CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY BLA REVIEW AND EVALUATION

Application number:	125521
Supporting document/s:	SDN 1
Applicant's letter date:	3/23/2015
CDER stamp date:	3/23/2015
Product:	TALTZ™, single-dose prefilled autoinjector (80 mg/mL)
Indication:	moderate-to-severe plaque psoriasis
Applicant:	Eli Lilly
Review Division:	DDDP
Reviewer:	Jill C Merrill, PhD
Supervisor/Team Leader:	Barbara Hill, PhD
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Template Version: September 1, 2010

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1 Executive Summary

1.1 Introduction

TALTZ™ (ixekizumab) is a humanized immunoglobulin G subclass 4 (IgG4) monoclonal antibody (MAb) that neutralizes the cytokine interleukin 17A (IL-17A, also known as IL-17). LY2439821 was developed by humanization and optimization of mouse anti-human IL-17 antibody. It has high affinity (b) (4) for and neutralizes the activity of both human and monkey IL-17. It has high specificity to IL-17A and no cross reactivity to other IL-17 family members (IL-17B through IL-17F).

TALTZ™ binds to IL-17A, inhibiting its interaction with the IL-17 receptor. Preventing the cytokine/receptor interaction neutralizes the bioactivity of IL-17A and inhibits the subsequent release of proinflammatory cytokines, chemokines and mediators of tissue damage.

IL-17 is a proinflammatory cytokine produced primarily by a subset of CD4+ T cells, called Th17 cells, which represent a third subset of CD4+ "helper" lymphocytes, besides the classically described CD4+ Th1 and Th2 populations. IL-17 has been shown to be important for host defense against a variety of microbial infections in both clinical and nonclinical models. Aberrant Th17 responses and IL-17 production have been implicated in a variety of autoimmune diseases, including rheumatoid arthritis (RA) and psoriasis.

The sponsor believes IL-17 inhibition could be efficacious in psoriasis, but recognizes that neutralizing IL-17 may increase the risk of infections. The sponsor is developing ixekizumab for the treatment of (b) (4) psoriasis (IND 100834, DDDP) (b) (4) (b) (4).

1.2 Brief Discussion of Nonclinical Findings

Ixekizumab crossreacts with cynomolgus monkey IL-17A, but not with the rodent IL-17A, making the cynomolgus monkey the most appropriate nonclinical species. Repeat-dose toxicity, fertility, embryofetal development and peri- and postnatal development studies have been conducted with the cynomolgus monkey.

In a 9-month toxicity study in cynomolgus monkeys subcutaneous injections of ixekizumab (0, 0.5, 5, 50 mg/kg/week) caused no adverse compound-related clinical signs at ≤5 mg/kg/week. A dose of 50 mg/kg/week exceeded the maximum-tolerated dose for one animal due to injection site reactions resulting in suspension of dosing, but was otherwise well tolerated. One male given 5 mg/kg/week was found dead 6 days after the 20th weekly injection (Day 140). Although the cause of death could not be determined, it was not considered compound-related. Ixekizumab administration did not produce any remarkable changes in the peripheral blood immunophenotyping (total T cells, helper T cells, cytotoxic T cells, total B cells, natural killer cells, and helper-to-

cytotoxic T cell ratio) or natural killer cell assay data. Based on the injection site reactions requiring dose suspension, the NOAEL for this 9-month study was 5 mg/kg/week.

Fertility, embryofetal development and peri- and postnatal development studies have been conducted with ixekizumab in cynomlgus monkeys treated by subcutaneous injection with up to 50 mg/kg/week. No treatment-related effects were observed during these studies. Neonatal deaths occurred in the infants of two monkeys administered ixekizumab at 5 mg/kg/week and two monkeys administered ixekizumab at 50 mg/kg/week. The cause and/or clinical significance of these findings is unknown.

1.3 Recommendations

1.3.1 Approvability

BLA 125521 is approvable from a pharmacology/toxicology perspective.

1.3.2 Additional Non Clinical Recommendations

None.

1.3.3 Labeling

Revisions to the sponsor's proposed wording for the nonclinical and related sections of the label are provided below. With the exception of the Section 8 subheading "Risk Summary" which the sponsored underlined per PLLR specifications, it is recommended that the underlined wording be inserted into and the ~~strikeout~~ wording be deleted from the TALTZ™ label text. Additionally although the PLLR-specified subheading "Animal Data" had been added by the sponsor, it was incorrectly underlined and not italicized per PLLR formatting requirements. Recommended revisions for the nonclinical information contained in Section 8 of the label are made below. Refer to the clinical review for recommended revisions for the clinical information contained in Section 8 of the label. A clean copy of these revised labeling sections is provided in the Appendix as Attachment # 1.

HIGHLIGHTS OF PRESCRIBING INFORMATION
INDICATIONS AND USAGE
TALTZ™ is a (b)(4) humanized interleukin-17A antagonist indicated for the treatment of adults (b)(4) with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. (1)

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Risk Summary

There are no [redacted] available data on TALTZ use in pregnant women to [redacted] inform any drug associated risks. [redacted] Human IgG is known to cross the placental barrier; therefore, TALTZ may be transmitted from the mother to the developing fetus. An embryofetal [redacted] developmental study [redacted] conducted [redacted] in pregnant monkeys [redacted] at doses [redacted] up to 19 times the maximum recommended human dose (MRHD) revealed no evidence of harm to the fetus [redacted]

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

An embryofetal development study was conducted in cynomolgus monkeys administered [redacted] ixekizumab. [redacted] No malformations or embryofetal toxicity were observed in fetuses from pregnant monkeys administered ixekizumab weekly by subcutaneous injection [redacted] during organogenesis [redacted] at doses up to [redacted] 19 times the [redacted] MRHD (on a mg/kg basis [redacted] of 50 mg/kg/week). Ixekizumab crossed the placenta in monkeys.

In a pre- and post-natal development toxicity study, pregnant cynomolgus monkeys were administered weekly subcutaneous doses of ixekizumab up to 19 times the MRHD from the beginning of organogenesis to parturition. Neonatal deaths occurred in the [redacted] of two monkeys administered ixekizumab at 1.9 times the MRHD (on a mg/kg basis of 5 mg/kg/week) and two monkeys administered ixekizumab at 19 times the MRHD (on a mg/kg basis of 50 mg/kg/week). The [redacted] clinical significance of these findings are unknown. [redacted] No ixekizumab-related effects on [redacted] functional or immunological development [redacted] were observed in the infants from birth through ~~6~~ six months of age [redacted]

8.2 Lactation

Risk Summary

(b) (4) There are no data on the presence of ixekizumab in human milk (b) (4) the effects on the breastfed infant, or the effects on milk production. (b) (4) (b) (4) Ixekizumab was detected in the milk of lactating cynomolgus monkeys. (b) (4) (b) (4) The developmental and health (b) (4) benefits of breastfeeding should be considered along with the mother's clinical need for TALTZ and any potential adverse effects on the breastfed (b) (4) infant from TALTZ or from the underlying maternal condition.

CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ixekizumab is a (b) (4) humanized IgG4 monoclonal antibody that selectively binds ~~with~~ (b) (4) (b) (4) the interleukin 17A (IL-17A) (b) (4) cytokine and inhibits its interaction with the IL-17 receptor. IL-17A is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. (b) (4) Ixekizumab inhibits the release of proinflammatory cytokines and chemokines. (b) (4) (b) (4)

NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies have not been conducted to evaluate the carcinogenic or mutagenic potential of TALTZ. Some published literature suggests that IL-17A directly promotes cancer cell invasion (b) (4) whereas other reports indicate IL-17A promotes T-cell mediated (b) (4) tumor rejection. Depletion of IL-17A with a neutralizing antibody inhibited tumor development in mice. The relevance of experimental findings in mouse models for malignancy risk in humans is unknown.

No effects on fertility parameters such as reproductive organs, menstrual cycle length, or sperm were observed in sexually mature cynomolgus monkeys that were administered ixekizumab for 13 weeks at a subcutaneous dose of 50 mg/kg/week (b) (4) ((b) (4) (b) (4) 19 times the MRHD (b) (4) on a mg/kg basis). The monkeys were not mated to evaluate fertility (b) (4).

2 Drug Information

2.1 Drug

Generic Name: humanized monoclonal IgG4 antibody against IL-17A

Code Name: LY243981 (formerly known as LA426-3C3)

USP/USAN: ixekizumab

Molecular Formula: $C_{6492}H_{10038}N_{1726}O_{2028}S_{46}$ (b) (4)

Molecular Weight: 146,158 Da

Biochemical Description: LY2439821 is a humanized MAb. The heavy chain is the human IgG4 isotype (b) (4). The light chain (b) (4) (b) (4)

(b) (4)

Pharmacologic Class: humanized interleukin 17-A antagonist

2.2 Relevant INDs, BLAs and MFs

IND 100834 (DDDP) psoriasis

(b) (4)

2.3 Drug Formulation

Table 3.2.P.1.1-1 Composition of Ixekizumab Injection, 80 mg/1 mL

Ingredient	Quantity(mg) per Syringe	Function	Reference to Standards
Active Ingredient			
Ixekizumab	80	Active Ingredient	Internal Standard: See Section S.4.1, Specifications
Other Ingredients			
Sodium Citrate Dihydrate	5.11	(b) (4)	USP, Ph.Eur., JP
Citric Acid Anhydrous	0.51		USP, Ph.Eur., JP
Sodium Chloride	11.69		USP, Ph.Eur., JP
Polysorbate 80	0.30		USP, Ph.Eur., JP
Water for Injection	(b) (4)		USP, Ph.Eur., JP

Ixekizumab is supplied as a solution ready for administration via subcutaneous injection (80 mg/mL) in a 1 mL prefilled glass syringe.

2.4 Comments on Novel Excipients

None.

2.5 Comments on Impurities/Degradants of Concern

None.

2.6 Proposed Clinical Population and Dosing Regimen

TALTZ is a human interleukin-17A antagonist indicated for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. TALTZ is administered as 160 mg by subcutaneous injection (two 80 mg injections) at week 0, followed by an 80 mg injection at Weeks 2, 4, 6, 8, 10, and 12, then 80 mg every 4 weeks.

2.7 Regulatory Background

- 11/02/2007 IND received
- 06/22/2011 Guidance meeting
- 11/07/2012 Guidance meeting
- 10/29/2014 preBLA meeting

3 Studies Submitted

3.1 Studies Reviewed

Pharmacology

Neutralization of human IL-17 by LY2439821: In vitro study using the human cell line Hs27 (Report bTDR07).

Neutralization of human IL-17 by LY2439821: In vivo study using C57BL/6NHsd mice (Report bTDR08).

Specificity measurement of LY2439821 to human IL-17A, IL-17B, IL-17C, IL-17D, IL-17E and IL-17F: In vitro study using recombinant proteins (Report bTDR09)

In vitro binding kinetics of LY2439821: Surface plasmon resonance analysis (Report bTDR10)

In vivo efficacy of a surrogate anti-mouse IL-17 monoclonal antibody in mouse collagen-induced arthritis (CIA; Report bTDR11).

In vivo efficacy of a surrogate anti-mouse IL-17 antibody: Activity in a mouse model of experimental autoimmune encephalomyelitis (EAE; Report bTDR12)

Neutralization of human and cynomolgus monkey IL-17 by LY2439821: In vitro study using the human cell line HT-29 (Report bTDR13)

The effect of anti-murine IL-17 on in vivo T cell-dependent an T-cell-independent antibody responses in mice (Report bTDR57)

LY2439821 blocks IL-17 binding to IL-17 receptor: Surface plasmon resonance analysis (Report BTDR68)

In vitro binding kinetics of the surrogate antibodies for murine IL-17: Surface Plasmon resonance analysis (Report bTDR69)

Neutralization of murine IL-17 by the surrogate antibodies: In vitro study using NIH/3T3 fibroblasts (Report bTDR70)

Neutralization of mouse or rat IL-17 by the monoclonal antibodies LSN2805474 and LSN2886817: In vitro study using 4TI cells (LY2439821; Report bTDR79)

In vitro evaluation of IL-17-secreting cells in peripheral blood from psoriasis patients (LY2439821; Report bTDR80)

In vitro binding kinetics of the surrogate antibodies for rat and human IL-17: Surface plasmon resonance analysis (bTDR90)

In vitro epitope mapping for LY2439821 (Report bTDR113)

In vitro epitope mapping for the surrogate antibodies (LSN2805474 and LSN2886817) for mouse IL-17 (Report bTDR114).

