CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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NON-CLINICAL 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

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Product:	Lyumjev (pending)
Indication:	Diabetes Mellitus
Applicant:	Eli-Lilly and Company
Review Division:	Division of Diabetes, Lipid Disorders, and Obesity
Reviewer:	D. Minck
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1 Executive Summary

1.1 Introduction

Eli Lilly and Company (applicant) has submitted a BLA 351(a) for LY900014, (b) (4) rapid acting formulation of insulin lispro, to improve glycemic control in patients with type 1 or type 2 diabetes. The LY900014 formulation contains the same active ingredient (insulin lispro) used in their Humalog® product along with two additional excipients (treprostinil and sodium citrate) (b) (4)

1.2 Brief Discussion of Nonclinical Findings

The nonclinical support for this application primarily consisted of an assessment of the excipient treprostinil as the active component insulin lispro was previously evaluated in support of Humalog® (approved in 1996). A micro-dose of treprostinil is included in the LY900014 formulation as an excipient (b) (4) Treprostinil, a prostacyclin analog with vasodilatory activity, is the active ingredient of marketed products (Remodulin, Orenitram, and Tyvaso) approved for use in the treatment of pulmonary arterial hypertension (PAH) to systemically lower blood pressure. The applicant conducted their own series of nonclinical studies with treprostinil to support its use as an excipient in LY900014. The dose of treprostinil in LY900014 (15 ng/kg/day[1] based on a 100 kg person administered 150 U/day of LY900014) is well below the starting dose of treprostinil (1800 ng/kg/day) used in the marketed product Remodulin® (which is administered by intravenous or subcutaneous injection).

Pharmacology studies were conducted with LY900014 while safety pharmacology, pharmacokinetic, and toxicology studies were conducted with treprostinil alone.

In multiple nonclinical pharmacology studies conducted with LY900014 , increased insulin levels and more rapid declines in glucose levels were evident as compared to that seen with Humalog®.

Safety pharmacology studies with treprostinil revealed no effects on respiratory or central nervous system functioning. Cardiovascular safety pharmacology studies in dogs revealed prolonged QT/QTc times only at multiples >50-fold the clinical exposure to treprostinil in LY900014.

Treprostinil was rapidly absorbed in nonclinical species with peak levels reached within 40 minutes. It is widely distributed with the highest levels found at the injection site, liver, kidney, and plasma. It is primarily excreted in bile and feces.

[1] Based on an estimated insulin lispro dose of 1.5 U/kg/day administered to a 100 kg patient with T2DM, 150 U/day of insulin lispro containing 1500 ng/day of treprostinil (15 ng/kg/day) would be administered (5 ng/kg pre-prandial dose 3 times/day)

Repeat-dose toxicity studies of up to 6 months in duration were conducted with treprostinil in the rat and dog. Treprostinil-related effects in both species consisted of red discoloration of the skin on the face, ears, and/or forelimbs considered related to its pharmacologic activity. These signs were evident for a short period after dosing. No adverse effects were seen on other parameters or tissues evaluated in these studies. Treprostinil showed no evidence of genotoxocity and it had no effects on fertility or embryofetal development. The exposure to treprostinil at the NOAEL dosages in the repeat-dose and reproductive toxicity studies was greater than 250-fold the exposure to treprostinil in a 100 kg patient administered 150 U/day of LY900014.

There was no evidence of injection site irritation in a study in which Humalog® (up to 201 U/kg) and Remodulin® (up to 2290 ng/kg) were administered alone or in combination. However, there was evidence of dermal irritation with treprostinil at a dose of 2000 mg/kg and ocular irritation at a concentration of 20% (w/v), dosages/concentrations well above those that would be encountered clinically.

1.3 Recommendations

1.3.1 Approvability

This BLA is approvable from the PharmTox perspective

1.3.2 Additional Nonclinical Recommendations

None

1.3.3 Labeling

Treprostinil did not induce toxicity at high multiples of its exposure in the LY90014 formulation. As a result, the nonclinical sections of the label for this product can use verbiage consistent with that summarizing the insulin lispro data in the approved Humalog® label.

