CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125545Orig1s000

NON-CLINICAL REVIEW(S)

MEMORANDUM

Date: June 1, 2017
From: Natalie Simpson, PhD
Pharmacology/Toxicology Reviewer
Division of Hematology Oncology Toxicology (DHOT)
Office of Hematology and Oncology Products (OHOP)
Re: Responses to CRL for Preliminary Review
BLA: 125545
Drug: RETACRIT ("Epoetin Hospira", a proposed biosimilar to US-Epogen/Procrit)
Indication: Being developed for the same indications as approved for the reference product US-licensed Epogen/Procrit
Applicant: Hospira, Inc.

"Epoetin Hospira" is a proposed biosimilar to US-Epogen/Procrit, an erythropoietin stimulating agent. The Applicant initially submitted the 351 (k) BLA in December of 2014, along with animal studies to support marketing approval. Comparative animal studies were reviewed by the Agency and from the Pharmacology/Toxicology perspective, there were uncertainties regarding the overall similarity of "Epoetin Hospira" to US-Epogen/Procrit that would be addressed by other disciplines (see Nonclinical Review in DARRTS dated 09/11/15). The Applicant was issued a Complete Response Letter (CRL) by the Agency on October 16, 2015 due to clinical deficiencies and product quality deficiencies pertaining to analytical similarity.

On December 22, 2016, BLA 125545 was resubmitted by the Applicant with responses to the deficiencies. No new nonclinical (e.g., animal data) information was submitted. However, with more Agency experience with biosimilar products since the initial submission of this application, the language of the Pharmacology/Toxicology recommendation for approval changed. During the previous review cycle, it was concluded that "Epoetin Hospira" should not be recommended for approval due uncertainties in the animal data. However, the current Agency thinking is that the animal studies should not be included along with the clinical and analytical similarity studies to support a demonstration of biosimilarity since the animal studies were designed and conducted prior to passage of the BPCI Act to support a stand alone biologic 351 (a) BLA. This change in thinking has no major effect on the regulatory recommendation for approval, which like the previous review cycle, will still be based on clinical and analytical similarity data.

Pharmacology/Toxicology presented at the ODAC Meeting on May 25, 2017 conclusions made from the animal studies comparing head-to-head "Epoetin Hospira" and US-Epogen/Procrit for completeness, even though the studies were not designed to support a demonstration of biosimilarity. Also noted during the presentation was that a more tailored approach can be taken to the amount and type of animal data needed to support a demonstration of biosimilarity depending on the strength of the analytical similarity data (*FDA Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product*).

No labeling negotiations with the Applicant were initiated due to the anticipated complete response of the resubmission due to manufacturing site (Facilities) deficiencies. Labeling will therefore be addressed in the subsequent review cycle and will be consistent with the nonclinical sections of the reference product, US-Epogen/Procrit label.

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/s/

NATALIE E SIMPSON
06/01/2017

CHRISTOPHER M SHETH
06/02/2017
I concur

MEMORANDUM

Date: September 11, 2015
From: Christopher Sheth, PhD
Division of Hematology Oncology Toxicology (DHOT)
Office of Hematology and Oncology Products (OHOP)
Re: Approvability for Pharmacology and Toxicology
BLA: 125545
Drug: Referred to as "Epoetin Hospira"[1] by the Applicant
Indication: Anemia due to Chronic Kidney Disease; anemia due to zidovudine in HIV – infected patients; anemia due to chemotherapy in patients with cancer; reduction of allogeneic red blood cell transfusions in patients undergoing elective, noncardiac, nonvascular surgery.
Applicant: Hospira, Inc.

Hospira submitted the 351(k) BLA 125545 requesting marketing approval for "Epoetin Hospira" as a proposed biosimilar to the erythropoietin reference product US-licensed Epogen.

Epoetin Hospira was compared head-to-head with US-licensed Epogen in two 13-week GLP-compliant repeated-dose animal toxicology studies assessing the pharmacodynamics, toxicity, toxicokinetics, and immunogenicity of the two products. The two products were compared following intravenous administration in the Beagle dog and following subcutaneous administration in the Sprague-Dawley rat. The drugs were administered three times per week in both animal studies, which is consistent with the approved dosage and administration recommendations on the US-licensed Epogen label.

The toxicological findings were similar for Epoetin Hospira and US-licensed Epogen and were related to the exaggerated pharmacology of erythropoietin (see Nonclinical Review). Intravenous administration of either Epoetin Hospira or US-Epogen resulted in similar pharmacodynamic responses in dogs as measured by effects on red blood cell counts, hematocrit, hemoglobin, and absolute reticulocyte counts. There was minimal immunogenicity in dogs. While the toxicokinetics in dogs were variable, no toxicologically meaningful differences in pharmacodynamic responses or target organs were observed between "Epoetin Hospira" and US-Epogen by the end of the 13-weeks of intravenous administration. Subcutaneous administration was associated with a greater immunogenic response than that observed in dogs, and the production of anti-drug antibodies in rats, which was associated with lower exposures and lesser pharmacodynamic responses in rats given US-licensed Epogen as compared to those given the proposed biosimilar.

The nonclinical studies needed to support product labeling were reviewed by Dr. Natalie Simpson. The nonclinical findings are summarized in the "Executive Summary" of the BLA review.

[1] For purposes of this review, we generally refer to Hospira's proposed product by the Hospira descriptor "Epoetin Hospira." FDA has not yet designated a nonproprietary name for Hospira's proposed biosimilar product that includes a distinguishing suffix (see Draft Guidance on Nonproprietary Naming of Biological Products).

Recommendation: I concur with the pharmacology/toxicology reviewer that from a nonclinical perspective that because of the differences observed with subcutaneous administration, there are discipline-specific uncertainties regarding the similarity of "Epoetin Hospira" to US-Epogen. Therefore from a Pharmacology/Toxicology perspective, approval is not recommended.

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/s/

CHRISTOPHER M SHETH
09/11/2015

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:	125545
Supporting document/s:	1
Applicant's letter date:	December 15, 2014
CDER stamp date:	December 16, 2014
Product:	RETACRIT (referred to as "Epoetin Hospira" by the Applicant*)
Indication:	Being developed for the same indications as approved for the reference product US-licensed Epogen
Applicant:	Hospira, Inc.
Review Division:	Division of Hematology Oncology Toxicology (DHOT) for Division of Hematology Products (DHP)
Reviewer:	Natalie E. Simpson, PhD
Team Leader:	Christopher M. Sheth, PhD
Division Director:	John Leighton, PhD, DABT (DHOT) Ann Farrell, MD (DHP)
Project Manager:	Beatrice Kallungal

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of BLA 125545 are owned by Hospira, Inc. or are data for which Hospira, Inc. has obtained a written right of reference. Any information or data

* For purposes of this review, we generally refer to Hospira's proposed product by the Hospira descriptor "Epoetin Hospira." FDA has not yet designated a nonproprietary name for Hospira's proposed biosimilar product that includes a distinguishing suffix (see Draft Guidance on Nonproprietary Naming of Biological Products).

necessary for approval of BLA 125545 that Hospira, Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of BLA 125545.

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1 Executive Summary

1.1 Introduction

Hospira, Inc. is requesting marketing approval for “Epoetin Hospira”, as a proposed biosimilar product to the erythropoietin reference product, US-licensed Epogen (also referred in this review as US-Epogen). US-Epogen was approved in 1989 and the current label includes indications and usage information for treatment of: (1) anemia due to chronic kidney disease (CKD) in patients on dialysis and not on dialysis, Zidovudine in HIV-infected patients, and the effects of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy; and, (2) reduction of allogeneic RBC transfusions in patients undergoing elective, noncardiac, nonvascular surgery. US-Epogen is approved for administration via the intravenous (IV) and subcutaneous (SC) routes.

Erythropoietin protein is a glycosylated cytokine with the primary function of stimulating the proliferation and differentiation of erythroid precursors in the bone marrow. It is induced in response to a lower than normal blood oxygen content and produced primarily by a subset of peritubular fibroblasts in the kidney localized in the cortex, close to the boundary with the medulla. It may interact with the homodimeric erythropoietin receptor on particular cells in the erythropoietic lineage (including Burst Forming Unit-Erythroid (BFU-E), Colony Forming Unit-Erythroid (CFU-E), pro-erythroblast, and basophilic erythroblast) to prevent apoptosis in cells as they mature. According to the approved US-Epogen labeling, US-Epogen stimulates erythropoiesis by the same mechanism as endogenous erythropoietin and increases the reticulocyte count within 10 days of initiation, followed by increases in the red blood cell count, hemoglobin, and hematocrit, usually within 2 to 6 weeks.

