CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761063Orig1s000

NON-CLINICAL REVIEW(S)

Tertiary Pharmacology Review

By: Paul C. Brown, Ph.D., ODE Associate Director for Pharmacology and Toxicology, OND IO
BLA: 761063
Submission date: 9/27/17
Drug: galcanezumab (a calcitonin gene-related peptide antagonist)
Applicant: Eli Lilly and Company
Indication: prophylaxis of migraine in adults

Reviewing Division: Division of Neurology Products

Discussion/Conclusions:
The pharmacology/toxicology reviewer and supervisor conducted a thorough evaluation of the nonclinical information submitted in support of this BLA. Both found the information sufficient to support approval.

Galcanezumab is a monoclonal antibody that binds to and inhibits the activity of α and β calcitonin gene-related peptide (CGRP).

The potential for cardiovascular effects from inhibiting CGRP were discussed. Based on the Agency's independent review of published literature, primarily on a well-established peptide probe, no nonclinical post-marketing studies to investigate this theoretical concern were recommended.

I concur that the nonclinical information is adequate to support approval for this indication.

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/s/

PAUL C BROWN
09/27/2018

MEMORANDUM

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

Division of Neurology Products (HFD-120)
Center for Drug Evaluation and Research

Date: September 27, 2018
From: Lois M. Freed, Ph.D.
Supervisory Pharmacologist

Subject: BLA 761063 (Emgality, galcanezumab, LY2951742)

BLA 761063 was submitted by Eli Lilly and Co. on September 26, 2017, to request licensure of galcanezumab for migraine prophylaxis in adults; the BLA was filed 60 days after receipt of the application (*Filing Communication, December 8, 2017*), with no filing review issues identified. Clinical development of galcanezumab was conducted under IND 111295 (prevention of migraine pain) (b) (4)

The nonclinical data submitted to support clinical development (IND 111295) were reviewed by Dr. D. Charles Thompson (*Pharmacology/Toxicology IND Review and Evaluation, April 4, 2011, August 19, 2015*). The BLA review was conducted by Dr. Ed Nesti (*Pharmacology/Toxicology BLA Review and Evaluation, BLA 761063, Edward Nesti, Ph.D., September 27, 2018*). Based on that review, Dr. Nesti has concluded that the nonclinical data support approval of galcanezumab for the proposed indication.

The following provides a brief discussion of selected nonclinical data; a detailed description and discussion of the studies may be found in Dr. Nesti's review.

Summary and Discussion

Pharmacology

Galcanezumab is a humanized IgG4 monoclonal antibody that binds to both α and β isoforms of calcitonin gene-related peptide (CGRP) and prevents their binding to the CGRP receptor. Galcanezumab is pharmacologically active in rat, rabbit, and human, as characterized in a series of binding and functional in vitro assays. Binding affinity was slightly lower for rat CGRP compared to human CGRP (K_D's of 31 and 250 pM, respectively); binding affinity was not assessed for monkey CGRP. In cell-based assays, the IC_{50} for inhibition of CGRP receptor activation by human α- and β-CGRP were 0.35 and 0.18 nM, respectively, and the K_b for inhibition of rabbit or human CGRP binding to the human CGRP receptor were 4.1 and 44.2 pM, respectively. Binding to monkey CGRP was not assessed because its sequence is identical to that of human CGRP; therefore, binding affinity was assumed to be similar in both species. In in vivo

functional assays, galcanezumab decreased capsaicin-induced dermal blood flow in male Lewis rat (~80% at 4 mg/kg SC) and cynomolgus monkey (86% at 5 mg/kg IV).

No stand-alone safety pharmacology studies were conducted for galcanezumab.

Cardiovascular risk: Because of the potent vasodilatory properties of CGRP, concerns were raised regarding long-term antagonism of the CGRP in humans, particularly in patients with cardiovascular risk factors. The sponsor was asked to provide a review of relevant published literature and data available to the sponsor. Since this request was made, the Agency has conducted an independent evaluation of available published literature, primarily on a well-established probe ($CGRP_{(8-37)}$), to investigate the potential for antagonism of CGRP to induce vasoconstriction or adversely affect coronary vessel size, blood flow, or coronary infarct size under ischemic conditions. The results of this evaluation suggest that regulation of vascular tone in healthy patients and those with cardiovascular risk factors involves multiple endogenous factors, of which CGRP is only one, and that there is limited understanding of the role of CGRP in normal hemodynamic processes or response to ischemic events. It was, therefore, concluded that there is insufficient information to dismiss the original concerns but that additional basic research is needed to further understand the role of CGRP in these processes. Without a better understanding of the role of CGRP, it is unlikely that nonclinical studies of galcanezumab could be designed and conducted that would provide useful information; therefore, no post-marketing study to further assess the cardiovascular safety of galcanezumab is recommended.

PK/ADME

The only PK/ADME studies conducted were acute-dose studies in male Sprague-Dawley rat and cynomolgus monkey. In the rat study, distribution into CNS tissues (dura mater, spinal cord, prefrontal cortex, cortex, cerebellum, and hypothalamus), trigeminal ganglia, spleen, csf, and plasma were evaluated 1, 3, and 7 days following a single 4-mg/kg subcutaneous (SC) injection of galcanezumab. In all CNS tissues examined, concentrations of galcanezumab were <1% of plasma. Galcanezumab concentrations in trigeminal ganglia (4.5%) and dura mater were 4.5 and ~11% of plasma at 7 days post dose; concentrations in spleen were ~10% of plasma at 7 days post dose. Concentrations in all tissues were similar at 3 and 7 days post dose, consistent with a prolonged $t_{1/2}$.

In the monkey study, PK parameters for galcanezumab following an acute intravenous (IV) dose of 2 mg/kg were: $AUC_{(0-\infty)}$ of 342 μg*day/mL, Cl of 0.015 L/day, V_{ss} of 0.14 L, and $t_{1/2}$ of 7/6 days.

Toxicology

The pivotal (GLP) subcutaneous (SC) toxicity studies (6-week + 9-week recovery, 3-month + 6-week recovery, and 6-month) were conducted in Sprague-Dawley rat and cynomolgus monkey. In rat, the highest dose tested in the 6-week (0, 1.5, 15, or 100 mg/kg QW) and 3-month (0, 1.5, or 100 mg/kg QW) studies was the no-adverse-effect level (NOAEL). In the 6-month study (0, 20, and 250 mg/kg QW), the high dose resulted in 2 spontaneous deaths in males (Day 169 [main study animal] or Day 108 [TK animal], for which a galcanezumab-related cause could not be "definitively ruled out." Plasma $AUC_{(0\text{-}7\ days)}$ in males and females on Day 176 of the 6-month

study was 1220 and 1280 μg*day/mL, respectively, at the low dose and 2440 and 3430 μg*day/mL, respectively, at the high dose.

In monkey, the high dose tested in the 6-week (0, 1.5, 15, or 100 mg/kg QW), 3-month (0, 15, or 100 mg/kg QW), and 6-month (0, 2, or 100 mg/kg QW) studies was the NOAEL in all studies. Plasma $AUC_{(0\text{-}7\ days)}$ at the high dose in males and females on Day 176 of the 6-month study was 23800 and 24500 μg*day/mL, respectively.

Reproductive and Developmental Toxicology

A standard battery of reproductive and developmental toxicology studies was conducted in Sprague-Dawley rat and New Zealand White rabbit. In rat, effects on male fertility were assessed in a separate study (0, 30, or 250 mg/kg SC QW). In female rat, galcanezumab was tested in two combined fertility and embryofetal development studies (dosing prior to and throughout the mating period in males and continuing throughout gestation in females) at doses of 0, 30, or 100 mg/kg SC QW or 0 or 250 mg/kg SC Q3D and in a pre- and postnatal development study (dosing throughout gestation and lactation) at doses of 0, 30, or 250 mg/kg SC Q3D. In rabbit, SC doses of 0, 30, or 100 mg/kg SC were administered on GDs 7, 12, 16, and 20.

No drug-related effects were observed in the fetuses/offspring of either species. The only maternal finding of note was a death (Lactation Day 15) at the high dose in the pre- and postnatal study; the cause of death was not identified.

The plasma AUC data are summarized in the following table:

STUDY	SAMPLING TIME	DOSE (mg/kg)	$AUC_{(0\text{-}last^*)}$ (μg*hr/mL)		Concentration (μg/mL)	
			F_0		Maternal	Fetus
			M	F		
male rat fertility	Day 35	250	29300			
female rat fertility and EFD	GD 13	100		40200		
	GD 20				50.7-87.0	15.8-34.2[+]
female rat fertility and EFD	GD 18	250		61100		
rabbit EFD	GD 20	100		102000		
	GD 29				48.5-318	214-433[+]
rat pre- and postnatal	GD21	250		117000		

[*] $AUC_{(0\text{-}168\ hr)}$ for male rat fertility at 250 mg/kg and female rat fertility and EFD at 100 mg/kg; $AUC_{(0\text{-}72\ hr)}$ for studies in female rat at 250 mg/kg; $AUC_{(0\text{-}72\ hr)}$ for rabbit EFD

[+] Fetal concentrations were 0.32X maternal concentrations in rat and ~2X maternal concentrations in rabbit

Genetic Toxicology

Genetic toxicology studies are typically considered not applicable to biologic products and were not required.

Carcinogenicity

The sponsor was asked to provide a weight-of-evidence evaluation of the carcinogenic potential of galcanezumab. Based on published studies in CGRP knockout animals and on the biological activity of CGRP (e.g., promotion of angiogenesis) and on the results from the sponsor's studies

of galcanezumab, it was concluded that standard carcinogenicity studies of galcanezumab were not needed.

Conclusions and Recommendations
The nonclinical studies are adequate to support approval of galcanezumab for the proposed use.

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/s/

LOIS M FREED
09/27/2018

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

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	761063
Supporting document/s:	1
Applicant's letter date:	September 27, 2017
CDER stamp date:	September 27, 2017
Product:	Galcanezumab
Indication:	Migraine prevention
Applicant:	Eli Lilly and Company
Review Division:	DNP
Reviewer:	Edmund Nest, PhD
Supervisor:	Lois M. Freed, PhD
Division Director:	Billy Dunn, MD
Project Manager:	Emilios Papanastasiou, PharmD

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1 Executive Summary

1.1 Introduction

Galcanezumab is a humanized IgG4 monoclonal antibody that binds the alpha and beta calcitonin gene-related peptide (CGRP), inhibiting binding to the CGRP receptor. During a migraine attack, CGRP levels increase, causing vasodilation and nociceptive signaling. It is hypothesized that inhibiting the binding of CGRP to its receptor will prevent migraine. The sponsor is proposing galcanezumab for migraine prophylaxis.

1.2 Brief Discussion of Nonclinical Findings

Galcanezumab has high affinity and specificity for human, monkey, rat, and rabbit alpha and beta CGRP without off target binding to human Fcγ receptors, complement component C1q, CGRP receptor, or nonCGRP calcitonin family members. A tissue cross-reactivity study assessing galcanezumab binding positively stained select human, monkey, and rat tissues that were consistent with the association of CGRP with neurons and innervated tissues; however, specific binding was also observed in tissues not expected to express CGRP (i.e., tubular epithelium of the kidney). The observed staining in the gray matter of the spinal cord did not concentrate in the in the dorsal horn where high CGRP expression is expected. In pharmacodynamics studies, single SC and IV doses of ≥4 mg/kg galcanezumab inhibited capsaicin-induced dermal blood flow increases in a short-duration study (5 days) in rat and a long-duration study (up to 29 days) in monkey. The toxicology package consisted of general toxicology studies up to 6 months in rat and monkey, which included a safety pharmacology assessment in monkeys; fertility and embryofetal development studies in rat and rabbit; a pre- and postnatal development study in rat; and a juvenile animal toxicology study in rat. Overall, the most notable findings were two unexplained HD deaths in the 6-month general toxicology study in rat and one unexplained HD death in a dam in the pre- and postnatal development study in rat. The most common finding was injection site inflammation in both rats and monkeys, which was not considered adverse. There were no adverse cardiovascular (CV), reproductive, developmental, or juvenile animal effects. Carcinogenicity studies were not required, based on the potential for galcanezumab to counter CGRP associated angiogenesis and immunosuppression, specificity of galcanezumab for CGRP, lack of structural alerts on galcanezumab, and submitted toxicity and clinical studies, which indicated that galcanezumab has a low potential for carcinogenicity.