2 Drug Information

2.1 Drug

Insulin Lispro
CAS Registry Number: 133107-64-9

Code Name: LY900014

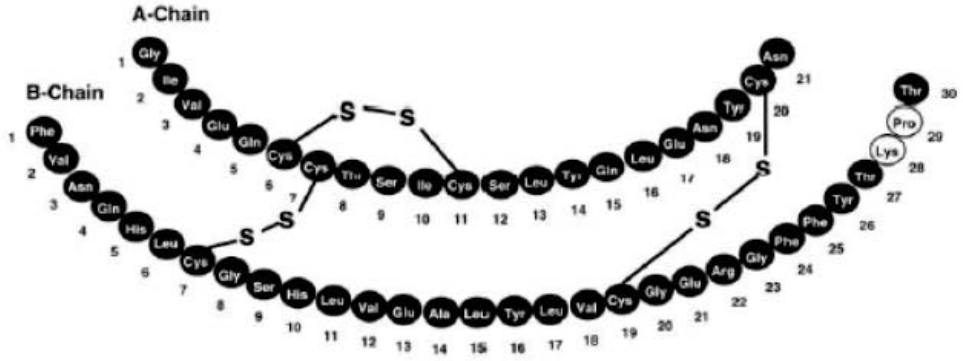
Chemical Name: Insulin lispro is a 2-chain peptide containing 51 amino acids. The A-chain is composed of 21 amino acids and the B-chain is composed of 30 amino acids. Insulin lispro is nearly identical in structure to human insulin, only differing in amino acid sequence at positions 28 and 29 of the B chain. Human insulin is Pro(B28), Lys(B29), whereas insulin lispro is Lys(B28), Pro(B29).

1. 8A-L-threonine-10A-L-isoleucine-28B-L-lysine-29B-Lproline-30B-L-threonine insulin (ox)
2. 28B-L-lysine-29B-L-proline insulin (human)

Molecular Formula/Molecular Weight: $C_{257}H_{383}N_{65}O_{77}S_6$

Structure or Biochemical Description:

Figure 1: Structure of Insulin Lispro



Representation of the primary structure of insulin lispro.

Pharmacologic Class: insulin analog

Treprostinil

Added as an excipient to the LY900014 formulation [redacted] (b) (4)

CAS Registry Number: 81846-19-7

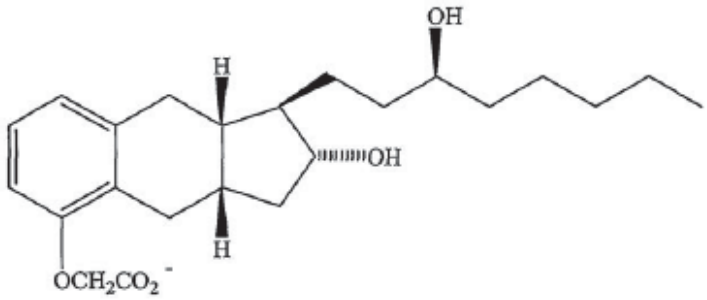
Code Name: LY3326777 sodium, Compound 3354125, LSN3354125

Chemical Name: 2-[[(1R,2R,3aS,9aS)-2,3,4,9,9a-hexahydro-2-hydroxy-1-[(3S)-3-hydroxyoctyl]-1H-benz[f]inden-5-yl]oxy]-acetic acid

Molecular Formula/Molecular Weight: $C_{23}H_{34}0_5$ / 390.5

Structure or Biochemical Description:

Figure 2: Structure of Treprostinil



Pharmacologic Class: Prostacycline vasodilator

2.2 Relevant INDs, NDAs, BLAs and DMFs

- NDA 020563 - Humalog® [insulin lispro (rDNA origin)]; initial approval 14 Jun 96
- NDA 018781 - Humulin® N (human insulin [rDNA origin] isophane suspension); initial approval 28 Oct 82
- NDA 21272 and 208276 - Remodulin® (treprostinil); initial approval 21 May 02
- IND 127210 – The IND for this formulation of insulin lispro with sodium citrate and treprostinil

2.3 Drug Formulation

LY900014 will be administered by subcutaneous (sc) or intravenous (iv) injection. It will be available at dosage strengths of 100 or 200 U/mL. The formulation strengths to be marketed (analogous to that used in the phase 3 clinical trials) are compared to that of the Humalog® formulation in the reviewer table below:

Table 1: LY900014 Formulation Composition

Ingredient	Test Article		
	Humalog	LY900014	LY90014
	Quantity per mL		
Insulin lispro[a]	100 U	100 U	200 U
Treprostinil[b]	-	1.06 µg	1.06 µg
Sodium citrate dihydrate	-	4.41 mg (15mM)	4.41 mg (15mM)
Dibasic sodium phosphate heptahydrate	1.88 mg	-	-
Zinc oxide	19.7 µg	39 µg	52 µg
Magnesium chloride hexahydrate	-	1.02 mg (5mM)	1.02 mg (5mM)
Metacresol	3.15 mg	3.15 mg	3.15 mg
Glycerol	16 mg	12.1 mg	12.1 mg
Water for injection	q.s. to 1 mL	q.s. to 1 mL	q.s. to 1 mL

