and end of the analysis period.

% Gain = percentage bodyweight gain between base period and end of the analysis period.

Group 1 - 0 mg/kg/day

Group 2 - 30 mg/kg/day

Group 3 - 100 mg/kg/day

Group 4 - 300 mg/kg/day

TABLE 5A – SUMMARY OF BODY WEIGHT GAINS – GROUP 1 vs. GROUPS 2-4 (CONTINUED)

RTA023-04/02

Provantis (v.8.2.0.8)

Date: 09/29/2014 11:06

Bodyweights - Intergroup Comparison of Bodyweight Gains

AD58ET.7G8R.BTL:LX1606 hippurate: 26-Week Repeated Dose Oral Carcinogenicity Study in Tg.rasH2 Mice

		Body Weight Gain (Grams)									
Day numbers relative to Start Date											
Group	Sex	Base Weight	From:	113	127	141	155	169	Abs Gain	% Gain	
		Day 1	To:	127	141	155	169	183	183	183	
1	f	17.44	Mean	0.09	1.19	-0.61	0.68	0.08	6.02	34.66	
		0.85	S.D.	0.86	1.03	1.41	0.99	1.25	1.30	7.32	
		25	N	24	24	24	21	21	21	21	
2	f	17.44	Mean	0.43	1.07	-0.90	1.11	0.23	6.03	34.72	
		0.67	S.D.	0.73	0.81	1.47	1.46	0.58	1.08	6.69	
		25	N	24	24	24	24	23	23	23	
3	f	17.35	Mean	0.25	1.17	-0.22	0.34	0.54	6.20	35.94	
		0.82	S.D.	0.56	0.95	0.99	1.08	1.06	1.33	8.63	
		25	N	25	25	25	25	25	25	25	
4	f	17.09	Mean	0.15	1.00	-0.08	0.45	0.10	6.14	36.06	
		0.82	S.D.	0.70	0.59	0.81	0.84	0.53	1.09	6.53	
		25	N	24	24	24	24	24	24	24	

Statistical analysis (Dunnett's Test) did not reveal any significant differences when the test-article treated groups were compared to the vehicle control (Group 1).

Abs Gain = absolute bodyweight gain between base period and end of the analysis period.

% Gain = percentage bodyweight gain between base period and end of the analysis period.

Group 1 - 0 mg/kg/day

Group 2 - 30 mg/kg/day

Group 3 - 100 mg/kg/day

Group 4 - 300 mg/kg/day

Feed Consumption: There were no clear treatment-related changes.

Organ Weights: Increased kidney weight and decreased liver weights were noted in the treatment groups. The results are presented in the sponsor's table below.

Text Table 6: Organ Weights

Parameter	Sex	Group No.	Dose Level (mg/kg/day)	Significant Difference compared to Control	% Difference from Vehicle Control
Absolute Kidney	M	4	300	↑	6.8%
Relative Liver		2	30	↓	4.6%
Absolute Kidney	F	2	30	↑	8.0%
Relative Kidney			30	↑	7.3%
Relative Liver		4	300	↓	5.1%

↑= increased when compared to the vehicle control, Group 1.

↓= decreased when compared to the vehicle control, Group 1.

Gross Pathology: No treatment-related changes were observed.

Histopathology

The tissues and organs examined are listed in the sponsor's table below.

Tissues/Organs	
Adrenal glands	Ovaries
Aorta	Pancreas
Bone (femur and sternum)	Parathyroid glands
Bone marrow (femur and sternum)	Pituitary gland
Brain	Prostate gland
Epididymides	Salivary gland
Esophagus	Sciatic nerve
Eyes	Seminal vesicles
Gall bladder	Skeletal muscle (thigh)
Gross lesions	Small intestine (duodenum, jejunum, and ileum)
Harderian gland	
Heart	Spinal cord (cervical, thoracic, and lumbar)
Kidneys	Spleen
Large intestine (cecum, colon, rectum)	Stomach
Liver	Testes
Lungs and bronchi	Thymus
Lymph nodes (mesenteric and mandibular)	Thyroid glands
Skin from mammary area (male and female mice)	Trachea
	Urinary bladder
Mammary gland (females only)	Uterus
Nasal Cavity	Vagina

Peer Review: Yes.

Non-Neoplastic Changes:

Hyperplasia of non-glandular stomach was found in four male mice in the high-dose group (see table from study report below).

Text Table 7: Stomach, Non-Glandular Hyperplasia - Male

Number Examined	Group 1	Group 2	Group 3	Group 4
	25	25	25	25
Minimal	0	0	0	1
Mild	0	0	0	3

Nominal Dose:

Group 1 – Vehicle control

Group 2 - 30 mg/kg/day

Group 3 - 100 mg/kg/day

Group 4 - 300 mg/kg/day

An increased incidence of nasal inflammation was noted in the treatment groups, as shown in the following table (taken from the study report).

Text Table 10: Nasal Cavity, Exudative Inflammation

MALES				
Number Examined	Group 1	Group 2	Group 3	Group 4
	25	25	25	25
Minimal	0	3	2	6
Mild	0	0	0	3
Moderate	1	0	0	2
FEMALES				
Number Examined	Group 1	Group 2	Group 3	Group 4
	25	25	25	25
Minimal	2	0	7	5
Mild	0	0	0	9
Moderate	0	0	1	3

Group 1 - Vehicle control

Group 2 - 30 mg/kg/day

Group 3 - 100 mg/kg/day

Group 4 - 300 mg/kg/day

Neoplastic Changes:

The positive control article produced a marked increase in the incidence of lung tumors, as shown in the following table (taken from the study report).

Text Table 7: Tumors in Lungs

MALES						
	Group 1	Group 2	Group 3	Group 4	Group 5	HCR (%) Range
Number Examined	25	25	25	25	10	
Adenoma, single	1	2	0	1	0	0-24
Adenoma, multiple	0	0	1	0	10*	0-8
Carcinoma	1	0	1	0	0	0-8
Total Lung Tumors	2	2	2	1	10*	NA

Nominal Dose:

Group 1 – Vehicle control

Group 2 - 30 mg/kg/day

Group 3 - 100 mg/kg/day

Group 4 - 300 mg/kg/day

Group 5 – Urethane (1000 mg/kg/day)

HCR: (b) (4) Historical Control Range % in vehicle control mice based on 25 mice in each dose group

NA: Not applicable

* Statistically significant when compared to vehicle control (see Pathology report, [Appendix C](#)).**Text Table 7: Tumors in Lungs – Continued**

FEMALES						
	Group 1	Group 2	Group 3	Group 4	Group 5	HCR (%) Range
Number Examined	25	25	25	25	10	
Adenoma, single	1	2	0	1	0	0-24
Adenoma, multiple	0	0	1	0	10*	0-4
Carcinoma	2	1	2	0	0	0-4
Total Lung Tumors	3	3	3	1	10*	NA

Nominal Dose:

Group 1 – Vehicle control

Group 2 - 30 mg/kg/day

Group 3 - 100 mg/kg/day

Group 4 - 300 mg/kg/day

Group 5 – Urethane (1000 mg/kg/day)

HCR: (b) (4) Historical Control Range % in vehicle control mice based on 25 mice in each dose group

NA: Not applicable

* Statistically significant when compared to vehicle control (see Pathology report, [Appendix C](#)).

The incidence of hemangiosarcomas and hemangiomas in various organs, including spleen, are summarized in the following tables (taken from the study report).

**Text Table 8: Incidence of Hemangiosarcomas and Hemangiomas in
Different Organs, Including Spleen**

MALES					
	Group 1	Group 2	Group 3	Group 4	HCR (%)
Number Examined	25	25	25	25	Range
Spleen	0	1 ¹	0	0	0-16
Ear (skin), hemangiosarcoma	1	0	0	0	0-4
Hindlimb (skin), hemangiosarcoma	0	1	0	0	0-4
Bone, Sternum, Hemangiosarcoma	0	0	0	1	0-4
Total Animals	1	2	0	1	NA

1 = Multicentric hemangiosarcoma observed in this animal, which included spleen and bone marrow.

Nominal Dose:

Group 1 – Vehicle control

Group 2 - 30 mg/kg/day

Group 3 - 100 mg/kg/day

Group 4 - 300 mg/kg/day

HCR: (b) (4) Historical Control Range % in vehicle control mice based on 25 mice in each dose group

NA: Not applicable.

**Text Table 8: Incidence of Hemangiosarcomas and Hemangiomas in
Different Organs, Including Spleen - Continued**

FEMALES					
	Group 1	Group 2	Group 3	Group 4	HCR (%)
Number Examined	25	25	25	25	Range
Spleen	2	2 ²	1	2	0-16
Multicentric Hemangiosarcoma	1	0 ²	0	0	0-4
Uterus, Hemangiosarcoma	0	0	1	0	0-8
Uterus, Hemangioma	0	1	0	0	NPO
Skin, Mammary, Hemangiosarcoma	1	0	0	0	0-4
Total Animals	4	3	2	2	NA

2 = Multicentric hemangiosarcoma observed in one animal, which included spleen and uterus.

Nominal Dose:

Group 1 – Vehicle control

Group 2 - 30 mg/kg/day

Group 3 - 100 mg/kg/day

Group 4 - 300 mg/kg/day

HCR: (b) (4) Historical Control Range % in vehicle control mice based on 25 mice in each dose group

NA: Not applicable.

NPO: Not Previously Observed in the (b) (4) Historical Control Database.

Treatment with LX1606 did not significantly increase the incidence of hemangiomas or hemangiosarcomas as compared to the vehicle control group. The positive control article, however, produced a statistically significant increase in the incidence of splenic hemangiosarcomas (100% in males and 90% in females) as compared to the vehicle control.

The incidence of other types of tumors is presented in the following table (taken from the study report).

Text Table 9: Other Tumors

MALES					
	Group 1	Group 2	Group 3	Group 4	HCR (%)
Number Examined	25	25	25	25	Range
Multicentric, Lymphoma	0	0	1	0	0-4
Hepatocellular adenoma	0	0	0	1	0-4
Kidney, cystadenoma	0	0	0	1	NPO
Multicentric mesothelioma	0	0	0	2	0-4
Heart, Sarcoma	1	0	0	0	0-4
Thymus, Lymphoma	0	0	0	1	0-4
Harderian Gland, Adenoma	0	1	0	0	0-8
Nasal Cavity, Osteosarcoma	1	0	0	0	NPO
Nasal Cavity, Ameloblastoma ¹	0	0	0	1	NPO
Nasal Cavity, Adenocarcinoma	0	0	0	2	NPO ²
FEMALES					
	Group 1	Group 2	Group 3	Group 4	HCR (%)
Number Examined	25	25	25	25	Range
Multicentric Histiocytic Sarcoma	0	0	1	0	NPO
Multicentric Basal Cell Carcinoma	0	1	0	0	NPO
Nasal Cavity, Adenocarcinoma	0	0	1	1	0-4
Ear, Papilloma	0	0	0	1	0-4
Harderian Gland, Adenoma	0	1	1	0	0-16
Salivary Gland, Adenocarcinoma	0	1	0	0	NPO
Muscle, Sarcoma ³	0	0	1	0	0-4
Forelimb, Papilloma	0	1	0	0	0-4

¹Originating in the tooth of nasal cavity section.

²Although adenocarcinomas not recorded in males, nasal cavity adenomas were recorded with a range of 0-8%.

³Involves muscles around salivary gland.

Nominal Dose:

Group 1 – Vehicle control

Group 2 - 30 mg/kg/day

Group 3 - 100 mg/kg/day

Group 4 - 300 mg/kg/day

HCR: (b) (4) Historical Control Range % in vehicle control mice based on 25 mice in each dose group

(b) (4)

NPO: Not Previously Observed in the (b) (4) Historical Control Database.

Treatment with LX1606 did not significantly increase the incidence of these tumors as compared to the vehicle control group.

The tumor incidences were within the historical control ranges from the testing laboratory. The FDA statistical review of this study concluded that treatment with LX1606 did not significantly increase the tumor incidences in either males or females,

as compared to the vehicle control (see table below from Dr. Feng Zhou's review). The following tumor combinations were analyzed for statistical significance:

1. alveolar-bronchiolar adenoma + carcinoma (both sexes)
2. uterine hemangioma + hemangiosarcoma
3. multiple organ hemangiosarcoma (both sexes)
4. multiple organ hemangioma + hemangiosarcoma (females only)
5. multiple organ papilloma (females only)
6. multiple organ lymphoma (males only)

Table 2A: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons with Vehicle Control – Male Mice

Organ Name	Tumor Name	0 mkd VC N=25	30 mkd LD N=25	100 mkd MD N=25	300 mkd HD N=25	P-Value			
						Dos Response	C vs. LD	C vs. MD	C vs. HD
bone, sternum	hemangiosarcoma	0	0	0	1	0.2371	.	.	0.4792
cavity, nasal	adenocarcinoma	0	0	0	2	0.0543	.	.	0.2243
	ameloblastoma	0	0	0	1	0.2371	.	.	0.4792
	osteosarcoma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	hemangiosarcoma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
harderian glands	adenoma	0	1	0	0	0.7423	0.4898	.	.
heart	sarcoma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
hindlimb	hemangiosarcoma	0	1	0	0	0.7423	0.4898	.	.
kidneys	cystadenoma	0	0	0	1	0.2371	.	.	0.4792
liver	hepatocellular adeno	0	0	0	1	0.2371	.	.	0.4792
lungs with bronchi	alveolar-bronchiolar carcinoma	1	0	1	0	0.7474	1.0000	0.7551	1.0000
	alveolar-bronchiolar adenoma	1	2	1	1	0.5905	0.4844	0.7551	0.7340
	C_alveolar_carcinoma+adenoma	2	2	2	1	0.7149	0.6798	0.6954	0.8670
multicentric	Hemangiosarcoma	0	1	0	0	0.7423	0.4898	.	.
	Lymphoma	0	0	1	0	0.4948	.	0.5000	.
	Mesothelioma	0	0	0	2	0.0618	.	.	0.2449
thymus	Lymphoma	0	0	0	1	0.2371	.	.	0.4792
Multiple Organs	C_hemangiosarcoma	1	2	0	1	0.6085	0.4844	1.0000	0.7340
	C_lymphoma	0	0	1	1	0.1778	.	0.5000	0.4792

Table 2B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons with Vehicle Control – Female Mice

Organ Name	Tumor Name	0 mkd VC N=25	30 mkd LD N=25	100 mkd MD N=25	300 mkd HD N=25	P-Value			
						Dos Response	VC vs. LD	VC vs. MD	VC vs. HD
cavity, nasal	adenocarcinoma	0	0	1	1	0.1921	.	0.5208	0.5106
ear	papilloma	0	0	0	1	0.2577	.	.	0.5208
forelimb	papilloma	0	1	0	0	0.7604	0.5106	.	.
	C_papilloma	0	1	0	1	0.3275	0.5106	.	0.5208
harderian glands	adenoma	0	1	1	0	0.6368	0.5106	0.5208	.
lungs with bronchi	alveolar-bronchiolar adenoma	1	2	1	1	0.6249	0.5163	0.7757	0.7660
	alveolar-bronchiolar carcinoma	2	1	2	0	0.8933	0.8908	0.7270	1.0000
	C_alveolar_carcinoma+adenoma	3	3	3	1	0.8774	0.6878	0.7067	0.9504
multicentric	basal cell carcinoma	0	1	0	0	0.7604	0.5106	.	.
	hemangiosarcoma	1	1	0	0	0.9445	0.7660	1.0000	1.0000
	histiocytic sarcoma	0	0	1	0	0.5104	.	0.5208	.
salivary glands	adenocarcinoma	0	1	0	0	0.7604	0.5106	.	.
	sarcoma	0	0	1	0	0.5104	.	0.5208	.
skin (mammary area)	hemangiosarcoma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
spleen	hemangiosarcoma	2	1	1	2	0.4031	0.8830	0.8901	0.6957
uterus	hemangioma	0	1	0	0	0.7604	0.5106	.	.
	hemangiosarcoma	0	0	1	0	0.5104	.	0.5208	.
	C_hemangiosarcoma/hemangioma	0	1	1	0	0.6368	0.5106	0.5208	.
Multiple Organs	C_hemangiosarcoma	4	2	2	2	0.7211	0.8961	0.9053	0.8961
	C_hemangiosarcoma/hemangioma	4	3	2	2	0.7829	0.7742	0.9053	0.8961

Toxicokinetics: The TK data for both LX1606 and metabolite LP-778902 were summarized in the following tables (taken from the study report).