Neutralization of human IL-17A/F heterodimer by LY2439821: In vitro study using the human cell line HT-29 (Report bTDR130)

In vitro binding kinetics of LY2439821 for human IL-17A/F heterodimer: Surface Plasmon resonance analysis (Report bTDR131)

In vitro analysis of human Fc receptor and complement binding of the interleukin-17A antibody (LY2439821) (bTDR171)

Pharmacokinetics

Pharmacokinetics of LA426-3C3 in cynomolgus monkeys following a single intravenous or subcutaneous dose of 1 mg/kg LA426-3C3 for 4 weeks (Study 6180-791)

Repeat Dose Toxicology

A repeat-dose toxicity, toxicokinetic, and immunotoxicology study in cynomolgus monkeys given LY2439821 by subcutaneous injection once weekly for 9 months with a 4-month recovery (Covance 7608-478)

Reproductive Toxicology

A repeat-dose fertility study in cynomolgus monkeys given LY2439821 by subcutaneous injection once weekly for 3 months (20003965)

An assessment of LY2439821 on pre- and postnatal development when administered by subcutaneous injection once weekly to pregnant cynomolgus monkeys (20018253)

Other
Cross-reactivity of LY2439821 with human and cynomolgus monkey tissues ex vivo (KTA00027)

The hemolytic potential and compatibility of LY2439821 in human and monkey blood and sera (N00024)

3.2 Studies Not Reviewed

The nonclinical studies listed in this section have been previously reviewed under IND 100834. A summary of the pivotal information from these nonclinical studies is provided in this document in the corresponding sections.

A repeat-dose toxicity and toxicokinetic study in cynomolgus monkeys given LY2439821 once weekly by intravenous injection for 8 weeks with a 6-week recovery (6180-918)

An assessment of the effects of LY2439821 on embryo-fetal development when administered weekly by subcutaneous injection to pregnant cynomolgus monkeys from gestation day 20 through 139 (SNBL.010.15)

3.3 Previous Reviews Referenced

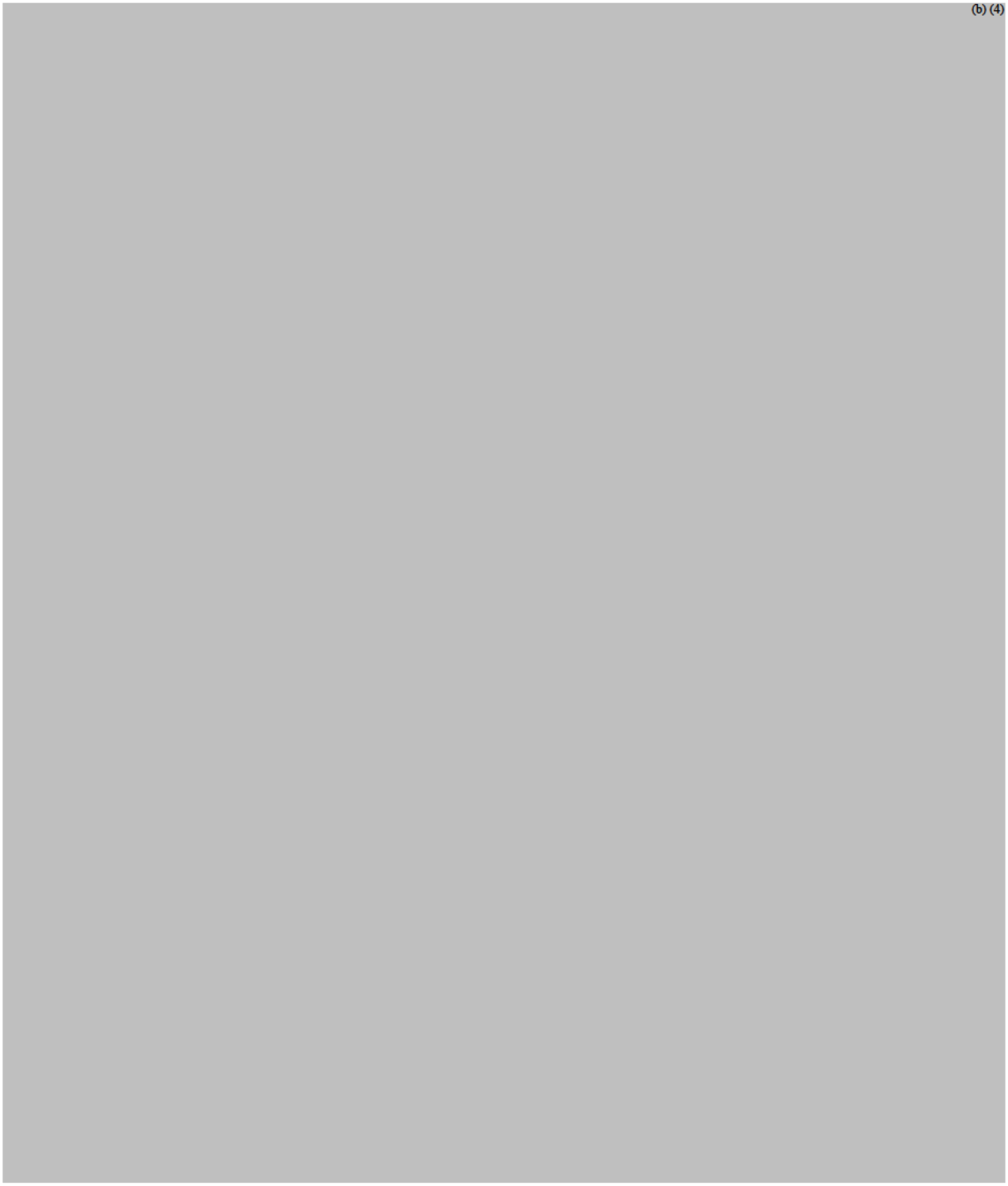
IND 100834 Pharmacology/Toxicology reviews

4 Pharmacology

4.1 Primary Pharmacology

Ixekizumab is a humanized IgG4 monoclonal antibody that binds to human and monkey IL-17A. Ixekizumab does not bind to mouse or rat IL-17A. In psoriasis, the IL-17A ligand plays a major role in driving excess keratinocyte proliferation and activation. The sponsor proposes that neutralization of IL-17A by ixekizumab will inhibit these actions and be useful in the treatment of psoriasis.

Epitope mapping studies (Report bTDR113) were performed to determine the specific amino acids in human IL-17A that are required for ixekizumab binding. Using (b) (4) mass spectrometry the predominant epitope for ixekizumab was determined to be amino acids (b) (4), with additional amino acids (b) (4) potentially contributing to the antibody binding site. Alignment of the amino acid sequences for human, cynomolgus monkey, mouse, and rat IL-17A confirms many amino acid differences in these regions in the two rodent species compared to human and cynomolgus monkey. While there are significant differences between human and mouse IL-17A in these regions, there are minor differences between rat and mouse (Figure 1, taken directly from sponsor's submission). The sequence differences observed between human and rodent IL-17A in the region identified as the binding epitope for ixekizumab explains the species specificity of the antibody.



LSN2805474 and LSN2886817 are rat antibodies that specifically bind mouse IL-17A and neutralize its biological activity. Epitope mapping studies were performed to determine the amino acids in mouse IL-17A that were required for binding of these antibodies (Report bTDR114). A single amino acid was identified as essential for the binding of LSN2805474 to mouse IL-17A since LSN2805474 was unable to neutralize

mouse IL-17A when this amino acid was altered. LSN2886817 has a similar but distinct epitope on mouse IL-17A because alteration of this same amino acid decreased the ability of LSN2886817 to neutralize mouse IL-17A.

4.2 Secondary Pharmacology

Psoriasis has long been considered primarily a disorder of Th1 cells, but there appears to be a strong link with the newly described type 17 helper T (Th17) cells. Th17 cells secrete proinflammatory cytokines, including IL-17A, a member of the proinflammatory interleukin-17 cytokine family. The sponsor performed a study to measure the number of IL-17-secreting cells and the production of IL-17, IL-17F and IL-22 from peripheral blood cells from psoriasis patients (Report bTDR80). The data showed that psoriasis patients tended to have a significant increase in the number of IL-17-secreting cells and cells from these patients produced more IL-17, IL-17F and IL-22 compared with cells from healthy donors. Thus neutralization of IL-17 may be an effective treatment for psoriasis.

Murine IL-17 antibodies are able to neutralize murine IL-17-induced IL-6 secretion from NIH/3T3 cells (murine embryonic fibroblast cell line established from NIH Swiss mouse embryos; Report bTDR70), suggesting that these antibodies are potential candidates for in vivo neutralization of mouse IL-17.

IL-17 (also known as IL-17A) can stimulate fibroblasts and epithelial cells to secrete IL-8. Ixekizumab neutralized IL-17-induced IL-8 secretion from the human foreskin fibroblast cell line Hs27 (Report bTDR07).

Although the IL-17 family of cytokines share 20% to 50% amino acid homology to IL-17A, considerable heterogeneity exists in their expression patterns and known functions. Study bTDR09 was designed to determine specificity and/or cross-reactivity of ixekizumab with the recombinant proteins human IL-17A, IL-17B, IL-17C, IL-17D, IL-17E, IL-17F, IL-22 and mouse IL-17 by ELISA. Ixekizumab was able to bind to human IL-17A, but no binding was detected with human IL-17B to F, mouse IL-17 or control cytokine IL-22, suggesting ixekizumab is specific to human IL-17A.

The in vitro binding kinetics and affinity of ixekizumab was determined against purified recombinant human, cynomolgus monkey, rabbit, mouse, and rat IL-17 (Report bTDR10). The results demonstrate that ixekizumab binds human and cynomolgus monkey IL-17 with similar affinities in a concentration dependent manner. Ixekizumab also binds to rabbit IL-17, but the affinity is lower and heterogenous. However, ixekizumab shows no binding to both mouse and rat IL-17.

IL-17 can stimulate epithelial cells to secrete growth-regulated oncogene alpha (GROα). Ixekizumab was able to completely neutralize human and cynomolgus monkey IL-17-induced GROα secretion from the human colorectal adenocarcinoma epithelial cell line HT-29 (Report bTDR13). Human IL-17 is able to bind and stimulate the mouse IL-17

receptor, leading to an elevation of mouse keratinocyte chemoattractant (KC) chemokine (mouse homologue of human GROα) in the plasma of C57BL/6NHsd mice. Ixekizumab administration decreased hIL-17 induced KC secretion in C57BL/6NHsd mice (Report bTDR08).

IL-17 production has been associated with several inflammatory diseases, including multiple sclerosis (MS), rheumatoid arthritis (RA) and inflammatory bowel disease (IBD). The effect of blocking IL-17 on disease severity was evaluated in an animal model for MS (Report bTDR12). The immunization protocol led to the induction of an autoimmune response to myelin, resulting in gradually increasing paralysis. A reduction in disease severity was observed when animals were treated with anti-IL-17 as compared to isotype control groups. Histology of spinal cords from these mice revealed that the inflammatory cell infiltration to the spinal cord was reduced in anti-IL-17 treated groups. High levels of IL-17 have been detected in the synovial fluid of patients with RA. Treatment with a monoclonal antibody directed against mouse IL-17 was conducted in a collagen induced arthritis (CIA) mouse model and found to reduce clinical signs of arthritis in terms of inflammation and bone destruction (Report bTDR11).

Since IL-17 is a proinflammatory cytokine with effects on many cell types and plays a role in host defense, the sponsor investigated the ability of mice to generate an antibody response after neutralization of IL-17 (Report bTDR57). The data showed that in vivo neutralization of IL-17 did not significantly alter the ability of a mouse to produce a normal T cell-dependent or T cell-independent response. The response was normal in terms of magnitude and isotype profile.