[a] (b) (4) 100 U formulation (b) (4) 200 U formulation
[b] Calculated to provide 1 µg/mL

2.4 Comments on Excipients

The excipients in LY900014 that are not present in Humalog® are treprostinil, sodium citrate, and magnesium chloride while zinc oxide is used at a higher level. Treprostinil is used in marketed drugs at a higher level than in LY900014 and the sponsor has also qualified its use. The levels of other excipients are within the ranges listed in the FDA inactive ingredient database and/or were qualified at the listed concentration in the chronic toxicity studies.

2.5 Comments on Impurities/Degradants of Concern

There are no impurities or degradants of concern.

2.6 Proposed Clinical Population and Dosing Regimen

Adults with diabetes.

2.7 Regulatory Background

Summarized below are the major project milestones and interactions with the applicant in which nonclinical issues were a key component:

- Pre-IND package submitted 20 Oct 15. Applicant indicates nonclinical development fill follow FDA guidance for excipients. FDA agreed with this concept 1 Dec 15.
- Sponsor submitted justification for why carcinogenicity studies would not be informative on 28 Mar 16. The Division agreed that a carcinogenicity assessment was not needed on 27 Apr 16.
- End of Phase 2 meeting held 19 Apr 17. PharmTox agreed that nonclinical safety information provided to date would support marketing authorization provided remaining studies did not identify risks. Also agreed that a juvenile animal study would not be necessary provided no unexpected effects occur in pre/postnatal toxicity study.
- Pre-BLA meeting held 22 May 19. No nonclinical issues.
- BLA filed 15 Aug 19.

3 Studies Submitted

3.1 Studies Reviewed

The applicant conducted a nonclinical pharmacology study with LY900014 while safety pharmacology, pharmacokinetic, and toxicology studies were conducted with treprostinil to support its use in the LY900014 formulation. The studies reviewed are summarized in the table below:

Table 2: Nonclinical Studies Reviewed

Study Number	Brief Title
Pharmacology	
DBT172	Effect of treprostinil on skin blood flow
DBT173	Effect of treprostinil on insulin lispro PK/PD in diabetic mini-swine
DBT188	Effect of formulation B on vascular permeability
DBT198	Effect of remodulin® on insulin lispro PK/PD at a fixed dose volume in diabetic mini-swine
DBT199	Effect of remodulin® on insulin lispro PK/PD following sc dosing in diabetic mini-swine
DBT216	Insulin lispro transport across endothelial cells
DBT231	Effects of citrate, treprostinil, and citrate + treprostinil on glucodynamics and PK of insulin lispro in diabetic mini swine
DBT232	Effect of varying citrate concentration + fixed treprostinil concentrations on glucodynamics and PK of insulin lispro in diabetic mini swine
DBT233	Effect of fixed citrate concentration + varying treprostinil concentrations on glucodynamics and PK of insulin lispro in diabetic mini swine
DBT253	Glucodynamics and insulin lispro PK in mini swine administered LY900014
Safety Pharmacology	
150715FMD	Effect of treprostinil in hERG assay
8328214	Cardiovascular safety pharm of treprostinil in dogs
Pharmacokinetics	
8329342	PK, bioavailability, distribution, metabolism, and elimination of treprostinil in rats
8329343	Metabolite profiling of treprostinil in rats
8333362	In vitro metabolism of treprostinil
Toxicology	
8327887	3-month rat with treprostinil
8340039	6-month rat with treprostinil
8327888	3-month dog with treprostinil
8340050	6-month dog with treprostinil
Genotoxicity	
8327866	Chromosome aberration assay with treprostinil
8327885	Bacterial reverse mutation assay with treprostinil
8327890	Rat micronucleus assay with treprostinil
Reproductive Toxicity	
8338440	Fertility and early embryonic development in male rat with treprostinil
8338441	Fertility and early embryonic development in female rat with treprostinil
8338439	Embryofetal development dose-ranging in rabbit with treprostinil
8338442	Embryofetal development in rat with treprostinil
8338443	Embryofetal development in rabbit with treprostinil
20104727	Pre- and post-natal toxicity in rats with treprostinil
Other Toxicology	
8330849	Tolerability study in rats given humalog® and remodulin® alone or in combination
15AI000.350055	Bovine corneal opacity and permeability with treprostinil
20085992	Dermal irritation in rats administered treprostinil

These nonclinical studies were reviewed in detail under the IND (reviews dated 3 Feb 16, 16 Mar 16, 19 May 16, 13 Oct 16, 4 Jan 17, 11 May 17, and 27 Jun 18). This current document summarizes the key findings from many of these studies.