1.3 Recommendations

1.3.1 Approvability

The nonclinical BLA package supports approval of galcanezumab.

1.3.2 Additional Nonclinical Recommendations

None

1.3.3 Labeling

Statements were removed in sections 8.1, (b) (4) 12.1, (b) (4) 13.1, (b) (4)

2 Drug Information

2.1 Drug

CAS Registry Number: 1578199-75-3

Generic Name: Galcanezumab

Code Name: LY2951742

Chemical Name: n/a

Molecular Weight: 144,084 Da

Structure or Biochemical Description: Sponsor's figure

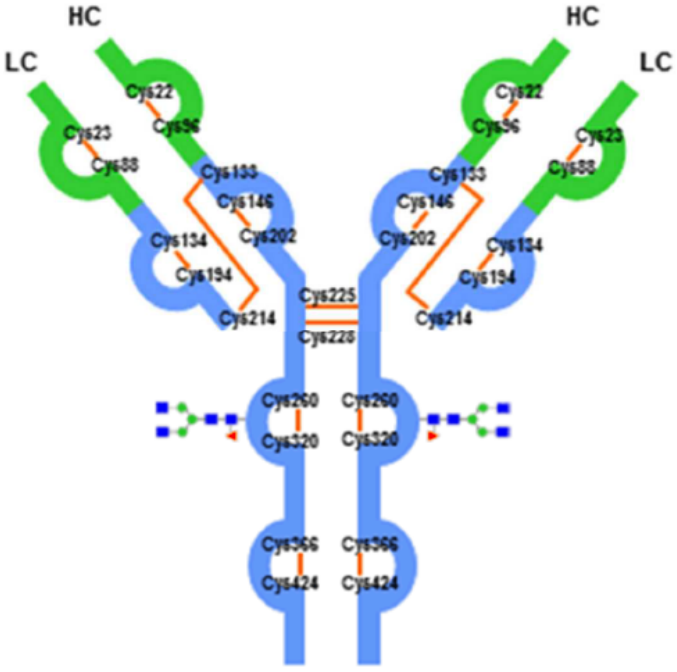

Figure 3.2.S.1.2-3 Schematic Diagram of Galcanezumab

The 32 Cys residues that are involved in the intra-chain and inter-chain disulfide bonding are shown. The variable region is shown in green, and the constant region is shown in blue. Orange color lines between Cys residues indicate disulfide bonds. The location of the *N*-linked glycosylation at Asn296 in each heavy chain is also illustrated.

Pharmacologic Class: Humanized IgG4 monoclonal antibody that binds alpha and beta CGRP.

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND: 111295

2.3 Drug Formulation

Table 3.2.P.1.2-1 Composition of Galcanezumab Injection

Ingredient	Quantity (mg) per Syringe[1]	Function	Reference to Standards
Active Ingredient			
Galcanezumab	120	Drug Substance	Internal Standard: See Section 3.2.S.4.1, Specification
Other Ingredients			
L-Histidine	0.5	(b) (4)	USP, Ph. Eur.
L-Histidine Hydrochloride Monohydrate	1.5		Ph. Eur.
Sodium Chloride	8.8		USP, Ph. Eur.
Polysorbate 80	0.5		USP, Ph. Eur.
Water for Injection	*q.s.* (b) (4)		USP, Ph. Eur.

Abbreviation: Ph. Eur. = European Pharmacopoeia; *q.s.* = quantity sufficient; USP = United States Pharmacopoeia.

[1] (b) (4)

Sponsor's Table

2.4 Comments on Novel Excipients

No novel excipients are included in the drug product.

2.5 Comments on Impurities/Degradants of Concern

No concerns.

2.6 Proposed Clinical Population and Dosing Regimen

Indication	(b) (4)	Dosing Regimen
Migraine prophylaxis		120 mg SC monthly dosing, following a 240 mg loading dose.

2.7 Regulatory Background

At the PreBLA meeting, a summary of the relevant information related to the potential for CV of galcanezumab in humans was requested.

3 Studies Submitted

3.1 Studies Reviewed

- *In vitro* binding: BTDR169, BTDR344, BTDR370, MSK112.
- Cell based activity: MSK113.
- *In vivo* pharmacodynamics: MSK115, MSK116, PM123, QSB39.
- *In vivo* pharmacokinetics: 8214340LO, PM120.
- General toxicity: 8297947, 504703, 503647, 8297946, 504702, 503646.
- Reproduction and development: 8316570, 20096436, 902585, 902586 (b) (4) 353310, (b) (4) -353311, 20092502, 20093122.
- Tissue cross-reactivity: 20000687.
- Literature support for carcinogenicity and vasospasm: CARCI-ASSESS, VASOSPASM-ASSESS.
- Analytical methods and validation reports: 320328, 320329, 320335, AR3142, AR3146.

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

IND 111295, D. Charles Thompson, Ph.D., April 4, 2011.
IND 111295, D. Charles Thompson, Ph.D., August 19, 2015.

4 Pharmacology

4.1 Primary Pharmacology

An *in vitro* characterization of galcanezumab binding to human and rat CGRP demonstrated equilibrium dissociation constants (K_D) of 31 and 250 pM, respectively. A comparison of galcanezumab functional activity, measured by the inhibition of cAMP induction in SK-N-MC cells, on human and rabbit CGRP peptides demonstrated IC_{50} values of 0.23 and 0.06 nM, respectively. An assessment of the ability of galcanezumab to inhibit human CGRP or amylin on the human AMY-1 receptor, expressed in CHO-K1 cells, demonstrated an IC_{50} of 0.9 nM for CGRP and no inhibition for amylin, as measured by cAMP inhibition. Galcanezumab inhibited α- and β-CGRP-induced formation of cAMP in human SK-N-MC cells, with IC_{50} values of 0.35 and 0.18 nM, respectively. SC administration of 4 mg/kg galcanezumab reduced capsaicin-induced increase in rat dermal blood flow by ~81% 5 days after administration. IV administration of 5 mg/kg galcanezumab provided long-term inhibition of capsaicin-induced increases in forearm dermal blood flow in cynomolgus monkeys. On Days 1, 15, and 29, capsaicin-induced blood flow was reduced by 87, 71, and 63%, respectively.

(Summarized from Pharmacology/Toxicology IND Review and Evaluation, IND 111295*, D. Charles Thompson, Ph.D.,* April 4, 2011*)*

4.2 Secondary Pharmacology

In vitro analysis to determine off target binding of galcanezumab showed no binding to human Fcγ receptors I, IIa, and IIIa, complement component C1q, CGRP-R, or nonCGRP calcitonin family members (amylin, calcitonin, adrenomedullin, and intermedin).

4.3 Safety Pharmacology

Safety pharmacology assessments were incorporated into the 6-week and 6-month toxicity studies in monkey.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Galcanezumab serum concentrations were measured in rat, rabbit, and monkey using enzyme-linked immunosorbent assays (ELISA). The lower limit of quantification for galcanezumab in serum was 30 ng/mL and the upper limit was 1500 ng/mL.

The $t_{1/2}$ of a 2 mg/kg IV dose of galcanezumab administered to cynomologus monkeys was 184 h.

The peripheral and central nervous system distribution of galcanezumab was assessed in rat. Following a 4 mg/kg SC dose, plasma drug levels peaked at 72 hours and persisted until study end at ~168 h. There was no statistically significant difference between the distributions of drug compared to control (IgG4). The distribution of drug in

the peripheral tissues (including trigeminal ganglia) ranged from 5 to 11% of plasma levels, while CNS tissues had a distribution of <0.4%. The rank order of distribution was dura mater = spleen > trigeminal ganglia >> hypothalamus = spinal cord = prefrontal cortex = cerebellum = CSF.

6 General Toxicology

6.2 Repeat-Dose Toxicity

Study title: A 6-week Subcutaneous Injection Toxicity and Toxicokinetic Study in Sprague-Dawley Rats Given LY2951742 Followed by a 9-week Recovery Period

Study no.:	503646
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	April 7, 2010
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and concentration:	LY2951742; lot # 18646-71-AP1; concentration: 56.9 mg/mL

Key Study Findings

The NOAEL was the HD, with Day 36 $AUC_{0\text{-}168\ h}$ values of 13,916 (M) and 106,331 (F) µg*h/mL.

Methods

Doses:	0, 1.5, 15, and 100 mg/kg
Frequency of dosing:	Once weekly (6 weeks)
Route of administration:	SC
Dose volume:	2 mL/kg
Formulation/Vehicle:	10 mM Sodium Citrate buffer, 150 mM Sodium Chloride, 0.02% Polysorbate 80 diluted in Sterile Water for Injection USP, pH 6.0
Species/Strain:	Rat, Sprague Dawley
Number/Sex/Group:	10/sex/group (Main Study); 5/sex/group (Recovery); 12/sex/group (TK and Immunogenicity)
Age:	At dosing initiation: 8 to 9 weeks
Weight:	At dosing initiation: 185 to 335 g
Satellite groups:	Recovery and TK (with immunogenicity)
Unique study design:	Recovery period included control and MD (not HD animals).
Deviation from study protocol:	There were minor deviations, with no impact on study validity.

Observations and Results

Animals were assessed for clinical observations, body weight, food consumption, clinical pathology, ophthalmoscopy, hematology, urinalysis, organ weights, histopathology (with adequate battery), TK, and antidrug antibodies (ADA; no data provided). There were no animal deaths. Drug-related histopathology findings consisted of inflammatory responses at the injection sites and mandibular lymph nodes, and oligospermia in the epididymis in 2 HD males. TK data showed exposure increased less than dose proportionally, following a single dose on Day 1. Drug accumulated following repeat dosing at the LD and MD. At the HD, between Days 1 and 36, drug concentrations decreased, which was attributed to ADA; however, no ADA data were provided. The NOAEL was the HD.

(Based on Pharmacology/Toxicology IND Review and Evaluation, IND 111295*, D. Charles Thompson, Ph.D.,* April 4, 2011*)*

Study title: A 3-month Subcutaneous Injection Toxicity and Toxicokinetic Study in Rats Given LY2951742 Followed by a 6-week Recovery Period

Study no.:	504702
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	November 10, 2011
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and concentration:	LY2951742; lot # 18646-71-AP1; concentration: 56.9 mg/mL

Key Study Findings

The NOAEL was the HD, with Day 78 C_{max} and $AUC_{0\text{-}168\ h}$ values of 621 µg/mL and 35,362 µg*h/mL, respectively.

Methods

Doses:	0, 15, and 100 mg/kg
Frequency of dosing:	Once weekly (12 weeks)
Route of administration:	SC
Dose volume:	2 mL/kg
Formulation/Vehicle:	10 mM Sodium Citrate buffer, 150 mM Sodium Chloride, 0.02% Polysorbate 80 diluted in Sterile Water for Injection USP, pH 6.0
Species/Strain:	Rat, Sprague Dawley
Number/Sex/Group:	Main Study: 10/sex/group; Recovery: 5/sex/group; TK: 3/sex/group (vehicle), 9/sex/group (LY2951742).
Age:	At dosing initiation: 8 weeks
Weight:	At dosing initiation: M: 238 to 289 g; F: 193 to 233 g
Satellite groups:	Recovery and TK
Unique study design:	Recovery period included HD animals only.
Deviation from study protocol:	There were minor deviations, with no impact on study validity.

Observations and Results

Mortality and Clinical Signs

Observations were made twice daily, with detailed examinations weekly.

There were no drug-related findings.

Body Weights and Food Consumption

Measured weekly.

There were no drug-related findings.

Ophthalmoscopy

None

ECG

None

Hematology, Coagulation, and Clinical Chemistry (measured prior to necropsy)

There were no drug-related findings.

Urinalysis

There were no drug-related findings.

Gross Pathology

There were no drug-related findings.

Organ Weights

Adrenal glands, brain, epididymides, heart, kidneys, liver, ovaries, prostate, spleen, testes, thymus, thyroid lobes, and parathyroid glands were assessed.