Two surrogate antibodies that cross react with murine IL-17 were used in nonclinical collagen-induced arthritis (CIA) and experimental autoimmune encephalomyelitis (EAE) models. The binding kinetics and affinity of these two surrogate antibodies to murine IL-17 were measured by surface Plasmon resonance (SPR; Report bTDR69). MAB421, a rat anti-mouse IgG2a antibody, binds to murine IL-17 with an on-rate of ~8.25 x 10^5 $M^{-1}s^{-1}$, and off-rate of ~1.52 x 10^{-4} s^{-1} and a K_D of ~185 pM. A rat anti-mouse IgG1 from clone TC11-18H10 binds to murine IL-17 with an on-rate of ~5.3 x 10^6 $M^{-1}s^{-1}$, and off-rate of ~1.7 x 10^{-5} s^{-1} and a K_D of 4.0 pM (Table 1; taken directly from the study report).

Table 1: In Vitro Binding Parameters of Surrogate Antibodies to Murine IL-17 Determined Using Surface Plasmon Resonance

antibodies	k_{on} (1/Ms)	k_{off} (1/s)	K_D (M)
Rat anti-mouse IL-17, Mab421 (IgG2a)	$8.25x10^{5}$	$1.52x10^{-4}$	$1.85\ x10^{-10}$
Rat anti-mouse IL-17[a] (IgG1, TC11-18H10)	$5.3\ (\pm1.5)\ x10^{6}$	$1.7\ (\pm2.1)\ x10^{-5}$	$4.0\ (\pm5.4)\ x10^{-12}$

[a] The value reported are averages ± standard deviations calculated from several independent measurements.

KD is calculated using koff/kon for each measurement, and the final value is average of several independent measurements.

Using SPR, ixekizumab was observed to block human IL-17 binding to the human IL-17 receptor (Report bTDR68).

IL-17A can exist as a homodimer or pair with IL-17F to make an IL-17A/F heterodimer. Ixekizumab is known to have neutralizing activity against human IL-17A; SPR analysis was performed to determine the binding affinity of ixekizumab for human IL-17A and IL-17A/F (Report bTDR131).

The human colorectal adenocarcinoma epithelial cell line HT-29 secretes growth regulated oncogene-alpha (GROα) in response to stimulation with either IL-17A or IL-17A/F, in a dose-dependent manner. Ixekizumab was able to completely neutralize human IL-17A and IL-17A/F-induced GROα secretion from HT29 cells (Report bTDR130). Thus, ixekizumab can neutralize the effects of IL-17A and IL-17A/F in this in vitro model.

The ability of anti-IL-17 monoclonal antibodies to neutralize mouse IL-17 or rat IL-17-induced KC chemokine (CXCL1) secretion from mouse 4T1 cells was tested in vitro (Report bTDR79). Two antibodies, specifically LSN2886817 (rat IgG2a anti-mouse IL-17) and LSN2805474 (rat IgG1 anti-mouse IL-17), are able to completely neutralize mouse IL-17-induced KC secretion from 4T1 cells. With regards to neutralization of rat IL-17, LSN2886817 completely neutralizes rat IL-17-induced KC secretion, whereas LSN2805474 did not neutralize rat IL-17 under the conditions tested.

4.3 Safety Pharmacology

Safety pharmacology evaluations incorporated within the 8-week and 9-month repeat-dose toxicity studies indicated that ixekizumab did not affect cardiovascular, respiratory or central nervous system functions.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

The pharmacokinetics of ixekizumab were evaluated following a single intravenous or subcutaneous administration of 1 mg/kg to male cynomolgus monkeys (2 monkeys /group; Study 6180-791). Plasma samples were collected prior to dosing and at 0.083 (intravenous group only), 0.25, 0.5, 1, 3, 6, 12, 24, 48, 72, 96, 120, 168, 240, 312, 384, 456, 528, 600 and 672 hours postdose. Plasma concentrations of ixekizumab were determined by antigen-capture ELISA using IL-17 as the capture antigen. Plasma concentrations were subsequently used to determine the pharmacokinetic parameters (summarized in the table below, taken directly from the study report). After intravenous dosing, ixekizumab was cleared from the plasma with an average half-life of 156 hours (6.5 days). The total body clearance and volume of distribution were 0.448 mL/h/kg and 87 mL/kg, respectively. After subcutaneous dosing of ixekizumab an average maximal plasma concentration of 11.1 µg/mL was achieved 72 hours postdose.

Parameter	Animal I01897	Animal I01903	Mean	Animal I02281	Animal I02282	Mean
Route	Intravenous			Subcutaneous		
AUC_{last} (h*µg/mL)	2792	1714	2253	3771	2857	3314
t ½ (h)	192	120	156	287	204	246
CL (mL/h/kg)	0.323	0.573	0.448	0.207	0.317	0.262
Vss (mL/kg)	88.7	85.2	87.0	ND	ND	ND
Cmax (µg/mL)	18.2	24.0	21.1	12.4	9.8	11.1
Tmax (h)	ND	ND	ND	96	48	72
%F			ND			147

Abbreviations: AUC_{last}, area under the concentration curve; t ½, half-life; CL, clearance; Vss, volume of distribution; C_{max}, maximum concentration; T_{max}, time to maximum concentration; %F, bioavailability = (mean AUC_{SC}/mean AUC $_{IV}$) x 100; ND, not determined.

5.2 Toxicokinetics

(included in toxicity study)

6 General Toxicology

6.1 Single-Dose Toxicity

No single-dose toxicity studies have been conducted with ixekizumab.

6.2 Repeat-Dose Toxicity

The sponsor has performed a repeat-dose toxicity and toxicokinetic study in cynomolgus monkeys (6180-918, reviewed under IND 100834) given ixekizumab once

weekly by intravenous injection at doses of 0, 5, 15, and 50 mg/kg for 8 weeks with a 6-week recovery period (control and 50 mg/kg/groups only). This study is summarized below.

The 8-week treatment phase (9 weekly doses total) consisted of 3 monkeys/sex/group, with an additional 3 monkeys per sex in the control and 50 mg/kg groups continuing through the recovery phase. There were no important compound-related adverse effects observed for clinical signs, central nervous system (CNS)/behavioral signs, respiratory parameters, body temperature, body weight, feed consumption, ophthalmic changes, electrocardiogram (ECG) parameters, hematology or coagulation parameters, clinical chemistry parameters, urinalysis parameters, organ weights, or histopathologic parameters. No changes in cellular immune parameters, including peripheral blood B cells and T cell subsets occurred at any dose levels. No changes occurred in humoral immunity parameters with regard to immunoglobulin G (IgG) or M (IgM) response to keyhole limpet hemocyanin (KLH). No LY2439821-reactive antibodies (immunogenicity) were detectable; although serum concentrations of LY2439821 may have interfered with the detection of reactive antibodies, there were no changes in toxicokinetic parameters to suggest formation of ixekizumab-reactive antibodies. As such, the highest dose tested, 50 mg/kg, was considered the no observed adverse effect level (NOAEL) for this 8-week treatment study.

Study title: A repeat-dose toxicity, toxicokinetic, and immunotoxicology study in cynomolgus monkeys given LY2439821 by subcutaneous injection once weekly for 9 months with a 4-month recovery

Study no.:	(b) (4) 7608-478
Study report location:	Electronic document
Conducting laboratory and location:	(b) (4)
Date of study initiation:	6-20-07
GLP compliance:	yes
QA statement:	yes
Drug, lot #, and potency:	LY2439821, 14685-057F, 26.4 mg/mL

Key Study Findings

Once weekly subcutaneous injections of ixekizumab for 9 months in cynomolgus monkeys caused no adverse compound-related clinical signs at ≤5 mg/kg/week. A dose of 50 mg/kg/week exceeded the maximum-tolerated dose for one animal due to injection site reactions resulting in suspension of dosing but was otherwise well tolerated. One male given 5 mg/kg was found dead 6 days after the 20th weekly injection (Day 140); the cause of death could not be determined, but it was not considered compound-related. Mean C_{max} and $AUC_{0\text{-}168hr}$ values increased from Day 1 to Day 267 at the 50 mg/kg/dose level, indicating accumulation of ixekizumab following multiple dosing. Increases in mean C_{max} and $AUC_{0\text{-}168hr}$ on Day 1 were generally dose proportional. The NOAEL for this 9-month monkey study was 5 mg/kg/week.

Methods

Doses:	0, 0.5, 5, 50 mg/kg
Frequency of dosing:	weekly
Route of administration:	Subcutaneous in dorsal region. Dose administration was rotated among four injection sites (A, B, C, D).
Dose volume:	2 mL/kg for Groups 1, 2, 3; 1.89 mL/kg for Group 4
Formulation:	Clinical formulation. Vehicle control: 10 mM sodium citrate buffer (pH 6.0 ±0.2); 150 mM NaCl; 0.02% Polysorbate 80, prepared in sterile water for injection, USP
Species/Strain:	*Macaca fascicularis*/cynomolgus monkey
Number/Sex/Group:	4/sex/group
Age:	2-4 years*
Weight:	Males: 2.4 – 4.6 kg; females: 2.3 – 4.1 kg
Satellite groups:	Recovery: 2/sex for control and high dose
Unique study design:	none
Deviation from study protocol:	None significant to integrity of results

Group	No. of Animals		Dose Level	Dose Concentration
	Male	Female	(mg LY2439821/kg)[a]	(mg LY2439821/mL)[a]
1 (Control)[b,c]	6	6	0	0
2 (Low)	4	4	0.5	0.25
3 (Mid)	4	4	5	2.5
4 (High)[c]	6	6	50	26.4

a Animals were dosed once weekly. The dose level refers to the level of each weekly dose. The dose volume was 2 mL/kg for Groups 1, 2, and 3; the dose volume was 1.89 mL/kg for Group 4.
b Animals in Group 1 received the control article only.
c The last two animals/sex/group in the control and high-dose groups were designated as recovery animals and were dosed with test article or control article for 39 doses, after which dosing was discontinued and the animals were observed for reversibility, persistence, or delayed occurrence of toxic effects for at least 16 weeks posttreatment.

**Reviewer's comment: Based on a review article (Morford et al., Birth Defects Research, 2011) these animals would have been considered to be juvenile (up to 36 months) to adolescent (3-5 years) with respect to sexual maturity.*

Observations and Results

Mortality

Observed twice daily. A mid-dose male (I03242) was found dead 6 days after the 20th weekly injection (Day 140). No adverse clinical signs, changes in clinical pathology or immunophenotyping parameters were observed at necropsy. There was no evidence of parasitic infection. All microscopic findings were considered spontaneous and likely not compound-related. No qualitative or quantitative abnormalities were identified on review

of the electrocardiographic examinations predose or 48 hours postdose (Day 85). Cause of death for this animal was not determined. Since no deaths occurred in the higher dose group and no compound-related adverse effects were noted at this dose level or higher that could account for the death, this death was not attributed to the test article.

Clinical Signs

Observed twice daily. Injection site reactions occurred mainly in treated groups, but were relatively sporadic and typically resolved by the next dose (see Text Table 2, taken directly from study report).

Text Table 2
Incidence of Injection Site Observations During the Dosing Phase

	Total Number of Incidences[a] (Number of Animals with Sign Each Day)							
Sex	Males				Females			
mg LY2439821/kg	0	0.5	5[b]	50	0	0.5	5	50[c]
Swollen-Dose Site	0(0)	2(2)	4(2)	2(1)	0(0)	0(0)	3(1)	49(2)
Scab(s)-Dose Site	1(1)	0(0)	0(0)	0(0)	1(1)	0(0)	3(1)	28(1)
Red skin-Dose Site	0(0)	0(0)	0(0)	0(0)	2(1)	0(0)	0(0)	15(2)

a Table represents number of incidences that occurred during the dosing phase.
b One male given 5 mg/kg was found dead on Day 140 of the dosing phase.
c Dosing was halted for one female given 50 mg/kg as of Day 210 of the dosing phase (last dose received on Day 204) due to severe injection site observations; this animal received one single dose 2 days prior to sacrifice on Day 266.

However, starting on Day 94 one 50 mg/kg female had injection site reactions which worsened over time, often on several of the four alternating sites. Observations at injection site D first required treatment with an antibiotic and non-steroidal anti-inflammatory drug on Day 192 and again on Day 210 at which time dosing was stopped. Clinical pathology findings on Day 210 suggested inflammation; animal also had a total of 18 days of low feed consumption and 4 days of nonformed feces. Immunophenotyping parameters (evaluated as percent change and relative values) were all within normal variation. Starting on Day 22 of the dosing phase this animal had lower predose test article concentration values than those for other animals in the same dosing group.