3.2 Studies Not Reviewed

The applicant re-submitted nonclinical pharmacology, pharmacokinetic, and toxicology studies that were originally relied upon to support the initial marketing application for insulin lispro. None of these studies were reviewed to provide support for this reformulation of insulin lispro.

Studies supporting the marketing application of treprostinil were not reviewed.

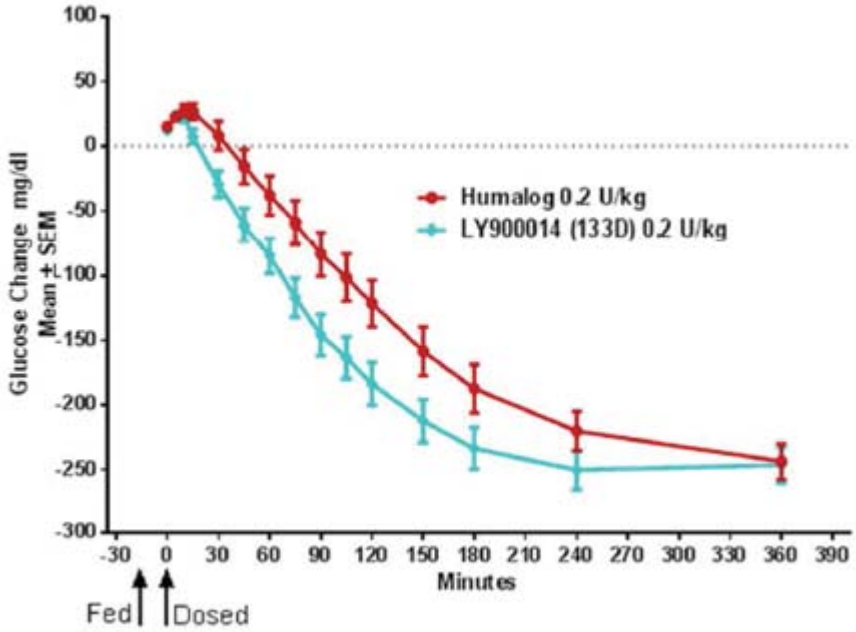
4 Pharmacology

4.1 Primary Pharmacology

A series of studies were conducted to demonstrate that citrate and treprostini (b) (4) in rats following subcutaneous administration of citrate-containing formulations as assessed using the Miles assay. Insulin lispro formulations containing various concentrations of sodium citrate revealed dose-dependent increases in insulin lispro levels across microvascular endothelial cells. Treprostinil administration elicited (b) (4) laser doppler imaging. Various levels of citrate and treprostinil were subsequently evaluated in insulin lispro formulations administered to diabetic swine in order to determine the optimal concentration of each excipient. These studies revealed faster lowering of plasma glucose levels with one or more of the excipients as compared to that induced by Humalog alone.

In diabetic swine, the final commercial formulation of LY900014 caused a more rapid reduction in glucose levels as compared to that occurring with Humalog as shown in the applicant figure below:

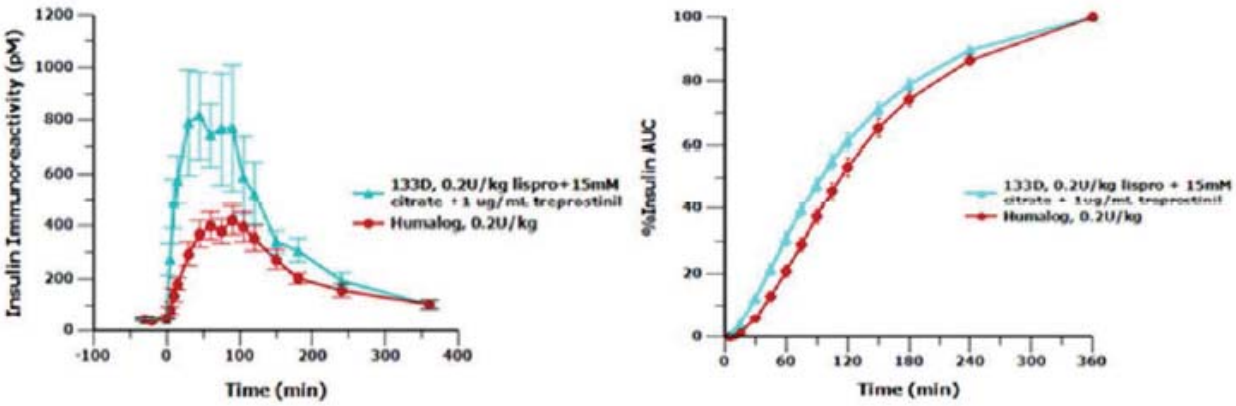
Figure 3: Glucose Change from Baseline in Diabetic Swine