There were no drug-related findings.

Histopathology

abnormalities	injection sites
animal identification[a]	jejunum
adrenals	kidneys
aorta (thoracic)	liver (sample of 2 lobes)
bone and marrow (sternum)***	lungs+
bone (femur) (to include articular surface of the distal end)***	lymph nodes (axillary bilateral and mesenteric)
brain (cerebrum, cerebellum, midbrain and medulla oblongata)	mammary gland (inguinal)
cecum	optic nerves**++
colon	ovaries
dorsal root (cervical, thoracic, lumbar), bilateral	pancreas
dorsal ganglion (cervical, thoracic, lumbar), bilateral	pituitary
duodenum	prostate
epididymides*	salivary glands (mandibular)
esophagus	sciatic nerve
eyes**	seminal vesicles
GALT/peyer's patch (ileum)	skeletal muscle (quadriceps femoris)
heart (including section of aorta)	skin (inguinal)
ileum	spinal cord (thoracic)
thymus	spleen
thyroid lobes (and parathyroids)++	stomach
tongue	testes*
trachea	urinary bladder
	uterus (horns, body and cervix)
	vagina

* Fixed in modified Davidson's fluid.
** Fixed in Davidson's fluid
*** Bone decalcified prior to sectioning.
\+ Infused with neutral buffered 10% formalin
++ At least one parathyroid/optic nerve was present on the slide.
a Retained but not processed.

Sponsor's table

Adequate Battery: Yes

Signed pathology report: Yes

Peer Review: No

Histological Findings

There were no drug-related findings.

Special Evaluation

Immunogenicity
Samples were collected from the Main study animals on Day 85 and the Recovery animals on Day 120.

There was no difference in ADA between sexes. On Day 85 (one day after the last dose), ADA was observed in 2/20 (vehicle), 6/20 (LD), and 12/20 (HD) animals. On Day 120 (6 weeks after the last dose), all but 1 LD and 1 HD animal were positive for ADA (individual animal data were not provided).

Toxicokinetics

Blood samples were collected on Days 1 and 78.

Exposure increased dose proportionally on Day 1 and increased less than dose proportionally on Day 78. At the LD, $AUC_{0\text{-}168\ h}$ values were 2.5-fold higher on Day 78 compared to Day 1; however, at the HD, $AUC_{0\text{-}168\ h}$ values were approximately 37% higher on Day 1 compared to Day 78 (see sponsor's table below).

Text Table 7 Analytical Results - Summary of Main Toxicokinetic Parameters

	Administered Dose (mg/kg/dose)	
Parameter	15	100
Sex	Male	Male
LY2951742		
Day 1		
T_{max} (Hours)	72	72
C_{max} (ng/mL)	100046 ± 6225	444154 ± 95626
$AUC_{0\text{-}168}$ (ng*Hours/mL)	13776196 ± 375265	56338112 ± 3675718
$T_{1/2}$ (Hours)	RNR	RNR
Day 78		
T_{max} (Hours)	1	24
C_{max} (ng/mL)	279514 ± 57960	620646 ± 608466
$AUC_{0\text{-}168}$ (ng*Hours/mL)	32986966	35362305
$AUC_{0\text{-}1008}$ (ng*Hours/mL)	100776308 ± 24720545	160769018 ± 109444991
$T_{1/2}$ (Hours)	163	NE

T_{max}	Time of maximum observed concentration
C_{max}	Maximum observed concentration
$AUC_{0\text{-}168}$	Area Under the Curve during the dosing interval
$AUC_{0\text{-}1008}$	Area Under the Curve from time zero to 1008 hours postdose on Day 78
$T_{½}$	Terminal elimination half-life
RNR	Result not reported because the $AUC_{(0\text{-}inf)}$ was extrapolated by > 20% or Rsq was <0.800.
NE	Parameter not estimable from data set.

Dosing Solution Analysis: The mean concentrations of the first and last dose preparations were within ±10% of nominal.

Study title: A Repeat-Dose Toxicity and Toxicokinetic Study in Rats Given LY2951742 by Subcutaneous Injection Once Weekly for 6 months.

Study no.:	8297946
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	May 20, 2014
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and concentration:	LY2951742; lot # EL01456-007-API-F; concentration: 57.2 mg/mL

Key Study Findings

The NOAEL was the LD, with Day 176 C_{max} and $AUC_{0\text{-}168\ h}$ values of 212 µg/mL and 29,900 µg*h/mL, respectively.

Methods

Doses:	0, 20, and 250 mg/kg
Frequency of dosing:	Once weekly
Route of administration:	SC
Dose volume:	5 mL/kg
Formulation/Vehicle:	10 mM Sodium Citrate buffer, 150 mM Sodium Chloride, 0.02% Polysorbate 80 diluted in Sterile Water for Injection USP, pH 6.0
Species/Strain:	Rat, Sprague Dawley
Number/Sex/Group:	Main Study: 15/sex/group; TK: 3/sex/vehicle, 12/sex/LY2951742.
Age:	At dosing initiation: 6 to 7 weeks.
Weight:	At dosing initiation: M: 166 to 231 g; F: 152 to 184 g.
Satellite groups:	Recovery and TK
Unique study design:	Two dosing levels.
Deviation from study protocol:	There were minor deviations, with no impact on study validity.

Observations and Results

The sponsor stated that the HD is the MFD, based on a SC dose volume of 5 mL/kg and a drug formulation of 50 mg/mL. Animals were assessed for clinical observations, body weight, food consumption, clinical pathology, ophthalmoscopy, hematology, urinalysis, organ weights, histopathology (adequate battery), and TK. There were 3 HD deaths, 2 males on Days 108 and 169, respectively, and 1 female on Day 176. No cause of death was identified in the male animals. The female was sacrificed due to an inguinal mass which was identified histologically as a fibrosarcoma in the skin. In both sexes, there was an increased incidence and/or severity, compared to control, of histological injection site findings; however, these findings were not considered adverse.

Exposure values were similar between sexes. C_{max} and $AUC_{0\text{-}168\ h}$ values increased less than dose proportionally between the LD and HD. At the LD, $AUC_{0\text{-}168\ h}$ values were 50% higher on Day 176 compared to Day 1; however, at the HD, $AUC_{0\text{-}168\ h}$ values were 50% lower on Day 176. The sponsor attributed the decrease in HD $AUC_{0\text{-}168\ h}$ values on Day 176 to ADA, although ADA was not assessed in this study.

(Based on Pharmacology/Toxicology IND Review and Evaluation, IND 111295*, D. Charles Thompson, Ph.D.,* August 19, 2015*)*

Dr. Thompson considered the NOAEL to be the HD; however, because no cause of death was determined for the 2 HDM, a drug-related cause of death cannot be ruled out. Therefore, the NOAEL was the LD.

Study title: A 6-week Subcutaneous Injection Toxicity and Toxicokinetic Study in Cynomolgus Monkeys Given LY2951742 Followed by a 9-week Recovery Period

Study no.:	503647
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	March 30, 2010
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and concentration:	LY2951742; lot # 18646-71-AP1; concentration: 56.9 mg/mL

Key Study Findings

The NOAEL was the HD, with $AUC_{0\text{-}168\ h}$ values of 462,969,831 and 409,939,416 ng•h/mL in males and females, respectively.

Methods

Doses:	0, 1.5, 15, and 100 mg/kg
Frequency of dosing:	Once weekly (6 weeks)
Route of administration:	SC
Dose volume:	2 mL/kg
Formulation/Vehicle:	10 mM Sodium Citrate buffer, 150 mM Sodium Chloride, 0.02% Polysorbate 80 diluted in Sterile Water for Injection USP, pH 6.0
Species/Strain:	*Macaca fascicularis, Cynomolgus monkey*
Number/Sex/Group:	Main study: 3/sex/group; Recovery: 3/sex/group
Age:	At dosing initiation: 2.5 to 3.0 years
Weight:	At dosing initiation 2.1 to 2.9 kg
Satellite groups:	Recovery
Unique study design:	Only MD animals were maintained through the Recovery Period.
Deviation from study protocol:	There were minor deviations, with no impact on study validity.

Observations and Results

Monkeys were assessed for clinical observations, body weight, food consumption, clinical pathology, ophthalmoscopy, CV function, hematology, urinalysis, organ weights, histopathology (adequate battery), TK, and ADA (no individual animal data provided). All animals survived to necropsy. There were drug-related histopathology findings consistent with inflammatory response at the injection site that consisted of mononuclear cell infiltration, which did not resolve in many animals during the recovery period (≥1.5 mg/kg F, ≥15 mg/kg M). In the recovery period, one female had ulceration at the injection site.

There were no sex differences in exposure (C_{max} and $AUC_{0\text{-}168\ h}$). Exposure values increased dose proportionally after both single and repeat dosing. After 6 weeks of dosing, there was a 2-fold accumulation in drug. Recovery data showed $t_{1/2}$ was between 235 and 297 hours. Because the injection site findings were not considered adverse, the NOAEL was the HD.

(Based on Pharmacology/Toxicology IND Review and Evaluation, IND 111295*, D. Charles Thompson, Ph.D.,* April 4, 2011*)*

Study title: A 3-month Subcutaneous Injection Toxicity and Toxicokinetic Study in Cynomolgus Monkeys Given LY2951742 Followed by a 6-week Recovery Period

Study no.:	504703
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	November 29, 2011
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and concentration:	LY2951742; lot # 18646-71-API; concentration: 56 mg/mL

Key Study Findings

The NOAEL was the HD, with Day 78 C_{max} and $AUC_{0\text{-}168\ h}$ values of 2,425,169 ng/mL and 334,964,042 ng•h/mL, respectively.

Methods

Doses:	0, 15, and 100 mg/kg
Frequency of dosing:	Once weekly (12 weeks)
Route of administration:	SC
Dose volume:	2 mL/kg
Formulation/Vehicle:	10 mM Sodium Citrate buffer, 150 mM Sodium Chloride, 0.02% Polysorbate 80 diluted in Sterile Water for Injection USP, pH 6.0
Species/Strain:	*Macaca fascicularis, Cynomolgus monkey*
Number/Sex/Group:	3/sex/group (Main Study); 1/sex/HD (Recovery)
Age:	At dosing initiation: 2.0 to 3.5 years
Weight:	At dosing initiation: 2.0 to 3.0 kg
Satellite groups:	Recovery
Unique study design:	Only one HDM and one HDF were maintained through recovery.
Deviation from study protocol:	There were minor deviations, with no impact on study validity.

Observations and Results

Mortality and Clinical Signs

Observations were made twice daily, with detailed examinations weekly.

All animals survived and there were no drug-related clinical signs.

Body Weights

Measured weekly.

There were no drug-related findings.

Food Consumption

Food consumption was evaluated by visual inspection daily.

There were no drug-related findings.

Ophthalmoscopy

None

ECG

None

Hematology, Coagulation, and Clinical Chemistry

Parameters were measured prior to commencement of treatment, during Weeks 6 and 13, and at the end of the recovery period.

There were no drug-related findings.

Urinalysis

Urine was collected during pretreatment, Weeks 6 and 12, and at the end of the recovery period.

There were no drug-related findings.

Gross Pathology

There were no drug-related findings.

Organ Weights

Adrenal glands, brain, epididymides, heart, kidneys, liver, ovaries, prostate, spleen, testes, thymus, thyroid lobes, and parathyroid glands were assessed.

There were no drug-related findings.