Injection site reactions were considered compound-related because they occurred with greater frequency in the treated animals and the severity in one 50 mg/kg female required dosing suspension. Observations in other animals were sporadic, relatively mild and transient.

The observation of liquid feces was noted with a slightly increased frequency in treated groups. The observation of red feces was noted in a dose-related manner in males, but not females.

Clinical signs of alopecia, vomitus, broken or red skin (not at dose site), swollen tail, prolapsed rectum, thin appearance, and discolored feces (green in color) were seen sporadically across all groups and were not considered compound-related.

These findings are consistent with a LOAEL of 50 mg/kg/week because they were sporadic in nature and resolvable.

No compound-related clinical signs were noted during the recovery period. At the end of the recovery phase, the only compound-related finding at injection sites was minimal inflammation, indicating injection site reactions were generally reversible.

Body Weights

Weekly. No treatment-related effects were observed during either the dosing or recovery phases.

Ophthalmoscopy

Ophthalmoscopy was performed predose, during Week 38 of dosing phase and during the final week of the recovery phase.

No lesions were observed during the predose, dosing, and recovery phases.

Neurological examinations

Neurological examinations (not otherwise described) were done on all animals (unanesthetized) once during the predose phase, approximately 48 hours postdose for days 1 and 260 of the dosing phase and during Week 16 of the recovery phase.

During all neurological examinations, all animals were observed as normal with no remarkable findings.

ECG

ECG measurements were performed twice predose (at ~ same time as predose and ~48 hours postdose evaluations); predose and ~48 hours postdose for days 85, 176; ~48 hours postdose for day 260; and once at the end of the recovery phase. Quantitative evaluation of cardiovascular measurements included: heart rate, QT interval, and corrected QT interval (QTc) using Bazett method.

All electrocardiograms were qualitatively and quantitatively within normal limits. No arrhythmias were found. No test article-related effect on heart rate or QTc intervals was found at any dose level comparing predose and postdose group mean values and based on comparison with control values.

Hematology

Blood was collected twice during the predose phase, once during Weeks 4, 13, 26, 30, 34 of the dosing phase, at termination, once during Weeks 4, 8, and 12 of the recovery phase and at the end of the recovery phase. The following parameters were evaluated: white blood cell count, red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin concentration, mean corpuscular hemoglobin,

platelet count, percent neutrophils, percent lymphocytes, percent monocytes, percent eosinophils, percent basophils, percent large unstained cells, absolute segmented neutrophils, absolute lymphocytes, absolute monocytes, absolute eosinophils, absolute basophils, absolute large unstained cells, percent reticulocyte, absolute reticulocyte, activated partial thromboplastin, prothrombin time.

With the exception of results for the high dose group female requiring dosage suspension because of injection site reactions, compound-related effects were not observed after treatment or at the end of the recovery period. For the high dose female requiring dose suspension, hematology findings included minimally to mildly lower red cell mass and higher leukocyte counts.

Clinical Chemistry

Blood was collected twice during predose phase, once during Weeks 4, 13, 26, 30, 34 of dosing phase, at termination, once during Weeks 4, 8, and 12 of the recovery phase and at the end of the recovery phase. The following parameters were evaluated: glucose, urea nitrogen, creatinine, total cholesterol, aspartate aminotransferase, alanine aminotransferase, alkaline aminotransferase, total protein, albumin, calcium, total bilirubin, inorganic phosphorus, triglyceride, gamma glutamyltransferase, sodium, potassium, chloride, creatine kinase, albumin/globulin ratio, globulin.

With the exception of the high dose female requiring dosage suspension because of injection site reactions, compound-related effects were not observed after treatment or at the end of the recovery period. For the single female requiring dosage suspension, lower albumin and high globulin counts resulted in lower albumin-to-globulin ratio.

Urinalysis

Urine was collected once predose and at terminal and recovery sacrifice. The following parameters were evaluated: glucose, ketones, blood, nitrite, protein, bilirubin, specific gravity, pH, urobilinogen, volume, clarity, and color.

Compound-related effects were not observed after treatment or at the end of the recovery period.

Gross Pathology

Gross pathology was conducted for each animal at scheduled necropsy.

One male given 5 mg/kg was found dead on Day 140 of the dosing phase. Significant macroscopic observations or important microscopic findings were not noted. The cause of death was undetermined. Because no deaths occurred in the higher dose group and no compound-related lesions were noted, this death was not attributed to the compound.

In general, dosing phase animals had reversible compound-related macroscopic findings consisting of thickened or discolored injection sites. The remaining macroscopic findings were incidental and not-compound-related. No compound-related macroscopic findings were noted at the end of the recovery phase.

Organ Weights

The following organs were weighed at scheduled sacrifices: adrenals, brain, epididymis, heart, kidney, liver with gallbladder (drained), pituitary gland, prostate, spleen, testis, thymus, thyroid with parathyroid.

No compound-related organ weight effects were observed at the final dosing phase necropsy or the final recovery phase necropsy.

Histopathology

When present, the following tissues were retained from each animal and preserved in 10% neutral-buffered formalin, unless otherwise specified: adrenal, aorta, brain stem, cerebellum, cerebrum, cecum, cervix, colon, duodenum, epididymis (Davidson's fixative), esophagus, eye (Davidson's fixative), femur with bone marrow (articular surface of the distal end), gallbladder, heart, ileum, injection sites (test article), injection sites (KLH), jejunum, kidney, lacrimal gland, lesions, liver, lung with large bronchi, lymph node (mandibular), lymph node (mesenteric), mammary gland (females), optic nerve (Davidson's fixative), ovary, pancreas, pituitary gland, prostate, rectum, salivary gland (mandibular), sciatic nerve, seminal vesicle, skeletal muscle (quadriceps femoris), skin, spinal cord (cervical, thoracic, lumbar), spleen, sternum with bone marrow, stomach, testis, thymus, thyroid (2 lobes) with parathyroid, tongue, trachea, urinary bladder, uterus, vagina.

Adequate Battery -yes

Peer Review – independent peer review performed by the sponsor

Histological Findings

Compound-related microscopic findings were seen at the subcutaneous injection sites in animals given 5 or 50 mg/kg. Compared with controls, the incidence and average severity score of inflammation and hemorrhage at the injection sites were increased in animals given 5 or 50 mg/kg. Inflammation was characterized by various combinations of infiltrating lymphocytes, macrophages, neutrophils, and esosinophils accompanied by edema and variable fibrosis. Necrosis, seen as accumulation of karyorrhectic nuclei and degeneration of collagen, was noted at a low incidence at the most recent injection site (Site C). Overall, the reactions were most prominent in the most recently injected site (Site C) and least prominent in the site that had received an injection 22 days prior to necropsy (Site D).

There were no findings of vasculitis, necrosis, and/or hemorrhage at the injection site of all recovery phase animals, supporting complete reversibility of these findings.

Review of individual animal data indicates that most males were sexually immature with testis, prostate and epididymis described as immature (see partial excerpt from Table

50, Individual Animal Data, taken directly from the study report). This observation correlates with the stated age range (2 – 4 years).

Table 50
Individual Animal Data

Animal: I03233	Sex: Male	Group: 1	Dose level: 0.0 mg/kg
Day/Week of death:268/39 Dosing phase	Status: Final phase sacrifice		Terminal body weight (kg): 3.10

<< Pathology Observations >>

Tissue	Histopathologic diagnoses / Special histological comments
Prostate	Required tissue. Immature, Present.
Seminal Vesicle	Required tissue. Immature, Present.
Testis	Required tissue. Immature, Present.
Epididymis	Required tissue. Immature, Present.
Subcutan Site B	Required tissue.

Minimal infiltrates in the heart tissue were also a common finding (see partial excerpt from Table 50, Individual Animal Data, taken directly from the study report).

Table 50
Individual Animal Data

Animal: I03231	Sex: Male	Group: 1	Dose level: 0.0 mg/kg
Day/Week of death:268/39 Dosing phase	Status: Final phase sacrifice		Terminal body weight (kg): 2.90

<< Pathology Observations >>

Tissue	Histopathologic diagnoses / Special histological comments
Heart	Required tissue. Infiltrate, Lymphocytes/Macrophages, Minimal.
Subcutan Site C	Required tissue. Inflammation, Subacute, Minimal

Histologic evaluation for the 5 mg/kg male that died on study day 140 appears below and did not reveal a cause of death:

Table 50
Individual Animal Data

Animal: I03242	Sex: Male	Group: 3	Dose level: 5.0 mg/kg
Day/Week of death:140/20 Dosing phase	Status: Found dead		Terminal body weight (kg): -----

<< Pathology Observations >>

Tissue	Histopathologic diagnoses / Special histological comments
Testis	Required tissue. Immature, Present.
Epididymis	Required tissue. Immature, Present.
Heart	Required tissue. Infiltrate, Lymphocytes/Macrophages, Minimal.
Subcutan Site A	Required tissue. Inflammation, Subacute, Slight.
Subcutan Site E	Required tissue. Not Examined, Present. /No KLH (Subcutaneous Site E) present due to animal sacrifice prior to day 244 as per protocol.
Death Comment	Required tissue. Undetermined, Present. /Histopathology evaluation did not reveal a cause of death. All changes noted at microscopic examination were compatible with spontaneous/incidental background changes of the cynomolgus monkey.

The following tissues are unremarkable:

Bone, Femur	Marrow, Femur	Bone, Sternum	Marrow, Sternum	Spinal Cord
Nerve, Sciatic	Pituitary	Adrenal, Medulla	Aorta	Trachea
Thyroid	Parathyroid	Lung	Liver	Gallbladder
Urinary Bladder	Esophagus	Stomach, Gl	Duodenum	Colon
Ileum	Jejunum	Cecum	Rectum	Pancreas
Gl, Mandib Saliv	Thymus	Muscle, Bi Fem	Tongue	Skin/Subcutis
Eye	Nerve, Optic	Gl, Lacrimal	Brain	Subcutan Site B
Subcutan Site C	Subcutan Site D			

Special Evaluation

Peripheral blood was collected for immunophenotyping analysis from all animals on Days 13 and 21 of the predose phase; on Days 28, 91, 182, 210, 238, and 268 of the dosing phase; and Days 27, 55, 83, and 113 of the recovery phase.

Ixekizumab administration did not produce any remarkable changes in the peripheral blood immunophenotyping (total T cells, helper T cells, cytotoxic T cells, total B cells, natural killer cells, and helper-to-cytotoxic T cell ratio) or natural killer cell assay data.

T-cell dependent antibody response (TDAR) analysis using keyhole limpet hemocyanin (KLH) as the antigen was evaluated. There were no treatment-related changes in the anti-KLH IgG or IgM responses either during the dosing or recovery phases.

At the end of the recovery period, one high dose female was positive for anti-drug neutralizing antibody. Another high dose animal was observed to have high titers but could not be evaluated against pretreatment values for assignment of treatment-induced "positive" immunoreactivity. However, the presence of ixekizumab in serum samples can interfere with the accuracy of the anti- ixekizumab Ig analysis. Thus there is a potential for false negatives or underestimated titers due to the presence of ixekizumab in group 4 serum samples.

Toxicokinetics

Blood samples for toxicokinetic evaluation were collected ~3, 6, 24, 48, 72, 120, and 168 hours postdose on Day 1 and on Days 15, 22, 29, 71, 134, and 211 of the dosing phase and at weekly intervals during the recovery phase. The lower limit of quantitation was 7.5 ng/mL.

No measurable concentrations of ixekizumab (all<7.5 ng/mL) were found in any of the serum samples from control animals.

After subcutaneous administration, ixekizumab was slowly absorbed with mean T_{max} values ranging from 40 to 102 hours. Values for mean T_{max} decreased with increasing dose level on Day 1. After reaching C_{max}, concentrations slowly declined, with estimated mean $t_{1/2}$ values of 337 hours for males and 188 hours for females in Group 4 (50 mg/kg) on Day 267. Due to the lack of a distinct terminal elimination phase (collections only out to 168 hours), $t_{1/2}$ values could not be estimated for Day 1.

Predose concentration values on days 15, 22, 29, 71, 134, 211, and 267 indicated that the concentration values generally increased after multiple dosing. Concentration values for two high dose females showed decreased concentrations by Day 22 (Animal I03265) and following the last dose on Day 267 (Animal I03269). Immunogenicity results confirmed a positive response for Animal I03269. A high anti-ixekizumab-reactive antibody titer was observed in Animal I03265, but could not be confirmed as a positive response because the pretreatment sample was not reportable for this animal.