Text Table 11: Toxicokinetic parameters for LX1606 on Day 177

Group	Dose (mg/kg/day)	Sex	C _{max} (ng/mL)	T _{max} (hr)	AUC ₀₋₂₄ (ng·hr/mL)
2	30	M	0.994	0.500	1.31
		F	0.956	0.500	NC
3	100	M	2.14	0.500	8.75
		F	1.66	1.00	6.74
4	300	M	1.94	2.00	24.5
		F	2.73	0.500	34.7

NC=Not calculated

Text Table 12: Toxicokinetic parameters for LP-778902 on Day 177

Group	Dose (mg/kg/day)	Sex	C _{max} (ng/mL)	T _{max} (hr)	AUC ₀₋₂₄ (ng·hr/mL)	Metabolite: Parent Ratio AUC ₀₋₂₄
2	30	M	2330	0.500	5340	4080
		F	4130	0.500	8250	NA
3	100	M	6340	1.00	20400	2330
		F	8310	0.500	29100	4310
4	300	M	8990	2.00	64100	2620
		F	15600	0.500	101000	2900

Dosing Solution Analysis: All dosing formulations analyzed were within the acceptance criteria of 85-115% of target concentration.

RAT:

The 2-year rat carcinogenicity study will be submitted post-approval as agreed in the End of Phase 2 Meeting on April 11, 2012 and in the pre-NDA meeting on February 24, 2015. The doses used in this study were recommended by the Executive Carcinogenicity Assessment Committee (see meeting minutes in Appendix 2). The 2-year rat carcinogenicity study was initiated in September, 2015, and the in-life phase will be completed in September 2017. The final study report is expected in the third quarter of 2018. The sponsor provided a safety update for this study on July 27, 2016 (SD # 22). The update covers the study through the end of 26 weeks of treatment. No treatment-related clinical or mass observations were noted.

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

Study title: LX1606: Oral (Gavage) Study of Fertility and Early Embryonic Development in the Rat

Study no.: 8247231
Study report location: N/A
Conducting laboratory and location: (b) (4)
Date of study initiation: May 24, 2011
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: LX1606 hippurate (see table below)

The test article, LX1606 hippurate, was received at (b) (4) as follows:

(b) (4) lot number	Batch number	Quantity	Purity (%)	Date of receipt (b) (4)
1	AA-020763-BATCH-04-2008	2 x (b) (4) g	98.35	20 May 2011

Key Study Findings

Male rats were treated with LX1606 for 4 weeks prior to pairing, during the pairing period and until the day prior to necropsy for more than 10 weeks. Females were dosed for 2 weeks prior to pairing, during the pairing period, and until Day 6 of gestation. The females were terminated on Day 13 of gestation.

Treatment with LX1606 induced mouth rubbing, paddling, and salivation in all treatment groups. Treatment with LX1606 did not adversely affect reproductive performance, fertility, or embryo-fetal viability at doses up to 500 mg/kg/day.

Methods

Doses: 0, 100, 200, and 500 mg/kg/day
 Frequency of dosing: daily
 Dose volume: 10 ml/kg
 Route of administration: oral
 Formulation/Vehicle: 0.25% (w/v) methylcellulose
 Species/Strain: rat/Crl:CD(SD)
 Number/Sex/Group: 22/sex/group
 Satellite groups: none
 Study design: See table below
 Deviation from study protocol: There were no deviations that had a significant impact on the study outcome.

The study design is shown in the table below (taken from the study report).

Group number	Group description	Dose level (mg/kg/day)	Dose concentration (mg/mL)	Dose volume (mL/kg)	Number of animals	
					Male	Female
1	Control	0	0	10	22	22
2	Low	100	10	10	22	22
3	Intermediate	200	20	10	22	22
4	High	500	50	10	22	22

The sponsor provided the following rationale for dose selection: *“The high dose of 500 mg/kg/day was selected as it was expected to be a pharmacologically active dose level”*. Male rats were treated with LX1606 for four weeks prior to pairing, during the pairing period, and until the day prior to necropsy, for a total duration of more than 10 weeks. Females were dosed for two weeks prior to pairing, during the pairing period, and until Day 6 of gestation. The females were terminated on Day 13 of gestation.

Observations and Results

Mortality: There were no treatment-related deaths. One control male was found dead due to a dosing error. One high-dose male was sacrificed due to tail injury unrelated to drug treatment.

Clinical Signs: Mouth rubbing, paddling, and salivation were noted in all treatment groups.

Body Weight: There were no treatment-related changes.

Feed Consumption: There were no treatment-related changes.

Necropsy: All mating and fertility parameters including sperm parameters, estrous cycling, pre-coital time, pregnancy rate, fertility index, and mating index were not

affected. There were 21, 22, 22, and 22 pregnancies in the control, low, mid, and high dose groups, respectively. The results are summarized in the sponsor's tables below.

Table 6
Group mating data

Test Article		Control		LX1606	
Group		1	2	3	4
Level (mg/kg/day)		0	100	200	500
6.1 Mating performance					
		Group 1	Group 2	Group 3	Group 4
Group size at pairing:					
Male		22	22	22	22
Female		22	22	22	22
Number mating on Day of pairing	1	6	8	7	8
	2	6	4	2	7
	3	2	4	3	3
	4	8	6	10	4
	Total:	22	22	22	22
Median pre-coital time (days)		2	2	3	2

Table 6
Group mating data

Test Article		Control		LX1606	
Group		1	2	3	4
Level (mg/kg/day)		0	100	200	500
6.2 Summary of mating record					
		Group 1	Group 2	Group 3	Group 4
Number of females paired					
		22	22	22	22
Pregnant:					
Mating from vaginal plug <i>in situ</i>				3	1
Mating from positive smear:					
Sperm/oestrus/pro-oestrus		3	4	2	1
Sperm/metoestrus/dioestrus					
Sperm/stage of oestrus not recorded		18	18	17	20
Absence of positive smear					
Pregnancy rate (%)		95.5	100.0	100.0	100.0
Non-pregnant:					
Vaginal plug <i>in situ</i>					
Positive smear		1			
Absence of positive smear					
Total showing vaginal plug <i>in situ</i> or positive smear		22	22	22	22

Table 6
Group mating data

	Test Article	Control				Statistics
	Group	1	2	3	4	
	Level (mg/kg/day)	0	100	200	500	
6.3 Mating indices						
	Group 1	Group 2	Group 3	Group 4		
Number of paired males	22	22	22	22		
Number of paired females	22	22	22	22		
Number of mated males	22	22	22	22		
Number of mated females	22	22	22	22		
Number of males inducing pregnancy	21	22	22	22		
Number of pregnant females	21	22	22	22		
Mating index %	100.0	100.0	100.0	100.0		F-
Fertility index % : male	95.5	100.0	100.0	100.0		F-
: female	95.5	100.0	100.0	100.0		F-
Fecundity index % : male	95.5	100.0	100.0	100.0		F-
: female	95.5	100.0	100.0	100.0		F-
F- = Cochran-Armitage and Fisher's Exact (lower tail)						

F- = Cochran-Armitage and Fisher's Exact (lower tail)

Table 7
Group mean uterine/implantation data

Test Article Group Level (mg/kg/day)	Control 1 0	LX1606 2 3 4 100 200 500			
	Group 1	Group 2	Group 3	Group 4	Statistics
Number of females with live fetuses on Day 13 gestation	21	22	22	22	
Mean number of corpora lutea per female	17.6	17.3	18.4	17.3	J
Mean number of implantations per female	15.6	15.9	16.8	16.0	J
Pre-implantation loss:					
mean%	11.5	7.6	7.3	6.9	
number of dams affected	15	11	11	12	F+
Early intrauterine deaths:					
mean number	0.8	0.7	1.0	1.0	
number of dams affected	13	9	12	12	F+
Late intrauterine deaths:					
mean number	0.0	0.0	0.0	0.0	
number of dams affected	0	0	0	0	X
Dead fetuses:					
mean number	0.0	0.0	0.0	0.0	
number of dams affected	0	0	0	0	X
Post-implantation loss:					
mean%	4.7	4.0	5.5	6.0	
number of dams affected	13	9	12	12	F+
Mean number of fetuses per female	14.8	15.2	15.8	15.1	J

F+ = Cochran-Armitage and Fisher's Exact (upper tail)

J = Kruskal-Wallis, Terpstra-Jonckheere, Wilcoxon

X = not analysed

Table 8
Summary of seminology data

Test Article	Control	LX1606		
Group	1	2	3	4
Level (mg/kg/day)	0	100	200	500
	Group 1	Group 2	Group 3	Group 4
Number of males examined	21	22	22	21
Mean total sperm count (10 ⁶ /mL)	19.0	30.2	24.9	29.9
Mean % motile	94	95	94	94
Mean VAP (µm/s)	179.7	175.6	181.3	186.7
Mean VCL (µm/s)	314.6	306.4	318.2	324.3
Mean VSL (µm/s)	130.4	127.8	132.1	134.8
Mean STR (%)	71	71	72	71
Mean abnormal sperm (%)	1.1	-	-	1.1
VAP = average path velocity VSL = straight line velocity VCL = curvilinear velocity STR = straightness (VSL:VAP)				

Toxicokinetics: Not measured.

Dosing Solution Analysis:

The formulation samples were analyzed. The results indicated that the mean values were 119.0%, 122.3%, and 122.4% of the nominal concentration for the dosing formulations used in the 100, 200, and 500 mg/kg/day groups, respectively, on week 9. The concentrations in the high-dose formulation were slightly higher than 120% of the nominal concentration at week 3.

9.2 Embryo-Fetal Development

Study title: Oral Gavage Study for Effects on Embryo-fetal Development and Toxicokinetics of LP-778914 in Rats

Study no.:	7648-298
Study report location:	N/A
Conducting laboratory and location:	(b) (4)
Date of study initiation:	July 9, 2008
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	See table below

Test Article	Batch No.	Storage	Purity	Stability	Reserve (Archive) Sample
LP778914	AA-020763-Batch-01-2008	2-8°C, protect from light, with desiccant	98%	See footnote a	Not required

a The sponsor established 9 month accelerated stability from the time of manufacturing (07 March 2008). As the study terminated prior to the end of this 9 month period, the test article was deemed stable during the time frame of dose administration on this study.

Key Study Findings

Pregnant rats were treated with LP-778914 at oral doses of 0 (vehicle control), 250, 500, or 750 mg/kg/day during gestation days (GD) 7-17. Maternal toxicity (mortality and impaired bodyweight gain) occurred at 750 mg/kg/day, whereas no adverse effects on embryo-fetal development were observed. The NOAEL was 500 mg/kg/day for maternal toxicity, and ≥ 750 mg/kg/day for embryo-fetal development. LP-778914 was not teratogenic in this testing system.

Methods

Doses: 250, 500, or 750 mg/kg/day
 Frequency of dosing: daily
 Dose volume: 10 ml/kg
 Route of administration: oral
 Formulation/Vehicle: 0.25% (w/v) methylcellulose
 Species/Strain: Rat/Crl:CD(SD)
 Number/Sex/Group: 25
 Satellite groups: 6/sex/group (3 in control group)
 Study design: See sponsor's table below
 Deviation from study protocol: There were no deviations that had a significant impact on the study outcome.

The study design is shown in the table below (taken from the study report).

Group ^a	No. of Females	Dose Level (mg/kg/day)	Dose Concentration (mg/mL)	Dosing Schedule Days of Gestation
Main Study Animals				
1 (Control)	25	0	0	6-17
2 (Low)	25	250	25	6-17
3 (Mid)	25	500	50	6-17
4 (High)	25	750	75	6-17
Toxicokinetic Animals				
5 (Control)	3	0	0	6-17
6 (Low)	6	250	25	6-17
7 (Mid)	6	500	50	6-17
8 (High)	6	750	75	6-17

a Groups 1 and 5 received control article only.

Pregnant rats were treated with LP-778914 at oral doses of 0 (control), 250, 500, or 750 mg/kg/day during GD 7-17. At initiation of treatment, the animals were approximately 12 weeks old, and their body weights ranged from 221 to 285 g.

The dose selection was based on the results of the dose-ranging study (study #7648-296). In this study, maternal and embryo-fetal toxicity were observed in one female treated with the highest dose tested (750 mg/kg/day). The effects included decreased body weight gain, lower food consumption, absence of viable fetuses, and early resorptions.

Observations and Results

Mortality:

One high-dose female was found dead on GD 20. This animal had body weight loss, decreased food consumption, and clinical signs of toxicities including paleness and hunched posture, squinted eyes, rough haircoat, red and/or brown haircoat, nonformed feces, and few or no feces. Another female was sacrificed on gestation day 18 due to moribund condition, with clinical signs including hunched posture, opaque eyes, rough haircoat, red and/or brown haircoat, and red/black anal discharge. This female also had body weight loss and decreased food consumption. Both deaths are considered as treatment related.

Clinical Signs: Clinical signs of toxicity were limited to the two dead animals as mentioned above.

Body Weight: Body weight gain during GD 6-18 was significantly lower (~31%) in the high dose group as compared to the control.

Food Consumption: Significant decreases in mean maternal food consumption (~6%) were noted in the high dose group during the study (GD 4-20).

Necropsy

Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.):

One high-dose female had no viable fetuses (all early resorptions). All other surviving dams were pregnant with viable fetuses. There were no treatment-related effects on the corpora lutea, implantations, litter sizes, live fetuses, early and late resorptions, sex ratio of fetuses, or mean fetal weights. The results are presented in the following tables (taken from the study report).