Histopathology

abnormalities
animal identification[a]
adrenals
aorta (thoracic)
bone and marrow (sternum)[***]
bone (femur)[***]
brain (cerebrum, cerebellum, midbrain and medulla oblongata)
cecum
cervix
colon
dorsal root (cervical, thoracic, lumbar), bilateral
dorsal root ganglion (cervical, thoracic,

lumbar), bilateral
duodenum
epididymides*
esophagus
eyes**
heart (including section of aorta)
gallbladder
ileum
injection sites (thighs)
jejunum
kidneys
lacrimal glands
liver (sample of 2 lobes)
lungs+
lymph nodes (mandibular, unilateral, and mesenteric)
mammary gland (thoracic – females only)
optic nerves**
ovaries
pancreas
pituitary
prostate
rectum[a]
salivary glands (submandibular)
sciatic nerve
seminal vesicles
skeletal muscle (quadriceps femoris)
skin (ventral thoracic)
spinal cord (thoracic, cervical, lumbar)
spleen
stomach
testes*
thymus
thyroid lobes (and parathyroids)++
tongue
trachea
urinary bladder
uterus (body and cervix)
vagina

* Fixed in modified Davidson's fluid.
** Fixed in Davidson's fluid
*** Bone decalcified prior to sectioning.
\+ Infused with neutral buffered 10% formalin.
++ At least one parathyroid was present on the slide.
[a] Retained but not processed.

Sponsor's table

Adequate Battery: Yes

Signed pathology report: Yes

Peer Review: No

Histological Findings
Drug-related findings consisted of minimal to slight mononuclear cell infiltration, comprised primarily of lymphocytes, at the injection sites. After the 6-week Recovery Period, these findings resolved in one of the two monkeys.

Text Table 6: Incidence and Severity of Noteworthy Histopathological Changes in the Injection Sites

Tissue/Finding	Sex	Male			Female		
Dose (mg/kg/dose)		0	15	100	0	15	100
Injection Site (left hindlimb)							
Number examined		3	3	3	3	3	3
Infiltration: mononuclear cell							
Total Number affected		0	2	2	1	1	3
Minimal		—	2	2	1	1	2
Slight		—	—	—	—	—	1
Injection Site (right hindlimb)							
Number examined		3	3	3	3	3	3
Infiltration: mononuclear cell							
Total Number affected		0	1	1	1	0	1
Minimal		—	—	1	1	—	1
Slight		—	1	—	—	—	—

Sponsor's table

Special Evaluation

Immunogenicity
Samples were collected from the Main study animals on Day 85 and the Recovery animals on Day 120.

No animals tested positive for ADA.

Toxicokinetics

Blood samples were collected on Days 1 and 78.

C_{max} and $AUC_{0\text{-}168\ h}$ values were similar between sexes and increased dose proportionally on Days 1 and 78, between 15 and 100 mg/kg. After 78 days of weekly dosing, accumulation ratios ranged between 2- and 3-fold. $T_{1/2}$ was 316 hours post-dose on Day 78 during the Recovery Period (HD).

Parameter	Administered Dose (mg/kg/dose)			
	15		100	
Sex	Male	Female	Male	Female
LY2951742				
Day 1				
T_{max} (Hours)	32.0 ± 13.9	24.0 ± 0.00	30.0 ± 12.0	36.0 ± 13.9
C_{max} (ng/mL)	162031 ± 24192	185258 ± 23370	1239617 ± 41592	1208044 ± 73856
$AUC_{0\text{-}168}$ (ng*Hours/mL)	23222758 ± -	24456910 ± 3213060	160715987 ± 6512914	145089232 ± 4295677
$T_{1/2}$ (Hours)	-	-	-	-
Day 78				
T_{max} (Hours)	32.0 ± 13.9	26.7 ± 20.1	30.0 ± 12.0	42.0 ± 23.0
C_{max} (ng/mL)	454468 ± 72656	375747 ± 21393	2478117 ± 122332	2372221 ± 404242
$AUC_{0\text{-}168}$ (ng*Hours/mL)	61610305 ± 15363618	49701380 ± 6145806	339525311 ± 31310684	330402772 ± 74717290
$AUC_{0\text{-}1008}$ (ng*Hours/mL)	N/A	N/A	990445708[a]	1276098137[b]
$T_{1/2}$ (Hours)	-	-	316[a]	316[b]

T_{max} Time of maximum observed concentration.
C_{max} Maximum observed concentration.
$AUC_{0\text{-}168}$ Area Under the Curve during the dosing interval.
$AUC_{0\text{-}1008}$ Area Under the Curve from time zero to 1008 hours postdose on Day 78.
$T_{½}$ Terminal elimination half-life.
[a] Result for recovery Animal No. 3004 only.
[b] Result for recovery Animal No. 3504 only.
N/A Not applicable.
- Not calculated.

Sponsor's table

Dosing Solution Analysis: Samples were taken from the dose formulations prepared on November 28, 2011, February 13, 2012, and February 22, 2012. The mean drug concentrations were within 10% of nominal.

Study title: A Repeat-Dose Toxicity and Toxicokinetic Study in Monkeys Given LY2951742 Once Weekly by Subcutaneous Injection for 6 Months

Study no.:	8297947
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	April 10, 2014
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and concentration:	LY2951742; lot # EL01456-007-API-F; concentration: 57.2 mg/mL

Key Study Findings

The NOAEL was the HD, with C_{max} and $AUC_{0\text{-}168\ h}$ values of 4,490 µg/mL and 579,500 µg*h/mL, respectively.

Methods

Doses:	0, 2, and 100 mg/kg
Frequency of dosing:	Once weekly
Route of administration:	SC
Dose volume:	4 mL/kg
Formulation/Vehicle:	10 mM Sodium Citrate buffer, 150 mM Sodium Chloride, 0.02% Polysorbate 80 diluted in Sterile Water for Injection USP, pH 6.0
Species/Strain:	*Macaca fascicularis, Cynomolgus monkey*
Number/Sex/Group:	4/sex/group
Age:	At dosing initiation: 3 to 4 years
Weight:	At dosing initiation: M: 2.7-3.9 kg; F: 2.4-3.0 kg
Satellite groups:	None
Unique study design:	None
Deviation from study protocol:	There were minor deviations, with no impact on study validity.

Observations and Results

Monkeys were assessed for mortality, clinical observations, body weight, food consumption, clinical pathology, ophthalmoscopy, hematology, urinalysis, organ weights, ophthalmoscopy, respiratory examinations, neurological examinations, body temperature, ECG, histopathology (adequate battery), and TK. Drug-related findings consisted of liquid or non-formed feces in males and histological observations of minimal to slight perivascular mononuclear cell infiltrate in the subcutis at the injection site in LDF and HDF. There were no sex differences in exposure. C_{max} and $AUC_{0\text{-}168\ h}$ increased dose proportionally between Days 1 and 176. At the end of the dosing period (Day 176), drug was not detectable in 1 LDM, 3 LDF, and 1 HDF. The sponsor speculated the lack of detectable drug in these animals was due to ADA because

exposure in other animals increased up to 4.4-fold following repeat dosing. The NOAEL was the HD.

(Based on Pharmacology/Toxicology IND Review and Evaluation, IND 111295*, D. Charles Thompson, Ph.D.,* August 19, 2015*)*

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

Study title: Male Fertility and Toxicokinetic Study in Rats Given LY2951742 by Six Weekly Subcutaneous Injections

Study no.:	8316570
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	March 3, 2015
GLP compliance:	Yes
QA statement:	Yes
Drug, batch #, and protein concentration:	LY2951742, batch # EL01456-007-API-F, protein concentration: 57.2 mg/mL

Key Study Findings

The NOAEL was the HD, with C_{max} and $AUC_{0\text{-}168\ h}$ values of 286 µg/mL and 29300 µg*h/mL, respectively.

Methods

Doses:	0, 30, 250 mg/kg
Frequency of dosing:	Once weekly (6 weeks)
Dose volume:	5 mL/kg
Route of administration:	SC
Formulation/Vehicle:	10 mM sodium citrate buffer, 150 mM sodium chloride, and 0.02% polysorbate 80 in Sterile Water for Injection, USP, pH 6.0
Species/Strain:	Rat/Sprague-Dawley
Number/Sex/Group:	25/sex/group-females were not dosed (Main Study); 3/male/group (TK)
Satellite groups:	TK
Study design:	Main study males were mated to untreated females to assess male fertility. Dosing began 28 days prior to mating and continued during mating (2 weeks).
Deviation from study protocol:	There were minor deviations, with no impact on study validity.

Observations and Results

Mortality

Observations were made twice daily.

There were no animal deaths.

Clinical Signs

Detailed observations were made weekly.

There were no drug-related findings.

Body Weight

Measurements were made twice weekly.

There were no drug-related findings.

Food Consumption

Measurements were made weekly.

There were no drug-related findings.

Reproductive performance

Mating, fecundity, and fertility were assessed.

There were no drug-related findings.

Toxicokinetics

Samples were collected on dosing Days 0 and 35.

On Day 0, C_{max} and $AUC_{0\text{-}168\ h}$ increased less than dose proportionally; on Day 35, C_{max} and $AUC_{0\text{-}168\ h}$ did not increase with increasing dose. The LD C_{max} and $AUC_{0\text{-}168\ h}$ values were > 2-fold higher on Day 35 compared to Day 0; however, the HD values were > 2-fold lower.

Covance 8316570

Table 1
Mean Toxicokinetic Parameters of LY2951742 in Male Rats Following Once Weekly Subcutaneous Injection Administration of 30 or 250 mg/kg LY2951742: Days 0 and 35, Study 8316570

Day	Dose Group	Dose Level (mg/kg)		C_{max} (µg/mL)	T_{max} (hr)	$AUC_{0\text{-}168hr}$ (µg·hr/mL)
0	2	30	Mean	170	72.0	21600
			SD	24.4	0.00	2930
			N	3	3	3
	3	250	Mean	846	72.0	111000
			SD	187	0.00	24200
			N	3	3	3
35	2	30	Mean	335	72.0	50400
			SD	58.4	0.00	8400
			N	3	3	3
	3	250	Mean	268	56.0	29300
			SD	246	27.7	29000
			N	3	3	3

Sponsor's table

Dosing Solution Analysis

The mean concentrations of samples collected were within ±10% of nominal.

Necropsy

A cesarean section was performed on GD 13. The uterus from each gravid animal was examined for the number and placement of live fetuses, resorptions, and abnormalities. The ovaries were examined for the number of corpora lutea.

There were no drug-related findings.

Gross pathology

There were no drug-related findings.

Organ weight

The following organs were weighed:

Organ/Tissue		Organ/Tissue	
epididymis (left)[a]	WP	testis (left)[b]	WP
epididymis (right)[a]	WP	testis (right)[b]	WP
prostate	WP	seminal vesicles (with coagulating gland)	WP
brain	WP	lesions	P

W = weighed; P = preserved
a - Epididymis designated for sperm assessment (total sperm count) was stored frozen until processed for analysis.
b - Preserved in Modified Davidson's solution

Sponsor's table

There were no drug-related findings.

Sperm Assessment
All Main study males were evaluated for sperm motility. The first 12 males in the C and HD were assessed for sperm count.

There were no drug-related findings.

Signed pathology report: Yes

Peer review: Yes

Complete battery: The following tissues were assessed in all control and HD males:
Coagulating gland, epididymides, prostate, seminal vesicles, testes, and brain.

Histopathology
There were no drug-related findings.

9.2 Embryonic Fetal Development

Study title: A Subcutaneous Injection Enhanced Pilot Embryo-Fetal Development Study of LY2951742 in Sprague Dawley Rats

Study no.:	902585
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	November 14, 2011
GLP compliance:	No
QA statement:	No
Drug, lot #, and concentration:	LY2951742, lot # 18646-71-API, concentration: 56.9 mg/mL

Methods

Doses:	0, 15, and 100 mg/kg/day
Frequency of dosing:	Days 6, 12, and 18 of gestation.
Dose volume:	2 mL/kg
Route of administration:	SC
Formulation/Vehicle:	10 mM Sodium Citrate buffer, 150 mM Sodium Chloride, 0.02% Polysorbate 80 diluted in Sterile Water for Injection USP, pH 6.0
Species/Strain:	Rat/Sprague Dawley
Number/Sex/Group:	Main study: 7/F/group; TK: 2/F/group
Satellite groups:	TK
Study design:	Treatment period: GDs 6 through 18; Cesarean Sections: GD 21.
Deviation from study protocol:	There were minor deviations, with no impact on study validity.

Observations and Results

Mortality

Observations were made twice daily.

No deaths occurred during the study.

Clinical Signs

Detailed examinations were made on Days: 0, 3, 6, 9, 12, 15, 18, and 21 of gestation.

There were no drug-related findings.