Mean C_{max} and $AUC_{0\text{-}168hr}$ values were similar between males and females (see Text Table 1, taken directly from the study report). Mean C_{max} and $AUC_{0\text{-}168hr}$ values increased from Day 1 to Day 267 at the 50 mg/kg/dose level, indicating accumulation of ixekizumab following multiple dosing. Increases in mean C_{max} and $AUC_{0\text{-}168hr}$ on Day 1 were generally dose proportional.

Text Table 1
Mean Serum Toxicokinetic Data Summary

Parameter		Administered Dose (mg LY2439821/kg)					
		0.5		5		50	
	Sex	M	F	M	F	M	F
LY2439821							
Day 1							
C_{max} (µg/mL)		5.11	4.62	43.9	45.8	423	450
$AUC_{0\text{-}168hr}$ (µg·hr/mL)		705	615	6043	6166	57160	58312
Day 267							
C_{max} (µg/mL)		NA	NA	NA	NA	1215	855
$AUC_{0\text{-}168hr}$ (µg·hr/mL)		NA	NA	NA	NA	168595	119305

Abbreviations: M = male, F = female, C_{max} = maximum observed serum concentration, hr = hour, $AUC_{0\text{-}168\ hr}$ = area under the serum concentration curve, NA = not applicable.

Dosing Solution Analysis

Concentration verification analysis was completed for each concentration of the test article formulations used for dosing on Days 1, 71, 134, and 267. Concentrations were between 93 and 103% of theoretical and considered acceptable for use in this study.

7 Genetic Toxicology

Based on ICH S6 (Guideline for the Safety Evaluation of Biotechnology-Derived Pharmaceuticals) guidelines, no genetic toxicology studies were conducted with ixekizumab.

8 Carcinogenicity

There are no carcinogenic concerns related to ixekizumab structure or metabolism. Since ixekizumab is a monoclonal antibody, this large protein is not expected to gain access to the nucleus and directly interact with DNA. It will be catabolized to peptides and constituent amino acids via normal metabolic pathways.

Ixekizumab acts by inhibiting the binding of IL-17A to the IL-17A receptor, thereby preventing IL-17A-mediated cellular responses, highlighted by the release of cytokines

and chemokines designed to recruit and activate both neutrophils and memory T-cells to the site of injury or inflammation and maintain a proinflammatory state. However, assessments of immunotoxicity and immune-modulation in the monkey repeat-dose toxicity studies identified no remarkable changes. There was no alteration (reduction or increase) in lymphocyte subsets (helper T cells, cytotoxic T cells, B cells, NK cells), no change in NK cell function, no effects on immune response (IgG and IgM) to KLH, and no histopathological changes in lymphoid organs in the adult monkeys or in their infants exposed to ixekizumab in utero.

The literature supports a protumor role for IL-17A based on its high expression in a variety of tumor types and its ability to promote angiogenesis, attract proinflammatory cells and provide pro-survival signals to tumor cells. A strong association between chronic inflammation and increased incidence of malignancy is well established. Inflammatory responses can promote tumorigenesis through multiple mechanisms, including promotion of malignant cell transformation, pro-proliferative effects, enhanced angiogenesis and metastasis and suppression of cytotoxic T-cell (adaptive immune cell) responses (Mantovani *et al.*, 2008). Tartour *et al.* (1999) and Kato *et al*. (2001) found that transduction of cDNA encoding IL-17A into human or mouse cancer cell lines promoted tumor growth, compared to the parental tumor, when transplanted into athymic nude mice. Kato's group further demonstrated the enhanced tumor growth was associated with angiogenic activity of IL-17A. They found that the IL-17A-transduced tumors had significantly increased vascular density and that both tumor angiogenesis and growth were inhibited when IL-17A activity was blocked. Subsequently the group correlated IL-17A expression with increased microvessel density in a majority of ovarian cancer tissues (Kato *et al.*, 2001).

Prabhala *et al.* (2010) showed that IL-17A-producing Th17 cells promote human multiple myeloma cell growth. They found that IL-17A directly promoted myeloma cell growth in vitro and in a murine xenograft model of multiple myeloma. In addition, they showed that IL-17A synergized with IL-22 to inhibit the production of IFN-γ-producing Th1 T cells, thereby inhibiting tumor immunity. Zhu *et al.* (2008) identified IL-17A-expressing infiltrating macrophages in human breast tumors and further demonstrated that IL-17A directly promoted breast cancer cell invasion in vitro.

Using a model of 7,12-dimethylbenz(*a*)anthracene (DMBA)-induced cutaneous skin carcinogenesis, Yusuf *et al.* (2008) showed that mice lacking Toll-like receptor 4 (TLR4) produced a strong Th17 cell response resulting in larger and more frequent tumors, that developed more rapidly and were more vascular than in control animals. Analysis of tumor lysates demonstrated reduced IFN-*γ* and significant increases in IL-17A, as well as VEGF, and macrophage inflammatory protein-2 (MIP-2; CXCL2) that likely contributed to the increased vasculogenesis.

Conversely, several researchers have observed an anti-tumor effect of IL-17A. Kryzcek *et al.*, (2009) studied the effect of IL-17 on tumor growth in IL-17-deficient mice. MC38, a murine colon cancer cell line, was subcutaneously inoculated into the wild-type and IL-17-deficient mice. The IL-17-deficient mice exhibited an accelerated tumor growth

compared with the control mice (P<0.01). They also compared the metastatic potential of MC38 cells by intravenously inoculating cells into wild-type and IL-17-deficent mice and observed more metastatic foci of tumors in the lungs of IL-17-deficient mice (59 ±8) than in control mice (12 ± 5; P=0.01). The effect was accompanied by reduced IFN-γ levels in tumor-infiltrating NK cells and T cells. These data suggest that endogenous IL-17 may play a protective role in tumor immunity. In addition, IL-17 has been shown to inhibit the growth of hematopoietic tumors such as mastocytoma and plasmocytoma by enhancing cytolytic T-lymophocytes (Benchetrit *et al*., 2002). Although IL-17 has been shown to promote tumor growth by inducing angiogenesis, the same process provides the channel through which the immune cells can invade and assault the relatively inaccessible tumor cells at the core of the solid tumor mass (Murugaiyan and Saha, 2009). Thus IL-17-induced angiogenesis might also promote antitumor immunity by being a supply channel for immune cells to reach and attack the inner mass of a solid tumor.

Other investigations of tumorigenesis in IL-17A-deficient mice have produced mixed results. Martin-Orozco *et al.* (2009) found that in IL-17A-deficient mice, adaptive T cell therapy with tumor-specific Th17 cells prevented the development of poorly immunogenic lung melanoma tumors as well as helped control growth of established lung melanoma tumors; the Th17 cells maintained their Th17 cell cytokine production and did not convert to Th1 cells. The proposed anti-tumor mechanism was Th17-cell mediation of dendritic cell recruitment and subsequent activation of CD8+ T cells against the tumor. According to the authors, their data indicated an active role of IL-17A in immunosurveillance since IL-17A deficiency resulted in reduced leukocyte infiltration into the tumor and increased tumor development. The authors further commented that their findings were consistent with the notion that the effects of IL-17A on tumor development are directly influenced by the existence of an adaptive immune system; in the presence of lymphocytes, IL-17A promotes tumor rejection, while in their absence, IL-17A favors tumor growth and angiogenesis.

Rare human genetic disorders resulting in, but not necessarily limited to, defective IL-17A signaling exhibit susceptibility to recurrent or chronic oral *Candida* infection which, if not controlled, may predispose to oral and/or esophageal squamous cell carcinoma (Husebye *et al*., 2009).

The overall weight-of-evidence suggests that neutralization of IL-17A with ixekizumab is expected to create a less favorable environment for tumor growth. Assessment of the frequency of malignancy reports during postmarketing surveillance in comparison to the background rates in patient populations will ultimately provide the most accurate determination of cancer risk for ixekizumab.

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

Study title: A repeat-dose fertility study in Cynomolgus monkeys given LY2439821 by subcutaneous injection once weekly for 3 months

Study no.:	20003965
Study report location:	Electronic document
Conducting laboratory and location:	(b) (4)
Date of study initiation:	7-21-2010
GLP compliance:	yes
QA statement:	yes
Drug, lot #, and % purity:	LY2439821, EL01025-012-API-F, protein content = 34.95 mg/mL

Key Study Findings

Once-weekly subcutaneous administration of ixekizumab to cynomolgus monkeys for 3 months at doses of 50 mg/kg/week did not have a drug related effect on fertility parameters measured (sperm analysis, menstrual cycling, reproductive organ weight and histopathology). The NOAEL was considered to be 50 mg/kg/week (Day 85 ixekizumab male $AUC_{0\text{-}168h}$ 179279 μg*hours/mL and female $AUC_{0\text{-}168h}$ 153865 μg*hours/mL).

Methods

Doses:	0 and 50 mg/kg/week
Frequency of dosing:	weekly
Dose volume:	2 mL/kg
Route of administration:	Subcutaneous injection
Formulation:	Clinical formulation. Vehicle control: 10 mM sodium citrate buffer (pH 6.0 ±0.2) with 150 mM NaCl and 0.02% polysorbate 80, prepared in sterile water for injection.
Species/Strain:	Cynomolgus monkeys
Number/Sex/Group:	6/sex/group
Satellite groups:	none
Study design:	See chart below taken directly from the study report
Deviation from study protocol:	None relevant to integrity of test results

Group Identification	Dose Level mg/kg/week[a]	Dose Concentration mg/mL	Dose Volume[b] mL/kg	Animal Numbers	
				Male	Female
1 Vehicle Control	0	0	2	1101, 1002, 1003, 1004, 1105, 1006	1601, 1502, 1503, 1604, 1605, 1506
2 LY2439821	50	25[a] (nominal)	2	2001, 2002, 2003, 2104, 2105, 2006	2601, 2502, 2503, 2604, 2505, 2506

[a] Concentrations were corrected for lot-specific test article protein content.
[b] The final dose volume/kg was based on test article protein content.

Reviewer's comment: Sexual maturity was demonstrated based on the following data obtained prestudy:

Males: hormone levels (testosterone), descended testicles, testicular volume, ability to produce an ejaculate and semen analysis including sample volume, sperm concentration, count and % motility.
Females: menstrual cycling (assessed daily for at least 3 months)

Parameters evaluated: mortality, clinical signs, body weight, feed consumption, menstrual cycling, sperm analysis (sperm concentration, count-per-ejaculate, motility, morphology), and reproductive organ weight and histopathology.

Study design
Groups were administered 0 or 50 mg/kg weekly by subcutaneous injection for a total of 13-weeks. Animals were not mated.

Observations and Results

Mortality

Animals were examined for mortality twice daily (am and pm). All animals survived to scheduled necropsy.

Clinical Signs

Animals were examined for clinical signs once daily. There were no test article-related clinical findings.

Body Weight

Body weight was recorded weekly. There was no test article-related change in either body weight or body weight gain.

Feed Consumption

Feed consumption was evaluated daily by counting the biscuits remaining. There was no change in feed consumption.

Toxicokinetics

Blood samples (~1 mL per timepoint) were collected by venipuncture on days 1, 43 and 85 (see TK Sample Collection Schedule).

TK Sample Collection Schedule

	Sample Collection Time Points (Time Post Dose)					
Study Day	0 (predose)	8 hr	24 hr	48 hr	96 hr	168±1 hr
1	-	X	X	X	X	X
43	X	-	-	X	-	-
85	X	X	X	X	X	X

Serum was collected, shipped on dry ice and analyzed for ixekizumab content using a previously validated ELISA method (lower limit of quantitation (LLOQ) = 7.5 ng/mL).