Applicant figure

Insulin concentrations and exposure were also increased with LY900014 as compared to that with Humalog, with t_{max} occurring earlier, a higher C_{max} and AUC, and a slower clearance of insulin noted. Data are shown in the applicant figures below:

Figure 4: Insulin Concentration and Exposure in Diabetic Swine



Applicant figure

The pharmacokinetics of insulin based on this study are summarized in the applicant table below:

Table 3: Insulin Pharmacokinetics in Diabetic Swine

Mean ± SEM Pharmacokinetic Parameters of Total Insulin in Male Diabetic Pigs Administered 0.2 U/kg Humalog or 0.2 U/kg of Insulin Lispro in the LY900014 formulation (Report DBT253)

Formulation	C_{max} (pmol/L)	$AUC_{0-\infty}$ (pmol•h/L)	Cl/F (L/h)	t_{max} (min)	Early 50% t_{max} (min)	Late 50% t_{max} (min)
100 U/mL insulin lispro (Humalog)	525 ± 54	1700 ± 233	42.6 ± 4.7	92.5 ± 9	29.7 ± 3.7	169 ± 16
100 U/mL insulin lispro+ 1.0 µg/mL treprostinil + 15 mM citrate (LY900014)	1090 ± 240 p≤0.001[a]	2550 ± 400 p≤0.001[a]	30.0 ± 3.2 p≤0.001[a]	54.7 ± 6.7 p=0.0049[a]	12.9 ± 1.9 p=0.0002[a]	129 ± 11 p=0.011[a]

Abbreviations: $AUC_{0-\infty}$ = area under the serum concentration versus time curve from time 0 to infinity; C_{max} = maximum observed serum concentration; CL/F = apparent y clearance; Early 50% t_{max} = time to early half C_{max}; Late 50% t_{max} = time to half maximum observed drug concentration after t_{max}; SEM = standard error of the mean; t_{max} = time of maximum observed concentration.

[a] Comparison versus Humalog (no citrate or treprostinil).

Note: Number of animals per group = 15 to 18 used in PK and statistical analyses. Statistical comparisons to the Humalog control group were made using a mixed effects ANOVA with fixed effects of formulation and period and random animal effect, and the log of PK parameters were taken to stabilize the variance.

Applicant table

4.2 Secondary Pharmacology

NA

4.3 Safety Pharmacology

The applicant conducted a series of cardiovascular safety pharmacology studies with treprostinil. A hERG study revealed minimal inhibition (3.3%) of the hERG channel at a concentration of 298 µM.

Cardiovascular endpoints were evaluated in dogs as part of the toxicological assessment the applicant performed with treprostinil. Treprostinil dosages of 0.004, 0.015, and/or 0.07 mg/kg were administered once or repeatedly for up to 6-months. Cardiovascular effects observed in these studies included prolongation of QT/QTc intervals by up to 9 msec at 0.07 mg/kg following a single dose but not after multiple dosing; no effects were observed on PR, QRS, or QT/QTc intervals. Reductions in systolic, diastolic, and mean arterial pressure and pulse pressure (<50%) occurred at dosages ≥ 0.015 mg/kg; there were corresponding increases (up to 55%) in heart rate at 0.07 mg/kg. These effects were of short duration (<2.5 hours). The NOEL for cardiovascular effects was 0.004 mg/kg. The C_{max} at this dose (from day 1 of the 6-month study) was 1.58 ng/mL (52-fold the C_{max} of treprostinil (0.03 ng/mL) at 1500 ng/day in humans).