Table 8
Summary of Cesarean Section Data

DOSE LEVEL		GROUP 1 0 MG/KG/DAY	GROUP 2 250 MG/KG/DAY	GROUP 3 500 MG/KG/DAY	GROUP 4 750 MG/KG/DAY
Females Mated	N	25	25	25	25
Pregnant	N	25	25	25	24
	%	100	100	100	96
Aborted	N	0	0	0	0
	%	0.0	0.0	0.0	0.0
Died	N	0	0	0	2
	%	0.0	0.0	0.0	8.0
Delivered Early	N	0	0	0	0
	%	0.0	0.0	0.0	0.0
Pregnant at C-section	N	25	25	25	22
Dams with Viable Fetuses	N	25	25	25	21
	%	100	100	100	95
Dams with no Viable Fetuses	N	0	0	0	1
	%	0.0	0.0	0.0	4.5
Corpora Lutea	MEAN	14.7	14.6	14.1	14.5
	S.D.	1.8	2.1	1.6	1.9
	N	25	25	25	22
	TOTAL	367	364	352	320
Implantation Sites	MEAN	14.0	13.8	13.8	13.4
	S.D.	1.5	1.9	1.4	1.9
	N	25	25	25	22
	TOTAL	349	346	345	295
Preimplantation Loss	MEAN%	4.4	4.6	1.8	7.8
	S.D.	7.4	6.2	3.5	6.5

STATISTICAL ANALYSES WERE CONDUCTED. IF SIGNIFICANT DIFFERENCES OCCUR, THEY ARE DENOTED AS FOLLOWS: * = P≤0.05 ** = P≤0.01.

TABLE 8
SUMMARY OF CESAREAN SECTION DATA

DOSE LEVEL		GROUP 1 0 MG/KG/DAY	GROUP 2 250 MG/KG/DAY	GROUP 3 500 MG/KG/DAY	GROUP 4 750 MG/KG/DAY
Pregnant at C-section	N	25	25	25	22
Resorptions: Total	MEAN	0.5	0.2	0.3	1.0
	S.D.	0.9	0.5	0.7	3.3
	N	25	25	25	22
	TOTAL	12	6	7	21
	MEAN%	3.4	1.7	1.9	6.5
	S.D.	6.5	3.6	4.9	21.8
Early	MEAN	0.5	0.2	0.3	1.0
	S.D.	0.9	0.5	0.7	3.3
	N	25	25	25	22
	TOTAL	12	6	7	21
	MEAN%	3.4	1.7	1.9	6.5
	S.D.	6.5	3.6	4.9	21.8
Late	MEAN	0.0	0.0	0.0	0.0
	S.D.	0.0	0.0	0.0	0.0
	N	25	25	25	22
	TOTAL	0	0	0	0
	MEAN%	0.0	0.0	0.0	0.0
	S.D.	0.0	0.0	0.0	0.0
Dead Fetuses	TOTAL	0	0	0	0
Postimplantation Loss	MEAN%	3.4	1.7	1.9	6.5
	S.D.	6.5	3.6	4.9	21.8

STATISTICAL ANALYSES WERE CONDUCTED. IF SIGNIFICANT DIFFERENCES OCCUR, THEY ARE DENOTED AS FOLLOWS: * = P≤0.05 ** = P≤0.01.

TABLE 8
SUMMARY OF CESAREAN SECTION DATA

DOSE LEVEL		GROUP 1 0 MG/KG/DAY	GROUP 2 250 MG/KG/DAY	GROUP 3 500 MG/KG/DAY	GROUP 4 750 MG/KG/DAY
Pregnant at C-section	N	25	25	25	22
Live Fetuses	MEAN	13.5	13.6	13.5	12.5
	S.D.	1.6	1.9	1.4	3.5
	N	25	25	25	22
	TOTAL	337	340	338	274
	MEAN%	96.6	98.3	98.1	93.5
	S.D.	6.5	3.6	4.9	21.8
Females	MEAN	6.8	7.2	7.2	6.3
	S.D.	2.1	2.6	2.0	2.3
	N	25	25	25	21
	TOTAL	169	180	181	132
	MEAN%	50.9	53.1	53.4	48.2
	S.D.	16.8	17.5	12.4	15.3
Males	MEAN	6.7	6.4	6.3	6.8
	S.D.	2.6	2.6	1.8	2.4
	N	25	25	25	21
	TOTAL	168	160	157	142
	MEAN%	49.1	46.9	46.6	51.8
	S.D.	16.8	17.5	12.4	15.3
Sex Ratio M:F		50:50	47:53	46:54	52:48

STATISTICAL ANALYSES WERE CONDUCTED. IF SIGNIFICANT DIFFERENCES OCCUR, THEY ARE DENOTED AS FOLLOWS: * = P≤0.05 ** = P≤0.01.

TABLE 8
SUMMARY OF CESAREAN SECTION DATA

DOSE LEVEL		GROUP 1 0 MG/KG/DAY	GROUP 2 250 MG/KG/DAY	GROUP 3 500 MG/KG/DAY	GROUP 4 750 MG/KG/DAY
Pregnant at C-section	N	25	25	25	22
Dams with Viable Fetuses	N	25	25	25	21
Resorptions:	Total	MEAN	0.5	0.2	0.3
		S.D.	0.9	0.5	0.9
		N	25	25	21
		TOTAL	12	6	6
		MEAN%	3.4	1.7	2.1
		S.D.	6.5	3.6	6.5
	Early	MEAN	0.5	0.2	0.3
		S.D.	0.9	0.5	0.9
		N	25	25	21
		TOTAL	12	6	6
Late		MEAN%	3.4	1.7	2.1
		S.D.	6.5	3.6	6.5
		MEAN	0.0	0.0	0.0
		S.D.	0.0	0.0	0.0
		N	25	25	21
		TOTAL	0	0	0
		MEAN%	0.0	0.0	0.0
		S.D.	0.0	0.0	0.0
	Dead Fetuses	TOTAL	0	0	0
	Postimplantation Loss	MEAN%	3.4	1.7	2.1
		S.D.	6.5	3.6	6.5

STATISTICAL ANALYSES WERE CONDUCTED. IF SIGNIFICANT DIFFERENCES OCCUR, THEY ARE DENOTED AS FOLLOWS: * = $P \leq 0.05$ ** = $P \leq 0.01$. MEANS CALCULATED EXCLUDING DAMS WITH NO VIABLE FETUSES.

TABLE 8
SUMMARY OF CESAREAN SECTION DATA

DOSE LEVEL		GROUP 1 0 MG/KG/DAY	GROUP 2 250 MG/KG/DAY	GROUP 3 500 MG/KG/DAY	GROUP 4 750 MG/KG/DAY
Pregnant at C-section	N	25	25	25	22
Dams with Viable Fetuses	N	25	25	25	21
Live Fetuses	MEAN	13.5	13.6	13.5	13.0
	S.D.	1.6	1.9	1.4	2.1
	N	25	25	25	21
	TOTAL	337	340	338	274
	MEAN%	96.6	98.3	98.1	97.9
	S.D.	6.5	3.6	4.9	6.5
Females	MEAN	6.8	7.2	7.2	6.3
	S.D.	2.1	2.6	2.0	2.3
	N	25	25	25	21
	TOTAL	169	180	181	132
	MEAN%	50.9	53.1	53.4	48.2
	S.D.	16.8	17.5	12.4	15.3
Males	MEAN	6.7	6.4	6.3	6.8
	S.D.	2.6	2.6	1.8	2.4
	N	25	25	25	21
	TOTAL	168	160	157	142
	MEAN%	49.1	46.9	46.6	51.8
	S.D.	16.8	17.5	12.4	15.3
Sex Ratio M:F		50:50	47:53	46:54	52:48

STATISTICAL ANALYSES WERE CONDUCTED. IF SIGNIFICANT DIFFERENCES OCCUR, THEY ARE DENOTED AS FOLLOWS: * = $P \leq 0.05$ ** = $P \leq 0.01$. MEANS CALCULATED EXCLUDING DAMS WITH NO VIABLE FETUSES.

Table 9
Summary of Mean Fetal Weights (g)

DOSE LEVEL		GROUP 1 0 MG/KG/DAY	GROUP 2 250 MG/KG/DAY	GROUP 3 500 MG/KG/DAY	GROUP 4 750 MG/KG/DAY
of all Viable Fetuses	MEAN	3.70	3.72	3.86	3.76
	S.D.	0.24	0.24	0.25	0.24
	N	25	25	25	21
Covariate Adjusted MEAN		3.70	3.72	3.86	3.76
of Male Fetuses	MEAN	3.79	3.84	3.96	3.85
	S.D.	0.26	0.27	0.25	0.28
	N	25	25	25	21
Covariate Adjusted MEAN		3.79	3.84	3.96	3.85
of Female Fetuses	MEAN	3.59	3.62	3.78	3.66
	S.D.	0.27	0.22	0.27	0.23
	N	25	25	25	21
Covariate Adjusted MEAN		3.59	3.62	3.78	3.66

STATISTICAL ANALYSES WERE CONDUCTED. IF SIGNIFICANT DIFFERENCES OCCUR, THEY ARE DENOTED AS FOLLOWS: * = P≤0.05 ** = P≤0.01.

Offspring (Malformations, Variations, etc.)

External alterations:

Fetal external malformations were limited to umbilical hernia (high-dose), rudimentary tail (control and mid-dose) and anal atresia (mid-dose). None of these effects are considered to be treatment related. The results are summarized in the table below (taken from the study report).

Table 11
Summary of Fetal External Malformations

DOSE LEVEL		GROUP 1 0 MG/KG/DAY	GROUP 2 250 MG/KG/DAY	GROUP 3 500 MG/KG/DAY	GROUP 4 750 MG/KG/DAY
Litters Evaluated	N	25	25	25	21
Fetuses Evaluated	N	337	340	338	274
Live	N	337	340	338	274
Dead	N	0	0	0	0
UMBILICAL HERNIA					
Fetal Incidence	N	0	0	0	1
	%	0.0	0.0	0.0	0.4
Litter Incidence	N	0	0	0	1
	%	0.0	0.0	0.0	4.8
RUDIMENTARY TAIL					
Fetal Incidence	N	1	0	1	0
	%	0.3	0.0	0.3	0.0
Litter Incidence	N	1	0	1	0
	%	4.0	0.0	4.0	0.0
ANAL ATRESIA					
Fetal Incidence	N	0	0	1	0
	%	0.0	0.0	0.3	0.0
Litter Incidence	N	0	0	1	0
	%	0.0	0.0	4.0	0.0
TOTAL FETAL EXTERNAL MALFORMATIONS					
Fetal Incidence	N	1	0	1	1
	%	0.3	0.0	0.3	0.4
Litter Incidence	N	1	0	1	1
	%	4.0	0.0	4.0	4.8

STATISTICAL ANALYSES WERE CONDUCTED. IF SIGNIFICANT DIFFERENCES OCCUR, THEY ARE DENOTED AS FOLLOWS: * = P≤0.05 ** = P≤0.01.
N = Number

Fetal Soft Tissue Alterations:

Fetal soft tissue malformations were limited to a single occurrence of retroesophageal aortic arch in the high-dose group. The results are summarized in the sponsor's table below.

Table 13
Summary of Fetal Soft Tissue Malformations

DOSE LEVEL		GROUP 1 0 MG/KG/DAY	GROUP 2 250 MG/KG/DAY	GROUP 3 500 MG/KG/DAY	GROUP 4 750 MG/KG/DAY
Litters Evaluated	N	25	25	25	21
Fetuses Evaluated	N	165	170	170	140
Live	N	165	170	170	140
Dead	N	0	0	0	0
RETROESOPHAGEAL AORTIC ARCH					
Fetal Incidence	N	0	0	0	1
	%	0.0	0.0	0.0	0.7
Litter Incidence	N	0	0	0	1
	%	0.0	0.0	0.0	4.8
TOTAL FETAL SOFT TISSUE MALFORMATIONS					
Fetal Incidence	N	0	0	0	1
	%	0.0	0.0	0.0	0.7
Litter Incidence	N	0	0	0	1
	%	0.0	0.0	0.0	4.8

STATISTICAL ANALYSES WERE CONDUCTED. IF SIGNIFICANT DIFFERENCES OCCUR, THEY ARE DENOTED AS FOLLOWS: * = P≤0.05 ** = P≤0.01.
N = Number

Fetal Skeletal Alterations: There were no treatment-related changes. The results are summarized in the sponsor's table below.

Table 15
Summary of Fetal Skeletal Malformations

DOSE LEVEL		GROUP 1 0 MG/KG/DAY	GROUP 2 250 MG/KG/DAY	GROUP 3 500 MG/KG/DAY	GROUP 4 750 MG/KG/DAY
Litters Evaluated	N	25	25	25	21
Fetuses Evaluated	N	172	170	168	134
Live	N	172	170	168	134
Dead	N	0	0	0	0
VERTEBRA(E) ABSENT					
Fetal Incidence	N	1	0	1	0
	%	0.6	0.0	0.6	0.0
Litter Incidence	N	1	0	1	0
	%	4.0	0.0	4.0	0.0
FUSED ARCHES					
Fetal Incidence	N	0	0	1	0
	%	0.0	0.0	0.6	0.0
Litter Incidence	N	0	0	1	0
	%	0.0	0.0	4.0	0.0
RIB(S) ABSENT					
Fetal Incidence	N	0	0	1	0
	%	0.0	0.0	0.6	0.0
Litter Incidence	N	0	0	1	0
	%	0.0	0.0	4.0	0.0
TOTAL FETAL SKELETAL MALFORMATIONS					
Fetal Incidence	N	1	0	1	0
	%	0.6	0.0	0.6	0.0
Litter Incidence	N	1	0	1	0
	%	4.0	0.0	4.0	0.0

STATISTICAL ANALYSES WERE CONDUCTED. IF SIGNIFICANT DIFFERENCES OCCUR, THEY ARE DENOTED AS FOLLOWS: * = P≤0.05 ** = P≤0.01.
N = Number

Toxicokinetics:

Plasma exposure to LP-778902 (the active metabolite) was much higher than that of the unchanged drug, as shown in the tables below (taken from the study report).

Table 3. Toxicokinetic Parameters for LP-778902 in Female Rat Plasma

Interval	Group	LX1606 Dose Level (mg/kg/day)	C _{max} (ng/mL)	DN C _{max} [(ng/mL)/ (mg/kg/day)]	T _{max} (hr)	AUC ₀₋₄ (ng·hr/mL)	AUC ₀₋₂₄ (ng·hr/mL)	DN AUC ₀₋₂₄ [(ng·hr/mL)/ (mg/kg/day)]	AUC _{0-∞} (ng·hr/mL)	t _{1/2} (hr)
GD 6	6	250	3930	15.7	2.00	13713	13713	54.9	13779	3.49
	7	500	1657	3.31	1.00	18809	18809	37.6	NC	NC
	8	750	1647	2.20	1.00	14635	14635	19.5	NC	NC
GD 17	6	250	1617	6.47	1.00	12880	12880	51.5	NA	3.75
	7	500	2483	4.97	2.00	26878	26878	53.8	NA	5.76
	8	750	3073	4.10	1.00	47563	47563	63.4	NA	NC

Very limited plasma concentrations of the parent compound, LX1606, were detected. The results are summarized in the following table (taken from the study report).