As part of Hospira’s developmental strategy for “Epoetin Hospira”, “Epoetin Hospira” was compared head-to-head with US-Epogen as the comparator in two animal studies assessing pharmacodynamics (PD), toxicity, toxicokinetics (TK), and immunogenicity. The nonclinical development of “Epoetin Hospira” involved selecting doses, routes of administration, and a dosing regimen consistent with the currently approved labeling of US-Epogen. The nonclinical data indicate that “Epoetin Hospira” is similar to US-Epogen for the intravenous route of administration, but not for subcutaneous administration, based on the original “pilot-scale” “Epoetin Hospira” formulation. Considering the differences observed with subcutaneous administration, there are discipline-specific uncertainties regarding the similarity of “Epoetin Hospira” to US-Epogen.

1.2 Brief Discussion of Nonclinical Findings

The nonclinical data submitted to the BLA demonstrate the similarity (i.e., similar PD characteristics and similar toxicity) of “pilot scale” “Epoetin Hospira” and US-licensed Epogen via the intravenous route.

Two GLP-compliant 13-week comparative toxicology studies were submitted to support the similarity of "Epoetin Hospira" to US-Epogen. Subcutaneous and IV injection routes of administration, with a three times weekly dosing regimen for 13 weeks, were assessed in Sprague-Dawley rats and Beagle dogs, respectively, at doses of 150, 450, and 1500/900 IU/kg for "Epoetin Hospira" and US-Epogen. The rat comparative toxicology study does not support similarity via that SC route of administration due to the lower exposures and differences in several PD endpoints, including lower red blood cell count (RBC), hemoglobin (HGB), hematocrit (HCT), and absolute reticulocytes (RETIC) in US-Epogen treated rats compared to those treated with "Epoetin Hospira". These differences were associated with a higher incidence of anti-drug antibody (ADA) development to the reference product compared to "Epoetin Hospira". The Applicant suspects that the high incidence of ADA is related to the route of administration (evidence supports SC is more immunogenic than IV administration) and the presence of human serum albumin (HSA) as a stabilizer in the reference product. In dogs, PD endpoints, including RBC, HGB, HCT, and RETIC were similar for "Epoetin Hospira" and US-Epogen, supporting similarity via the IV route of administration.

Both the rat and dog comparative toxicology studies revealed similar pharmacologically driven mechanisms of toxicity for "Epoetin Hospira" and US-Epogen. However, there were some differences between "Epoetin Hospira" and US-Epogen toxicokinetics (lower exposure for the biosimilar compared to the reference product in both rats and dogs on Day 1 and faster clearance in dogs on Day 89), but differences were generally within the range of individual animal variability.

Overall, the toxicological findings between "Epoetin Hospira" and the reference product administered intravenously in the comparative dog toxicology study were similar and related to the exaggerated pharmacology of erythropoietin – early mortality associated with multi-organ congestion, hemorrhage, infarction, and necrosis; body weight loss and reduced body weight gain; increased vascular retinal pattern (size) and tortuosity of the eye (of note, this finding was more pronounced in high dose "Epoetin Hospira" treated dogs compared to US-Epogen treated dogs); and, pharmacologically driven/inflammatory related microscopic findings in organs of the hematopoietic (bone marrow, spleen, lymph nodes, and thymus), digestive (stomach, small intestine, large intestine), and nervous (brain, sciatic nerve, and spinal cord) systems, as well as the kidney, liver, heart, and lungs. Skeletal muscle (moderate edema or marked infarction) was observed only in high dose "Epoetin Hospira" treated animals, but at low incidence.

The totality of the nonclinical data indicate that "Epoetin Hospira" is similar to US-Epogen for the intravenous route of administration, based on the original "pilot-scale" "Epoetin Hospira" formulation, but does not support similarity for subcutaneous administration. Considering the differences observed with subcutaneous administration, there are discipline-specific uncertainties regarding the overall similarity of "Epoetin Hospira" to US-Epogen from the Pharmacology/Toxicology perspective.

1.3 Recommendations

1.3.1 Approvability

From the Pharmacology/Toxicology perspective, the nonclinical data leads to uncertainties regarding the overall similarity of "Epoetin Hospira" to US-Epogen. Therefore, from a Pharmacology/Toxicology perspective, approval is not recommended.

1.3.2 Additional Non Clinical Recommendations

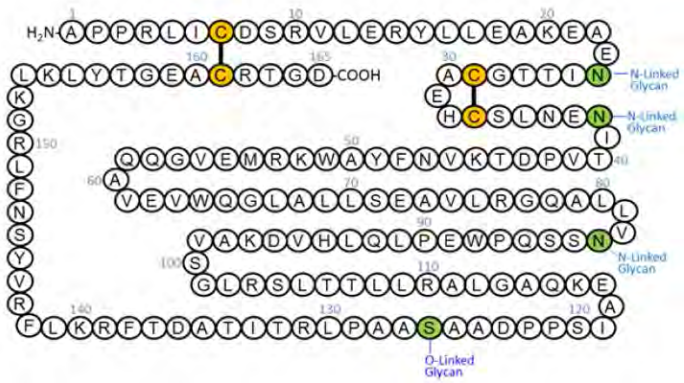
None

1.3.3 Labeling

A labeling review was not conducted due to the Complete Response determination.

2 Drug Information

2.1 Drug

CAS Registry Number	113427-24-0
Code Name	"Epoetin Hospira"; Erythropoetin; Epoetin; EPO; CMO1030 (b) (4) 11341672 (Hospira drug code computer number)
Chemical Name	1-165-Erythropoietin (human clone λHEPOFL13 protein moiety), glycoform α (9CI)
Molecular Formula/ Molecular Weight	$C_{809}H_{1301}N_{229}O_{240}S_5$ / 30.4 kDa
Structure or Biochemical Description	
Pharmacologic class	Recombinant erythropoietin

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 100685; BLA 103234 (US-licensed Epogen)

2.3 Drug Formulation

"Epoetin Hospira" is formulated as a sterile, colorless solution for IV or SC injection in water for injection and contains the excipients sodium monohydrogen phosphate, sodium dihydrogen phosphate, sodium chloride, calcium chloride, polysorbate 20, glycine, leucine, isoleucine, threonine, glutamic acid, and phenylalanine. Single-dose

vials in strengths of 2000 Units/mL, 3000 Units/mL, 4000 Units/mL, 10,000 Units/mL, and 40,000 Units/mL are proposed. These strengths are identical to those of the reference product.

Table 1 Quantitative Model Composition of "Epoetin Hospira" Drug Substance

(Excerpted from Module 3.2.P.2.)

Ingredient	Concentration
Epoetin alfa	(b) (4)
Sodium Phosphate Monobasic, USP or MC	
Sodium Phosphate Dibasic, USP or MC	
Sodium Chloride, MC	
(b) (4)	
WFI, USP	

USP, Unites States Pharmacopeia; MC, Multi-compendial; NF, National Formulary; WFI, Water for Injection;

(b) (4)

Table 2 Target Quantity of "Epoetin Hospira" Drug Product Excipients per Unit Dose, Quality Standards and Functions

(Excerpted from Module 3.2.P.2.)

Components	Compendial Quality Standard	Quantity per Unit Dose	Function
Sodium Phosphate Monobasic, Monohydrate [1]	USP	1.3 mg 1.5 mg [2]	(b) (4)
Sodium Phosphate Dibasic, Anhydrous [1]	USP, EP	4.9 mg 5.7 mg [2]	
Calcium Chloride, Dihydrate	USP	0.01 mg	
Glycine	USP, EP, JP	7.5 mg	
Leucine	USP	1.0 mg	
Isoleucine	USP	1.0 mg	
Threonine	USP	0.25 mg	
L-Glutamic Acid	EP	0.25 mg	
Phenylalanine	USP	0.50 mg	
Sodium Chloride [1]	USP, EP, BP, JP	2.4 mg 2.2 mg [2]	
Polysorbate 20	NF, EP	0.1 mg	
(b) (4)			
Water for Injection	USP	q.s. to 1 mL	
(b) (4)			

q.s., quantity sufficient; A.R., As Required

[1] The target quantity is calculated. The calculation is provided in *Module 3, Section 3.2.P.3.3, Description of Manufacturing Process and Process Controls.*

[2] This quantity per unit dose is applicable to Epoetin Hospira DP 40,000 U/mL only.