Respiratory and CNS endpoints were evaluated in a second 3-month toxicity study with treprostinil in which dosages of 0.01, 0.03, and 0.1 mg/kg were administered. No adverse effects on respiratory or CNS parameters were identified.

5 Pharmacokinetics/ADME/Toxicokinetics

The *in-vivo* pharmacokinetic profile of treprostinil was determined following single subcutaneous (sc) or intravenous (iv) dose administration in rats while the toxicokinetic profile was determined in rats, pregnant rabbits, and dogs in conjunction with repeat dose toxicity studies in these species.

Following single sc (0.4 mg/kg) or iv (0.2 mg/kg) administration of treprostinil, absorption is rapid with t_{max} reached at 0.5 to 0.625 hours, respectively, post dosing and the half-life in plasma was 1.5 to 2 hours following either route of administration. With both routes, treprostinil is the most abundant component in plasma followed by 3 oxidative metabolites. In rat and human hepatocytes, treprostinil is primary metabolized via oxidation; there were no metabolites observed in humans that were not also observed in rats. Hepato-biliary/fecal excretion is the major route of elimination following sc dosing. Urinary excretion was minimal at around 5% following both sc and iv administration. Radioactivity was widely distributed following sc administration. In pigmented rats, the highest levels occurred at 0.5 hours post-dose (first time point) and were found at the dose site, liver, and various parts of the kidney. In non-pigmented rats the highest levels were seen at 1 hour (first time point) after dosing and occurred at the dose site, liver, and various portions of the kidney. High levels were also detected in GI track contents and bile. Radioactivity was not detected in CNS tissues nor was there an indication of an association with melatonin containing tissues.

The toxicokinetics of treprostinil were determined as part of the toxicity testing. The t_{max} was reached within 40 minutes of dose administration and exposure (C_{max} and AUC) generally increased in a dose-proportional manner. There was no sex effect or evidence of accumulation with repeated dosing.

6 General Toxicology

The applicant conducted a series of repeat dose, genotoxicity, and reproductive and developmental toxicity studies with treprostinil to support its use as an excipient. For all toxicology studies, the exposure to treprostinil at the NOAEL dosage was >250-fold that at the highest projected exposure to treprostinil in patients administered LY900014. Key observations from these studies with treprostinil are summarized below:

6.1 Single-Dose Toxicity

NA

6.2 Repeat-Dose Toxicity

Treprostinil was administered to rats and dogs for up to 6 months by daily subcutaneous injection.

In the rat, dosages of 0.01, 0.03, or 0.1 mg/kg were administered for 3- and 6-months. Effects observed included red discoloration of the skin noted on ears, feet, legs, and/or nose that resolved within an hour of dose administration. These effects were considered related to vasodilation associated with the pharmacologic activity of the drug. Also observed at 0.1 mg/kg were slightly lower but non-adverse effects on body weights (decreased up to 13%) and hypocellularity of the marrow in the sternum with associated hematologic changes (platelet, white blood cell, reticulocyte, neutrophil, and/or monocyte counts reduced by <36%). The NOAEL for the 3- and 6-month rat toxicity studies was considered the highest dose administered (0.1 mg/kg). Following 6-months of treatment, the exposures (AUC_{0-24}) were approximately 55 and 36 ng·hr/mL in males and females, respectively.

Dosages of 0.004, 0.015, or 0.07 mg/kg were administered by daily subcutaneous injection for 3- or 6-months to dogs. Drug-related effects were limited to reductions in systolic and pulse pressures with corresponding increases in heart rate at 0.07 mg/kg (<50% relative to baseline and/or controls). These effects were transient and lasted <2.5 hours. There were no consistent effects on waveform. These effects were considered related to the pharmacologic actions of the drug, and none were adverse. There were no adverse drug-related microscopic effects. The high dose of 0.07 mg/kg was considered the NOAEL in both studies. Following 6-months of treatment, the exposures (AUC_{0-24}) were approximately 29 and 17 ng·hr/mL in males and females, respectively.

7 Genetic Toxicology

An Ames, chromosome aberration, and rat micronucleus assay conducted with treprostinil were all negative for evidence of genotoxicity.

8 Carcinogenicity

The agency has previously agreed that carcinogenicity studies with treprostinil would not be necessary.