Table 1. Toxicokinetic Parameters for LX1606 in Female Rat Plasma

Interval	Group	LX1606 Dose Level (mg/kg/day)	C _{max} (ng/mL)	DN C _{max} [(ng/mL)/ (mg/kg/day)]	T _{max} (hr)	AUC ₀₋₄ (ng·hr/mL)	AUC ₀₋₂₄ (ng·hr/mL)	DN AUC ₀₋₂₄ [(ng·hr/mL)/ (mg/kg/day)]	AUC _{0-∞} (ng·hr/mL)	t _{1/2} (hr)
GD 6	6	250	5.28	0.0211	2.00	22.5	37.3	0.149	NC	NC
	7	500	4.69	0.00938	8.00	76.0	76.0	0.152	NC	NC
	8	750	3.04	0.00406	8.00	57.4	57.4	0.0765	NC	NC
GD 17	6	250	6.83	0.0273	8.00	43.0	97.7	0.391	NA	NC
	7	500	10.8	0.0215	8.00	155	155	0.309	NA	NC
	8	750	12.2	0.0163	8.00	216	216	0.288	NA	NC

Dosing Solution Analysis: The drug concentrations in the dosing formulations (105 to 109% of target concentration) were within the acceptance criteria.

Study title: Oral Gavage Embryo-fetal Developmental and Toxicokinetic Study of LP-778914 in Rabbits

Study no.: 7648-299
 Study report location: N/A
 Conducting laboratory and location: (b) (4)
 Date of study initiation: September 7, 2008
 GLP compliance: Yes
 QA statement: Yes
 Drug, lot #, and % purity: See table below

Test Article	Batch No.	Storage	Purity	Stability	Reserve (Archive) Sample
LP-778914	AA-020763-Batch-01-2008	2-8°C, protect from light, with desiccant	98%	See footnote ^a	1 g

^a The sponsor established 9-month accelerated stability from the time of manufacturing (07 March 2008). As the study terminated prior to the end of this 9-month period, the test article was deemed stable during the time frame of dose administration on this study.

Key Study Findings

Pregnant rabbits were treated with LP-778914 by oral gavage once daily on gestation days (GD) 7 through 19 at doses of 0 (control), 125, 250, and 500 mg/kg/day. Treatment resulted in mortality in the high-dose group, and decreased body weight gain and food consumption in the mid- and high-dose groups. The test article produced post-implantation loss in the mid- and high-dose groups and decreased fetal weight in the high-dose group. There were no clear treatment-related malformations. LP-778914 was not teratogenic in this testing system. The NOAEL for embryo-fetal development and maternal toxicity was 125 mg/kg/day.

Methods

Doses: 0 (control), 125, 250, and 500 mg/kg/day.
Frequency of dosing: daily
Dose volume: 10 ml/kg
Route of administration: oral
Formulation/Vehicle: 0.25% (w/v) methylcellulose
Species/Strain: Female Hra:(NZW)SPF rabbits
Number/Sex/Group: 20 females/group
Satellite groups: 3/group
Study design: See table below
Deviation from study protocol: There were no deviations that had a significant impact on the study outcome.

The study design is shown in the sponsor's table below.

Group ^a	No. of Females	Dose Level (mg/kg/day)	Dose Concentration ^b (mg/mL)	Dosing Schedule Days of Gestation
Main-Study Animals				
1 (Control)	20	0	0	7-20
2 (Low)	20	125	12.5	7-20
3 (Mid)	20	250	25	7-20
4 (High)	20	500	50	7-20
Toxicokinetic Animals				
5 (Control)	3	0	0	7-20
6 (Low)	3	125	12.5	7-20
7 (Mid)	3	250	25	7-20
8 (High)	3	500	50	7-20

a Groups 1 and 5 received control article only.

b All dose concentrations were corrected for salt content (correction factor = 1.312).

Pregnant rabbits were treated with LP-778914 by oral gavage once daily on GD 7 through 19 at doses of 0 (control), 125, 250, and 500 mg/kg/day.

The dose selection was based on the results of a dose range-finding study (study #7648-297) in pregnant NZW rabbits. In this study, pregnant rabbits were with LP-778914 during GD 7 through 19. Mortality was observed at 2000 mg/kg/day, and no adverse effects were noted at 300 mg/kg/day. Hence, a high dose of 500 mg/kg/day was selected for the current study.

In the present study, there were no signs of maternal toxicity and no adverse effects in fetuses.

Observations and Results

Mortality:

One doe in the 125 mg/kg/day group (F68375) was found dead on GD 19. Both horns of the gravid uterus were noted as being filled with a large amount of dark red fluid. The death of the 125 mg/kg/day doe is considered incidental, not due to LP-778914, and possibly related to pregnancy complications (as evidenced by the large amount of dark fluid in the uterus). This conclusion is based on the isolated occurrence in the low-dose group and the fact that no deaths occurred in the mid-dose group.

Two high-dose females were found dead on GD 10 and 20. No remarkable clinical observations were noted. The causes of death were not provided. However, these deaths are considered as treatment related since they were in the high-dose group.

Clinical Signs: Few or no feces, thin appearance and hypoactivity were observed in the high dose group.

Body Weight: Body weight gains in the mid- and high-dose groups were reduced by ~21 and 42%, respectively, as compared to the control group during the initiation of dosing to study termination (Days 7-29).

Food Consumption: Decreased food consumption during gestation days 7-21 were noted in the mid- and high-dose groups (~14 and 44%, respectively).

Necropsy

Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.):

Post-implantation loss (early and late) was increased in the mid- and high-dose groups. The control and low-dose groups had one litter each with post-implantation loss, and the mid- and high-dose groups had 5 and 7 litters with post-implantation loss, respectively. The live fetuses were decreased at these dose levels. The results are summarized in the sponsor's tables below.

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Table 7
Summary of Cesarean Section Data

DOSE LEVEL		GROUP 1 0 MG/KG/DAY	GROUP 2 125 MG/KG/DAY	GROUP 3 250 MG/KG/DAY	GROUP 4 500 MG/KG/DAY
Females Mated	N	20	20	20	20
Pregnant	N	19	19	19	16
	%	95	95	95	80
Aborted	N	0	0	0	0
	%	0.0	0.0	0.0	0.0
Died	N	0	1	0	1
	%	0.0	5.0	0.0	5.0
Delivered Early	N	0	0	0	0
	%	0.0	0.0	0.0	0.0
Pregnant at C-section	N	19	18	18	15
Dams with Viable Fetuses	N	19	18	18	15
	%	100	100	100	100
Dams with no Viable Fetuses	N	0	0	0	0
	%	0.0	0.0	0.0	0.0
Corpora Lutea	MEAN	9.6	9.7	9.2	8.5
	S.D.	2.9	2.0	1.7	2.0
	N	19	18	18	15
	TOTAL	183	174	166	127
Implantation Sites	MEAN	9.1	8.8	8.6	7.9
	S.D.	2.4	2.1	1.3	2.1
	N	19	18	18	15
	TOTAL	173	158	155	118
Preimplantation Loss	MEAN%	4.7	9.4	5.9	7.3
	S.D.	6.7	9.2	5.8	9.7

STATISTICAL ANALYSES WERE CONDUCTED. IF SIGNIFICANT DIFFERENCES OCCUR, THEY ARE DENOTED AS FOLLOWS: * = P≤0.05 ** = P≤0.01.

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TABLE 7 SUMMARY OF CESAREAN SECTION DATA					
DOSE LEVEL		GROUP 1 0 MG/KG/DAY	GROUP 2 125 MG/KG/DAY	GROUP 3 250 MG/KG/DAY	GROUP 4 500 MG/KG/DAY
Pregnant at C-section	N	19	18	18	15
Resorptions: Total	MEAN	0.2	0.1	0.4	0.5
	S.D.	0.9	0.2	0.8	0.5
	N	19	18	18	15
	TOTAL	4	1	7	7
	MEAN%	1.2	0.6	4.5	6.0*
	S.D.	5.4	2.6	8.2	6.9
Early	MEAN	0.1	0.1	0.3	0.3
	S.D.	0.2	0.2	0.6	0.5
	N	19	18	18	15
	TOTAL	1	1	5	5
	MEAN%	0.3	0.6	3.2	3.9
	S.D.	1.3	2.6	6.4	5.9
Late	MEAN	0.2	0.0	0.1	0.1
	S.D.	0.7	0.0	0.3	0.4
	N	19	18	18	15
	TOTAL	3	0	2	2
	MEAN%	0.9	0.0	1.3	2.1
	S.D.	4.0	0.0	3.9	5.5
Dead Fetuses	TOTAL	0	0	0	0
Postimplantation Loss	MEAN%	1.2	0.6	4.5	6.0*
	S.D.	5.4	2.6	8.2	6.9

STATISTICAL ANALYSES WERE CONDUCTED. IF SIGNIFICANT DIFFERENCES OCCUR, THEY ARE DENOTED AS FOLLOWS: * = P≤0.05 ** = P≤0.01.

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		TABLE 7 SUMMARY OF CESAREAN SECTION DATA			
DOSE LEVEL		GROUP 1 0 MG/KG/DAY	GROUP 2 125 MG/KG/DAY	GROUP 3 250 MG/KG/DAY	GROUP 4 500 MG/KG/DAY
Pregnant at C-section	N	19	18	18	15
Live Fetuses	MEAN	8.9	8.7	8.2	7.4
	S.D.	1.8	2.1	1.4	2.1
	N	19	18	18	15
	TOTAL	169	157	148	111
	MEAN%	98.8	99.4	95.5	94.0*
Females	S.D.	5.4	2.6	8.2	6.9
	MEAN	4.3	4.8	3.8	3.7
	S.D.	2.0	1.7	1.4	2.0
	N	19	18	18	15
	TOTAL	82	86	68	55
Males	MEAN%	48.0	55.2	45.1	48.4
	S.D.	19.9	15.0	12.8	21.5
	MEAN	4.6	3.9	4.4	3.7
	S.D.	1.8	1.6	1.0	1.7
	N	19	18	18	15
Sex Ratio M:F	TOTAL	87	71	80	56
	MEAN%	52.0	44.8	54.9	51.6
	S.D.	19.9	15.0	12.8	21.5
	Sex Ratio M:F	51:49	45:55	54:46	50:50

STATISTICAL ANALYSES WERE CONDUCTED. IF SIGNIFICANT DIFFERENCES OCCUR, THEY ARE DENOTED AS FOLLOWS: * = P≤0.05 ** = P≤0.01.

Decreases in fetal weights (~9%) were noted in the high-dose litters (see sponsor's table below).

Table 8
Summary of Mean Fetal Weights (g)

DOSE LEVEL		GROUP 1 0 MG/KG/DAY	GROUP 2 125 MG/KG/DAY	GROUP 3 250 MG/KG/DAY	GROUP 4 500 MG/KG/DAY
FETAL WEIGHTS	UNITS: GRAMS				
	of all Viable Fetuses				
	MEAN	39.49	39.64	38.93	37.99
	S.D.	5.35	3.72	4.56	5.47
	N	19	18	18	15
	Covariate Adjusted MEAN	40.23	40.14	38.75	36.68
	of Male Fetuses				
	MEAN	39.62	39.71	39.23	37.81
	S.D.	4.90	3.36	4.41	6.06
	N	19	18	18	15
	Covariate Adjusted MEAN	40.24	40.13	39.08	36.70
	of Female Fetuses				
	MEAN	39.61	39.64	38.43	38.13
	S.D.	6.37	4.99	5.36	5.57
	N	19	18	18	15
	Covariate Adjusted MEAN	40.44	40.21	38.22	36.64

STATISTICAL ANALYSES WERE CONDUCTED. IF SIGNIFICANT DIFFERENCES OCCUR, THEY ARE DENOTED AS FOLLOWS: * = P≤0.05 ** = P≤0.01.

Offspring (Malformations, Variations, etc.)**External alterations:**

There were no treatment-related changes. The results are summarized in the following tables (taken from the study report).

Table 9
Summary of Fetal External Variations

DOSE LEVEL		GROUP 1 0 MG/KG/DAY	GROUP 2 125 MG/KG/DAY	GROUP 3 250 MG/KG/DAY	GROUP 4 500 MG/KG/DAY
Litters Evaluated	N	19	18	18	15
Fetuses Evaluated	N	169	157	148	111
Live	N	169	157	148	111
Dead	N	0	0	0	0
TOTAL FETAL EXTERNAL VARIATIONS					
Fetal Incidence	N	0	0	0	0
	%	0.0	0.0	0.0	0.0
Litter Incidence	N	0	0	0	0
	%	0.0	0.0	0.0	0.0

STATISTICAL ANALYSES WERE CONDUCTED. IF SIGNIFICANT DIFFERENCES OCCUR, THEY ARE DENOTED AS FOLLOWS: * = P≤0.05 ** = P≤0.01.
N = Number

Table 10
Summary of Fetal External Malformations

DOSE LEVEL		GROUP 1 0 MG/KG/DAY	GROUP 2 125 MG/KG/DAY	GROUP 3 250 MG/KG/DAY	GROUP 4 500 MG/KG/DAY
Litters Evaluated	N	19	18	18	15
Fetuses Evaluated	N	169	157	148	111
Live	N	169	157	148	111
Dead	N	0	0	0	0
OPEN EYE(S)					
Fetal Incidence	N	1	0	0	0
	%	0.6	0.0	0.0	0.0
Litter Incidence	N	1	0	0	0
	%	5.3	0.0	0.0	0.0
TOTAL FETAL EXTERNAL MALFORMATIONS					
Fetal Incidence	N	1	0	0	0
	%	0.6	0.0	0.0	0.0
Litter Incidence	N	1	0	0	0
	%	5.3	0.0	0.0	0.0

STATISTICAL ANALYSES WERE CONDUCTED. IF SIGNIFICANT DIFFERENCES OCCUR, THEY ARE DENOTED AS FOLLOWS: * = P≤0.05 ** = P≤0.01.
N = Number

Fetal Soft Tissue Alterations:

Most fetal soft tissue variations and malformations were the type commonly seen in this strain of rabbit, with the exception of reduced spleen in the control (1 fetus) and high-dose groups (2 fetuses).

Absent right subclavian was noted in one high-dose fetus. This variation is not in the historical control data of the conducting laboratory, nor is it in the historical control data of the Middle Atlantic Reproduction and Teratology Association. Therefore, its background frequency is unknown. The results are summarized in the sponsor's tables below.