[3] The final pH range of the Epoetin Hospira DP is provided in *Section 2.3.P.5.1, Specifications.*

Table 3 Composition of Epogen/Procrit (Reference Product), Non-HSA Containing Formulation (EU Marketed Product) and Test Formulations

(Excerpted from Module 3.2.P.2.2.)

Component	Function	Epogen/Procrit	Non-HSA Epoetin Formulation (EU Market)	Formulation 1	Formulation 2	Formulation 3	Formulation 4
Epoetin	Active Ingredient	X	X	(b) (4)			
Excipients:							
Human Serum Albumin	(b) (4)	X	--				
Polysorbate 20		--	X				
Polysorbate 80		--	--				
Sodium Phosphate Monobasic, Dihydrate		X[1]	X				
Sodium Phosphate Dibasic, Dihydrate		X[1]	X				
Sodium Citrate/Citric Acid		X	--				
Calcium Chloride, Dihydrate		--	X				
Glycine		X	X				
Leucine		--	X				
Isoleucine		--	X				
Threonine		--	X				
Glutamic Acid		--	X				
Phenylalanine		--	X				
Methionine		--	--				
Sodium Chloride		X	X				
Urea		--	X				
(b) (4)		--	--				
		--	--				
Water for Injection		X	X				
(b) (4)		X	X				

[1] Sodium phosphate is used only in the 40,000 Units/mL dose strength formulation

Table 4 Overview of "Epoetin Hospira" Drug Product (DP) Formulation Changes during Nonclinical and Clinical Development

The lot of "Epoetin Hospira" drug product used for both 13-week comparative toxicology studies was formulated based on bioactivity and contained the "Epoetin Hospira" drug substance manufactured at the 400 L "pilot-scale". This is different from the proposed commercial "Epoetin Hospira" drug substance manufacturing process, which was scaled to 20,000 L and determined the active epoetin component based on a target epoetin protein concentration rather than on the basis of in vivo bioactivity.

2.4 Comments on Novel Excipients

None.

2.5 Comments on Impurities/Degradants of Concern

None.

2.6 Proposed Clinical Population and Dosing Regimen

Hospira proposes clinical populations and dosing regimens that are consistent with current US-Epogen labeling. See approved US-Epogen label for more detailed information.

2.7 Regulatory Background

BLA 125545 was submitted on December 16, 2014 for the biologic product "Epoetin Hospira" under Section 351(k) of the Public Health Service Act (42 U.S.C. 262(k). The development program for "Epoetin Hospira" was initiated prior to the BPCI Act. Following passage of the BPCI Act, a series of Biosimilar Product Development

meetings under IND 100685 were held with the FDA to discuss development of "Epoetin Hospira" under the 351(k) pathway. To fulfill the nonclinical requirements for a biosimilar BLA, the Applicant submitted two 13-week comparative toxicology studies that included PK, PD, toxicity, and immunogenicity assessments of the similarity of "Epoetin Hospira" to US-licensed Epogen in side-by-side comparisons in the dog (IV) and rat (SC). An Application Orientation Meeting was held on January 26, 2015.

3 Studies Submitted

3.1 Studies Reviewed

Repeat-Dose Toxicology

Study No.	Title	Module
60486	"Epoetin Hospira": A 13-Week Intravenous Repeat Dose Comparative Toxicity Study Followed by a 4-Week Recovery Period in Beagle Dogs	4.2.3.2.
70882	"Epoetin Hospira": A 13-Week Subcutaneous Repeat Dose Comparative Toxicity Study Followed by a 4-Week Recovery Period in Sprague-Dawley Rats	4.2.3.2.

3.2 Studies Not Reviewed

Primary Pharmacology

Study No.	Title	Module
(b) (4) -631002	A Comparable Activity Study of Four Recombinant Erythropoietin (Epoetin) Products in Female Normocythemic Mice	4.2.1.1.

Single-Dose Toxicology

Study No.	Title	Module
60319	"Epoetin Hospira": An Acute Intravenous Toxicity Study in Beagle Dogs	4.2.3.1.
1632-07608	"Epoetin Hospira": An Acute Toxicity Study Following Subcutaneous Administration in Beagle Dogs	4.2.3.1.
70491	"Epoetin Hospira": An Acute Intravenous Toxicity Study in Sprague-Dawley CD® Rats	4.2.3.1.
1632-07617	"Epoetin Hospira": An Acute Toxicity Study Following Subcutaneous Administration in Sprague-Dawley Rats	4.2.3.1.

Repeat-Dose Toxicology

Study No.	Title	Module
60304	"Epoetin Hospira": A 4-Week Intravenous Toxicity Study with a 2-Week Recovery Period in Beagle Dogs	4.2.3.2.
60320	"Epoetin Hospira": A 2-Week Intravenous Dose Range-Finding Toxicity Study in Beagle Dogs	4.2.3.2.
1632-07766	"Epoetin Hospira": An Eight-Week Subcutaneous Repeat Dose Toxicity Study with a 4-Week Recovery Period in Beagle Dogs	4.2.3.2.
1632-07584	"Epoetin Hospira": A Two-Week Dose Range-Finding Study Following Subcutaneous Administration in Beagle Dogs	4.2.3.2.
70475	"Epoetin Hospira": A 4-Week Intravenous Toxicity Study with a 2-Week Recovery Period in Sprague-Dawley CD® Rats	4.2.3.2.
70487	"Epoetin Hospira": A 2-Week Intravenous Dose Range-Finding Toxicity Study in Sprague-Dawley CD® Rats	4.2.3.2.

1632-07767	"Epoetin Hospira": An Eight-Week Subcutaneous Repeat Dose Toxicity Study with a 4-Week Recovery Period in Sprague-Dawley Rats	4.2.3.2.
1632-07587	"Epoetin Hospira": A Two-Week Dose Range-Finding Study Following Subcutaneous Administration in Sprague-Dawley Rats	4.2.3.2.

3.3 Previous Reviews Referenced

None

4 Pharmacology

4.1 Primary Pharmacology

A comparative pharmacodynamic activity study of "Epoetin Hospira", US-Epogen, EU-Retacrit, and EPO Standard (BRP3) in normocythemic mice was submitted (Study No. (b) (4)-631002), but was not reviewed because it did not add value to the nonclinical assessment for biosimilarity, mainly since it did not model the clinical dosing regimen (single vs. repeat-dose), was conducted in only one sex (female), and was not GLP-compliant.

The comparative pharmacodynamic activity of "Epoetin Hospira" and US-Epogen administered via the IV route was assessed as part of the repeat-dose 13-week dog toxicology study (Study No. 60486). Meaningful comparisons of PD endpoints could not be made in the comparative toxicology study in Sprague-Dawley rats (Study No. 70882) evaluating the SC route of administration due to reduced exposure and pharmacodynamic activity of the reference product, associated with a high incidence of ADA development.

4.2 Secondary Pharmacology

No studies were submitted for review.

4.3 Safety Pharmacology

Not Applicable.

5 Toxicokinetics

5.2 TK

The toxicokinetics of "Epoetin Hospira" were evaluated in comparative toxicology studies 60486 and 70882 and are summarized below with the individual toxicology study summaries.

6 General Toxicology

6.1 Single-Dose Toxicity

No single-dose comparative toxicology studies were submitted. Single-dose toxicology studies submitted for "Epoetin Hospira" alone were not reviewed by the Agency.

6.2 Repeat-Dose Toxicity

The 13-week repeat-dose GLP comparative toxicology study (3 SC doses/week) in Sprague-Dawley rats (Study No. 70882) is summarized below. It was not fully reviewed by the Agency due to reduced AUC exposure on Days 26 and 89 and C_{max} on Day 89 for US-Epogen treated rats, associated with the development of neutralizing ADA at higher incidence in US-Epogen treated rats. Additionally, levels of PD biomarkers (RBC, HGB, HCT, and RETIC) in US-Epogen treated rats compared to Epogen Hospira treated rats were lower on Week 13.