All control group serum concentrations of ixekizumab were below the LLOQ with the exception of Male 1002 at the Day 43 predose time point which was 9.5 ng/mL. This single concentration was minimally above the LLOQ and therefore not considered to be due to misdosing and did not impact the toxicokinetic interpretation. Maximum concentrations of ixekizumab were generally reached by 48 hours postdose, but were observed at 96 hours postdose in a minority of animals. After T_{max}, the decline in ixekizumab concentration was slow enough that the terminal elimination phase could not be characterized for the dosing interval and therefore $t_{1/2}$ could not be estimated. There were no consistent gender differences in exposure. The increase in ixekizumab exposure was generally greater on Day 85 than on Day 1, indicating some accumulation occurred with weekly administration. The predose and 48 hour postdose serum concentrations were similar between Days 43 and 85; thus steady state was considered

to have already been achieved by Day 43. Mean serum toxicokinetic data are summarized in the text table below (taken directly from the study report).

Parameter	Administered Dose (mg/kg/week)	
	50	
Sex	Male	Female
LY2439821		
Day 1		
T_{max} (Hours)	60.0 ± 29.4	48.0 ± 26.3
C_{max} (µg/mL)	426 ± 63.9	456 ± 60.6
AUC_{0-168} (µg*Hours/mL)	59995 ± 10771	63398 ± 6686
Day 85		
T_{max} (Hours)	40.0 ± 29.1	36.0 ± 13.1
C_{max} (µg /mL)	1238 ± 259	1073 ± 125
AUC_{0-168} (µg *Hours/mL)	179279 ± 40962	153865 ± 18128

Dosing Solution Analysis

The stability of bulk ixekizumab through completion of the study was determined and the results are listed below. Ixekizumab was considered stable over the course of the study.

Parameter	Result
Protein content	33.9 mg/mL
Purity	98.3 %
pH	6.0
Appearance	Slightly opalescent, colorless solution

Fertility Parameters

Vaginal swabs

Swabbing of the peri vaginal area was performed daily on all female animals to detect bleeding due to menstrual cycles beginning on Day -90 and continuing until necropsy. There were no changes in menstrual cycle lengths related to ixekizumab administration. Group mean menstrual cycle lengths were 29.2± 3.8 and 29.1± 2.6 days during the prestudy phase in the 0 and 50 mg/kg/week groups, respectively. During the dosing phase, group mean menstrual cycle lengths were 30.1± 6.5 and 32.5± 12.5 days in the 0 and 50 mg/kg/week groups, respectively. There was no effect of ixekizumab treatment on menstrual cycle lengths.

Sperm evaluation
Semen ejaculate samples were collected at two prestudy intervals (two weeks apart, Weeks -4 and -2), and during Weeks 12 and 13. From each ejaculate sample, two sperm morphology slides were prepared for staining with Eosin and evaluation. A minimum of 200 intact sperm cells/animal were examined for morphological development.

There were no test article-related effects on sperm motility, concentration, count-per-ejaculate or morphological development.

Mean sperm count-per-ejaculate was significantly reduced ($p \leq 0.05$) in the 50 mg/kg/week dose group at Weeks 12 and 13 compared to the concurrent control group values (see table below, taken directly from the study report). However, individual values for Group 2 males were comparable to Prestudy I and II values. The normal variability in sperm count-per-ejaculate is reflected in the data from the 0 and 50 mg/kg/week dose groups when comparing Prestudy I results (232.8 ± 172.2 and 101.8 ± 90.5 M, respectively) to Prestudy II results (168.0 ± 85.3 and 83.0 ± 54.1 M, respectively). This reduced sperm count-per-ejaculate is not considered biologically significant and is attributed to normal variability viewed within the context of a small group size.

Study: STUDY 20003965
Compound: See Study Protocol
Sex: M
Analysis Framework: 1-Factor ANOVA
Primary Factor: Treatment Group Code

Parameter: Count per Ejaculate Millions

GROUP	STATISTIC	PRESTUDY I	PRESTUDY II	WEEK 12	WEEK 13
1	Mean	232.83	168.03	298.26	230.30
	SD	172.18	85.30	102.50	86.54
	N	6	6	6	6
	Statistical Sig				
2	Mean	101.75	83.03	94.85	78.61
	SD	90.48	54.14	66.41	45.75
	N	6	6	6	6
	Statistical Sig			*	*

* ANOVA with Dunnett's/Dunn's (p <= 0.05)
Groups with n<3 were excluded from statistical analysis

Necropsy

All animals were euthanized under deep anesthesia followed by exsanguination on Day 92. All animals were subject to a complete necropsy examination which included evaluation of the carcass and musculoskeletal system; all external surfaces and orifices; cranial cavity and external surfaces of the brain; and thoracic abdominal and pelvic cavities with their associated organs and tissues. There were no test article-associated macroscopic findings in animals euthanized at the end of the dosing phase (Day 92).

The following organs were dissected free of fat and weighed: brain, epididymides, ovaries, prostate, testes, and uterus. There were no alterations in organ weights or organ weight ratios.

Histopathology

A complete set of tissues was retained and preserved from each animal. The following tissues were embedded in paraffin wax, sectioned, mounted on glass slides and stained with hematoxylin & eosin stain: cervix, epididymides, mammary gland, ovaries, pituitary gland, prostate, seminal vesicles, testes, uterus, vagina.

There were no test article-related findings in animals euthanized on Day 92. Two male animals dosed with 50 mg/kg/week of ixekizumab (Animal # 2003, 2105) had minimal multifocal hypocellularity of the germinal epithelium. This change consisted of a few cross-sections of seminiferous tubules (less than 5%) that had only a single cell layer, most likely Sertoli cells, and no germinal epithelium present. The change was bilateral in one animal and unilateral in the other. Most of the seminiferous tubules in these two animals were unremarkable. Similar unilateral and bilateral changes are occasionally observed as an incidental finding in control cynomolgus monkeys at the testing facility. Hypocellularity of the germinal epithelium in these two test article-treated males was considered to be incidental and unrelated to ixekizumab administration because of the similarity to previously observed background changes, the minimal focal nature of the change, and the absence of any indication of a test article effect on spermatogenesis. A peer review was performed by the Eli Lilly Company and was in complete agreement with the findings.

Reviewer's comment: Histopathology of the testis has been shown to be the most sensitive method for detection of effects on spermatogenesis (ICH S5(R2): Detection of Toxicity to Reproduction for Medicinal Products and Toxicity to Male Fertility). The lack of effect of treatment on histopathology of the testis in this study suggests that the previously noted reduced mean sperm count per ejaculate is not treatment-related.

9.2 Embryonic Fetal Development

The sponsor submitted an embryofetal development study (Study title: An assessment of the effects of LY2439821 on embryo-fetal development when administered weekly by subcutaneous injection to pregnant cynomolgus monkeys from gestation day 20 through 139, SNBL.010.15). The study was reviewed under IND 100834 and is summarized below.

There was no evidence of adverse compound-related systemic toxicity in maternal animals (12/group) or teratogenicity, embryotoxicity or adverse effects on immune system development in fetuses following once weekly subcutaneous administration of ixekizumab at dosages of 5 mg/kg or 50 mg/kg for 18

consecutive weeks (gestation day (GD) 20 to GD139) in cynomolgus monkeys. Samples of cord blood taken at C-section revealed ixekizumab distribution across the placenta to the fetus increased with dose, but was less than dose proportional. Based on the results of this test, the NOAEL for both maternal toxicity and embryofetal development was 50 mg/kg/week.

9.3 Prenatal and Postnatal Development

Study title: An Assessment of LY2439821 on Pre- and Postnatal Development When Administered by Subcutaneous Injection Once Weekly to Pregnant Cynomolgus Monkeys

Study no.:	20018253
Study report location:	Electronic document
Conducting laboratory and location:	(b) (4)
Date of study initiation:	11-23-2011
GLP compliance:	yes
QA statement:	yes
Drug, lot #, and protein content:	LY2439821, 111116-0055, 26 mg/mL

Key Study Findings

Three groups of 18 pregnant cynomolgus monkeys were administered weekly subcutaneous injections of ixekizumab (0, 5, 50 mg/kg) from gestation day (GD) 20 to parturition to evaluate potential adverse effects of ixekizumab on the pregnant female and on development of the conceptus. No dam died during this study and no ixekizumab-related abnormalities were observed in infants. However, maternal ixekizumab treatment was associated with neonatal deaths (5, 50 mg/kg) and maternal neglect (50 mg/kg). Under the experimental conditions, a NOAEL for prenatal and postnatal development could not be determined.

Methods

Doses:	0, 5, 50 mg/kg
Frequency of dosing:	Once weekly from GD20 to parturition (~GD160)
Dose volume:	2 mL/kg
Route of administration:	Subcutaneous injection with dosing site rotated through 4 possible sites
Formulation:	Clinical formulation. Vehicle control: 10 mM sodium citrate buffer (pH 6.0 ±0.2) with 150 mM NaCl and 0.02% polysorbate 80, prepared in sterile water for injection.
Species/Strain:	Cynomolgus monkey
Number /Group:	18
Satellite groups:	none
Study design:	See below
Deviation from study protocol:	None significant to the integrity of the results

Group Identification	Dose Level (mg/kg)	Dose Concentration (mg/mL)[a]	Dose Volume (mL/kg)	Number of Pregnant Adult Females
1 Vehicle Control	0	0	2	18
2 LY2439821	5	2.5	2	18
3 LY2439821	50	25	2	18

[a] Concentrations were corrected for lot specific test article potency.

Endpoints evaluated: In the F_0 (maternal) generation: survival, clinical signs, body weight, feed consumption, clinical pathology (hematology and serum biochemistry), duration of gestation, infant sex and viability, maternal behavior, toxicokinetics, immune response, milk analysis. In the F_1 generation: viability, clinical signs of toxicity, body weight, clinical pathology, immunological examination, functional development (electrocardiograph recordings and ophthalmology examinations), morphological development, immunological development, toxicokinetics and immune response, skeletal examinations, organ weight, and gross and histopathological examinations.

Observations and Results

F_0 Dams:

Survival
All females assigned to the study were pregnant and there were no maternal deaths.

Clinical signs
There were no notable changes in clinical condition in adult females. Red vaginal discharge at GD21 to GD42 was considered due to normal implantation bleeding and was unrelated to pregnancy outcome.

In-life measurements
There were no treatment-related abnormalities or effects on body weight, feed consumption, hematology and serum biochemistry (pretreatment and on GD70 and GD140).

Uterine content and reproductive parameters
All control females (Group 1) and Group 2 pregnant females that aborted or demonstrated evidence of embryonic death prior to GD50 had measurable levels of monkey chorionic gonadotropin (mCG) in blood samples collected between GD18 and 22 that were consistent with ultrasound confirmation of pregnancy.

Abortion (*in utero* death <GD140) or stillbirth (*in utero* death ≥ GD140) occurred in 4 dams in the control group (GD46, GD60, GGD152, GD160), 6 dams in the 5 mg/kg group (GD32, GD33, GD131, GD160, GD160, GD167), and 4 dams in the 50 mg/kg group (GD113, GD128, GD142, GD158). These losses were spread evenly over the 3 dose groups (22.2% [4/18] at 0 mg/kg, 33.3% [6/18] at 5 mg/kg and 22.2% [4/18] at 50 mg/kg) and were within the range of historical control data for embryo/fetal loss at the testing facility (47 embryo/fetal losses out of 197 pregnancies [23.9%]; range 6.7 to 38.9%). No ixekizumab-related findings were observed on gross evaluation of any available placentas or umbilical cords from fetal losses.

The mean gestation length of live infants was comparable among the three groups: 160 days, 158 days, and 157 days, respectively. A total of 14 Group 1 (control), 12 Group 2 (5 mg/kg) and 14 Group 3 (50 mg/kg) infants were delivered by natural birth. Abnormal nursing behavior was observed in one dam in group 2 (5 mg/kg; mother holding F_1 by the mandibles on BD1, F_0 had no milk present at lactation check on PPD1). Maternal neglect was observed in Group 3 (3/14, 21.4%). This is outside of the historical control range at the testing facility (9 incidences out of 161 live births [5.6%]; range 0% to 16.7%). Attempts to cross foster infants failed and infants were euthanized.

Reviewer's comment: All dams on this study were first time mothers (as per Section 2.4 Nonclinical Overview). The sponsor suggests maternal neglect is displayed more often among first time mothers and cites Maestripieri and Carroll, 1998. However, this view is not universally accepted (Jarvis et al., 2010). Although the maternal neglect at the high dose is not directly attributable to treatment, the cause is considered unknown.

F_0 necropsy: Adult females were released to breeding facility colony after euthanasia of their infant.