Body Weight and Food Consumption

Measurements were made on Days: 0, 3, 6, 9, 12, 15, 18, and 21 of gestation.

There were no drug-related findings.

Toxicokinetics

Blood samples were collected on Days 6 and 18 of gestation.

Drug concentrations were highly variable at the LD; increased with increasing dose; and did not accumulate after repeat dosing.

Table 1.2: Concentrations of LY2951742 in Female Sprague-Dawley Rat Serum Following Subcutaneous Injection of LY2951742

	Nominal	Group 2: 15 mg/kg - Concentration (ng/mL)		
	Time	Animal	Animal	
Occasions	(h)	2508	2509	Mean
Day 6 of Gestation	Predose	< LLOQ	< LLOQ	< LLOQ
	24	19601	78081	48841
	48	53347	89717	71532
Day 18 of Gestation	Predose	27146	54656	40901
	24	43177	70128	56652
	48	31863	58191	45027

< LLOQ = Below the lower limit of quantitation (LLOQ = 30.0 ng/mL).

Table 1.3: Concentrations of LY2951742 in Female Sprague-Dawley Rat Serum Following Subcutaneous Injection of LY2951742

Occasions	Nominal Time (h)	Group 3: 100 mg/kg - Concentration (ng/mL) Animal 3508	Animal 3509	Mean
Day 6 of Gestation	Predose	< LLOQ	< LLOQ	< LLOQ
	24	289129	342409	315769
	48	358338	393143	375740
Day 18 of Gestation	Predose	124827	151007	137917
	24	210085	209521	209803
	48	192265	188519	190392

< LLOQ = Below the lower limit of quantitation (LLOQ = 30.0 ng/mL).

Sponsor's tables

Dosing Solution Analysis

Samples were collected from each dose concentration and found to be within ±10% of nominal.

Necropsy

There were no gross pathology drug-related findings.

Cesarean Section Data

The following examinations were made: corpora lutea, implantation sites, placentae, live and dead fetuses, and early and late resorptions.

There were no drug-related findings.

Offspring

The following examinations were made: sex, external, visceral, skeletal, litter number, uterine distribution.

There were no drug-related findings.

Study title: A Combined Fertility, Embryo-Fetal Development and Toxicokinetic Study of LY2951742 Administered Weekly via Subcutaneous Injection to Female Sprague-Dawley Rats

Study no.:	353311
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	February 10, 2014
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and concentration:	LY2951742, lot # BR101353,

concentration: 55.7 mg/mL

Key Study Findings

The NOAEL was the HD, with GD 13 C_{max} and AUC_{last} values of 425 µg/mL and 40,200 µg*h/mL, respectively.

Methods

Doses:	0, 30, and 100 mg/kg
Frequency of dosing:	Female rats were dosed prior to mating through organogenesis. (Once on Study Days 0, 7, and 14 and GDs 6 and 13.)
Dose volume:	10 mL/kg
Route of administration:	SC
Formulation/Vehicle:	10 mM sodium citrate buffer, 150 mM sodium chloride, and 0.02% polysorbate 80 in water for injection, USP, pH 6.0
Species/Strain:	Rat/ Sprague Dawley
Number/Sex/Group:	Main study: 30/sex/group - males were not dosed TK: 4/sex/group (C), 12/sex/group (dosing) – males were not dosed.
Satellite groups:	TK
Study design:	30 females per group were administered drug on Study Days 0, 7, and 14 and GDs 6 and 13.
Deviation from study protocol:	There were minor deviations, with no impact on study validity.

Observations and Results

Mortality

Observations were made twice daily.

There were no drug-related deaths.

Clinical Signs

Observations were made once daily.

There were no drug-related findings.

Body Weight (female only)

Weights were recorded on Days 0, 1, 2, 3, 7, 10, and 14; GDs 0-6, 6-13, 13-20, and 0-20.

There were no drug-related findings.

Food Consumption

Consumption was recorded on Days 0, 1, 2, 3, 7, 10, and 14; GDs 0-18 (daily) and 20.

There were no drug-related findings.

Estrous Cycles

There were no drug-related findings.

Histopathology

The following tissues were assessed:

Ovaries and oviducts (2)	Uterus[a] with cervix and vagina
Pituitary gland	All gross lesions[b]

[a] = Uterus not retained if placed in ammonium sulfide solution.
[b] = Representative sections of corresponding organs from a sufficient number of controls were retained for comparison.

Sponsor's table

There were no drug-related findings.

Toxicokinetics

Blood was collected from the vehicle control groups on Study Day 0 and GD 13, and the dosing groups on Study Days 7 and 14 and GD 6.

C_{max} and AUC_{last} increased approximately dose proportionally on Study Day 0 and GD 13. Exposure was lower on GD 13 compared to Study Day 13 (accumulation ratios: 0.74 and 0.60, respectively). T_{max} occurred 72 h post LD and HD on Day 0, and 72 h and 24 h post LD and HD, respectively, on GD 13. Fetal drug concentrations on GD 20 ranged from 25 to 39% of maternal concentration.

Dose (mg/kg):	30	100
Study Day 0		
AUC_{last} (µg•hr/mL)	24,800	67,600
C_{max} (µg/mL)	176	512
T_{max} (hr)	72	72
Gestation Day 13		
AUC_{last} (µg•hr/mL)	18,300	40,200
C_{max} (µg/mL)	146*	425
T_{max} (hr)	72*	24

* = T_{max} was prior to dosing on Gestation Day 13, therefore, C_{max} and T_{max} after dosing are presented.
Abbreviations: AUC_{last} = area under the curve from 0 to T_{last} (168 hours post-dosing), C_{max} = maximum plasma concentration, and T_{max} = time of maximum plasma concentration.

Sponsor's table

Dosing Solution Analysis

Samples for concentration analysis were collected from the formulations used on the first day of dosing. Mean assayed concentrations ranged from 95.2 to 97.3% of nominal.

Necropsy

Laparohysterectomy

The number of corpora lutea, fetuses, resorptions, and implantations were recorded.

There were no drug-related findings

Offspring
The following assessments were made: skeletal, external, and visceral abnormalities, sex, and body weight.

There were no drug-related findings

Study title: A Combined Fertility, Embryo-Fetal Development and Toxicokinetic Study of LY2951742 (Compound (b) (4) Administered by Subcutaneous Injection in Female Rats

Study no.:	20096436
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	June 6, 2016
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and Protein content:	LY2951742, lot # EL01537-087-API-F, Protein content: 165.1 mg/mL

Key Study Findings

The NOAEL was the HD, with GD 18 C_{max} and $AUC_{0\text{-}72h}$ values of 995 µg/mL and 61,100 µg*h/mL, respectively.

Methods

Doses:	0 and 250 mg/kg
Frequency of dosing:	Once every 3 days.
Dose volume:	5 mL/kg
Route of administration:	SC
Formulation/Vehicle:	10 mM L-Histidine buffer, 150 mM Sodium Chloride, 0.02% Polysorbate 80, pH 5.8
Species/Strain:	Rat/Sprague Dawley
Number/Sex/Group:	Main Study: 26/F/group; TK: 4/F/C, 8/F/drug
Satellite groups:	TK
Study design:	Drug was administered 14 days prior to cohabitation through GD 18.
Deviation from study protocol:	There were minor deviations, with no impact on study validity.

Observations and Results

Mortality

Observations were made twice daily.

No mortalities occurred.

Clinical Signs

Observations were made daily.

There were no drug-related findings.

Body Weight

Measurements were recorded daily.

There were no drug-related findings

Food Consumption

Measurements were recorded weekly until cohabitation and on GDs 0, 3, 6, 9, 12, 15, 18, 21 (food left value).

There were no drug-related findings.

Estrous Cycle Evaluations

Vaginal cytometry samples were collected 14 days prior to dosing and then continuously until conformation of pregnancy.

There were no drug-related findings.

Mating and Fertility

There were no drug-related findings.

Toxicokinetics

Blood samples were collected on GDs 1 and 18.

Drug serum concentrations were detectable throughout the 72 h sampling period on Study Day 1 and GD 18. T_{max} was 72 h post dosing on Study Day 1 and 24 h post dosing on GD 18. There was no difference in C_{max} and $AUC_{0\text{-}72h}$ after repeat dosing. The accumulation ratio ($AUC_{0\text{-}72\ h,\ GD18}/AUC_{0\text{-}72\ h,\ SD1}$) was 0.769.

Text Table 17
Summary of Toxicokinetic Parameters

LY2951742 Dose Level (mg/kg) [a]	250
Day 1 of study (DS 1)	
T_{max} (hr)	72
C_{max} (µg/mL)	1550 ± 89.9
AUC_{0-72} (µg*hr/mL)	79400 ± 6870
Day 18 of gestation (DG 18)	
T_{max} (hr)	24
C_{max} (µg/mL)	995 ± 175
AUC_{0-72} (µg*hr/mL)	61100 ± 7420

[a]Results are composite (n = 4/time point).
T_{max} Time of maximum observed concentration.
C_{max} Maximum observed concentration.
AUC_{0-72} Area Under the Curve from time zero to 72 hours.

Sponsor's table

Dosing Solution Analysis

Samples were collected from the first and last dosing preparations. The samples were within ±10% of nominal.

Necropsy

A gross necropsy of the thoracic, abdominal, and pelvic viscera was performed.

There were no drug-related findings.

Cesarean Section Data

Litter averages for corpora lutea, implantations, percentage of pre-implantation loss, litter sizes, live fetuses, early and late resorptions, percentage of post-implantation loss, percentage of dead or resorbed conceptuses, percentage of live male fetuses, and fetal body weights were assessed.

There were no drug-related findings.

Offspring

The following assessments were made: skeletal, external, and visceral abnormalities, sex, and body weight.

There were drug-related decreases in incidence of short ribs and the mean number of ossified caudal vertebrae (see sponsor's table below).

Text Table 15
Summary of Skeletal Abnormalities

Dose Level (mg/kg)	0 (Control)	250	Historical Control Data[a]
Ribs: Short			
Litter Incidence N (%)	1 (4.0)	3 (12.5)	0 – 2 (0 – 12.5)
Fetal Incidence N (%)	1 (0.6)	4 (2.2)	0 – 2 (0 – 1.7)

[a] Historical Control Data for embryo-fetal development studies in (b) (4) CD(SD) rats June 2011 – January 2015.

Text Table 16
Summary of Mean Ossification Site Averages

Dose Level (mg/kg)	0 (Control)	250	Historical Control Data[a]
Vertebrae Caudal	6.43	5.88*	6.78 – 8.14

[a] Historical Control Data for embryo-fetal development studies in (b) (4) CD(SD) rats June 2011 – January 2015.
* - Significantly different from the control group value ($p \leq 0.05$)

Study title: A Subcutaneous Injection Enhanced Pilot Embryo-fetal Development Study of LY2951742 in Rabbits

Study no.:	902586
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	November 10, 2011
GLP compliance:	No
QA statement:	No
Drug, lot #, and potency:	LY2951742, lot # 18646-71-API, potency: 56.9 mg/mL

Methods

Doses:	0, 15, and 100 mg/kg/dose
Frequency of dosing:	Weekly
Dose volume:	2 mL/kg
Route of administration:	SC
Formulation/Vehicle:	10 mM sodium citrate buffer, 150 mM sodium chloride, 0.02% polysorbate 80 diluted in sterile water for injection USP, pH 6.0
Species/Strain:	Rabbit/New Zealand White
Number/Sex/Group:	Main Study: 6/F/group; TK: 3/F/group
Satellite groups:	TK
Study design:	Animals were dosed on Days 7, 13, and 20 of gestation.
Deviation from study protocol:	There were minor deviations, with no impact on study validity.

Observations and Results

Mortality

Observations were made twice daily.

All animals survived to necropsy.

Clinical Signs

Detailed observations were made on GDs 0, 4, 7, 10, 13, 16, 20, 23, 26, and 29.

There were no drug-related findings.

Body Weight

Measurements were made the same time as detailed observations (see above).

There were no drug-related findings.

Food Consumption

Measurements were recorded daily.

There were no drug-related findings.

Toxicokinetics

Blood samples were collected on GDs 7 and 20.