Summary

Table 5 Effects of SC Administration of "Epoetin Hospira" or US-Epogen on PD Biomarkers and TK

Dose (IU/kg)	150				450				1500/900			
Sex	Male		Female		Male		Female		Male		Female	
Test Item	EH	RP	EH	RP	EH	RP	EH	RP	EH	RP	EH	RP
Toxicokinetics												
Cmax (mIU/mL)												
Day 1	*72*	102	*68*	97	*278*	331	*235*	343	*913*	1439	*1015*	1649
Day 26	81	66	80	94	355	**141**	298	184	901	**572**	1311	1192
Day 89	119	**71**	164	183	429	**25**	360	327	989	**539**	903	**349**
AUC0-t (mIU·hour/mL)												
Day 1	*1265*	1752	*1221*	1845	*4548*	5742	*3863*	6035	*14847*	22788	*16338*	25192
Day 26	1157	1044	1140	1222	5054	**1936**	4539	**2273**	14146	**4786**	18377	**10180**
Day 89	1659	**824**	1999	3060	6099	**326**	6318	4702	14792	**2447**	12570	**4047**
Pharmacodynamic Biomarkers - Week 13												
RBC (10^{12}/L)	13	4.9	12.5	10.2	11.8	4.4	11.8	7.8	11.6	2.2	11.5	8.3
HGB (g/L)	236	90	242	198	219	80	240	157	208	38	243	160
HCT (L/L)	0.72	0.28	0.73	0.6	0.68	0.25	0.73	0.47	0.67	0.12	0.75	0.5
RETIC (10^{12}/L)	0.46	0.13	0.45	0.36	0.72	0.28	0.61	0.32	0.86	0.06	0.77	0.45

Abbreviations: EH = "Epoetin Hospira"; RP = reference product (US-Epogen); RBC= red blood cells; HGB = hemoglobin; HCT = hematocrit; RETIC = reticulocytes; *Italic* = noting lower exposures on Day 1 in EH- compared to RP-treated rats; **Bold** = noting ~50%+ reduced exposures first detected at Day 26 for RP-treated rats.

- PD biomarkers (RBC, HGB, and HCT) were similar; irrespective of dose level for "Epoetin Hospira" treated rats (see blue shaded cells in Table 5 above). Thus, PD effects appear to be elicited by the low dose, which is equivalent to the starting human dose.
- As observed with dogs, exposures to "Epoetin Hospira" were slightly lower than for US-Epogen on Day 1 (before exposures to US-Epogen dropped), but were generally within the range of individual animal variability.

Table 6 Effects of SC Administration of "Epoetin Hospira" and US-Epogen on ADA Response[1] (Nab[2)] in Rats

Dose (IU/kg)	150				450				1500/900				Response Type
Sex	Male		Female		Male		Female		Male		Female		
Test item	EH	RP	EH	RP	EH	RP	EH	RP	EH	RP	EH	RP	
Predose	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	ADA
	0/0	0/4	0/4	0/6	0/1	0/5	0/1	0/6	0/3	0/6	0/3	0/5	NAb
Week 2	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	ADA
	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	NAb
Week 4	0/6	2/6	2/6	3/6	0/6	3/6	0/6	4/6	1/6	6/6	2/6	1/6	ADA
	0/0	2/3	3/3	3/3	0/0	2/3	0/0	4/4	1/1	5/6	2/2	1/3	NAb
Week 6	0/6	4/6	3/6	4/6	0/6	5/6	1/6	4/6	1/6	6/6	2/6	4/6	ADA
	0/0	4/4	3/3	4/4	0/0	4/5	1/1	4/5	1/1	6/6	3/3	4/4	NAb
Week 9	0/6	3/6	3/6	5/6	0/6	5/6	1/6	6/6	3/6	6/6	2/6	4/6	ADA
	0/0	3/3	3/3	5/5	0/0	5/5	1/1	6/6	3/3	6/6	2/2	4/4	NAb
Week 11	0/6	2/5	2/5	5/5	0/5	5/6	1/6	4/6	1/6	6/6	2/6	4/6	ADA
	0/0	2/2	2/2	5/5	0/0	5/5	1/1	4/4	1/1	6/6	2/2	4/4	NAb
Week 13	0/6	2/5	0/3	3/4	1/5	5/6	1/6	3/5	0/5	4/4	1/5	4/6	ADA
	0/0	2/2	0/0	3/3	1/1	5/5	1/1	3/3	0/0	4/4	1/1	4/4	NAb
Week 15	1/6	2/5	1/3	3/4	1/5	4/5	1/6	4/5	0/5	2/2	1/5	3/4	ADA
	0/0	2/2	1/1	3/3	0/1	4/4	1/1	1/4	0/0	2/2	1/1	3/3	NAb
Week 17	0/6	2/5	1/3	3/4	1/5	4/5	1/6	3/5	0/5	1/1	1/5	2/4	ADA
	0/0	2/2	1/1	3/3	1/1	4/4	1/1	2/3	0/0	1/1	1/1	2/2	NAb

Abbreviations: EH = "Epoetin Hospira"; RP = reference product (US-Epogen); ADA = anti-drug antibodies; NAb = neutralizing antibodies; 1 = Number of animals with positive ADA response/total number of animals; 2 = number of animals with positive Nab response/number of animals with ADA response

Common toxicity findings between rats and dogs for "Epoetin Hospira" and US-Epogen were mortality (but at lower doses of 150 IU/kg in rats); clinical signs of hypoactivity, loss of limb function, dehydration and reduced fecal output; ↑ in PD biomarkers (for "Epoetin Hospira" only in rats); ↑ kidney, lung, and spleen weights; and, microscopic findings of hypercellularity of the bone marrow and congestion of multiple organs (liver, lung, GI tract, adrenals, etc). The kidney was a target organ in both species, but with different microscopic findings (infarction of the kidney and/or chronic progressive nephropathy and/or thrombosis in the rat and tubular regeneration and chronic cortical inflammation in the dog). Microscopic findings of infarctions, necrosis, and/or fibrosis in common target organs (stomach, adrenals, and/or liver) between species were observed in rats treated with both "Epoetin Hospira" and US-Epogen, but were generally not noted in dogs. Other common organs of toxicity with different pathology between species were the brain and heart, with ↑ heart weights and microscopic findings in the brain (infarction) and heart (thrombosis and/or diffuse muscular hypertrophy and/or congestion) in the rat; and, brain hemorrhage or dilation and ↑ brain weights and lower heart rates in "Epoetin Hospira" treated dogs. Increased ocular vascular pattern was also observed in both species, but there was also a qualitative increase of the red color of the retinal and uveal vascular pattern (red reflex) observed in "Epoetin Hospira" interim rats at Week 4.

Of note, the severe cardiovascular toxicities observed in rats, but not in dogs, are expected toxicities since increased mortality, myocardial infarction, stroke, and

thromboembolism at target hemoglobin concentrations > 11 g/dL is in the WARNINGS AND PRECAUTIONS section of the US-Epogen label.

Study title: "Epoetin Hospira": A 13-Week Intravenous Repeat Dose Comparative Toxicity Study Followed by a 4-Week Recovery Period in Beagle Dogs

Study no.:	60486
Study report location:	eCTD 4.2.3.2.
Conducting laboratory and location:	(b) (4)
Date of study initiation:	August 10, 2009 (first treatment)
GLP compliance:	Yes, signed
QA statement:	Yes, signed
Drug, lot #, and % purity:	"Epoetin Hospira" (10,000 IU/mL), Lot No. 09-0074, Purity: assumed 100%; referenced product (US-Epogen (10,000 IU/mL)), Lot No. P114925, Purity: assumed 100%

Key Study Findings

- Increases in PD parameters were similar for the biosimilar and reference product.
- Overall, the toxicological findings between the biosimilar and reference product were similar and related to exaggerated pharmacology of erythropoietin - early mortality associated with multi-organ congestion, hemorrhage, and necrosis; body weight loss and reduced body weight gain; and, pharmacologically driven/inflammatory-related microscopic findings in organs of the hematopoietic (bone marrow, spleen, lymph nodes and thymus), digestive (stomach, small intestine, large intestine), and nervous (brain, sciatic nerve, and spinal cord) systems, as well as the kidney, liver, heart, and lungs.
- While not deemed adverse by the ophthalmologist, more pronounced increased vascular retinal pattern (size) and tortuosity with "Epoetin Hospira" compared to the reference product is noted.
- Mean exposures were slightly lower following administration for "Epoetin Hospira" compared to US-Epogen at all assessment points and mean clearance rates were faster for "Epoetin Hospira" compared to US-Epogen on Day 89. However, these differences were generally within the range of individual animal variability.