Table 11
Summary of Fetal Soft Tissue Variations

DOSE LEVEL		GROUP 1 0 MG/KG/DAY	GROUP 2 125 MG/KG/DAY	GROUP 3 250 MG/KG/DAY	GROUP 4 500 MG/KG/DAY
Litters Evaluated	N	19	18	18	15
Fetuses Evaluated	N	169	157	148	111
Live	N	169	157	148	111
Dead	N	0	0	0	0
FLUID IN ABDOMINAL CAVITY					
Fetal Incidence	N	1	0	0	0
	%	0.6	0.0	0.0	0.0
Litter Incidence	N	1	0	0	0
	%	5.3	0.0	0.0	0.0
DILATATION OF LATERAL VENTRICLE(S)					
Fetal Incidence +	N	0	0	0	1
	%	0.0	0.0	0.0	0.9
Litter Incidence	N	0	0	0	1
	%	0.0	0.0	0.0	6.7
THYMUS DISCOLORED					
Fetal Incidence	N	1	0	0	0
	%	0.6	0.0	0.0	0.0
Litter Incidence	N	1	0	0	0
	%	5.3	0.0	0.0	0.0
LEFT CAROTID ARISES FROM THE INNOMINATE					
Fetal Incidence	N	15	11	16	6
	%	8.9	7.0	11	5.4
Litter Incidence	N	6	6	6	4
	%	32	33	33	27
ACCESSORY SUBCLAVIAN					
Fetal Incidence	N	10	3	6	2
	%	5.9	1.9	4.1	1.8
Litter Incidence	N	7	3	5	2
	%	37	17	28	13

STATISTICAL ANALYSES WERE CONDUCTED. IF SIGNIFICANT DIFFERENCES OCCUR, THEY ARE DENOTED AS FOLLOWS: * = P≤0.05 ** = P≤0.01.
N = Number
+ = Significant Positive Trend

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DOSE LEVEL		GROUP 1 0 MG/KG/DAY	GROUP 2 125 MG/KG/DAY	GROUP 3 250 MG/KG/DAY	GROUP 4 500 MG/KG/DAY
Litters Evaluated	N	19	18	18	15
Fetuses Evaluated	N	169	157	148	111
Live	N	169	157	148	111
Dead	N	0	0	0	0
ABSENT RIGHT SUBCLAVIAN					
Fetal Incidence +	N	0	0	0	1
	%	0.0	0.0	0.0	0.9
Litter Incidence	N	0	0	0	1
	%	0.0	0.0	0.0	6.7
INTERMEDIATE LOBE OF LUNG SMALL/MISSING					
Fetal Incidence	N	6	5	5	1
	%	3.6	3.2	3.4	0.9
Litter Incidence	N	2	2	5	1
	%	11	11	28	6.7
SMALL LUNG LOBES					
Fetal Incidence	N	0	0	1	0
	%	0.0	0.0	0.7	0.0
Litter Incidence	N	0	0	1	0
	%	0.0	0.0	5.6	0.0
GALL BLADDER SMALL					
Fetal Incidence +	N	0	0	0	1
	%	0.0	0.0	0.0	0.9
Litter Incidence	N	0	0	0	1
	%	0.0	0.0	0.0	6.7
STOMACH DISTENDED					
Fetal Incidence	N	1	1	0	0
	%	0.6	0.6	0.0	0.0
Litter Incidence	N	1	1	0	0
	%	5.3	5.6	0.0	0.0

STATISTICAL ANALYSES WERE CONDUCTED. IF SIGNIFICANT DIFFERENCES OCCUR, THEY ARE DENOTED AS FOLLOWS: * = P≤0.05 ** = P≤0.01.
N = Number
+ = Significant Positive Trend

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TABLE 11 SUMMARY OF FETAL SOFT TISSUE VARIATIONS					
DOSE LEVEL		GROUP 1 0 MG/KG/DAY	GROUP 2 125 MG/KG/DAY	GROUP 3 250 MG/KG/DAY	GROUP 4 500 MG/KG/DAY
Litters Evaluated	N	19	18	18	15
Fetuses Evaluated	N	169	157	148	111
Live	N	169	157	148	111
Dead	N	0	0	0	0
TOTAL FETAL SOFT TISSUE VARIATIONS					
Fetal Incidence	N	30	19	24	11
	%	18	12	16	9.9*
Litter Incidence	N	12	11	9	7
	%	63	61	50	47

STATISTICAL ANALYSES WERE CONDUCTED. IF SIGNIFICANT DIFFERENCES OCCUR, THEY ARE DENOTED AS FOLLOWS: * = P≤0.05 ** = P≤0.01.
N = Number

Table 12
Summary of Fetal Soft Tissue Malformations

DOSE LEVEL		GROUP 1 0 MG/KG/DAY	GROUP 2 125 MG/KG/DAY	GROUP 3 250 MG/KG/DAY	GROUP 4 500 MG/KG/DAY
Litters Evaluated	N	19	18	18	15
Fetuses Evaluated	N	169	157	148	111
Live	N	169	157	148	111
Dead	N	0	0	0	0
INCOMPLETE CLOSURE OF ABDOMINAL WALL					
Fetal Incidence	N	1	0	0	0
	%	0.6	0.0	0.0	0.0
Litter Incidence	N	1	0	0	0
	%	5.3	0.0	0.0	0.0
DILATATION OF PULMONARY TRUNK (MARKED)					
Fetal Incidence	N	1	0	0	0
	%	0.6	0.0	0.0	0.0
Litter Incidence	N	1	0	0	0
	%	5.3	0.0	0.0	0.0
DEVIATED SEPTUM					
Fetal Incidence	N	0	0	1	0
	%	0.0	0.0	0.7	0.0
Litter Incidence	N	0	0	1	0
	%	0.0	0.0	5.6	0.0
DIAPHRAGMATIC HERNIA					
Fetal Incidence	N	0	0	1	0
	%	0.0	0.0	0.7	0.0
Litter Incidence	N	0	0	1	0
	%	0.0	0.0	5.6	0.0
REDUCED SPLEEN					
Fetal Incidence	N	1	0	0	2
	%	0.6	0.0	0.0	1.8
Litter Incidence	N	1	0	0	1
	%	5.3	0.0	0.0	6.7

STATISTICAL ANALYSES WERE CONDUCTED. IF SIGNIFICANT DIFFERENCES OCCUR, THEY ARE DENOTED AS FOLLOWS: * = P≤0.05 ** = P≤0.01.
N = Number

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TABLE 12 SUMMARY OF FETAL SOFT TISSUE MALFORMATIONS					
DOSE LEVEL		GROUP 1 0 MG/KG/DAY	GROUP 2 125 MG/KG/DAY	GROUP 3 250 MG/KG/DAY	GROUP 4 500 MG/KG/DAY
Litters Evaluated	N	19	18	18	15
Fetuses Evaluated	N	169	157	148	111
Live	N	169	157	148	111
Dead	N	0	0	0	0
GALL BLADDER AGENESIS					
Fetal Incidence +	N	0	0	0	1
%	%	0.0	0.0	0.0	0.9
Litter Incidence	N	0	0	0	1
%	%	0.0	0.0	0.0	6.7
MALPOSITIONED KIDNEY(S)					
Fetal Incidence	N	0	0	1	0
%	%	0.0	0.0	0.7	0.0
Litter Incidence	N	0	0	1	0
%	%	0.0	0.0	5.6	0.0
TOTAL FETAL SOFT TISSUE MALFORMATIONS					
Fetal Incidence	N	2	0	2	3
%	%	1.2	0.0	1.4	2.7
Litter Incidence	N	2	0	2	2
%	%	11	0.0	11	13

STATISTICAL ANALYSES WERE CONDUCTED. IF SIGNIFICANT DIFFERENCES OCCUR, THEY ARE DENOTED AS FOLLOWS: * = P≤0.05 ** = P≤0.01.
N = Number
+ = Significant Positive Trend

Fetal Skeletal Alterations

Higher incidence of 26 presacral vertebrae and 13th full rib were noted in the mid- and high-dose groups. These variations were within the historical control data of the conducting laboratory. The results are summarized in the sponsor's table below.

(b) (4)
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Table 13
Summary of Fetal Skeletal Variations

DOSE LEVEL		GROUP 1 0 MG/KG/DAY	GROUP 2 125 MG/KG/DAY	GROUP 3 250 MG/KG/DAY	GROUP 4 500 MG/KG/DAY
Litters Evaluated	N	19	18	18	15
Fetuses Evaluated	N	169	157	148	111
Live	N	169	157	148	111
Dead	N	0	0	0	0
ANGULATED HYOID WING(S)					
Fetal Incidence	N	15	21	8	9
%	%	8.9	13	5.4	8.1
Litter Incidence	N	10	8	6	5
%	%	53	44	33	33
UNOSSIFIED HYOID BODY					
Fetal Incidence	N	5	2	0	4
%	%	3.0	1.3	0.0*	3.6
Litter Incidence	N	3	2	0	2
%	%	16	11	0.0	13
UNOSSIFIED HYOID WING(S)					
Fetal Incidence	N	1	1	0	0
%	%	0.6	0.6	0.0	0.0
Litter Incidence	N	1	1	0	0
%	%	5.3	5.6	0.0	0.0
ACCESSORY BONE(S) IN SKULL					
Fetal Incidence	N	2	0	0	0
%	%	1.2	0.0	0.0	0.0
Litter Incidence	N	2	0	0	0
%	%	11	0.0	0.0	0.0
26 PRESACRAL VERTEBRAE					
Fetal Incidence +	N	9	5	22	24
%	%	5.3	3.2	15**	22**
Litter Incidence +	N	4	2	11	7
%	%	21	11	61*	47

STATISTICAL ANALYSES WERE CONDUCTED. IF SIGNIFICANT DIFFERENCES OCCUR, THEY ARE DENOTED AS FOLLOWS: * = P≤0.05 ** = P≤0.01.
N = Number
+ = Significant Positive Trend

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TABLE 13 SUMMARY OF FETAL SKELETAL VARIATIONS					
DOSE LEVEL		GROUP 1 0 MG/KG/DAY	GROUP 2 125 MG/KG/DAY	GROUP 3 250 MG/KG/DAY	GROUP 4 500 MG/KG/DAY
Litters Evaluated	N	19	18	18	15
Fetuses Evaluated	N	169	157	148	111
Live	N	169	157	148	111
Dead	N	0	0	0	0
LESS THAN 16 CAUDAL VERTEBRAE OSSIFIED					
Fetal Incidence -	N	14	10	6	4
	%	8.3	6.4	4.1	3.6
Litter Incidence	N	7	4	4	2
	%	37	22	22	13
24 PRESACRAL VERTEBRAE					
Fetal Incidence	N	1	0	0	2
	%	0.6	0.0	0.0	1.8
Litter Incidence	N	1	0	0	1
	%	5.3	0.0	0.0	6.7
5TH STERNEBRA UNOSSIFIED					
Fetal Incidence	N	24	19	14	12
	%	14	12	9.5	11
Litter Incidence	N	9	8	9	7
	%	47	44	50	47
5TH/6TH STERNEBRA(E) INCOMPLETE OSSIFICATION					
Fetal Incidence	N	32	24	20	14
	%	19	15	14	13
Litter Incidence	N	14	13	10	10
	%	74	72	56	67
STERNEBRAE EXTRA OSSIFICATION SITE(S)					
Fetal Incidence -	N	6	1	1	0
	%	3.6	0.6	0.7	0.0*
Litter Incidence	N	2	1	1	0
	%	11	5.6	5.6	0.0

STATISTICAL ANALYSES WERE CONDUCTED. IF SIGNIFICANT DIFFERENCES OCCUR, THEY ARE DENOTED AS FOLLOWS: * = P≤0.05 ** = P≤0.01.
N = Number
- = Significant Negative Trend

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TABLE 13 SUMMARY OF FETAL SKELETAL VARIATIONS					
DOSE LEVEL		GROUP 1 0 MG/KG/DAY	GROUP 2 125 MG/KG/DAY	GROUP 3 250 MG/KG/DAY	GROUP 4 500 MG/KG/DAY
Litters Evaluated	N	19	18	18	15
Fetuses Evaluated	N	169	157	148	111
Live	N	169	157	148	111
Dead	N	0	0	0	0
MINOR FUSION OF STERNEBRAE					
Fetal Incidence	N	1	2	2	2
	%	0.6	1.3	1.4	1.8
Litter Incidence	N	1	2	1	2
	%	5.3	11	5.6	13
6TH STERNEBRA UNOSSIFIED					
Fetal Incidence	N	6	15	14	5
	%	3.6	9.6*	9.5*	4.5
Litter Incidence	N	3	6	5	4
	%	16	33	28	27
STERNEBRA(E) ASYMMETRICALLY OSSIFIED					
Fetal Incidence	N	0	1	0	0
	%	0.0	0.6	0.0	0.0
Litter Incidence	N	0	1	0	0
	%	0.0	5.6	0.0	0.0
5TH/6TH STERNEBRA(E) BIPARTITE					
Fetal Incidence	N	0	1	2	0
	%	0.0	0.6	1.4	0.0
Litter Incidence	N	0	1	2	0
	%	0.0	5.6	11	0.0
13TH FULL RIB(S)					
Fetal Incidence +	N	55	44	71	52
	%	33	28	48**	47*
Litter Incidence	N	14	15	16	13
	%	74	83	89	87

STATISTICAL ANALYSES WERE CONDUCTED. IF SIGNIFICANT DIFFERENCES OCCUR, THEY ARE DENOTED AS FOLLOWS: * = P≤0.05 ** = P≤0.01.
N = Number
+ = Significant Positive Trend

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TABLE 13 SUMMARY OF FETAL SKELETAL VARIATIONS					
DOSE LEVEL		GROUP 1 0 MG/KG/DAY	GROUP 2 125 MG/KG/DAY	GROUP 3 250 MG/KG/DAY	GROUP 4 500 MG/KG/DAY
Litters Evaluated	N	19	18	18	15
Fetuses Evaluated	N	169	157	148	111
Live	N	169	157	148	111
Dead	N	0	0	0	0
13TH RUDIMENTARY RIB(S)					
Fetal Incidence	N	27	41	25	18
	%	16	26*	17	16
Litter Incidence	N	16	15	13	10
	%	84	83	72	67
13TH UNILATERAL FULL RIB					
Fetal Incidence	N	2	7	6	3
	%	1.2	4.5	4.1	2.7
Litter Incidence	N	2	6	4	3
	%	11	33	22	20
TALUS(I) UNOSSIFIED					
Fetal Incidence	N	1	0	0	1
	%	0.6	0.0	0.0	0.9
Litter Incidence	N	1	0	0	1
	%	5.3	0.0	0.0	6.7
TOTAL FETAL SKELETAL VARIATIONS					
Fetal Incidence	N	125	133	120	91
	%	74	85*	81	82
Litter Incidence	N	19	18	18	15
	%	100	100	100	100

STATISTICAL ANALYSES WERE CONDUCTED. IF SIGNIFICANT DIFFERENCES OCCUR, THEY ARE DENOTED AS FOLLOWS: * = P≤0.05 ** = P≤0.01.
N = Number

The fetal skeletal malformation of vertebral anomaly with associated rib anomaly was noted in one fetus in the high-dose group. This was within the historical control data. The incidence of skeletal malformations is summarized in the sponsor's table below.

Table 14
Summary of Fetal Skeletal Malformations

DOSE LEVEL		GROUP 1 0 MG/KG/DAY	GROUP 2 125 MG/KG/DAY	GROUP 3 250 MG/KG/DAY	GROUP 4 500 MG/KG/DAY
Litters Evaluated	N	19	18	18	15
Fetuses Evaluated	N	169	157	148	111
Live	N	169	157	148	111
Dead	N	0	0	0	0
MISALIGNED, FUSED AND/OR ABSENT CAUDAL VERTEBRA (E)					
Fetal Incidence	N	0	0	1	0
	%	0.0	0.0	0.7	0.0
Litter Incidence	N	0	0	1	0
	%	0.0	0.0	5.6	0.0
VERTEBRAL ANOMALY WITH/WITHOUT ASSOCIATED RIB ANOMALY					
Fetal Incidence +	N	0	0	0	1
	%	0.0	0.0	0.0	0.9
Litter Incidence	N	0	0	0	1
	%	0.0	0.0	0.0	6.7
MAJOR FUSION OF STERNEBRAE					
Fetal Incidence	N	2	4	0	1
	%	1.2	2.5	0.0	0.9
Litter Incidence	N	2	3	0	1
	%	11	17	0.0	6.7
TOTAL FETAL SKELETAL MALFORMATIONS					
Fetal Incidence	N	2	4	1	2
	%	1.2	2.5	0.7	1.8
Litter Incidence	N	2	3	1	2
	%	11	17	5.6	13

STATISTICAL ANALYSES WERE CONDUCTED. IF SIGNIFICANT DIFFERENCES OCCUR, THEY ARE DENOTED AS FOLLOWS: * = P≤0.05 ** = P≤0.01.
N = Number
+ = Significant Positive Trend

Toxicokinetics:

The TK data for unchanged drug and the active metabolite are shown in the tables below (taken from the study report).