Drug was quantifiable on GDs 7 and 20; however, there was high inter-animal variability. Nine days following the last LD dose, drug was not quantifiable; however, drug remained quantifiable after the HD. Drug exposure increased with increasing dose but did not accumulate following repeat administration.

Table 1.2: Concentrations of LY2951742 in Female New Zealand White Rabbit Serum Following Subcutaneous Injection of LY2951742

	Nominal	Group 2: 15 mg/kg - Concentration (ng/mL)			
	Time	Animal	Animal	Animal	
Occasions	(h)	2507	2508	2509	Mean ± SD
Day 7 of Gestation	Predose	< LLOQ	< LLOQ	< LLOQ	< LLOQ ± n/a
	24	98644	120069	113559	110757 ± 10984
	48	133267	151082	157956	147435 ± 12742
Day 20 of Gestation	Predose	131454	65.9	< LLOQ	43840 ± 75876
	24	161919	13719	6309	60649 ± 87781
	48	136457	463	< LLOQ	45640 ± 78650
Day 29 of Gestation	n/a	8327	< LLOQ	< LLOQ	2776 ± 4808

< LLOQ = Below the lower limit of quantitation (LLOQ = 30.0 ng/mL). The < LLOQ concentrations were assigned a value of zero.

n/a Not applicable.

Table 1.3: Concentrations of LY2951742 in Female New Zealand White Rabbit Serum Following Subcutaneous Injection of LY2951742

Occasions	Nominal Time (h)	Group 3: 100 mg/kg - Concentration (ng/mL) Animal 3507	Animal 3508	Animal 3509	Mean ± SD
Day 7 of Gestation	Predose	< LLOQ	< LLOQ	< LLOQ	< LLOQ ± n/a
	24	652843	669080	709740	677221 ± 29309
	48	852093	881822	1013038	915651 ± 85639
Day 20 of Gestation	Predose	884802	195127	767213	615714 ± 368953
	24	438295	1219081	1401380	1019585 ± 511598
	48	427617	1386434	1299642	1037897 ± 530297
Day 29 of Gestation	n/a	< LLOQ	83921	13145	32356 ± 45138

< LLOQ = Below the lower limit of quantitation (LLOQ = 30.0 ng/mL). The < LLOQ concentrations were assigned a value of zero.

n/a Not applicable.

Sponsor's tables

Dosing Solution Analysis

Samples were collected from each dose concentration and were found to be within ±10% of nominal.

Necropsy

There were no drug-related gross pathology findings.

Cesarean Section Data

The following were examined: corpora lutea, implantations, resorptions, placentas, and fetuses.

There were no drug-related findings.

Offspring

External, visceral, and skeletal structures were examined, and sex and body weights were recorded.

There were no drug-related findings.

Study title: An Embryo-Fetal Development and Toxicokinetic Study of LY2951742 Administered Via Subcutaneous Injection on GDs 7, 12, 16, and 20 in New Zealand White Rabbits

Study no.:	353310
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	February 18, 2014
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and protein content:	LY2951742, lot # BR101353, protein content: 55.7 mg/mL

Key Study Findings

The NOAEL was the HD, with GD 20 C_{max} and $AUC_{0\text{-}72\ h}$ values of 1660 µg/mL and 102000 µg*h/mL, respectively.

Methods

Doses:	0, 30, and 100 mg/kg
Frequency of dosing:	GDs 7, 12, 16, and 20
Dose volume:	2 mL/kg
Route of administration:	SC
Formulation/Vehicle:	10 mM sodium citrate buffer, 150 mM sodium chloride, and 0.02% polysorbate 80 in water for injection, USP, pH 6.0
Species/Strain:	Rabbit/ New Zealand White
Number/Sex/Group:	Main study: 25/F/group; TK: 5/F/group
Satellite groups:	TK
Study design:	Animals were dosed on GDs 7, 12, 16, and 20 and euthanized for examination of reproductive parameters on Day 29.
Deviation from study protocol:	Minor deviations were reported, with no impact on study validity.

Observations and Results

Mortality

Observations were made twice daily.

All animals survived through GD 29.

Clinical Signs

Observations were made daily from receipt through GD 29.

One LD female delivered prior to scheduled necropsy on GD 29.

Body Weight

Measurements were recorded for Main Study and TK animals on GDs 5-20 (daily), 24, and 29.

The LD female that delivered prior to necropsy had a body weight reduction of 16% during GDs 15 to 24, compared to control. There were no drug-related findings in other animals.

Food Consumption

Food consumption was recorded daily between GDs 5 and 29.

The LD female that delivered prior to necropsy had a reduction in food consumption ranging from 0 to 50 g between GDs 16 and 24. There were no drug-related findings in other animals.

Toxicokinetics

Blood samples were collected on GDs 7, 12, 16, 20, and 29.

C_{max} and $AUC_{0\text{-}72\ h}$ increased approximately dose-proportionally on GDs 7 and 12 and greater than dose proportionally on GDs 16 and 20. Drug accumulated at the HD on GDs 12, 16, and 20, and the LD on GD 12. The fetal drug concentration on GD 29 ranged from 110 to 441% of the associated maternal concentration.

Dose (mg/kg):	30	100
Gestation Day 7		
$AUC_{0\text{-}72hr}$ (µg•hr/mL)	11200	47000
C_{max} (µg/mL)	240	1020
T_{max} (hr)	82	82
Gestation Day 12		
$AUC_{0\text{-}72hr}$ (µg•hr/mL)	21700	91500
C_{max} (µg/mL)	355	1430
T_{max} (hr)	24	24
Gestation Day 16		
$AUC_{0\text{-}72hr}$ (µg•hr/mL)	10000	117000
C_{max} (µg/mL)	211	1760
T_{max} (hr)	16	34
Gestation Day 20		
$AUC_{0\text{-}72hr}$ (µg•hr/mL)	2480	102000
C_{max} (µg/mL)	68.5	1660
T_{max} (hr)	24	15

Abbreviations: $AUC_{0\text{-}72hr}$ = plasma concentration time curve between 0 and 72 hours, C_{max} = maximum plasma concentration, and T_{max} = time of maximum plasma concentration.

Sponsor's table

Dosing Solution Analysis

The mean concentration of all dosing formulations ranged between 98.0 and 98.8% of nominal.

Necropsy

Laparohysterectomy Data

On GD 29, the following data were collected: number of corpora lutea, uterus weight, number and location of all fetuses, number of resorptions, number of implantation sites, and examination of the placenta.

There were no drug-related findings.

Offspring

Each viable fetus was individually weighed, sexed, counted, and examined (external: eyes, palate, external orifices; internal: sex, kidneys, head, and skeleton).

There were no drug-related findings.

9.3 Prenatal and Postnatal Development

Study title: A Developmental and Perinatal/Postnatal Reproduction Study of LY2951742 (Compound 2951742) Administered by Subcutaneous Injection in Rats, Including a Postnatal Behavioral/Functional Evaluation.

Study no.:	20092502
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	March 9, 2017
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and concentration:	LY2951742, lot # EL01537-087-API-F, and concentration: 165.1 mg/mL

Key Study Findings

The NOAEL was the LD for the dams and the HD for the offspring generation. Plasma exposure in the dams was: C_{max}: 293 µg/mL and $AUC_{0\text{-}168\ h}$: 31,300 µg*h/mL at the LD and C_{max}: 1320 µg/mL and $AUC_{0\text{-}168\ h}$: 128000 µg*h/mL at the HD.

Methods

Doses:	0, 30, and 250 mg/kg
Frequency of dosing:	GDs: 6, 9, 12, 15, 18, and 21; Lactation Days: 2, 5, 8, 11, 14, 17, and 20
Dose volume:	5 mL/kg
Route of administration:	SC
Formulation/Vehicle:	10 mM L-Histidine buffer, 150 mM Sodium Chloride, 0.02% Polysorbate 80, pH 5.8
Species/Strain:	Rat/Sprague Dawley
Number/Sex/Group:	Main Study (F0): 26/F/group; TK Study (F0): 4/F/control and 12/F/dosing. F1: 24/sex/group
Satellite groups:	TK
Study design:	F0 female rats (Main study and TK) were dosed during gestation and lactation periods. F1 pups were not directly dosed.
Deviation from study protocol:	There were minor deviations, with no impact on study validity.

Observations and Results

F_0 Dams

Survival: Observations were made twice daily.

One HDF was found dead on Lactation Day (LD) 15 (11 doses of test article). No cause of death was identified.

Clinical signs: Observations were made daily.

There were no drug-related findings.

Body weight: Measurements were made daily.

There were no drug-related findings.

Food consumption: Recorded on GDs: 6, 9, 12, 15, 18, 20, and 25; LDs: 1, 4, 7, 10 and 14.

There were no drug-related findings.

Delivery observations: Evaluations of clinical signs, duration of gestation, litter size, and pup viability were made.

There were no drug-related findings.

Necropsy observation: Ovaries, uterus, and the thoracic abdominal and pelvic viscera were examined.

There were no drug-related findings.

Toxicokinetics: Samples were collected on GDs 6 and 21, and LD 20.

T_{max} was at 48 h on GD 6, up to 72 h on GD 21, and up to 24 h on LD 20. C_{max} and $AUC_{0\text{-}72\ h}$ increased less than dose proportionally. Exposure increased with repeat dosing on GD 21, relative to GD 6, with accumulation ratios of 2.23 and 2.55 at the LD and HD mg/kg, respectively, but did not increase on LD 20 relative to GD 21. ADA was suspected in 2 of 12 females in both the LD and HD groups due to lower drug concentrations after LD 20.

Text Table 19
Summary of LY2951742 Toxicokinetic Parameters

Day of Collection	Dose (mg/kg)	T_{max} (hr)	C_{max} (µg/mL)	$AUC_{(0-72)}$ (hr*µg/mL)	$AUC_{(0-168)}$ (hr*µg/mL)	$T_{1/2}$ (hr)	R_{AUC} (RATIO)
DG 6	30	48	187	9170	NC	NC	NA
	250	48	882	45800	NC	NC	NA
DG 21	30	24	378	20500	NC	NC	2.23
	250	72	2110	117000	NC	NC	2.55
DL 20	30	24	293	15800	31300	NC	1.73
	250	8	1320	64300	128000	NRR	1.40

R_{AUC} = DG 21 or DL 20 $AUC_{(0-72)}$/DG 6 $AUC_{(0-72)}$
NC = Not calculated
NA = Not applicable
NRR = Not reported because Rsq was less than 0.800 or the extrapolation of AUC to infinity represented more than 20% of the total area.

Sponsor's table

Dosing Solution Analysis: All formulations were within ±10 of nominal.

F_1 Generation

Survival:	Observations were made twice daily.
	There were no drug-related deaths.
Clinical signs:	Observations were made once daily.
	There were no drug-related findings.
Body weight:	Recorded on Days 1, 4, 7, 10, 14, and 21.
	There were no drug-related findings.
Food consumption:	Recorded on Days 0, 7, 10, and 13.
	There were no drug-related findings.
Physical development:	Observations were made between Days 28 and 34 and between Days 70 and 76.
	There were no drug-related findings.
Neurological assessment:	Motor activity (Day 60) and Morris Water Maze (Days 73 to 87) performance were evaluated.
	There were no drug-related findings.
Reproduction:	Sexual maturation and estrous cycling, mating, and fertility were evaluated.
	There were no drug-related findings.
Preweaning necropsy observations (for pups not selected for post weaning observations):	There were no drug-related observations.
Necropsy:	There were no drug related findings.
Organ weights:	There were no drug-related findings.
Sperm motility, concentration, and morphology:	There were no drug-related findings.
Ovarian and Uterine contents:	Pregnancy rate and litter averages for corpora lutea, implantations, percentages of preimplantation loss, viability, and percentages of post implantation loss

were assessed. Placentas were examined for detectable abnormalities.

There were no drug-related findings.

10 Special Toxicology Studies

Study title: A Juvenile Toxicity Study of LY2951742 Administered Every Three Days by Subcutaneous Injection from PND 21 to 90 in Sprague-Dawley Rats

Study no.:	20093122
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	November 29, 2011
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and concentration:	LY2951742; lot # EL01537-096-API-F; concentration: 165.4 mg/mL

Key study findings

The NOAEL was the HD, with C_{max} and $AUC_{0\text{-}168\ h}$ values on PND 90 of approximately 2840 µg/mL and 354,500 µg*h/mL, respectively.