Methods

Doses:	See table below
Frequency of dosing:	3 times per week
Route of administration:	Intravenous
Dose volume:	See table below
Formulation/Vehicle:	0.9% NaCl for injection
Species/Strain:	Beagle dog
Number/Sex/Group:	See table below
Age:	Six to seven months old
Weight:	6.0 to 8.9 kg for males and from 5.0 to 8.3 kg for females
Satellite groups:	N/A
Unique study design:	Treatments were administered to improve animal condition
Deviation from study protocol:	Two week dosing holiday, followed by dose reduction from 1500 to 900 IU/kg in Groups 4 and 7 (see table below for more info)

(Table excerpted from the study report)

Group No	Group Designation	Dose Level (IU/kg)	Dose Conc. (IU/mL)	Dose Volume (mL/kg)	Number of Main Animals				Number of Recovery Animals			
					4-Week Interim Animals[a]		13-Week Animals		4-Week Interim Animals[b]		13-Week Animals[c]	
					M	F	M	F	M	F	M	F
1	Control*	0	0	1/0.6	4	4	4	4	2	2	2	2
2	Epoetin-150	150	1500	0.1	4	4	4	4	-	-	-	-
3	Epoetin-500	450	1500	0.3	4	4	4	4	-	-	-	-
4	Epoetin-1500	1500/900	1500	1/0.6	4#	4#	4**	4**	2#	2#	2**	2**
5	Epogen®-150	150	1500	0.1	-	-	4	4	-	-	-	-
6	Epogen®-500	450	1500	0.3	-	-	4	4	-	-	-	-
7	Epogen®-1500	1500/900	1500	1/0.6	-	-	4**	4**	-	-	2**	2**

* The Control animals received the control/vehicle article (0.9% Sodium Chloride for Injection, USP) only. The Controls animals were dosed at 1 mL/kg for a 9-week dosing period (Doses 1 to 27) following which the dose volume was reduced to 0.6 mL/kg for a period of 4 weeks (Doses 28 to 39) due to changes in the dose level and dose volume administered to the animals of the High dose groups (Groups 4 and 7).

a: Animals were sacrificed following 4 weeks of treatment (designated as Interim Main animals).

b: Animals were sacrificed after a 2-week recovery period following 4 weeks of treatment (designated as Interim Recovery animals).

c: Animals were sacrificed after a 4-week recovery period following 13 weeks of treatment (designated as Recovery animals)

\# The Group 4 Interim Main and Interim Recovery animals were dosed at 1500 IU/kg throughout the 4 weeks of dosing.

** Due to abnormal clinical signs, marked body weight loss and mortality observed as of Week 6 among both Epoetin Hospira and Epogen® treated animals at 1500 IU/kg, the Main and Recovery animals from Groups 4 and 7 received 1500 IU/kg for a period of 7 weeks (Doses 1 to 22) followed by a 2-week washout period (Weeks 8 and 9), after which dosing was resumed for 4 additional weeks (Weeks 10 to 13) at a dose of 900 IU/kg (Doses 23 to 34).

Of note, for the 13-week treatment period, animals received a total of 39 doses, except for the animals of Groups 4 and 7 which received 34 doses total (due to a dosing holiday).

Observations and Results

Mortality:	Twice daily
Clinical signs:	Cage side daily; detailed examinations taken once pretreatment, twice weekly, at necropsy*
Body weights:	Pretreatment, weekly during treatment
Food consumption:	Pretreatment, daily during treatment
ECG:	Pretreatment, Weeks 4, 8, and 13; Weeks 6 and 17 for recovery animals only
Ophthalmoscopy:	Pretreatment, Weeks 4 and 13; Weeks 6 and 17 for recovery animals only
Hematology:	Pretreatment, Weeks 4, 9 and 13; Weeks 6 and 17 for recovery animals
Clinical chemistry:	Pretreatment, Weeks 4, 9 and 13; Weeks 6 and 17 for recovery animals
Coagulation:	Pretreatment, Weeks 4, 9 and 13; Weeks 6 and 17 for recovery animals
Urinalysis:	Pretreatment, Weeks 4, 9 and 13; Weeks 6 and 17 for recovery animals
ADA analysis:	Pretreatment (at least 5 days prior to treatment), once during Weeks 2, 4, 6, 9, 11 and 13 (prior to the 1st dose/week) of the treatment period, and once during Weeks 15 and 17 during the recovery period
Gross pathology:	At necropsy*
Organ weights:	At necropsy*
Histopathology:	At necropsy*
Toxicokinetics (samples taken from jugular vein):	Day 1 and Week 4 (bioanalysis includes interim and 13-week animals); Week 13: - Taken from all dogs - Sampling time points: predose, within the first 2 minutes following dosing, at 5, 10 and 15 minutes postdose, and at 0.5, 1, 2, 4, 8, 12 and 24 hours postdose

* 4-week interim necropsy was conducted on Day 29 for "Epoetin Hospira" treated animals; recovery animals for this portion of the study were sacrificed 14 days later, on Day 43. Necropsy for the main study animals was conducted on Day 92; recovery animals for this portion were sacrificed 4 weeks later, on Day 120.

Note: some interim findings in "Epoetin Hospira" animals only (non-comparative portion of the study) are not included in this section of the review, but are tabulated in the Appendix for reference.

Mortality

All interim animals survived to scheduled necropsy. For 13-week animals, there was early death in 12.5% (1/8) and 25% (2/8) of dogs treated with 450 IU/kg "Epoetin Hospira" or US-Epogen, respectively. Also, there was early death in 33% (4/12) and 8% (1/12) of dogs treated with 1500/900 IU/kg "Epoetin Hospira" or US-Epogen, respectively.

Table 7 "Epoetin Hospira" Treated Dogs with Early Mortality

Dose EH (IU/kg)	Animal No. (Group and Sex)	Condition	Day (Week)	Clinical signs
450	3508H (Main Study F)	Moribund	80 (11)	Undigested food; loose, liquid feces; thin; on Day 80, extreme uncoordination
1500/900	4012J (Recovery M)	Moribund	78 (11)	Reduced, loose, liquid feces; decreased activity and appetite; salivation
	4511J (Recovery F)	Moribund	50 (7)	Loose feces
	4507G (Main Study F)	Found dead	84 (12)	Thin; autolysis precluded evaluation of digestive organs and pancreas
	4011J (Recovery M)	Moribund	48 (6)	Loose, liquid feces; forehead lesions; thin; on Day 48, extreme decreased activity, lying on cage floor, respiration labored, no righting reflex, salivation

EH = "Epoetin Hospira"; M = male; F = female

Table 8 US-Epogen Treated Dogs with Early Mortality

Dose US-licensed Epogen (IU/kg)	Animal No. (Group and Sex)	Condition	Day (Week)	Clinical signs
450	6003G (Main study M)	Moribund	76 (10)	Loose, liquid feces; thin; on Day 76, extreme decreased activity
	6504H (Main study F)	Moribund	72 (10)	Loose, liquid feces; loss of limb function of the left forelimb, activity decreased; on Day 72, lying on cage floor, thin, uncoordinated, vocalizing
1500/900	7603G (Main study F)	Moribund	52 (7)	Multiple lesions (forehead, head, right forelimb), loose feces; on Day 52, vomiting, circling, convulsion, uncoordination, salivation

Table 9 Comparative Microscopic Findings in Dogs with Early Mortality

Treatment-related microscopic findings in dogs with mortality									% of dogs with early death with finding	
Test Article	"Epoetin Hospira"					US-Epogen				
Dose (IU/kg)	450	1500/900				450	1500/900			
Animal with mortality	3508H	4012J	4511J	4507G	4011J	6003G	6504H	7603G	EH	RP
Adrenal gland *mild necrosis*					X				20%	0%
mild congestion							X		0%	33%
Brain *minimal hemorrhage*				X					**20%**	**0%**
Bone marrow *mild to moderate hypercellularity*	X	X	X	X	X	X	X	X	100%	100%
minimal to moderate fibrosis		X			X		X	X	40%	67%
mild congestion			X						20%	0%
Dosing site *hemorrhage/ inflammation*	X		X	X				X	**60%**	**33%**
Liver										