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Table 1. Summary of the Mean Toxicokinetic Parameters for LX1606 in Rabbit Plasma

Interval	Group	LX1606 Dose Level (mg/kg/day)		C _{max} (ng/mL)	DN C _{max} [(ng/mL)/ (mg/kg/day)]	T _{max} (hr)	AUC ₀₋₄ (ng·hr/mL)	AUC ₀₋₂₄ (ng·hr/mL)	DN AUC ₀₋₂₄ [(ng·hr/mL)/ (mg/kg/day)]	AUC _{0-∞} (ng·hr/mL)	t _{1/2} (hr)
GD 7	6	125	Mean	2.30	0.0184	0.500	NA	NA	NA	NA	NA
			SD	NA	NA	NA	NA	NA	NA	NA	NA
			N	2	NA	2	0	0	NA	0	0
	7	250	Mean	6.88	0.0275	0.500	22.2	41.4	0.165	NA	NA
			SD	2.65	NA	0	2.9	3.6	NA	NA	NA
			N	3	NA	3	3	3	NA	0	0
	8	500	Mean	3.98	0.00797	3.00	37.4	54.9	0.110	NA	NA
			SD	0.32	NA	4.33	25.9	12.5	NA	NA	NA
			N	3	NA	3	3	3	NA	0	0
GD 20	6	125	Mean	5.47	0.0438	0.667	10.0	13.6	0.109	NA	2.98
			SD	1.01	NA	0.289	5.4	6.6	NA	NA	NA
			N	3	NA	3	3	3	NA	NA	1
	7	250	Mean	15.3	0.0612	0.500	69.7	117	0.468	NA	NA
			SD	7.0	NA	0	23.4	51	NA	NA	NA
			N	3	NA	3	3	3	NA	NA	0
	8	500	Mean	7.81	0.0156	0.500	59.8	90.1	0.180	NA	NA
			SD	NA	NA	NA	NA	NA	NA	NA	NA
			N	2	NA	2	2	2	NA	NA	0

Table 3. Summary of the Mean Toxicokinetic Parameters for LP-778902 in Rabbit Plasma: GD 7

Interval	Group	LX1606 Dose Level (mg/kg/day)		C _{max} (ng/mL)	DN C _{max} [(ng/mL)/ (mg/kg/day)]	T _{max} (hr)	AUC ₀₋₄ (ng·hr/mL)	AUC ₀₋₂₄ (ng·hr/mL)	DN AUC ₀₋₂₄ [(ng·hr/mL)/ (mg/kg/day)]	AUC _{0-∞} (ng·hr/mL)	t _{1/2} (hr)
GD 7	6	125	Mean	2293	18.3	1.00	10126	10126	81.0	10168	2.97
			SD	1115	NA	0	3415	3415	NA	3428	0.28
			N	3	NA	3	3	3	NA	3	3
	7	250	Mean	4273	17.1	1.00	32233	32233	129	32396	3.25
			SD	1242	NA	0	6589	6589	NA	6616	0.20
			N	3	NA	3	3	3	NA	3	3
	8	500	Mean	10163	20.3	3.33	132156	132156	264	73112	2.58
			SD	2455	NA	1.15	51751	51751	NA	NA	NA
			N	3	NA	3	3	3	NA	1	1
GD 20	6	125	Mean	5673	45.4	1.33	24365	24365	195	NA	2.89
			SD	1396	NA	0.58	5182	5182	NA	NA	0.19
			N	3	NA	3	3	3	NA	NA	3
	7	250	Mean	8560	34.2	2.00	78626	78626	315	NA	2.81
			SD	2544	NA	0	15452	15452	NA	NA	0.15
			N	3	NA	3	3	3	NA	NA	3
	8	500	Mean	11635	23.3	5.00	176309	176309	353	NA	NA
			SD	NA	NA	NA	NA	NA	NA	NA	NA
			N	2	NA	2	2	2	NA	NA	0

Dosing Solution Analysis:

The drug concentration was measured, with the results showing 92.9-102% of the target concentrations.

9.3 Prenatal and Postnatal Development

Study title: Oral Gavage Study for Effects on Pre- and Postnatal Development, Including Maternal Function, with LX1606 in Rats

Study no.: 8300028
Study report location: N/A
Conducting laboratory and location: (b) (4)
Date of study initiation: May 14, 2014
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: See table below

Test Article ^a	Storage	Batch No.	Retest Date	Purity
LX1606 (also known as LP-778914 or LX1032)	In a refrigerator set to maintain 2 to 8°C.	PT-C10052511-C13001P	18 March 2017	99.5% (by HPLC)
a Test article disposition actions were completed according to (b) (4) Standard Operating Procedure.				

Key Study Findings

Pregnant females were treated with LX1606 at 0 (vehicle), 100, 200, and 500 mg/kg/day by oral gavage from Gestation Day (GD) 6 to Lactation Day (LD) 20. An increased incidence of pup mortality was observed during postnatal days 0-4 at the maternal dose of 500 mg/kg/day. No developmental abnormalities or effects on growth, learning and memory, or reproductive performance were observed through maturation of the surviving offspring at maternal doses of up to 500 mg/kg/day. The NOAEL in the offspring was 200 mg/kg/day, based on mortality at 500 mg/kg/day. The maternal NOAEL was $\geq$ 500 mg/kg/day.

Methods

Doses: 100, 200, and 500 mg/kg/day
 Frequency of dosing: daily
 Route of administration: oral gavage
 Dose volume: 10 ml/kg
 Formulation/Vehicle: 0.25% (w/v) methylcellulose
 Species/Strain: Rat/Crl:CD(SD)
 Number/Sex/Group: 24 females/group
 Age: 9.6 to 10.6 weeks old at initiation
 Weight: 209-302 g at initiation
 Satellite groups: No
 Unique study design: None
 Deviation from study protocol: There were no deviations that had a significant impact on the study outcome.

The study design is shown in the sponsor's table below.

Group ^a	Number of Mated Females (F ₀)	Dose Level (mg/kg/day)	Dose Concentration (mg/mL) ^b	Dosing Schedule
1 (Control)	24	0	0	GD 6 thru LD 20
2 (Low)	24	100	10.0	GD 6 thru LD 20
3 (Mid)	24	200	20.0	GD 6 thru LD 20
4 (High)	24	500	50.0	GD 6 thru LD 20

a Group 1 received control article only.

b Dose concentrations were corrected for salt content (correction factor = 1.312)

Pregnant females were treated with LX1606 at 0 (vehicle control), 100, 200, or 500 mg/kg/day by oral gavage from GD 6 to LD 20.

Observations and Results

F0 females:

There were no deaths. Some animals in the control and treatment groups were sacrificed due to total litter death including two control group animals, one low-dose animal, one mid-dose animal, and one high-dose animal. These animals had no visible teets and did not attend to their litters, and thus no visible milk was noted in the stomachs of their pups. In addition, one low-dose animal and one high-dose animal were sacrificed due to failure to produce a litter. These animals were confirmed as non-pregnant at necropsy.

There were no treatment related clinical signs of toxicity or effects on body weights. Food consumption was lower in the high-dose group. Treatment with LX1606 did not adversely affect delivery and litter parameters, pup survival parameters, pregnancy, gestation, parturition, or litter size. The results are summarized in the sponsor's tables below.

Table 8.9: Natural Delivery Data and Litter Data Summary – F₀ Generation

	DOSE LEVEL	CONTROL 0 mg/kg	GROUP 2 100 mg/kg	GROUP 3 200 mg/kg	GROUP 4 500 mg/kg
Females: Mated	N	24	24	24	24
Pregnant	N	24	23	24	23
	%	100	96	100	96
Delivering	N	24	23	24	23
	%	100	100	100	100
Duration of Gestation:	MEAN	23.3	23.3	23.2	23.1
	S.D.	0.4	0.4	0.4	0.3
	N	24	23	24	23
Females with Liveborn Pups	N	24	23	24	23
Gestation Index	%	100	100	100	100
with Stillborn Pups	N	5	1	3	2
	%	20.83	4.35	12.50	8.70
Females with no Liveborn Pups	N	0	0	0	0
	%	0.00	0.00	0.00	0.00
Pups Delivered	MEAN	276	272	287	258
	S.D.	11.50	11.83	11.96	11.22
	N	238	1.67	1.83	2.45
		24	23	24	23
Liveborn	MEAN	259	270	284	254
	S.D.	10.79	11.74	11.83	11.04
		2.95	1.66	1.93	2.23
Stillborn	MEAN	17	2	3	4
	S.D.	0.71	0.09	0.13	0.17
		2.05	0.42	0.34	0.65
Uncertain		0	0	0	0
Implantation Sites	MEAN	11.88	12.65	12.58	12.35
	S.D.	2.15	1.77	1.41	1.94
	N	24	23	24	23
Post Implantation Loss	MEAN	1.04	0.91	0.75	1.30
	S.D.	1.94	1.00	1.29	1.79
	%	8.91	6.97	6.04	10.17

N = Number of Females or Litters TOTAL = Number of Pups or Implants

Table 8.9
Natural Delivery Data and Litter Data Summary – F₀ Generation

DOSE LEVEL		CONTROL	GROUP 2	GROUP 3	GROUP 4
		0 mg/kg	100 mg/kg	200 mg/kg	500 mg/kg
Females:	Delivering Live Pups	24	23	24	23
	Died or Killed During Lactation	0	0	0	0
	Removed due to Total Litter Loss	2	1	1	1
	Surviving to Scheduled Sacrifice	22	22	23	22
Pup Survival Indices					
	Livebirth Index	MEAN%	94	99	99
	Day 4 Viability Index	MEAN%	91	94	86
	Weaning Index	MEAN%	89	95	96
Pup Disposition					
	Culled day 4	TOTAL	74	77	85
	Dead Pup		9	12	8
	Moribund Pup Sacrifice		3	0	1
	Cannibalized		1	0	3
	Missing		3	8	4
Pups Surviving at 21 days	TOTAL	169	173	183	163
Pups Dead Pup, Moribund Pup Sacrifice, Missing and/or Cannibalized					
	Days 0-4	13	18	15	36
	Days 5-21	3	2	1	0
Entire Litter Dead Pup, Moribund Pup Sacrifice, Missing and/or Cannibalized					
	Days 0-4	N	2	1	1
	Days 5-21	N	0	0	0

N = Number of Females or Litters TOTAL = Number of Pups or Implants

Table 8.10: Summary of Pup Survival – F₀ Generation

DOSE LEVEL		CONTROL	GROUP 2	GROUP 3	GROUP 4
		0 mg/kg	100 mg/kg	200 mg/kg	500 mg/kg
Total Number and Mean Males Percent by Litter					
Day 0		123	142	128	120
	MEAN%	50	53	47	48
Day 4 Precull		118	130	123	105
	MEAN%	48	51	46	50
Day 21		86	89	88	83
	MEAN%	51	52	48	53
Live Pups/Litter with Live Pups					
Day 0	MEAN	11.04	11.70	12.04	10.91
	S.D.	2.74	1.64	1.52	2.19
	N	23	23	23	23
Day 4 - Precull	MEAN	11.23	11.45	11.70	9.91
	S.D.	2.58	1.57	1.79	3.05
	N	22	22	23	22
Day 4 - Postcull	MEAN	7.86	7.95	8.00	7.41
	S.D.	0.47	0.21	0.00	1.50
	N	22	22	23	22

N = Number of Litters.

Table 8.10
Summary of Pup Survival – F₀ Generation

DOSE LEVEL		CONTROL 0 mg/kg	GROUP 2 100 mg/kg	GROUP 3 200 mg/kg	GROUP 4 500 mg/kg
Live Pups/Litter with Live Pups					
Day 7	MEAN	7.77	7.91	8.00	7.41
	S.D.	0.53	0.29	0.00	1.50
	N	22	22	23	22
Day 14	MEAN	7.73	7.86	7.96	7.41
	S.D.	0.55	0.35	0.21	1.50
	N	22	22	23	22
Day 21	MEAN	7.68	7.86	7.96	7.41
	S.D.	0.72	0.35	0.21	1.50
	N	22	22	23	22

N = Number of Litters.

F1 Generation:

Mortality: The incidence of deaths during postnatal days (PND) 0-4 and 5-21 is summarized above (see table 8.9). In the high-dose group, the total mortality including dead pups, moribund pups sacrificed, and pups categorized as missing and/or cannibalized was 36/254 liveborn pups during PND 0-4, as compared to 13/259 liveborn pups in the control group. Among these, 19/254 liveborn pups were reported as missing in the high-dose group, in contrast to the control group with only 3/259 liveborn pups reported as missing. Missing pups in rodent litters are generally assumed to have been cannibalized by their mother following the death or onset of moribund condition of the pups. One male in the mid-dose group was sacrificed due to moribund condition. This animal had a body lump at left lumbar.

Clinical Signs: There were no treatment-related changes.

Body weight: There were no treatment-related changes.

Food Consumption: There were no treatment-related changes.

Reproductive Performance:

Reproductive performance and litter information are summarized in the following tables (taken from the study report). Treatment with LX1606 did not adversely affect these parameters.