9 Reproductive and Developmental Toxicology

Fertility studies were conducted using rats in which treprostinil was administered subcutaneously at dosages of 0.01, 0.03, and 0.1 mg/kg. There were no adverse effects on mating, fertility, viability of the resultant embryo/fetus, sperm parameters, or reproductive organs. The only effects seen were clinical signs (e.g., red discoloration of skin) related to the vasodilatory activity of treprostinil. The NOAEL was the high dose of 0.1 mg/kg. The AUC_{0-24} was approximately 30 and 21 ng·hr/mL in males and females, respectively, at this dose.

The effects of treprostinil on embryofetal development were evaluated in the rat and rabbit. In the rat, subcutaneous dosages of 0.01, 0.03, and 0.1 mg/kg were administered from gestation day 6 to 17. The only drug-related effects on maternal rats were clinical signs related to the pharmacologic action of the drug. There were no effects on the number of implants, embryo/fetal viability, fetal weights or on fetal gross, visceral, or skeletal development. The NOAEL was considered the high dose of 0.1 mg/kg and the AUC_{0-24} at this dose was approximately 30 ng·hr/mL.

In the rabbit, subcutaneous dosages of 0.05, 0.14, or 0.4 mg/kg were administered from gestation day 7 - 19. Treatment with dosages $\geq$0.14 mg/kg was excessively toxic to maternal animals as there were significant reductions in food consumption and body weight during various intervals, with the effects at the high dose leading to early termination of three animals and abortion in a single animal. Increased post-implantation loss was evident at the HD resulting from slight increases in both early and late resorptions relative to the incidence in controls (although within the historical range). Similar findings occurred in the ranging study at the same dose, and the consistency of the findings across studies suggests a potential relationship to drug treatment. There were no clear drug-related effects on fetal gross morphological, visceral, or skeletal development. Based on the increased post-implantation loss, the MD of 0.14 mg/kg is considered the NOAEL for embryo/fetal development. At this dosage, the maternal exposure (AUC_{0-24}) at the end of dosing was 137 ng·hr/mL.

A pre-and post-natal toxicity study in rats revealed no effects on maternal ability to maintain a pregnancy, deliver a litter, and rear the offspring at subcutaneous dosages of 0.01, 0.03, and 0.1 mg/kg. Treprostinil had no effects on growth, maturation, behavioral/functional performance, or on mating/fertility of the F1 generation. The NOAEL for maternal toxicity and for growth and reproduction of the F_1 generation was considered the HD of 0.1 mg/kg. At this dose, the AUC_{0-24} at the end of the pre-weaning period in F_0 animals was approximately 19 ng·hr/mL.

10 Special Toxicology Studies

Commercial Humalog® (20.1 or 201 U/kg) and Remodulin® (216, 2160, or 2290 ng/kg) were administered alone or in combination to evaluate injection site tolerability. Test article(s) were administered to male Sprague-Dawley rats by subcutaneous injection once daily for 14 days.

The formulations that contained both Humalog® and Remodulin® were mixed and given as a single injection/day. The dosing sites were scored/graded using a modified Draize technique. No compound-related irritation was observed at any of the injection sites with either drug alone or in combination during the in-life phase of the study. There were no macroscopic or microscopic effects observed in any group during postmortem exams that were considered test-article related.

In an acute dermal toxicity study in rats, a single 2000 mg/kg dose of treprostinil was applied to a gauze pad that was subsequently secured to the back of 5 animals/sex to

evaluate its potential for skin irritation. Slight to moderate erythema was observed in all animals that was typically present for 2 to 5 days before resolving. Slight edema was also noted sporadically in 3 of 5 males and 3 of 4 females while flaking of the skin was seen in a single male and female; these effects fully resolved before study termination. Treprostinil was considered a slight skin irritant based on these results.

Treprostinil was evaluated for its potential to be an ocular irritant in a bovine corneal opacity and permeability assay. A 20% (w/v) solution of treprostinil was tested. Opacity (an indicator of damage) was increased relative to negative controls but not to the extent seen with a positive control. Permeability (an indicator of loss of function of the corneal barrier) was increased relative to both negative and positive controls. Treprostinil was considered a severe eye irritant based on the results.

11 Integrated Summary and Safety Evaluation

Eli Lilly has submitted a 351(a) BLA for a rapid-acting formulation (LY900014) of Humalog®. The active ingredient remains the same (insulin lispro) as in the marketed product. LY900014 differs from Humalog® by the addition of three components:

- sodium citrate (b) (4)
- treprostinil (b) (4)
- magnesium chloride (b) (4)

Since the active drug substance in LY900014 is the same as in Humalog®, the supportive nonclinical testing strategy did not include an assessment of insulin lispro. The applicant instead relied on the previous findings of safety that supported the marketing of Humalog®. Studies with insulin lispro supporting its original marketing application were re-submitted, but not reviewed.