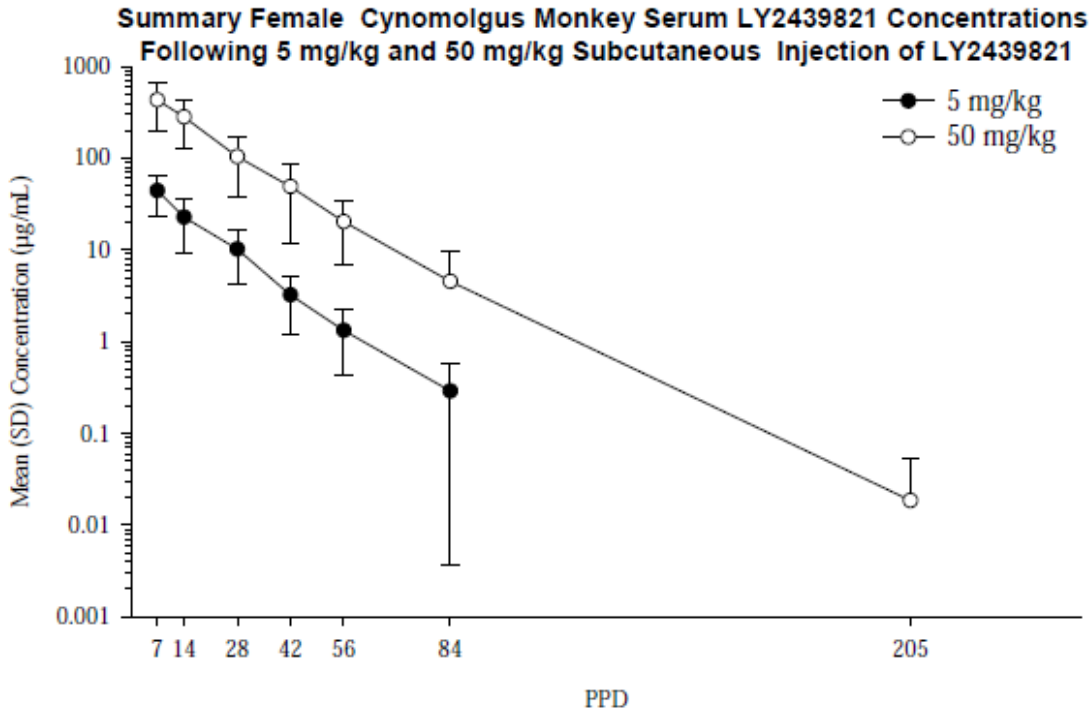
F_0 bioanalysis and milk analysis:

Ixekizumab serum concentrations in pregnant female monkeys were below the LLOQ (7.5 ng/mL) in all control samples. Ixekizumab serum concentrations were quantifiable in all samples collected from treated pregnant monkeys on GD20-22, GD70, and GD140, with the exception of Adult Female No. 2505 (5 mg/kg) for which ixekizumab was not quantifiable on GD70 and GD140, possibly due to anti-drug antibody.

Ixekizumab serum concentrations from Adult Female No. 2504 (5 mg/kg) on GD70 and GD140 and Adult female No. 3518 (50 mg/kg) on GD70 were remarkably lower than their dose-matched counterparts.

Ixekizumab serum concentrations in female monkeys post parturition were also below the LLOQ for all control group samples. With the exception of Adult Female No. 2505, post parturition serum concentrations in monkeys treated during pregnancy with 5 mg/kg were generally quantifiable up to PPD84 (see Figure 1.2, taken directly from the study report). At 50 mg/kg, ixekizumab serum concentrations in female monkeys post parturition were generally quantifiable throughout the sampling period (PPD7 to PPD205). Ixekizumab serum concentrations from two treated females (Adult Female No. 2502 treated with 5 mg/kg and Adult Female No. 3518 treated with 50 mg/kg) were remarkably lower than their dose-matched counterparts from PPD14.

Figure 1.2:



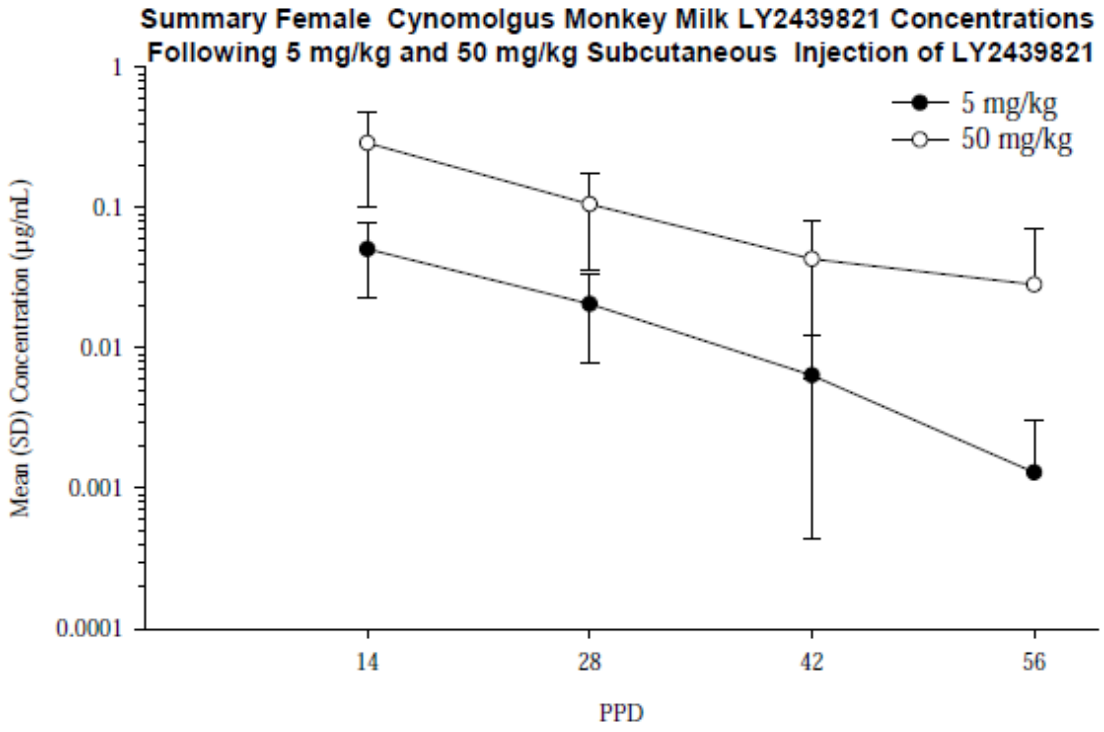
All dams except Female No. 2517 (5 mg/kg) had milk available at the lactation checks performed on PPD1. Female No. 2517 had no milk and the infant was euthanized on BD1.

Reviewer's comment: This single incidence of lactation failure at the low dose is considered to be unrelated to treatment.

Mean ixekizumab milk concentrations on PPD14 through PPD56 decreased over time from 50.9 to 1.30 ng/mL at 5 mg/kg and from 290 to 28.4 ng/mL at 50 mg/kg (see Figure

1.1, taken directly from the study report). Mean ixekizumab milk concentrations in Adult Female Nos. 2502, 2505, and 3518 were lower than their dose-matched counterparts throughout the milk sampling period, corresponding with the previously noted reduced serum concentrations.

Figure 1.1:



F_0 toxicokinetics:
Exposure to ixekizumab in pregnant females was dose related, with mean serum concentrations of ixekizumab 10-fold higher at 50 mg/kg relative to 5 mg/kg on GD20-22, GD70 and GD140. Ixekizumab mean concentrations were similar on GD70 and GD140 for both treatment groups, indicating steady state had been achieved by GD70.

Dosing solution analysis:
Mean ixekizumab concentrations for dose formulations used throughout the study ranged from 95% to 104% of theoretical values. The relative standard deviation was <1.9% for all analyses. Stability analysis of bulk ixekizumab at the end of the study indicates the compound was stable.

Immunophenotyping:
There were no ixekizumab-related changes in lymphocyte subsets in adult females.

F_1 generation:

Survival

Seven out of 40 (17.5%) delivered infants died or were euthanized within 6 days postpartum (see Text Table 17, Infant Mortality, taken directly from the study report). In three instances (Adult Females Nos. 2517, 3502, and 3513), the infants were delivered at an early gestational age (≤GD146). There were three incidences of maternal neglect in the 50 mg/kg dose group (Adult Female Nos. 3506, 3511, and 3513), including one where the infant was delivered early (Adult Female No. 3513). Attempts to cross foster the neglected infants were unsuccessful and the infants were terminated and dams released to the breeding facility.

Text Table 17 Infant Mortality

Dose Group (dose)	Adult Female No. / Infant No.	Infant Deaths (BD of loss/ GD of birth)	Total Surviving Infants (M/F)	Overall Percent Infant Loss
1 (0 mg/kg)	-	-	14 (7/7)	0
2 (5 mg/kg)	2501/2016 2517/2171	3/164 1/146	10 (2/8)	16.7% (2/12)
3 (50 mg/kg)	3502/3021 3506/3061[a] 3511/3116[a] 3513/3136[a] 3515/3151	5/145 6/164 2/154 2/142 1/164	9 (4/5)	35.7% (5/14)[b] 14.3% (2/14)[b]

[a] Maternal neglect.
[b] First line = total infant losses. Second line = losses adjusted for maternal neglect.
M/F = Male/Female

For fetuses that were aborted or stillborn, or infants that died early, there were no test article-related effects observed in the placenta or umbilical cord (when available), hematology, and there were no test article-related effects in the infant body weights, morphometric measurements, or external, visceral, heart, or skeletal evaluations, where applicable.

No ixekizumab-related changes in infant heart evaluations were noted in the infants that were euthanized or died prior to scheduled necropsy. All cardiac exams were normal for external, internal and overall evaluations, with some animals exhibiting variable patency of the ductus arteriosus and/or foramen ovale as expected for the time of evaluations relative to parturition.

The total number of male:female fetuses/infants in each group was 8:8, 5:11 and 9:9 at 0, 5, and 50 mg/kg, respectively. This is within the normal variation in male:female ratios in studies in nonhuman primates.

Morphological abnormalities: One 5 mg/kg dose group infant (Infant No. 2016) had a congenital defect (atresia ani, no anal opening) resulting in early euthanasia. A study of spontaneous congenital defects in cynomolgus monkey colonies over a more than 10-year period revealed atresia ani in 0 out of 965 cynomolgus monkeys. However, a single incidence at the lower dose and the lack of other congenital defects suggests this was incidental and not treatment related.

F_1 physical development: Neonatal deaths occurred in 2/12 (16.7%) infants in Group 2 (5 mg/kg/week) and 2/14 (14.3%) infants in Group 3 (50 mg/kg/week). No ixekizumab–related abnormalities in clinical signs, body weights, hematology or serum biochemistry were observed in neonates. Morphological development was assessed in F_1 animals by measuring fetal crown rump length, chest circumference, femur length, foot length, biparietal diameter, horizontal head circumference, and anogenital distance. There were no changes related to maternal ixekizumab treatment.

Neurobehavioral assessment: Neurobehavioral assessment was performed on neonates (BD7 and BD14) and on infants (BD91 and BD189). Neonatal assessment included: righting, palmar grasp, clasp-grasp, visual following, prone progression, lipsmack orient, oral reflexes (rooting, sucking, snout reflex), eye reflexes (pupil constriction, nystagmus, glabellar tap), moro reflex, negative geotaxis, buildup (increasing arousal levels in response to manipulation). Infant assessment included: general attitude and behavior, postural reactions, cranial nerve function, spinal nerve function (assessments of muscle tone, flexor reflex and perineal reflex). There were no effects on neonatal neurobehavioral evaluations or infant neurological evaluations in offspring exposed to ixekizumab at maternal doses of 5 or 50 mg/kg. Results were considered within the range of normal variability for neonatal and infant cynomolgus monkeys, and scores were similar between control- and test article-exposed infants.

Functional development: On BD1, BD28, BD98 and BD168 infant heart rates were recorded. There were no abnormalities detected in any infant. On BD119 all infants were lightly sedated (ketamine) and evaluated for ophthalmic parameters. There were no ixekizumab-related ophthalmic changes observed.