Table 8.25: Summary of Reproductive Performance – F₁ Generation (Males and Females)

Treatment Group	Males			
	Control	100 mg/kg	200 mg/kg	500 mg/kg
Total males	22	22	23	21
Unscheduled Deaths Prior to Cohabitation	0	0	0	0
Males Cohabitated	22	22	23	21
Unscheduled Deaths During Cohabitation	0	0	0	0
Males mating with at least 1 female	21	22	21	20
Males impregnating at least 1 female	21	21	19	20
Mating Index (%)	95	100	91	95
Fecundity Index (%)	100	95	90	100
Fertility Index (%)	95	95	83	95

Mating index % = (Number of males mating with at least 1 female / Number of males cohabitated with at least 1 female) x 100

Fecundity index % = (Number of males impregnating at least 1 female / Number of males mating with at least 1 female) x 100

Fertility Index % = (Number of males impregnating at least 1 female / Number of males cohabitated with at least 1 female) x 100

Table 8.25
Summary of Reproductive Performance – F₁ Generation (Males and Females)

Treatment Group	Females			
	Control	100 mg/kg	200 mg/kg	500 mg/kg
Total Females	22	22	23	21
Unscheduled Deaths Prior to Cohabitation	0	0	0	0
Females Cohabited	22	22	23	21
Unscheduled Deaths During Cohabitation	0	0	0	0
Females Mated	22	22	22	20
Pregnant Females	22	21	20	20
Non Pregnant Females	0	1	3	1
Matings Per Day Periods Of Cohabitation				
Day 1	10	5	8	7
Day 2	5	6	2	3
Day 3	3	4	8	6
Day 4	3	7	3	3
Day 6	0	0	0	1
Day 13	1	0	0	0
Mating Index %	100	100	96	95
Fecundity Index %	100	95	91	100
Fertility Index %	100	95	87	95

Mating index % = Mated females/females cohabited (excluding females sacrificed during Cohabitation) x 100

Fecundity Index % = Pregnant females/mated females (excluding females with an undetermined pregnancy status) x 100

Fertility Index % = Pregnant females/females cohabited (excluding females sacrificed during Cohabitation or with an undetermined pregnancy status) x 100

Table 8.26: Summary of Reproductive Performance – F₁ Generation (Cesarean)

Treatment Group	Females			
	Control	100 mg/kg	200 mg/kg	500 mg/kg
Total Females	22	22	23	21
Pregnant Females	22	21	20	20
Non Pregnant Females	0	1	3	1
Pregnant with Total Litter Loss	0	0	0	0
Females with Live Fetuses	22	21	19	20

Table 8.28: Summary of Cesarean Section Data – F₁ Generation

		Group			
		Control	100 mg/kg	200 mg/kg	500 mg/kg
Number of females pregnant at cesarean section	N	22	21	19	20
	Mean	1.0	1.0	1.0	1.0
	SD	0.00	0.00	0.00	0.00
Corpora Lutea	N	22	21	19	20
	Mean	16.6	17.4	16.8	16.6
	SD	2.89	2.40	2.22	2.80
Implantation Sites	N	22	21	19	20
	Mean	15.6	15.8	15.6	15.4
	SD	2.24	2.30	3.10	2.46
Preimplantation Loss	N	22	21	19	20
	Mean	1.0	1.7	1.3	1.3
	SD	1.35	2.31	2.31	2.05
Preimplantation Loss (%)	N	22	21	19	20
	Mean	5.4	8.8	7.6	6.8
	SD	6.63	12.03	13.89	10.17
Early Resorptions	N	22	21	19	20
	Mean	0.9	1.2	0.6	0.5
	SD	0.97	1.41	0.77	0.61

Table 8.28
Summary of Cesarean Section Data – F₁ Generation

		Group			
		Control	100 mg/kg	200 mg/kg	500 mg/kg
Late Resorptions	N	22	21	19	20
	Mean	0.0	0.0	0.0	0.0
	SD	0.00	0.00	0.00	0.00
Postimplantation Loss	N	22	21	19	20
	Mean	0.9	1.2	0.6	0.5
	SD	0.97	1.41	0.77	0.61
Postimplantation Loss (%)	N	22	21	19	20
	Mean	6.2	7.8	3.7	3.1
	SD	6.76	8.42	5.24	3.86
Live Fetuses	N	22	21	19	20
	Mean	14.7	14.5	15.0	14.9
	SD	2.62	2.40	3.11	2.32

Developmental Parameters:

During lactation, the following developmental parameters were assessed.

Test	Postnatal Day (PND) of Evaluation
Pinna unfolding	PND 1
Surface righting reflex	PND 4 (postculling)
Hair growth	PND 7
Incisor eruption	PND 7
Eye opening	PND 11

Vaginal opening was evaluated beginning on PND 30 and cleavage of the balanopreputial gland was evaluated beginning on PND 35. Estrous cycles were evaluated during week 6 of the postweaning maturation phase (approximately 10 weeks of age). There were no adverse effects on these parameters.

Neurobehavioral Performance:

Treatment with LX1606 did not have clear adverse effects in the acoustic startle or Morris water maze tests. The startle test was conducted on PNDs 28 and 62, and the Morris Water Maze testing started on the day following the startle assessment. Treatment with LX1606 did not have adverse effects on locomotor activity, but increased basic movements were noted in males in the low- and high-dose groups.

Toxicokinetics: Not performed.

10 Special Toxicology Studies

11 Integrated Summary and Safety Evaluation

Xermelo (telotristat ethyl) was developed under IND 78,749 for the treatment of diarrhea associated with carcinoid syndrome in patients that no longer respond to standard care with somatostatin analogues. This development program was designated as a Fast Track development program on May 19, 2008. LX1606 was designated as an orphan drug on March 9, 2012. A pre-NDA meeting was held February 24, 2015. All of the needed study reports are submitted in this NDA.

LX1606 (telotristat ethyl) is an inhibitor of L-tryptophan hydroxylase (TPH) which mediates serotonin synthesis in the mucosa of the gastrointestinal (GI) tract. LX1606 is rapidly converted in vivo to its active metabolite, LP778902 (telotristat). Both LX1606 and LP778902 inhibit TPH, thereby decreasing peripheral serotonin levels. However, the potency of telotristat exceeds that of telotristat ethyl by 29-fold and 38-fold for human TPH1 and TPH2, respectively. Furthermore, the systemic exposure to telotristat markedly exceeds that of the parent drug. Thus, the overall pharmacology and toxicology profile of telotristat ethyl should be attributed to the active metabolite, telotristat.

Carcinoid tumors are mostly derived from enterochromaffin cells of the midgut, and often produce and release large amounts of a variety of chemical signaling molecules and hormones, including 5-HT (serotonin). By reducing the peripheral serotonin levels, LX1606 is expected to be beneficial for patients with carcinoid syndrome, which is caused in part by excessive production and release of serotonin from metastatic carcinoid tumors.

In the present NDA, the sponsor seeks market approval for Xermelo for the (b) (4) treatment of carcinoid syndrome diarrhea in patients with metastatic neuroendocrine tumors who are receiving somatostatin analogue therapy. The recommended dose is 250 mg three times daily (b) (4). In support of this NDA, the following nonclinical studies were submitted: pharmacology studies, pharmacokinetic studies, oral acute toxicity studies in rats and dogs; 5-day, 2-week, 4-week, 13-week, and 6-month oral toxicity studies in rats; 7-day, 4-week, 13-week, and 9-month oral toxicity studies in dogs; Ames test, in vitro chromosomal aberration test in Chinese Hamster Ovary (CHO) cells, rat micronucleus test, two Ames tests with impurity (b) (4), 28-day dose ranging study in CByB6F1 mice, 26-week oral carcinogenicity study in Tg.rasH2 mice, mating and fertility study in rats, embryo-fetal developmental studies in rats and rabbits, and a pre- and post-natal developmental study in rats.

A single dose of telotristat ethyl by oral gavage at doses of 0 (control), 30, 100 and 200 mg/kg had no clear treatment-related effects on blood pressure, heart rate, or ECGs in conscious telemeterized dogs (study # 2572/016). Telotristat ethyl inhibited hERG current with an IC_{50} of 0.3 μ M (~172 ng/ml), and its active metabolite, LP-778902, had an IC_{50} > 10 μ M in the hERG assay (study # 7648-208).

The parent drug, telotristat ethyl, was rapidly converted to the active metabolite, LP-778902 (telotristat), following oral administration in animals. Oral bioavailability of LP-778902 was approximately 12% in mice following a single oral dose of telotristat ethyl at 50 mg/kg. The tissue distribution studies with ^{14} C-LX1606 in rats indicated that radioactivity was mainly present in liver, GI tract, and kidney, with no measurable radioactivity in the brain. Both the parent and active metabolite have high plasma protein binding (> 96% and > 98%, respectively) in mice, rats, dogs, monkeys, and humans. In rats, approximately 86.0% to 92.1% of the administered dose was excreted in feces by 24 hours after dosing, with <0.2% of the administered dose eliminated in urine.

LX1606 was tested at single oral doses up to 2000 mg/kg in rats (study 7648-199). There were no deaths in this study. Non-formed or liquid feces were noted in the high-dose animals.

LX1606 was tested at 1 mg/kg IV and oral doses up to 500 mg/kg in dogs (study 7648-211). No treatment-related changes were noted in the IV dose group. A dose-dependent emetic response was noted following oral dosing. Vomiting was severe at 200 mg/kg or higher.

In the 4-week oral toxicity study in rats, LX1606 was administered by oral gavage at 0, 100, 500, and 1000 mg/kg/day (study #7648-201). One male and 4 females in the high dose group were sacrificed on Day 12, and the remaining animals in this group were sacrificed on Day 13 due to clinical signs of toxicity, weight loss, and reduced food consumption. The clinical signs of toxicity noted in this group included hunched posture, thin appearance, liquid feces, rough or discolored haircoat, and piloerection. Distended or enlarged segments of the stomach, duodenum, jejunum, ileum, and/or cecum were noted in the high-dose group. The histopathological evaluation revealed submucosal edema localized to the limiting ridge of the nonglandular portion of the stomach in the high-dose group and enterocyte hypertrophy/hyperplasia in the duodenum and jejunum in the mid- and high-dose groups. The following clinical signs of toxicity were observed in the mid-dose group: audible respirations (1 male), few feces (1 female), and clear oral discharge (1 female). GI tract was the target organ of toxicity. The dose of 100 mg/kg/day is considered as NOAEL.

LP-778914 (LX1606) was tested at doses of 50, 200, and 500 mg/kg/day by oral gavage in rats for 3 months (study #7648-250). Treatment with 500 mg/kg/day produced a decrease in body weight gain. Based on the decreased body weight gain in the high dose group, the NOAEL was identified at 200 mg/kg/day, and the high dose was close to the MTD (maximum tolerated dose).

LP-778914 (LX1606) was tested at doses of 50, 200, and 500 mg/kg/day by oral gavage in rats for 26 weeks (study #7648-289). Two high-dose males were sacrificed due to moribund condition, including clinical signs of toxicity, decreased body weight and weight gain, and decreased food consumption. The major treatment-related changes were degeneration/necrosis in the non-glandular and/or glandular portions of the stomach and/or increased protein droplets in the glandular portion of stomach in the mid- and high-dose animals. The NOAEL was identified at 50 mg/kg/day.

LP-778914 (LX1606) was tested at doses of 30, 100, and 500/200 mg/kg/day by oral gavage in dogs for 4 weeks (study #7648-202). There were no deaths. Treatment with 500 mg/kg/day induced toxicities including clinical signs (dehydration, hypoactivity, thin appearance, and excessive struggling or vocalizing) and body weight loss. The dose of 500 mg/kg/day was reduced to 200 mg/kg/day on day 16. Vomitus and liquid/mucoid feces were noted in the animals treated with 100 and 500/200 mg/kg/day. The NOAEL was identified at 30 mg/kg/day.

LP-778914 (LX1606) was tested at doses of 30, 100, and 200 mg/kg/day by oral gavage in dogs for 13 weeks (study #7648-251). There were no deaths. The major treatment-related changes were clinical signs of toxicity including liquid feces in the mid- and high-dose groups. These were not considered as adverse effects. Hypospermatogenesis in testis was noted mainly in the low-dose group, therefore the clinical significance is uncertain. The NOAEL was identified at 200 mg/kg/day.

LP-778914 (LX1606) was tested at doses of 75, 150, and 300 mg/kg/day by oral gavage in dogs for 39 weeks (study #7648-288). There were no deaths. The major treatment-related changes were clinical signs of toxicity including liquid feces in the mid- and high-dose group. These were not considered as adverse effects. The NOAEL was identified at 300 mg/kg/day.

LX1606 was negative in the Ames test (study #7648-191), the in vitro chromosome aberration test (study #7648-192), and the in vivo rat micronucleus test (study #7648-193). The active metabolite, LP778902, was also negative in the Ames test and in the in vitro chromosome aberration test.

Impurity (b) (4) was tested in Ames test (study #8310730) at concentrations of 1.60, 5.00, 16.0, 50.0, 160, 500, 1600, and 5000 µg/plate with and without S9 using the plate incorporation method. The results suggest that the test article was positive with batch # 21094589, and negative with purer batch # P04574-025 in this test system. The sponsor repeated the Ames test (study #8321394) with impurity (b) (4). The results indicated that the (b) (4) was positive with batch # 21094589 and negative with purer batch # P04574-025 in this test system. The results of these studies suggest that the positive finding observed with batch # 21094589 was due to a mutagenic impurity.

In the 26-week oral carcinogenicity study in Tg.rasH2 mice, treatment with LX1606 hippurate at doses of 30, 100, and 300 mg/kg/day for 26 weeks did not increase the incidence of neoplastic lesions. Treatment-related non-neoplastic lesions included hyperplasia of the non-glandular stomach in high-dose group and exudative inflammation of the nasal cavity mainly in the mid- and high-dose groups. These lesions could be due to direct local irritation of the test drug. The FDA statistical review concluded that treatment with LX1606 hippurate did not produce any significant increase in tumor incidence. The Executive Carcinogenicity Assessment Committee concluded that there were no drug-related neoplasms (see Appendix 3).

The 2-year rat carcinogenicity study will be submitted post-approval as agreed in the End of Phase 2 Meeting on April 11, 2012 and in the pre-NDA meeting on February 24, 2015. Dosing in this study was initiated in September, 2015. The doses tested were recommended by the Executive Carcinogenicity Assessment Committee (see meeting minutes and review of the study protocols in Appendix 2).

In the fertility and general reproduction toxicity study in rats, male rats were treated orally with LX1606 for 4 weeks prior to pairing, during the pairing period and until the day prior to necropsy for a total period exceeding 10 weeks. Females were dosed for 2 weeks prior to pairing, during the pairing period, and until Day 6 of gestation. The females were terminated on Day 13 of gestation. Treatment with LX1606 induced mouth rubbing, paddling, and salivation in all treatment groups. Treatment with LX1606 did not adversely affect reproductive performance, fertility, and embryo/fetal viability at doses up to 500 mg/kg/day.

In the oral embryo-fetal development study in rats, pregnant rats were treated with LP-778914 at oral doses of 0 (control), 250, 500, or 750 mg/kg/day during gestation days 7-17. Maternal toxicity (mortality and impaired bodyweight gain) occurred at 750 mg/kg/day, whereas no adverse effects on embryo-fetal development were observed. The NOAEL was 500 mg/kg/day for maternal toxicity, and ≥ 750 mg/kg/day for embryo-fetal development.

In the oral embryo-fetal development study in rabbits, pregnant rabbits were treated with LP-778914 by oral gavage once daily on gestation days 7 through 19 at doses of 0 (control), 125, 250, and 500 mg/kg/day. Treatment resulted in mortality in the high-dose group and decreased body weight gain and food consumption in the mid- and high-dose groups. Treatment induced post-implantation loss in the mid- and high-dose groups and decreased fetal weights in the high-dose group. Thus, the adverse effect on embryo-fetal development (post-implantation loss) occurred only in association with maternal toxicity. There were no clear treatment-related malformations. The NOAEL for embryo-fetal and maternal effects was 125 mg/kg/day.

In the oral pre- and post-natal reproduction toxicity study in rats, pregnant females were treated with LX1606 at 0, (control), 100, 200, and 500 mg/kg/day by oral gavage from gestation day 6 through lactation day 20. Reproductive performance of both F0 and F1 generations was not affected by the test article. An increased incidence of pup mortality

was observed during postnatal days 0-4 at the maternal dose of 500 mg/kg/day. No developmental abnormalities or effects on growth, learning and memory, or reproductive performance were observed through maturation of offspring at maternal doses of up to 200 mg/kg/day.

Human PK parameters for the active metabolite, telotristat, are summarized in the sponsor's table below.