Methods

Doses:	0, 30, and 250 mg/kg
Frequency of dosing:	Once every 3 days beginning on PND 21 and continuing through PND 90
Route of administration:	SC
Dose volume:	5 mL/kg
Formulation/Vehicle:	10 mM L-Histidine buffer, 150 mM Sodium Chloride, 0.02% Polysorbate 80, pH 5.8
Species/Strain:	Rat/Sprague Dawley
Number/Sex/Group:	Main Study: 20/sex/dose; Recovery Study: 10/sex/dose; Neurobehavioral and Reproductive Study: 20/sex/group; Toxicokinetic Study: 6/sex/group;
Age:	At dosing initiation: PND21
Weight:	M: 54.4 g; F: 53.0 g.
Satellite groups:	Recovery and TK.
Unique study design:	Only two dosing groups.
Deviation from study protocol:	There were minor deviations, with no impact on study validity.

Observations and Results

Mortality

Observations were made twice daily.

There were no drug-related deaths.

Clinical Signs

Observations were made once daily on Main, Recovery, and Neurobehavioral and Reproductive study animals, with detailed observations on PND 52 and PND 118 on Main and Neurobehavioral and Reproductive study animals.

There were no drug-related findings.

Body Weights (Main, Recovery, and Neurobehavioral and Reproductive study animals)

Measured weekly during preweaning, daily during dosing, GDs 0, 3, 7, 8, 10, and 13 during reproduction, and weekly during the recovery periods.

There were no drug-related findings.

Food Consumption (Main, Recovery, and Neurobehavioral and Reproductive study animals)

Food consumption was recorded once weekly post weaning and on GDs 0, 3, 7, 8, 10, and 13.

There were no drug-related findings.

Sexual Maturation (Neurobehavioral and Reproductive study animals)

Evaluations were made from PND 28 in females or PND 39 in males and continued until vaginal opening or preputial separation.

There were no drug-related findings.

Neurobehavior (Main, and Neurobehavioral and Reproductive study animals)

Motor Activity (Main: PND 54; Neurobehavioral and Reproductive: PND 118), Acoustic Startle Habituation (Main: PND 54; Neurobehavioral and Reproductive: PND 118), and Morris Water Maze (Main: PND 65 to 80; Neurobehavioral and Reproductive: PND 115 to 130) were assessed.

There were no drug-related findings.

Estrous Cycle, Mating, and Fertility. (Neurobehavioral and Reproductive study animals)

Estrous cycle was evaluated for 14 days prior to cohabitation. Cohabitation occurred for 14 days in rats that were at least PND 126.

There were no drug related findings.

Ophthalmoscopy

None

ECG

None

Hematology, Coagulation, and Clinical Chemistry (Main and Recovery Study animals)

Samples were collected prior to scheduled euthanasia.

There were no drug-related findings.

Urinalysis (Main and Recovery Study animals)

Samples were collected prior to sacrifice.

There were no drug-related findings.

Gross Pathology

There were no drug-related findings.

Organ Weights

See histopathology table.

There were no drug-related findings.

Histopathology

Text Table 21
Tissue Collection and Preservation - Cohort A and Cohort B

Tissue	Weighed	Collected	Histology	Microscopic Evaluation	Comment
Animal identification	-	X	-	-	-
Artery, aorta	-	X	X	X	-
Body cavity, nasal	-	X	X	X	Level 4[a] processed to slide for evaluation of olfactory bulb. Nasal structures were not examined.
Bone marrow smear	-	X	-	-	Two bone marrow smears were collected from the femur at scheduled and unscheduled necropsies (for possible examination). Smears were not collected from animals that were euthanized moribund and then stored in the refrigerator prior to necropsy. Bone marrow smears were allowed to air dry and were not fixed in formalin.
Bone marrow	-	X	X	X	-
Bone, femur, left	-	X	X	X	To include the articular surface of the distal end. Retained in neutral buffered 10% formalin.
Bone, femur, right	-	X	-	-	To include the articular surface of the distal end. Retained whole, individually wrapped in saline soaked gauze and plastic wrap and placed in appropriately sized pouches on wet ice until stored in a freezer set to maintain -20°C within 2 hours of collection (scheduled euthanized animals only)[a].
Bone, sternum	-	X	X	X	-
Brain	X	X	X	X	Seven brain levels[a] were examined to include olfactory bulb (Examine in Body cavity, nasal section level 4[b]).
Cervix	-	X	X	X	-
Epididymis	X	X	X	X	Paired examination.
Esophagus	-	X	X	X	-
Eye	-	X	X	X	Collected with harderian gland and optic nerve. Paired examination; Preserved in Davidson's fixative.
Gland, adrenal	X	X	X	X	Paired examination.
Gland, harderian	-	X	X	X	Collected with optic nerve and eye. Only 1 required for microscopic examination.
Gland, mammary	-	X	X	X	Male and female.
Gland, parathyroid	X	X	X	X	Examined only if present in the routine section of thyroid.

Tissue	Weighed	Collected	Histology	Microscopic Evaluation	Comment
Gland, pituitary	X	X	X	X	-
Gland, prostate	X	X	X	X	-
Gland, salivary	-	X	X	X	Only 1 required for microscopic examination.
Gland, seminal vesicle	-	X	X	X	Paired examination.
Gland, thyroid	X	X	X	X	Paired fixed weight and examination; weight includes parathyroid.
Gross lesions/masses	-	X	X	X	-
Gut-associated lymphoid tissue	-	X	X	X	Examined only if present in routine section of intestine.
Heart	X	X	X	X	-
Kidney	X	X	X	X	Paired examination.
Large intestine, cecum	-	X	X	X	-
Large intestine, colon	-	X	X	X	-
Large intestine, rectum	-	X	X	X	-
Larynx	-	X	-	-	-
Liver	X	X	X	X	-
Lung	X	X	X	X	-
Lymph node, mandibular	-	X	X	X	Only 1 required for examination.
Lymph node, mesenteric	-	X	X	X	-
Lymph node, axillary	-	X	X	X	-
Muscle, skeletal	-	X	X	X	-
Nerve, optic	-	X	X	X	Examined only if present in the routine section of the eye. Preserved in Davidson's fixative.
Nerve, sciatic	-	X	X	X	Only 1 required for microscopic examination.
Ovary	X	X	X	X	Paired examination.
Pancreas	-	X	X	X	-
Site, Administration	-	X	X	X	All sites.
Skin	-	X	X	X	Inguinal skin.
Small intestine, duodenum	-	X	X	X	-
Small intestine, ileum	-	X	X	X	-
Small intestine, jejunum	-	X	X	X	-
Spinal cord	-	X	X	X	Examined one transverse and one longitudinal section from each of the following areas cranial cervical, mid-thoracic, lumbar (intumescence).
Spleen	X	X	X	X	-

Tissue	Weighed	Collected	Histology	Microscopic Evaluation	Comment
Stomach	-	X	X	X	-
Testis	X	X	X	X	Paired examination; preserve in Modified Davidson's fixative per Testing Facility SOP.
Thymus	X	X	X	X	-
Tongue	-	X	X	X	-
Trachea	-	X	X	X	-
Urinary bladder	-	X	X	X	-
Uterus	X	X	X	X	-
Vagina	-	X	X	X	-

X = Procedure conducted; - = Not applicable.

[a] Bolon, B., Garman, R. H., Pardo, I. D, Jensen, K., Sills, R., Roulois, A., Radovsky, A. E., Bradley, A., Andrews-Jones, L., Butt, M., Guimprecht, L. STP Position Paper: Recommended practices for sampling and processing the nervous system (brain, spinal cord, nerve and eye) during nonclinical general toxicity studies. Toxicol Pathol. 41, 2013. 1028-1048.

[b] Young, J. Histopathologic Examination of the Rat Nasal Cavity, Fundamental and Applied Toxicology, 1:309-312 (July/August 1981).

[c] For exceptions see Appendix A – Protocol, Amended Protocol, and Study Deviation Log.

Sponsor's table

Adequate Battery: Yes

Signed pathology report: Yes

Peer Review: Yes

Histological Findings
There were drug related findings at the injection sites of the LD and HD groups in both sexes that persisted through the recovery period.

Text Table 30
Incidence and Severity of LY2951742-related Histopathological Changes in Cohort A and Cohort B

Tissue/Finding	Sex	Male			Female		
	Dose (mg/kg)	0	30	250	0	30	250
Dose Period							
Number of Animals Examined		9	10	10	8	9	10
Administration Site 1-4[a] Infiltration, mononuclear cell	Number examined	36	40	40	32	36	40
	Total Number affected	1	18	25	1	11	17
	Minimal	1	14	25	1	11	15
	Mild	0	4	0	0	0	2
Recovery Period							
Number of Animals Examined		10	10	10	10	10	10
Administration Site 1-4[a] Infiltration, mononuclear cell	Number examined	40	39[b]	40	40	40	40
	Total Number affected	0	2	2	0	4	14
	Minimal	0	2	2	0	4	13
	Mild	0	0	0	0	0	1

[a] Findings for administration sites 1-4 were added together. On slides, administration sites were labeled as A, B, C, D.

[b] Administration site 2 was not examined (tissue lost during processing) in male 3977 at 30 mg/kg in Cohort B (Recovery Study).

Sponsor's figure

Bone densitometry
At 250 mg/kg, there were minimal decreases in distal femur metaphysis bone mass (decreased total and trabecular BMC) and density (decreased trabecular BMD) in both

sexes. These findings were not present in either sex at the end of the 46-day recovery period.

Male reproductive and sperm motility, concentration, and morphology assessments.

There were no drug-related findings.

Ovarian and Uterine Examinations
Examinations consisted of the following: number and distribution of corpora lutea, implantation sites, placentae (size, color or shape) and live and dead embryos.

There were no drug-related findings.

Special Evaluation

None

Toxicokinetics

Blood samples were collected on PND 21 or 90.

Exposure was similar between sexes. C_{max} and AUC values increased slightly greater than dose proportionally on PND 21 and less than dose proportionally on PND 90. After repeat dosing at the LD and HD, AUC_{0-72} values increased 9.4 and 2.5-fold, respectively.

Text Table 31
Summary of LY2951742 Toxicokinetic Parameters

Parameter[a]	Administered LY2951742 Dose (mg/kg)			
	30		250	
Sex	Male	Female	Male	Female
LY2951742				
PND 21				
T_{max} (hr)	24	72	72	24
C_{max} (µg/mL)	136 ± 7.97	129 ± 2.84	1250 ± 140	1470 ± 83.4
AUC_{0-72} (µg*hr/mL)	8030	7960	71400	81500
AUC_{0-168} (µg*hr/mL)	17500 ± 617	17400 ± 754	165000 ± 10600	172000 ± 8860
PND 90				
T_{max} (hr)	72	24	8	0
C_{max} (µg/mL)	692 ± 46.0	1430 ± 706	2360 ± 139	3320 ± 255
AUC_{0-72} (µg*hr/mL)	43400	74800	141000	205000
AUC_{0-168} (µg*hr/mL)	102000 ± 5380	141000 ± 22900	289000 ± 12000	412000 ± 19200

[a] Results are composite (n = 3/time point).
T_{max} Time of maximum observed concentration.
C_{max} Maximum observed concentration.
AUC_{0-72} Area Under the Curve from time zero to 72 hours.
AUC_{0-168} Area Under the Curve from time zero to 168 hours.

Sponsor's table

Dosing Solution Analysis: All samples collected on the first and last day of formulation preparation had mean concentrations within ±10% of nominal.

Study title: Tissue Cross-Reactivity of LY2951742 with Human, Cynomolgus Monkey, and Rat Tissues *Ex Vivo*

Study no.:	20000687
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	July 19, 2011
GLP compliance:	No
QA statement:	No
Drug, lot #, and concentration:	LY2951742; lot # 18646-71-API; concentration: 56.9 mg/mL

Objective: to determine the binding of LY2951742 in human, cynomolgus monkey, and rat tissues.