Treatment-related microscopic findings in dogs with mortality									% of dogs with early death with finding	
Test Article	"Epoetin Hospira"					US-Epogen				
Dose (IU/kg)	450	1500/900				450	1500/900			
Animal with mortality	3508H	4012J	4511J	4507G	4011J	6003G	6504H	7603G	EH	RP
mild to moderate centrilobular congestion	X	X	X	X	X	X	X	X	100%	100%
mild to moderate pigmentation	X	X	X	X	X		X	X	100%	67%
mild adhesion						X			0%	33%
Lung *minimal granulomatous inflammation*	X				X				**40%**	**0%**
minimal to mild inflammation			X					X	**20%**	**33%**
moderate congestion				X					**20%**	**0%**
Kidney *minimal to mild tubular regeneration*		X	X			X	X	X	**40%**	**100%**
minimal chronic inflammation		X				X	X	X	**20%**	**100%**
mild congestion			X	X	X			X	**60%**	**33%**
Lymph Nodes *minimal to mild hyperplasia*	X		X	X		X	X	X	**60%**	**100%**
Pancreas *mild congestion*			X					X	20%	33%
Pituitary gland *mild congestion*			X						**20%**	**0%**
Sciatic nerve *mild axonal degeneration*			X		X	X			40%	33%
Skeletal muscle *moderate edema*		X							**20%**	**0%**
Small and large intestine *minimal to mild congestion*	X		X				X	X	40%	67%
minimal necrosis of the duodenum		X							20%	0%
Spinal cord *minimal to mild hemorrhage*	X		X	X	X	X	X	X	80%	100%
Spleen *minimal to mild erythropoiesis*	X	X	X	X	X	X	X	X	100%	100%
Stomach *mild lymphocytic accumulation*	X				X	X	X	X	**40%**	**100%**
mild congestion			X						**20%**	**0%**
Thymus *minimal to moderate atrophy*	X	X	X		X	X	X	X	80%	100%
mild to moderate congestion	X		X	X			X	X	60%	67%

Treatment-related microscopic findings in dogs with mortality									% of dogs with early death with finding	
Test Article	"Epoetin Hospira"					US-Epogen				
Dose (IU/kg)	450	1500/900				450	1500/900			
Animal with mortality	3508H	4012J	4511J	4507G	4011J	6003G	6504H	7603G	EH	RP
mild necrosis			X			X			20%	33%
marked hemorrhage				X					20%	0%
Uterus *mild to moderate congestion*			X	X					**40%**	**0%**
Vagina *mild congestion*								X	**0%**	**33%**

EH="Epoetin Hospira"; RP = reference product (US-licensed Epogen); X = finding present in animal

- The percentages of microscopic findings per organ (adrenals, bone marrow, liver, sciatic nerve, spinal cord, small and large intestines, spleen, thymus) for "Epoetin Hospira" and US-Epogen treated dogs with early mortality were overall similar, except for findings (in brain, dosing site, lung, pituitary gland, skeletal muscle, and uterus) with higher incidence in the biosimilar groups; or, findings (in kidney, lymph node, stomach, and vagina) with higher incidence in the reference product groups. These differences (in bold in Table 9) generally did not hold up when looking at pathology data for dogs that survived to scheduled necropsy in this study and due to the presence of findings in the comparative rat toxicology study. However, findings in the skeletal muscle, even in the rat comparative toxicology study, were only noted with "Epoetin Hospira" treatment.

Clinical Signs

Table 10 Comparative Cage Side Observations in Dogs

Males:

Clinical Signs	No. of animals affected (No. of observations)						
Test article	Vehicle	"Epoetin Hospira"			US-licensed Epogen		
Group	1	2	3	4	5	6	7
Dose (IU/kg)	0	150	450	1500/900	150	450	1500/900
No. of animals examined (main/recovery)	4/2	4/0	4/0	4/2	4/0	4/0	4/2
Feces liquid*	1(3)/2(7)	3(6)/-	1(12)/-	2(16)/3(4)	2(3)/-	3(10)/-	2(3)/1(2)
Feces loose*	3(36)/2(19)	3(37)/-	3(74)/-	3(55)/3(28)	4(52)/-	4(59)/-	4(49)/2(12)
Material liquid*	1(1)/0(0)	2(2)/-	1(2)/-	2(2)/1(1)		1(1)/-	1(1)/0(0)
Material dry	1(3)/0(0)	1(1)/-	2(3)/-	1(1)/1(1)	2(2)/-	1(1)/-	1(1)/0(0)
Material mucoid*	1(1)/2(4)	1(1)/-	1(2)/-	2(4)/1(2)	3(3)/-	1(3)/-	3(4)/1(1)
Thin	2(47)/1(24)		1(5)/-	1(24)/1(6)		2(36)/-	1(43)/1(42)
Undigested food	1(1)/0(0)		1(2)/-	1(3)/1(1)			
Salivation			1(7)/-	0(0)/2(3)	1(1)/-		
Reduced fecal output			1(3)/-	0(0)/1(4)			
No feces*				0(0)/1(2)			1(1)/0(0)
Activity decreased*				1(8)/2(9)		1(1)/-	2(13)/1(34)
Loss of limb function*				1(28)/0(0)			1(8)/0(0)
Lesions				1(5)/1(19)			1(9)/0(0)

Clinical Signs	No. of animals affected (No. of observations)						
Test article	Vehicle	"Epoetin Hospira"			US-licensed Epogen		
Group	1	2	3	4	5	6	7
Dose (IU/kg)	0	150	450	1500/900	150	450	1500/900
No. of animals examined (main/recovery)	4/2	4/0	4/0	4/2	4/0	4/0	4/2
Appetite decreased				0(0)/1(3)			
Eyes closed				0(0)/1(1)			
Hair loss							0(0)/1(3)
Lying on cage floor				0(0)/1(1)			
Skin turgor slow				0(0)/1(1)			
Respiration labored				0(0)/1(1)			

Females:

Clinical Signs	No. of animals affected (No. of observations)						
Test article	Vehicle	"Epoetin Hospira"			US-licensed Epogen		
Group	1	2	3	4	5	6	7
Dose (IU/kg)	0	150	450	1500/900	150	450	1500/900
No. of animals examined (main/recovery)	4/2	4/0	4/0	4/2	4/0	4/0	4/2
Feces Liquid*	1(2)/0(0)	2(4)/-	3(7)/-	2(5)/1(8)	2(4)/-	3(5)/-	2(4)/1(26)
Feces Loose*	4(10)/0(0)	3(36)/-	3(13)/-	4(34)/2(45)	3(25)/-	3(23)/-	4(43)/2(21)
Discolored feces*				0(0)/1(1)			0(0)/1(5)
Material liquid*	0(0)/1(3)	2(2)/-	3(4)/-	1(1)/1(2)	2(4)/-		1(1)/1(4)
Material dry	0(0)/1(4)	2(2)/-	1(1)/-		1(2)/-	1(2)/-	1(1)/0(0)
Material mucoid*	3(3)/0(0)	2(2)/-	1(2)/-	2(3)/1(1)	1(1)/-	2(2)/-	3(9)/2(5)
Thin	1(12)/0(0)		2(33)/-	2(7)/0(0)	2(42)/-	1(1)/-	2(30)/1(46)
Undigested food*		1(1)/-	2(6)/-	2(5)/1(2)			0(0)/1(3)
Reduced fecal output	0(0)/1(1)						0(0)/1(2)
Activity decreased*				0(0)/1(9)		1(8)/-	1(2)/0(0)
Loss of limb function*		1(3)/-				1(13)/-	
Lesions	1(43)/0(0)		1(2)/-	0(0)/1(10)		1(20)/-	1(14)/0(0)

Abbreviations: No.= number; Empty cell = no observation present (or not assessed, in the case of recovery animals for Groups 2, 3, 5, and 6); "-" = observation present in main study animals was not assessed in recovery animals for Groups 2, 3, 5, and 6; * = observation could be observed 1-2 hours postdose in some instances.

- Fewer clinical signs were observed in interim animals and are noted in the Appendix.

Detailed Clinical Observations

Main study:

- Similar trends for cage side and detailed observations were observed, except, during detailed examinations, hot to touch was observed in one high dose (Group 4) "Epoetin Hospira" treated male on Day 92; skin discoloration was observed sporadically in Groups 4-7 males; and, teeth discoloration was observed after Day 67 in Groups 3-4 and Group 7 males, and in one Group 4 female.
- Also, during detailed observations, a Group 7 female vomited on Day 88 and one Group 7 female (Animal No. 7603G) was observed vomiting, circling, convulsing, retching, and uncoordinated on Day 52 preceding unscheduled euthanasia. One

Group 6 female (Animal No. 6504H) was found vocalizing, uncoordinated, with eye closed, and laying on the floor on Day 72.