Table 11.4 Pharmacokinetic Parameters of LP-778902 Following Administration of 100 mg QD, 250 mg QD, 500 mg QD, 500 mg BID, or 500 mg TID of LX1606 on Day 14, Pharmacokinetic Full Population

Dose		C _{max} (ng/mL)	t _{max} (hr) ^a	AUC _{0-τ} (ng*hr/mL)	AUC ₀₋₂₄ (ng*hr/mL)	t _{1/2} (hr)	CL/F _{ss} (L/hr)	Ro ^b
Cohort 1 100 mg QD	n	6	6	6	6	6	6	6
	Mean	149	2.00	453	453	3.65	248	1.11
	SD	55.4	2.00-2.00	185	185	1.36	86.5	0.289
Cohort 2 250 mg QD	n	6	6	6	6	6	6	6
	Mean	394	2.00	1216	1216	5.87	226	0.879
	SD	165	2.00-4.00	411	411	0.655	73.4	0.212
Cohort 3 500 mg QD	n	6	6	6	6	6	6	6
	Mean	835	4.00	2982	2982	7.34	170	0.816
	SD	114	2.00-4.00	444	444	2.99	20.6	0.137
Cohort 4 500 mg BID	n	4	4	4	4	4	4	4
	Mean	812	2.00	2471	2655	11.0	209	0.954
	SD	174	2.00-4.00	536	561	3.97	43.4	0.0530
Cohort 5 500 mg TID	n	6	6	6	6	6	6	6
	Mean	1028	4.00	3581	4238	11.7	152	0.997
	SD	344	2.00-4.00	1179	1441	1.74	45.7	0.177

a. t_{max} is presented as median (minimum-maximum)

b. Day 14 AUC_{0- τ} / Day 1 AUC_{0- τ}

Note: Summary data are presented to 3 significant digits for values up to 999, with numbers greater than this presented as whole integers. Summary data for t_{max} are presented to 2 decimals.

Source: Table 14.2.3

The value of 5371 ng•hr/ml was used as the estimated human AUC_{0-24 hr} for telotristat with administration 250 mg TID, in the calculations of animal/human exposure ratios in the table below, as recommended by the clinical pharmacology reviewer, Dr. Insook Kim. This value was extrapolated from AUC_{0- τ} for 500 mg TID (3581 ng•hr/ml), shown in the table above.

Study	NOAEL (mg/kg/day)	Telotristat AUC_{0-24 hr} (ng•hr/ml)	Animal/human AUC ratios
13-week rat toxicity	200	7760**	1.4
26-week rat toxicity	50	2727**	0.5
13-week dog toxicity	200	136304**	25
39-week dog toxicity	300	130834**	24
Fertility study in rats	500	Not measured	5*
Embryofetal development in rats	500 (maternal) 750 (fetal)	26878 47563	5 9
Embryofetal development in rabbits	125 (fetal and maternal)	24365	5
Pre- and post-natal development in rats	500	Not measured	5*

* Value from developmental toxicity study in rats (500 mg/kg/day group) was used.

** Mean of male and female AUC values.

The major findings in toxicology studies were degeneration/necrosis in the non-glandular and/or glandular portions of the stomach, and/or increased protein droplets in the glandular portions at doses of 200 mg/kg/day or higher in the 26-week oral toxicity study in rats (the animal to human exposure margin was approximately 2-6 at doses producing these effects). This was not seen in the 13-week and 39-week oral toxicity studies in dogs.

12 Appendix/Attachments

1. Executive CAC meeting minutes dated December 3, 2013

Executive CAC

Date of Meeting: December 3, 2013

Committee:

David Jacobson-Kram, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Paul Brown, Ph.D., OND IO, Member
David Joseph, Ph.D., DGIEP, Team Leader/Alternate Member
Ke Zhang, Ph.D., DGIEP, Presenting Reviewer

Author of Draft: Ke Zhang, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations.

The Committee did not address the Sponsor's proposed statistical evaluation for the carcinogenicity bioassay, as this does not affect the Sponsor's ability to initiate the bioassay. The Sponsor may seek guidance on the statistical evaluation of bioassay results from agency staff separately. Data files should be submitted electronically following the CDER/CBER Guidance for Industry, Providing Regulatory Submission in Electronic Format- Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008) and the associated Study Data Specifications document.

IND #: 78,749**Drug Name:** LX1606**Sponsor:** Lexicon Pharmaceuticals, Inc.
The Woodlands, TX

Background: LX1606 is an inhibitor of L-tryptophan hydroxylase which mediates serotonin synthesis in the mucosa of the gastrointestinal tract. LX1606 is rapidly converted *in vivo* to its active moiety, LP778902. The sponsor hypothesizes that by decreasing the peripheral serotonin level, LX1606 would be beneficial for patients with carcinoid syndrome, which is caused by excessive production and release of serotonin from metastatic carcinoid tumors. Currently the sponsor is developing LX1606 for the treatment of gastrointestinal symptoms (i.e. diarrhea) associated with carcinoid syndrome.

LX1606 was negative in the Ames test, in the *in vitro* chromosome aberration test, and in the *in vivo* rat micronucleus test. The active moiety, LP778902, was also negative in the Ames test and in the *in vitro* chromosome aberration test.

In the current submission, the sponsor provided a study protocol for a 26-week carcinogenicity study in Tg.rasH2 transgenic mice along with a 28-day dose ranging study in CByB6F1 mice.

Tg.rasH2 Mouse Carcinogenicity Study Protocol and Dose Selection:

The sponsor proposed doses of 0 (0.25% methylcellulose), 30, 100, and 300 mg/kg/day for the 26-week carcinogenicity study in Tg.rasH2 transgenic mice. The dose volume will be 10 mL/kg. A positive control article, urethane (1000 mg/kg/day), will be given by ip injection on study days 1, 3, and 5.

The dose selection was based on the toxicity observed in the 28-day dose ranging study in CByB6F1 mice. The doses used in this study were 0, 300, 750, and 1500 mg/kg/day in males, and 0, 300, 750, 2000, and 3000 mg/kg/day in females. A dose-dependent incidence of nasal cavity lesions was observed in the treatment groups (none in the control group). One male had acute inflammation and two females had serocellular exudates at 300 mg/kg/day. The incidence of these changes was higher at 750 mg/kg/day in both males and females. Two male mice given 750 mg/kg/day (main study) were sacrificed due to moribund condition (nasal cavity necrotizing inflammation). Four males in the 1500 mg/kg/day toxicokinetic group were sacrificed in moribund condition. The doses of 2000 and 3000 mg/kg/day produced death in all females.

Executive CAC Recommendations and Conclusions:

The Committee concurred with the sponsor's proposed doses of 0, 30, 100, and 300 mg/kg/day, by oral gavage, with the high dose based on the toxicity and mortality due to nasal cavity necrotizing inflammation.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:

/Division File, DGIEP

/Joseph, DGIEP

/Zhang, DGIEP

/Scherer, DGIEP

/ASeifried, OND IO

2. Executive CAC meeting minutes dated December 16, 2014

Executive CAC

Date of Meeting: December 16, 2014

Committee:

Abby Jacobs, Ph.D., OND IO, Acting Chair
Paul Brown, Ph.D., OND IO, Member
Linda Fossum, Ph.D., DPP, Alternate Member
David Joseph, Ph.D., DGIEP, Team Leader
Ke Zhang, Ph.D., DGIEP, Presenting Reviewer

Author of Draft: Ke Zhang, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations.

The Committee did not address the Sponsor's proposed statistical evaluation for the carcinogenicity bioassay, as this does not affect the Sponsor's ability to initiate the bioassay. The Sponsor may seek guidance on the statistical evaluation of bioassay results from agency staff separately. Data files should be submitted electronically following the CDER/CBER Guidance for Industry, Providing Regulatory Submission in Electronic Format- Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008) and the associated Study Data Specifications document.

IND #: 78,749
Drug Name: LX1606
Sponsor: Lexicon Pharmaceuticals, Inc.
The Woodlands, TX

Background: LX1606 is an inhibitor of L-tryptophan hydroxylase which mediates serotonin synthesis in brain and gastrointestinal tract mucosa. LX1606 is rapidly converted in vivo to its active moiety, LP778902. The sponsor hypothesizes that by decreasing the peripheral serotonin level, LX1606 would be beneficial for patients with carcinoid syndrome, which is caused by excessive production and release of serotonin from carcinoid tumors. The sponsor is developing LX1606 for the treatment of gastrointestinal symptoms (i.e. diarrhea) associated with carcinoid syndrome.

LX1606 was negative in the Ames test, the in vitro chromosome aberration test, and in the in vivo rat micronucleus test. The active moiety, LP778902, was also negative in the Ames test and in the in vitro chromosome aberration test.

In the current submission, the sponsor provided a protocol for a 2-year carcinogenicity study in rats.

2-year Rat Carcinogenicity Study Protocol and Dose Selection:

The sponsor proposed three dose levels for LX1606 (100, 200, and 300 mg/kg/day) and a vehicle control group (0.25% methylcellulose).

The dose selection was based on the results of a 6-month oral toxicity study in rats. In this study, LP-778914 (LX1606) was given by oral gavage to rats at 0, 50, 200, and 500 mg/kg/day for 26 weeks. Rough hair-coat was noted in 3 high dose females. The terminal body weight was lower in the high dose males (~18%) and females (~3%), compared to the respective controls. There were treatment related deaths in males and females in the high dose group.

The sponsor proposed doses of 100, 200, and 300 mg/kg/day for the carcinogenicity study for both males and females.

Executive CAC Recommendations and Conclusions:

The Committee did not concur with the sponsor's proposed doses. For both males and females, the Committee recommended doses of 0 (vehicle), 20, 60, and 170 mg/kg/day, by oral gavage, with the high dose based on lethality at 500 mg/kg/day.

Abby Jacobs, Ph.D.,
Acting Chair, Executive CAC

cc:

/Division File, DGIEP

/Joseph, DGIEP

/Zhang, DGIEP

/Strongin, DGIEP

/ASeifried, OND IO

3. Executive CAC meeting minutes dated August 9, 2016

Executive CAC**Date of Meeting:** August 9, 2016

Committee: Karen Davis Bruno, PhD, OND IO, Chair
Abby Jacobs, PhD, OND IO, Member
Paul Brown, PhD, OND IO, Member
Tim McGovern, PhD, OND IO, Member
Barbara Hill, PhD, DDDP, Alternate Member
David Joseph, PhD, DGIEP, Team Leader
Ke Zhang, PhD, DGIEP, Presenting Reviewer

Author of Draft: Ke Zhang, PhD

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA #: 208,794**Drug Name:** Xermelo / Telotristat Etiprate / LX1606

Sponsor: Lexicon Pharmaceuticals, Inc.
The Woodlands, TX

Background: LX1606 is an inhibitor of L-tryptophan hydroxylase which mediates serotonin synthesis in brain and gastrointestinal tract mucosa. LX1606 is rapidly converted in vivo to its active metabolite, LP778902. The sponsor hypothesizes that by decreasing the peripheral serotonin level, LX1606 would be beneficial for patients with carcinoid syndrome, in which excessive production and release of serotonin from carcinoid tumors is a major contributing factor. The sponsor is developing LX1606 for the treatment of carcinoid syndrome in patients with metastatic neuroendocrine tumors who are receiving somatostatin analogue therapy.

LX1606 was negative in the Ames test, the in vitro chromosome aberration test, and the in vivo rat micronucleus test. The active metabolite, LP778902, was also negative in the Ames test and the in vitro chromosome aberration test.

In the current submission, the sponsor provided the report of the 6-month Tg.rasH2 mouse carcinogenicity study.

Tg.rasH2 Mouse Carcinogenicity Study:

Tg.rasH2 mice were administered LX1606 at 0, 30, 100, or 300 mg/kg/day in 0.25% (w/v) methylcellulose by oral gavage for 26 weeks. The dose levels were recommended by the Executive Carcinogenicity Assessment Committee, based on the

toxicity and deaths due to nasal cavity necrotizing inflammation at higher doses. (see minutes from December 3, 2013 for IND 78,749). Administration of LX1606 did not increase the incidence of any neoplasm.

Executive CAC Recommendations and Conclusions:

1. The Committee concluded that the study was adequate, noting prior approval of the doses.
2. The Committee concluded that there were no drug-related neoplasms in the study.

Karen Davis Bruno, PhD
Chair, Executive CAC

cc:\n
/NDA 208,794/Division File, DGIEP
/David Joseph/Team Leader, DGIEP
/Ke Zhang/Reviewer, DGIEP
/Benjamin Vali/PM, DGIEP
/Adele Seifried, OND IO

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ADELE S SEIFRIED
08/11/2016

KAREN L DAVIS BRUNO
08/11/2016

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KE ZHANG
12/30/2016

DAVID B JOSEPH
12/31/2016
I concur.

Executive CAC

Date of Meeting: August 9, 2016

Committee: Karen Davis Bruno, PhD, OND IO, Chair
Abby Jacobs, PhD, OND IO, Member
Paul Brown, PhD, OND IO, Member
Tim McGovern, PhD, OND IO, Member
Barbara Hill, PhD, DDDP, Alternate Member
David Joseph, PhD, DGIEP, Team Leader
Ke Zhang, PhD, DGIEP, Presenting Reviewer

Author of Draft: Ke Zhang, PhD

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA #: 208,794

Drug Name: Xermelo / Telotristat Etiprate / LX1606

Sponsor: Lexicon Pharmaceuticals, Inc.
The Woodlands, TX

Background: LX1606 is an inhibitor of L-tryptophan hydroxylase which mediates serotonin synthesis in brain and gastrointestinal tract mucosa. LX1606 is rapidly converted in vivo to its active metabolite, LP778902. The sponsor hypothesizes that by decreasing the peripheral serotonin level, LX1606 would be beneficial for patients with carcinoid syndrome, in which excessive production and release of serotonin from carcinoid tumors is a major contributing factor. The sponsor is developing LX1606 for the treatment of carcinoid syndrome in patients with metastatic neuroendocrine tumors who are receiving somatostatin analogue therapy.

LX1606 was negative in the Ames test, the in vitro chromosome aberration test, and the in vivo rat micronucleus test. The active metabolite, LP778902, was also negative in the Ames test and the in vitro chromosome aberration test.

In the current submission, the sponsor provided the report of the 6-month Tg.rasH2 mouse carcinogenicity study.

Tg.rasH2 Mouse Carcinogenicity Study:

Tg.rasH2 mice were administered LX1606 at 0, 30, 100, or 300 mg/kg/day in 0.25% (w/v) methylcellulose by oral gavage for 26 weeks. The dose levels were recommended by the Executive Carcinogenicity Assessment Committee, based on the

toxicity and deaths due to nasal cavity necrotizing inflammation at higher doses. (see minutes from December 3, 2013 for IND 78,749). Administration of LX1606 did not increase the incidence of any neoplasm.

Executive CAC Recommendations and Conclusions:

1. The Committee concluded that the study was adequate, noting prior approval of the doses.
2. The Committee concluded that there were no drug-related neoplasms in the study.

Karen Davis Bruno, PhD
Chair, Executive CAC

cc:\n
/NDA 208,794/Division File, DGIEP
/David Joseph/Team Leader, DGIEP
/Ke Zhang/Reviewer, DGIEP
/Benjamin Vali/PM, DGIEP
/Adele Seifried, OND IO

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ADELE S SEIFRIED

08/11/2016

KAREN L DAVIS BRUNO

08/11/2016