The following tissues were tested:

Rat Tissue from Three Healthy Separate Animals

- Adrenal
- Bladder
- Blood[1]
- Bone Marrow
- Breast (with skin)
- Cerebellum
- Cerebral Cortex
- Colon
- Endothelium (aorta)
- Eye
- Fallopian Tube
- Gastrointestinal Tract[2]
- Heart
- Kidney (glomerulus)[3]
- Kidney (tubule)[3]
- Liver
- Lung
- Lymph Node
- Ovary
- Pancreas
- Parathyroid (with thyroid)
- Parotid Gland (salivary gland)
- Pituitary
- Prostate
- Skin (with breast)
- Spinal Cord
- Spleen
- Striated Muscle
- Testis
- Thymus
- Thyroid (with parathyroid)
- Uterus (cervix)
- Uterus (endometrium)

[1] Blood samples were evaluated by examination of a blood smear.
[2] Gastrointestinal tract was evaluated in a sample of small intestine.
[3] Kidney (glomerulus) and kidney (tubule) were both evaluated in the same tissue sample.

Human Tissue (Normal) from Three Healthy Separate Individuals

- Adrenal
- Bladder
- Blood[1]
- Bone Marrow
- Breast
- Cerebellum
- Cerebral Cortex
- Colon
- Endothelium (aorta)
- Eye
- Fallopian Tube
- Gastrointestinal Tract[2]
- Heart
- Kidney (glomerulus)[3]
- Kidney (tubule)[3]
- Liver
- Lung
- Lymph Node
- Ovary
- Pancreas
- Parathyroid
- Parotid Gland (salivary gland)
- Peripheral Nerve
- Pituitary
- Placenta
- Prostate
- Skin
- Spinal Cord
- Stomach
- Spleen
- Striated Muscle
- Testis
- Thymus
- Thyroid
- Tonsil
- Ureter
- Uterus (cervix)
- Uterus (endometrium)

[1] Blood samples were evaluated by examination of a blood smear.
[2] Gastrointestinal tract was evaluated in a sample of small intestine.
[3] Kidney (glomerulus) and kidney (tubule) were both evaluated in the same tissue sample.

The study was terminated prior to start of definitive experiments. No samples of the above tissues were evaluated.

Cynomolgus Monkey Tissue from Three Healthy Separate Animals

- Adrenal
- Bladder
- Blood[1]
- Bone Marrow
- Breast
- Cerebellum
- Cerebral Cortex
- Colon
- Endothelium (aorta)
- Eye
- Fallopian Tube
- Gastrointestinal Tract[2]
- Heart
- Kidney (glomerulus)[3]
- Kidney (tubule)[3]
- Liver
- Lung
- Lymph Node
- Ovary
- Pancreas
- Parathyroid
- Parotid Gland (salivary gland)
- Peripheral Nerve
- Pituitary
- Placenta
- Prostate
- Skin
- Spinal Cord
- Spleen
- Stomach
- Striated Muscle
- Testis
- Thymus
- Thyroid
- Tonsil
- Ureter
- Uterus (cervix)
- Uterus (endometrium)

[1] Blood samples were evaluated by examination of a blood smear.
[2] Gastrointestinal tract was evaluated in a sample of small intestine.
[3] Kidney (glomerulus) and kidney (tubule) were both evaluated in the same tissue sample.

The study was terminated prior to start of definitive experiments. No samples of the above tissues were evaluated.

Positive and Negative Control Tissues

- Human spinal cord tissue:
  - Positive control: human spinal cord (specifically the gray matter) or human dorsal root ganglia (DRG)
  - Negative control: human spinal cord (specifically the white matter)

Sponsor's tables

Results: LY2951742 positively stained select human, monkey, and rat tissues that were consistent with the association of CGRP with neurons and innervated tissues; however, specific binding was also observed in tissues not expected to express CGRP (i.e., tubular epithelium of the kidney). The observed staining in the gray matter of the spinal cord did not concentrate in the in the dorsal horn where high CGRP expression is expected.

11 Integrated Summary and Safety Evaluation

Pharmacology. Galcanezumab is a human monoclonal antibody that binds CGRP and inhibits its binding to the CGRP receptor. Both CGRP and its receptor are present in peripheral and central nervous system tissues. During a migraine episode, CGRP levels increase, which induces vasodilation and nociceptive signaling though the CGRP receptor in the trigeminal nervous system. It is hypothesized that inhibiting CGRP receptor binding will prevent migraine pain. The sponsor is proposing a monthly dosing regimen for migraine prophylaxis.

Galcanezumab has pM affinity for human, monkey, rat, and rabbit alpha and beta CGRP, without off target binding to human Fcγ receptors, complement component C1q, CGRP receptor, or nonCGRP calcitonin family members. In functional assays (in SK-N-MC cells), galcanezumab inhibited human and rabbit CGRP induction of cAMP, with IC_{50s} in the low nM range (≤0.9 nM), but did not inhibit amylin induction of cAMP, another peptide in the calcitonin family.

In a short-term pharmacodynamics study in rat, administration of a single 4 mg/kg SC dose of galcanezumab reduced capsaicin-induced increases in dermal blood flow by ~81% after 5 days. In a pharmacodynamics study in monkey, a single 5 mg/kg IV dose of galcanezumab inhibited capsaicin-induced increases in forearm dermal blood flow by 87, 71, and 63% on Days 1, 15, and 29, respectively.

Pharmacokinetics. In a pharmacokinetic study in monkey, the $t_{1/2}$ of galcanezumab was 184 h following a single 2 mg/kg IV dose. Tissue distribution of galcanezumab was assessed in rat following a single 4 mg/kg SC dose. There was no statistically significant difference between the distribution of galcanezumab compared to control (IgG4). In peripheral tissues (dura mater, spleen, and trigeminal ganglia), drug concentrations were 5 to 11% of plasma levels, while in CNS tissues (hypothalamus, prefrontal cortex, cerebellum, and spinal cord) drug distribution was <0.4%. Peak plasma concentrations were observed at 3 days and persisted for approximately 7 days.

Toxicology. In 6-week, 3-month, and 6-month general toxicology studies, weekly SC administration of galcanezumab was assessed in rat and monkey.

General toxicology studies			
Duration	**Dosing mg/kg**	**Species**	**# sex/group**
6-week	1.5, 15, 100	Rat	10
	1.5, 15, 100	Monkey	3
3-month	15, 100	Rat	10
	15, 100	Monkey	3
6-month	20, 250	Rat	15
	2, 100	Monkey	4

The most notable finding was 2 unexplained HDM deaths in the 6-month rat study. The most common finding was minimal to moderate drug-related injection site inflammation at doses ≥15 mg/kg in all rat and monkey studies. CV, respiratory, and/or central nervous system assessments in the 6-week and 6-month monkey studies showed no

drug-related findings. The NOAEL in the 6-month rat study was the LD, because a drug-related cause of death could not be ruled out in the 2 HDM. In the 6-month monkey study, the NOAEL was the HD, because the injection site irritation was not considered adverse.

In TK assessments, C_{max} and AUC values were similar between sexes in both the rat and monkey general toxicity studies. In the rat studies, plasma drug levels consistently decreased between the first and last day of dosing at the HD and sporadically decreased at the LD. In the 6-month monkey study, approximately half the monkeys at the LD and 1/8 the monkeys at the HD had undetectable drug levels at the end of the dosing period. The sponsor attributed the decreases in plasma drug levels following repeat dosing to ADA formation (no individual animal ADA data were provided).

The reproductive and development toxicity program consisted of a male fertility study in rat, embryofetal development studies in rat (included female fertility assessment) and rabbit, a pre- and postnatal development study in rat, and a juvenile animal study in rat. In the male fertility study, rats (25/group) were given SC doses of 0, 30, 250 mg/kg weekly. There were no drug-related effects on fertility or other toxicities observed; therefore, the NOAEL was the HD. At the HD, C_{max} and $AUC_{0\text{-}168h}$ values decreased 2-fold after repeat dosing (Day 0 and 35), which the sponsor attributed to ADA; no data were provided.

In two female fertility and embryofetal development studies, rats (26/group) were administered SC doses of up to 100 or 250 mg/kg once and every 3 days, respectively. There were no drug-related findings; therefore, the NOAEL was the HD for both dosing regimens. In the rabbit embryofetal development study, SC doses of up to 100 mg/kg (25/group) were administered every 4 to 5 days. There were no drug-related findings; therefore, the NOAEL was the HD. Repeat dosing in both rat and rabbit did not result in drug accumulation.

In the pre- and postnatal development study, rats (26/dose) were administered SC doses of 0, 30, and 250 mg/kg every 3 days. One HDF was found dead on Lactation Day 15, after the 11^{th} dose. No cause of death was identified. The NOAEL was the LD for the F0 based on the unexplained animal death. ADA was suspected in 2 LD and 2 HD animals due to lower drug concentrations after repeat dosing; no data were provided. There were no drug-related findings in the F1 generation; therefore, the NOAEL was the HD.

In the juvenile animal toxicity study, rats (20/sex/group) were administered SC doses of 0, 30, and 250 mg/kg, every 3 days from postnatal day 21 through 90. There were drug-related findings, consisting of minimal to mild injection site inflammation and minimal decreases in distal femur metaphysis bone mass and density. The injection site inflammation persisted through recovery; however, the decreases in bone mass and density reversed during the recovery period. These findings were not considered adverse; therefore, the NOAEL was the HD.

Carcinogenicity studies were not required based on the potential for galcanezumab to counter CGRP associated angiogenesis and immunosuppression, specificity of galcanezumab for CGRP, lack of structural alerts on galcanezumab, and submitted toxicity and clinical studies which indicated that galcanezumab has a low potential carcinogenicity.

Other Studies. In a tissue cross-reactivity study, galcanezumab positively stained select human, monkey, and rat tissues that were consistent with the association of CGRP with neurons and innervated tissues; however, specific binding was also observed in tissues not expected to express CGRP (i.e., tubular epithelium of the kidney). The observed staining in the gray matter of the spinal cord did not concentrate in the in the dorsal horn where high CGRP expression is expected.

Because CGRP is thought to cause vasodilation, there is the potential that CGRP blockage could potentiate ischemic events. At the pre-BLA meeting, the sponsor was asked to provide published literature and/or data to support their assessment of the CV safety of galcanezumab. However, based on the results of an independent review of published literature (primarily of a CGRP probe) conducted by the Agency, the decision was made that further investigation regarding this concern would not be warranted at this time.

Summary. Galcanezumab was shown to have high affinity for CGRP, relative to other family members, and effectively antagonizes CGRP activity. In short (5 day) and longer (up to 1 month) duration pharmacodynamics studies, a single dose ≥ 4 mg/kg of galcanezumab administered to rat or monkey by SC or IV, respectively, inhibited capsaicin-induced dermal blood flow increases. In the toxicity studies, the most notable findings were three unexplained HD deaths, two males in the 6-month general toxicology study in rats and one dam in the pre- and postnatal development study. The most common finding was injection site inflammation in both rats and monkeys, which was not considered adverse. The nonclinical BLA package supports approval of galcanezumab.

Safety Margins								
Study	**Species**	**Doses tested mg/kg**	**NOAEL Dose mg/kg**	**C_{max} µg/mL**	**Margin**	**$AUC_{1\text{-}168\ h}$ µg*h/mL**	**Margin**	**Adverse finding**
General Toxicology	Rat	0, 20, 250	20	213	7x	29900	1x	Unexplained death in 2 HD males
	Monkey	0, 2, 100	100	4490	143x	579500	21x	-
Embryo fetal development	Rat	0, 250	250	995	32x	61100	2x	-
	Rabbit	0, 30, 100	100	1660	35x	10200	<1	-
Pre- and postnatal development	Rat (F1)	0, 30, 250	250	1320	42x	128000	5x	-
Juvenile Toxicity	Rat	0, 30, 250	250	2840	90x	354500	13x	-
After a 240 mg SC dose in human C_{max}= 31.5 µg/mL; $AUC_{0\text{-}t\ last,\ 0\text{-}141\ h}$= 27360 µg*h/mL								

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/s/

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09/27/2018

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