Recovery:

- The recovery Group 4 male (Animal No. 4011J) with labored respiration and lying on the cage floor on Day 48, also had no righting reflex during detailed observations.
- One recovery Group 4 female (Animal No. 4511J) was hot to touch, lying on cage floor, increased respiration, uncoordinated, and skin discoloration prior to unscheduled euthanasia on Day 50.

Timed observations (one to 2 hours postdose)

In addition to what is noted by an asterisk (*) in Table 10, the following were observed:

- Salivation on Day 26 in one Group 7 male,
- One Group 3 and one Group 4 female each was found dead on Days 80 and 84, respectively,
- Swelling in one Group 7 female on Days 71-80.

Body Weights

Figure 1 Comparative Mean Body Weights in Male Dogs – 13-Week Groups

(Excerpted from the study report)

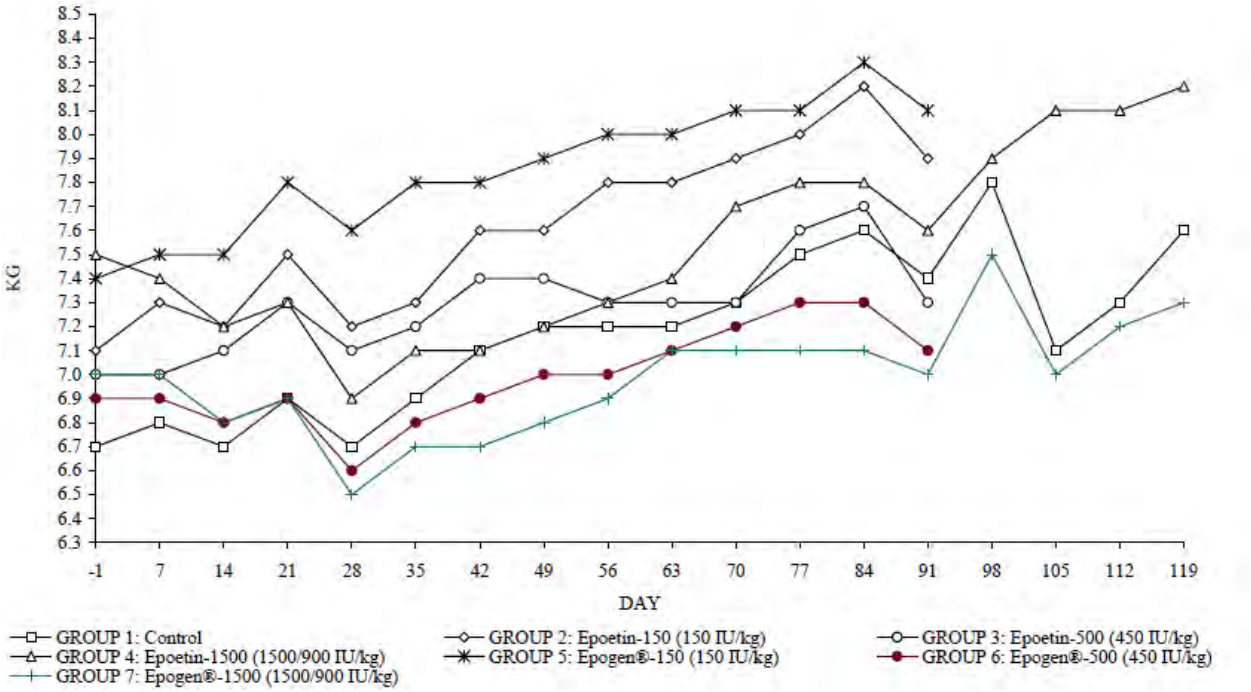
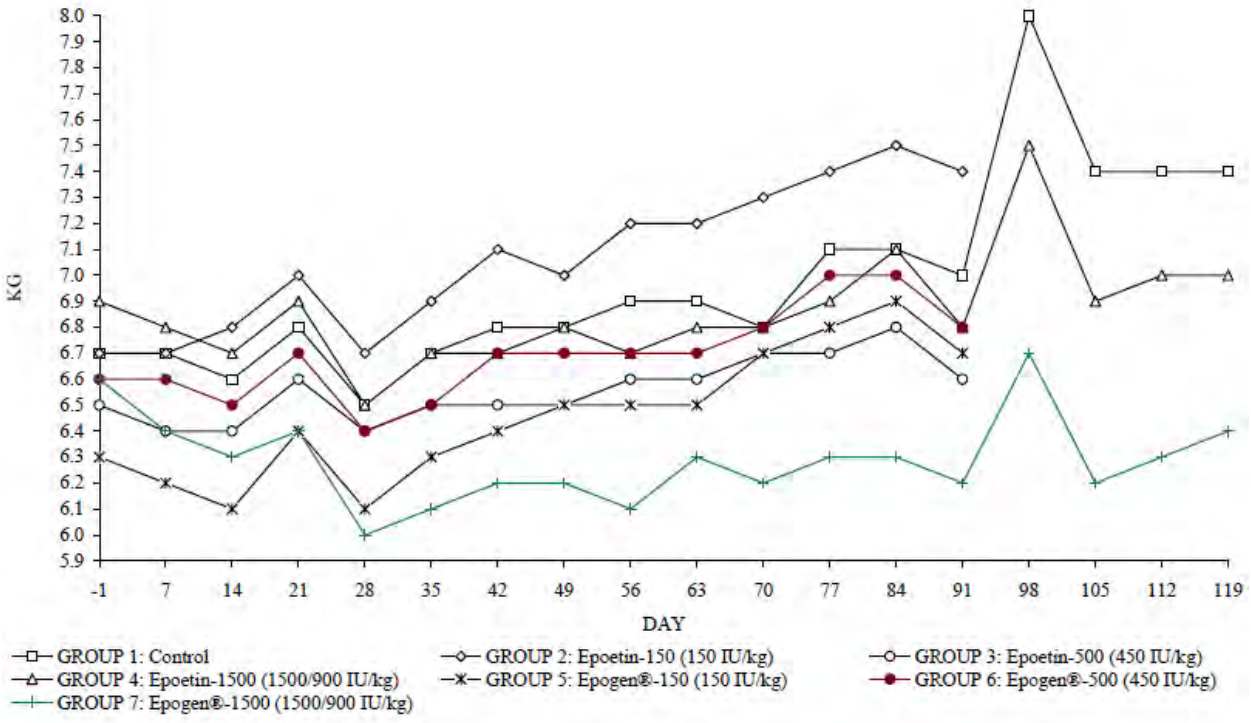


Figure 2 Comparative Mean Body Weights in Female Dogs – 13-Week Groups

(Excerpted from the study report)



- Similar observations of body weight loss in males and females on Day 28 for "Epoetin Hospira" interim animals are tabulated in the appendix.

Table 11 Tabulated Comparative Mean Body Weight and Body Weight Gain Changes after 13 Weeks and 4-Week Recovery

Changes in mean BW compared to control (Days 91/119)

Dose (IU/kg)	Males				Females			
	"Epoetin Hospira"		US-Epogen		"Epoetin Hospira"		US-Epogen	
	BW (kg)	%Δ control	BW (kg)	%Δ control	BW (kg)	%Δ control	BW (kg)	%Δ control
150	7.9	7%↑	8.1	9%↑	7.4	6%↑	6.7	4%↓
450	7.3	1%↓	7.1	4%↓	6.6	6%↓	6.8	3%↓
1500/900	7.6/8.2	3%↑/8%↑	7.0/7.3	5%↓/4%↓	6.8/7.0	3%↓/5%↓	6.2/6.4	11%↓/14%↓

BW = body weight; %Δ control = percent change compared to the control mean (main study/recovery control means for males = 7.4 kg/7.6 kg; females = 7.0 kg/ 7.4 kg)

Changes in BW gain compared to control (Days -1 to 91/119)

Dose (IU/kg)	Males				Females			
	"Epoetin Hospira"		US-Epogen		"Epoetin Hospira"		US-Epogen	
	BWG (kg)	%Δ control	BWG (kg)	%Δ control	BWG (kg)	%Δ control	BWG (kg)	%Δ control
150	0.8	12.5%↑	0.7	0	0.7	133%↑	0.4	33%↑
450	0.3	57%↓	0.2	71%↓	0.1	67%↓	0.2	33%↓
1500/900	0.1/0.7	86%↓/22%↓	0/0.3	100%↓/67%↓	-0.1/0.1	133%↓/86%↓	-0.4/-0.2	157%↓/128%↓

BWG = body weight gain; %Δ control = percent change compared to the control mean (main study/recovery control means for males = 0.7 kg/0.9 kg; females = 0.3 kg/0.7 kg)

Food Consumption

- Decreases in mean BW and BW gain in 1500 IU/kg interim treated animals correlated with decreased food consumption up to 13% relative to controls in males and 15% in females relative to the pretreatment mean on Day -1.
- Changes in food consumption were similar for "Epoetin Hospira" and US-Epogen treated dogs based on results from the 13-week study, however, body weight changes do not appear to be fully explained by changes in food consumption alone.