Two ingredients are added to the LY900014 formulation (b) (4) A micro-dose of treprostinil is included (b) (4) A 100 kg individual administered 150U/day of LY900014 would receive 15 ng/kg/day of treprostinil (1800 ng/kg/day is the therapeutic starting dose in marketed products for PAH). At this low level, treprostinil is considered an excipient in the formulation and it was evaluated in a series of nonclinical studies (consistently with the FDA Guidance for Industry: "Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients"; May 2005). These studies comprise the majority of data submitted in support of this application. Sodium citrate was added to the formulation (b) (4) No testing was done with it as the level used in LY900014 is in the range of that used in other marketed parenteral products administered chronically. The other excipients are used in parenteral drug products at higher levels and no nonclinical studies were necessary to support their use in LY900014.

Sodium citrate and treprostinil (b) (4)

glucose levels with one or more of the excipients as compared to that induced by Humalog alone. Studies in diabetic swine demonstrated quicker rises in insulin levels and a more rapid lowering of glucose levels following treatment with LY900014 as compared to that seen with Humalog®.

Safety pharmacology studies with treprostinil revealed prolongation of QT/QTc intervals at a dose that was >50-times that occurring clinically. An effect on the hERG current was also observed, but only at a concentration greater than 10^5-fold the concentration of treprostinil in LY900014.

Peak levels of treprostinil were generally observed within 40 minutes of dosing across nonclinical species following subcutaneous administration. It is widely distributed with the highest levels occurring at the injection site, liver, kidney, and plasma. In plasma from intact rats, treprostinil is the primary circulating component (35%). Three additional oxidative metabolites comprise an additional 43%. The remaining metabolites comprise less than 5% each. Excretion is via hepatobiliary/fecal excretion, with excretion in bile accounting for approximately 93% of the administered radioactivity.

Repeat-dose toxicity studies with treprostinil were conducted in the rat and dog. Treprostinil was administered at high dosages (relative to the clinical level of treprostinil in LY900014) in studies of 3- and 6-months duration in both species. In these studies, clinical signs were limited to the transient appearance of red discoloration of the skin on the face, ears, and forelimbs of test species that were considered related to the pharmacologic action of the drug. There were no adverse effects observed during the in-life phase of the repeat dose toxicity studies in rats or dogs. There also was no indication of target organ toxicity at necropsy. Genotoxicity revealed no evidence of mutagenicity and reproductive toxicity studies did not reveal effects on fertility or pre-/post-natal development. Increased post-implantation loss was observed in the rabbit, but only at an exposure many thousand-fold above the potential clinical exposure.

In a study in which high doses of Humalog® (up to 201 U/kg) and Remodulin® (up to 2290 ng/kg) were administered alone or in combination to rats, no evidence of irritation at the injection site was noted. However, treprostinil was considered a dermal irritant at a concentration of 20% and an ocular irritant at 2000 mg/kg; these dosages are well above the clinical range.

The NOAEL dose in the pivotal toxicity studies was associated with exposures that ranged from many hundreds to many thousands of times the clinical exposure. The exposure multiples at the NOAEL doses relative to a clinical dose of 1500 ng/day are summarized in the table below:

Table 4: Treprostinil Exposure Multiples

Study / Species	NOAEL Dose (mg/kg)	AUC_{0-24} at NOAEL (ng·hr/mL)	Safety Margin Based on AUC[a]
3-month rat	0.1	40.2[b]	574x
6-month rat	0.1	45.4[b]	649x
3-month dog	0.07	27.7[b]	396x
6-month dog	0.07	22.9[b]	327x
Fertility male rat	0.1	30.2	431x
Fertility female rat	0.1	21.4	306x
EFD rat	0.1	29.8	426x
EFD rabbit	0.14	137	1957x
Pre-/postnatal rat	18.7	18.7	267x

a) AUC in human of 0.07 ng·hr/ml at 1500 ng/day (derived from exposure data generated at 1000 and 2000 ng/day from study ITAO)
b) mean of males and females

In summary, there was no adverse toxicity caused by treprostinil at high dose/exposure multiples of its level in the LY900014 formulation. Consequently, its inclusion as an excipient does not poses a risk from a toxicologic perspective.

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/s/

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05/04/2020 01:02:08 PM

FEDERICA BASSO
05/05/2020 12:35:42 PM
I concur