Bioanalysis- infant serum: Blood (0.5 mL at <BD91, 1 mL at ≥BD91) was collected from lightly sedated infants by venipuncture (in-life), as possible, on BD7, BD28, BD98, and BD205 ±2. Infant ixekizumab serum concentrations were below the LLOQ in all control group samples. On BD7, mean serum concentrations of ixekizumab were ~ 20-fold higher in infants born of mothers dosed with 50 mg/kg during gestation than in infants born of mothers dosed with 5 mg/kg during gestation. No clear gender differences were observed in infant serum concentration values. With the exception of one infant for which ixekizumab was not quantifiable at any occasion, ixekizumab was quantifiable in

all 5 mg/kg group infant serum samples up to BD84 and was below the LLOQ on BD205. At 50 mg/kg, ixekizumab was quantifiable up to BD84 in 9/9 infants and up to BD205 in 5/9 infants.

Immunophenotyping: No ixekizumab-related changes were observed in lymphocyte subsets in infants. In addition, there were no changes in innate or humoral immunity, as evaluated by NK cell activity and T-cell dependent antibody response, respectively, in infants exposed to maternal doses of ixekizumab.

F_1 toxicokinetics: On BD7 mean serum concentrations of ixekizumab were approximately 20-fold higher in infants born of mothers dosed with 50 mg/kg during gestation than in infants born of mothers dosed with 5 mg/kg during gestation. No clear gender differences were observed in the infant serum concentration values.

Infant histopathology (early deaths): No ixekizumab-related histopathologic findings were identified in the infants that were euthanized early or died prior to scheduled necropsy. Artesia ani identified within female Infant No. 2016 (5 mg/kg ixekizumab) was of singular incidence and considered likely incidental. Mild thymic involution of Male Infant No. 3061 was of single incidence in early deaths, was considered related to debilitation associated with maternal neglect, and was not toxicologically relevant. No ixekizumab-related skeletal findings were noted in the infants that were euthanized or died prior to scheduled necropsy.

Terminal necropsy: At terminal necropsy of infants at ~ BD205 there were no gross, body/organ weight or organ weight ratio, morphometric measurement, external, visceral or heart evaluation, or histopathologic observations that were considered related to the test article.

10 Special Toxicology Studies

The sponsor has evaluated the tissue binding specificity of ixekizumab in normal human and cynomolgus monkey tissues (KTA00027). Ixekizumab was applied to tissue cryosections concentrations of 0.5 μg/mL and 2.5 μg/mL. Ixekizumab binding was assessed immunohistochemically using a biotinylated mouse anti-human IgG4 secondary antibody and chromogenic detection reagent. Appropriate controls were included in the study to validate the adequacy of tissue sections for immunohistochemistry.

No specific ixekizumab staining was observed in any human or cynomolgus monkey tissues examined at either concentration. This lack of cross-reactivity indicates that IL-17A is not present in normal human or cynomolgus monkey tissues.

The potential for ixekizumab and the vehicle without compound (10 mM citrate, pH 6.0, 150 mM sodium chloride, and 0.02% (w/v) polysorbate 80) to cause in vitro hemolysis and serum flocculation using whole blood and serum obtained from cynomolgus monkey and human volunteers was evaluated (N00024). No important compound-

related hemolysis occurred when 200 μL of ixekizumab at concentrations of 0, 5, and 25 μg/mL were mixed with an equal volume of human or monkey whole blood. The resulting concentrations of ixekizumab were 0, 2.5, and 12.5 mg/mL, respectively. Minor compound-related effects consisted of minimal, dose-dependent hemolysis in monkey and human whole blood when mixed with 5 or 25 mg/mL of ixekizumab (Table 2, taken directly from the study report). These changes were not considered important as they were of a small magnitude. Based on the results of this study, intravenous administration of ixekizumab in either species is unlikely to result in hemolysis.

Table 2: Percent Hemolysis for Solutions of LY2439821 and a Solution of the Vehicle Without Compound When Mixed in a 1:1 Ratio With Whole Blood From Cynomolgus Monkeys or Humans, Study N00024

Compound Concentration (mg/mL)	Final Compound Concentration in Mixture (mg/mL)	Monkey Hemolysis Percent (%)	Human Hemolysis Percent (%)
0	0	0.20	0.03
5.0	2.5	0.64	0.52
25.0	12.5	4.32	7.41

Serum flocculation was not detected for either the solutions(s) containing ixekizumab at concentrations of 0, 5 and 25 mg/mL or the vehicle without compound when mixed with monkey or human serum (Table 3, taken directly from the study report).

Table 3: Serum Flocculation Results for Solutions of LY2439821 and for a Solution of the Vehicle without Compound When Mixed With Serum from Cynomolgus Monkeys or Humans, Study N00024

Compound Concentration		Compound: Serum Ratio			
(mg/mL)	Incubation	1:2	1:5	1:20	1:50
0.0 (Vehicle)	Room Temperature (30 minutes)	Neg.	Neg.	Neg.	Neg.
	37°C (60 minutes)	Neg.	Neg.	Neg.	Neg.
5.0	Room Temperature (30 minutes)	Neg.	Neg.	Neg.	Neg.
	37°C (60 minutes)	Neg.	Neg.	Neg.	Neg.
25.0	Room Temperature (30 minutes)	Neg.	Neg.	Neg.	Neg.
	37°C (60 minutes)	Neg.	Neg.	Neg.	Neg.

Neg. = Negative, no flocculation observed.
Trace = Slight cloudiness was observed, light is readily transmitted through the mixture.
1+ = Cloudy, but readily transmit light.
2+ = Cloudy, transmission of light is partially blocked.
3+ = Very cloudy with heavy flocculation, no light is transmitted.

11 Integrated Summary and Safety Evaluation

In the pivotal cynomolgus monkey toxicity study, subcutaneous injections of ixekizumab (0, 0.5, 5, 50 mg/kg/week) for 9 months caused no adverse compound-related clinical signs at ≤5 mg/kg/week. A dose of 50 mg/kg/week exceeded the maximum-tolerated dose for one animal due to injection site reactions resulting in suspension of dosing but was otherwise well tolerated. One male given 5 mg/kg/week was found dead 6 days after the 20th weekly injection (Day 140). Although the cause of death could not be determined, it was not considered compound-related. Ixekizumab administration did not produce any remarkable changes in the peripheral blood immunophenotyping (total T cells, helper T cells, cytotoxic T cells, total B cells, natural killer cells, and helper-to-cytotoxic T cell ratio) or natural killer cell assay data. Based on the injection site reactions requiring dose suspension, the NOAEL for this study was 5 mg/kg/week.

Weekly subcutaneous administration of up to 50 mg/kg/week ixekizumab to pregnant cynomolgus monkeys (gestation day 20 to 139) did not elicit maternal toxicity. No embryotoxicity or fetal malformations were observed in this study. Also, no treatment related effects on fertility or pre- and postnatal development were noted in cynomolgus monkeys treated with 50 mg/kg/week ixekizumab. Neonatal deaths occurred in the infants of two monkeys administered ixekizumab at 5 mg/kg/week and two monkeys administered ixekizumab at 50 mg/kg/week. The cause and/or clinical significance of these findings is unknown.

No genetic toxicity or carcinogenicity studies have been conducted with ixekizumab. The sponsor has conducted a literature review to assess the carcinogenic potential of inhibiting IL-17A which correlates to potential effects after treatment with ixekizumab. The literature results were not definitive but the majority of the literature references indicate no increased carcinogenic potential after inhibition of IL-17A. No nonclinical studies to address the carcinogenic potential of ixekizumab are recommended.

TALTZ is approvable for the treatment of moderate-to-severe plaque psoriasis from a pharmacology/toxicology perspective.

12 Appendix/Attachments

Appendix #1 Recommended label and supportive information

Multiples of human exposure have been derived based on a mg/kg basis.

Maximum recommended human dose:

(2 x 80 mg) ÷ 60 kg = 2.67 mg/kg

Multiples of clinical dose

NOAEL in monkey EFD study = 50 mg/kg

50 mg/kg ÷ 2.67 mg/kg = ~19

Recommended Label.

HIGHLIGHTS OF PRESCRIBING INFORMATION
INDICATIONS AND USAGE

TALTZ™ is a humanized interleukin-17A antagonist indicated for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. (1)

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on TALTZ use in pregnant women inform any drug associated risks. Human IgG is known to cross the placental barrier; therefore, TALTZ may be transmitted from the mother to the developing fetus. An embryofetal development study conducted in pregnant monkeys at doses up to 19 times the maximum recommended human dose (MRHD) revealed no evidence of harm to the fetus due to ixekizumab *[see Data]*.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

An embryofetal development study was conducted in cynomolgus monkeys administered ixekizumab. No malformations or embryofetal toxicity were observed in fetuses from pregnant monkeys administered ixekizumab weekly by subcutaneous injection during organogenesis at doses up to 19 times the MRHD (on a mg/kg basis (b) (4) (b) (4) of 50 mg/kg/week). Ixekizumab crossed the placenta in monkeys.

In a pre- and post-natal development toxicity study, pregnant cynomolgus monkeys were administered weekly subcutaneous doses of ixekizumab up to 19 times the MRHD [redacted]. Neonatal deaths occurred in the infants of two monkeys administered ixekizumab at 1.9 times the MRHD (on a mg/kg basis of 5 mg/kg/week) and two monkeys administered ixekizumab at 19 times the MRHD (on a mg/kg basis of 50 mg/kg/week). The [redacted] clinical significance of these findings are unknown. No ixekizumab-related effects on [redacted] functional or immunological development were observed in the infants from birth through six months of age.

8.2 Lactation

Risk Summary

There are no data on the presence of ixekizumab in human milk, the effects on the breastfed infant, or the effects on milk production. Ixekizumab was detected in the milk of lactating cynomolgus monkeys. [redacted]
The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TALTZ and any potential adverse effects on the breastfed infant from TALTZ or from the underlying maternal condition.

CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ixekizumab is a humanized IgG4 monoclonal antibody that selectively binds to the interleukin 17A (IL-17A) cytokine and inhibits its interaction with the IL-17 receptor. IL-17A is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Ixekizumab inhibits the release of proinflammatory cytokines and chemokines.

NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies have not been conducted to evaluate the carcinogenic or mutagenic potential of TALTZ. Some published literature suggests that IL-17A directly promotes cancer cell invasion in vitro, whereas other reports indicate IL-17A promotes T-cell mediated tumor rejection. Depletion of IL-17A with a neutralizing antibody inhibited tumor development in mice. The relevance of experimental findings in mouse models for malignancy risk in humans is unknown.

No effects on fertility parameters such as reproductive organs, menstrual cycle length, or sperm were observed in sexually mature cynomolgus monkeys that were administered ixekizumab for 13 weeks at a subcutaneous dose of 50 mg/kg/week (19 times the MRHD on a mg/kg basis). The monkeys were not mated to evaluate fertility.

Appendix #2- References

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/s/

JILL C MERRILL
11/02/2015

BARBARA A HILL
11/02/2015

Pharmacology/Toxicology Supervisory Memorandum

BLA number: 125521
SDN/date/type of submission: 1 / March 23, 2015/ New BLA
Applicant: Eli Lilly
Supervisor name: Barbara Hill
Division name: Division of Dermatology and Dental Products
Date: November 2, 2015
Drug: TALTZ (ixekizumab)
Pharmacologic class: Humanized interleukin-17A antagonist
Indication: Moderate to severe psoriasis

General comments:

- I concur with the overall assessment and conclusions contained in Dr. Jill Merrill's Pharmacology/Toxicology review for this biologic product.
- I concur that there are no nonclinical approval issues for this biologic product and that this BLA is approvable from a Pharmacology/Toxicology perspective.
- I concur that there are no nonclinical Post-Marketing Requirements recommended for this BLA.
- I concur with the recommended nonclinical labeling changes proposed by Dr. Merrill for TALTZ contained in section 1.3.3 of her review which include:
    - Pharmacologic Class designation of "humanized interleukin-17A antagonist"
    - The revisions proposed for Sections 8.1, 8.2, 12.1 and 13.1 of the label

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/s/

BARBARA A HILL
11/02/2015

Comments on BLA 125521 Ixekizumab

From: A. Jacobs AD

Date: Sept 11, 2015

1. There were no pharm-tox related approval issues.
2. I have discussed some nonclinical labeling comments with the reviewer and she will address them as appropriate.

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/s/

ABIGAIL C JACOBS
09/11/2015