Table 12 Comparative Food Consumption on Days 28, 47, 91, and 119 in Dogs – 13-Week Groups

Males:

Dose (IU/kg)	Day 28		Day 47		Day 91		Day 119	
	EH	RP	EH	RP	EH	RP	EH	RP
150	-	-	21%↓	27%↓	21%↓	24%↓	NE	NE
450	-	-	35%↓**	28%↓	37%↓**	37%↓	NE	NE
1500/900	17%↓	16%↓	45%↓***	33%↓	20%↓	-	58%↓	-

Females:

Dose (IU/kg)	Day 28		Day 47		Day 91		Day 119	
	EH	RP	EH	RP	EH	RP	EH	RP
150		7%↓	22%↓	15%↓	-	7%↓	NE	NE
450	20%↓	12%↓	18%↓	26%↓	-	7%↓	NE	NE
1500/900	12%↓	-	2%↓	16%↓	13%↓	5%↓	-	3%↓

** $p < 0.01$; *** $p < 0.001$

Abbreviations: EH="Epoetin Hospira"; RP = reference product (US-Epogen); "-" = no toxicologically relevant change/differences fell within the range of variance among pretreatment and control values; NE=not evaluated

Ophthalmoscopy

At Week 4, a subjective qualitative observation consisting of an increased vascular retinal pattern (size) and tortuosity was made in animals of the 1500 IU/kg "Epoetin Hospira" (Group 4, interim and 13-week study) and US-Epogen treated (Group 7) groups, and to a lesser degree in some animals of the 450 IU/kg "Epoetin Hospira" (Group 3, interim and 13-week study) and US-Epogen treated (Group 6) groups. This is not an abnormal finding, but may reflect a possible increase in red blood cell count.

The same observation was observed at Week 13 in Groups 3 to 7, most apparent in Group 4 than in the other groups. At Week 17 (recovery), an animal of Group 4 (Animal No. 4105K) had a subjective qualitative observation consisting of an increased vascular retinal pattern (size) and tortuosity.

Reviewer comment: Based on the description above, provided in the ophthalmoscopy report (no individual data was provided), increased vascular retinal pattern (size) and tortuosity may be more pronounced with high dose "Epoetin Hospira" compared to the reference product groups.

ECG

Heart rate (bpm), PR (msec), QT (msec), QTc (msec), and QRS (msec) for most "Epoetin Hospira" and US-Epogen treated dogs were all within the range of pretreatment and control values, except:

- One 1500/900 IU/kg "Epoetin Hospira" treated male (Animal No. 7007G) had low heart rate (60 bpm) and shorter QTc interval (203 ms) at Week 8 (note: low heart rates may falsely lower QT interval).
- One 450 IU/kg and one 1500 IU/kg "Epoetin Hospira" treated female (Animal Nos. 3508H and 4507G) each had low heart rate at Week 4; animal 3508H was sacrificed in moribund condition on Day 80. A different 1500/900 IU/kg "Epoetin Hospira" treated female (Animal No. 4512J) had low heart rate on Week 13.

Hematology

Table 13 Comparative Hematology in Male Dogs

Males							
Test article	Vehicle	"Epoetin Hospira"			US-Epogen		
Dose (IU/kg)	0 Mean	150 %Δ	450 %Δ	1500/900 %Δ	150 %Δ	450 %Δ	1500/900 %Δ
RBC (10^{12}/L)							
Week 4	6.01	19↑**	41↑***	60↑***	32↑***	43↑***	60↑***
Week 9	6.27	43↑***	76↑***	83↑***	50↑***	78↑***	83↑***
Week 13	5.89	61↑***	109↑***	108↑***	76↑***	105↑***	101↑***
Recovery	6.30	--	--	67↑	--	--	33↑
HGB (g/L)							
Week 4	132	20↑**	39↑***	44↑***	32↑***	33↑***	37↑***
Week 9	142	36↑**	56↑***	39↑**	40↑**	49↑***	35↑*
Week 13	134	51↑***	75↑***	60↑***	61↑***	58↑***	52↑***
Recovery	142	--	--	22↑	--	--	7↑
HCT (L/L)							
Week 4	0.40	23↑	50↑***	58↑***	35↑*	50↑***	58↑***
Week 9	0.43	42↑	67↑***	53↑***	44↑	63↑***	56↑***
Week 13	0.40	58↑***	93↑***	83↑***	68↑***	75↑***	80↑***
Recovery	0.42	--	--	33↑	--	--	19↑
PLT (10^{9}/L)							
Week 4	376	3↑	16↓	2↓	9↓	1↓	30↑
Week 9	356	9↓	25↓	26↓	12↓	9↓	23↓
Week 13	336	13↓	32↓	24↓	20↓	6↓	17↓
Recovery	371	--	--	24↓	--	--	5↓
MCV (fL)							
Week 4	66.8	2↑	5↑	2↓	2↑	1↓	4↓
Week 9	68.4	2↓	5↓	15↓***	3↓	9↓**	14↓***
Week 13	68.2	3↓	8↓**	12↓***	5↓	15↓***	11↓***
Recovery	66.9	--	--	20↓	--	--	11↓
MCH (pg)							
Week 4	22.0	0	1↓	10↓***	0	7↓	14↓***
Week 9	22.6	5↓	11↓**	23↓***	6↓	17↓***	26↓***
Week 13	22.8	7↓	15↓***	23↓***	9↓*	23↓***	24↓***
Recovery	22.5	--	--	27↓	--	--	19↓
MCHC (g/dL)							
Week 4	329	2↓	6↓***	8↓***	2↓	6↓***	11↓***
Week 9	331	4↓**	6↓***	10↓***	3↓**	9↓***	13↓***
Week 13	334	4↓*	7↓***	12↓***	4↓**	10↓***	14↓***
Recovery	337	--	--	25↓	--	--	9↓

Males							
Test article	Vehicle	"Epoetin Hospira"			US-Epogen		
Dose (IU/kg)	0 Mean	150 %Δ	450 %Δ	1500/900 %Δ	150 %Δ	450 %Δ	1500/900 %Δ
Retic (10^{12}/L)							
Week 4	0.065	32↑	126↑***	200↑***	95↑**	89↑**	234↑***
Week 9	0.062	77↑	87↑	63↓*	20↑	98↑	58↓*
Week 13	0.044	73↑*	136↑***	330↑***	84↑**	157↑***	398↑***
Recovery	0.067	--	--	75↓	--	--	72↓
BASO (10^9/L)							
Week 4	0.07	43↑	128↑**	157↑**	57↑	100↑*	143↑***
Week 9	0.08	175↑	288↑***	150↑*	125↑*	263↑**	175↑**
Week 13	0.09	222↑***	311↑***	278↑***	122↑**	233↑***	222↑***
Recovery	0.11	--	--	82↑	--	--	36↑
LUC (10^9/L)							
Week 4	0.12	8↓	33↑	42↑	8↓	25↑	42↑
Week 9	0.09	22↑	100↑	89↑	0	78↑	67↑
Week 13	0.09	44↑	78↑	100↑*	11↑	100↑	67↑*
Recovery	0.14	--	--	14↑	--	--	0

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Abbreviations: RBC = red blood cells; HGB = hemoglobin; HCT = hematocrit; PLT = platelets; MCV = mean corpuscular volume; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; Retic.= reticulocytes; "—" = hematology parameters for low and mid dose recovery groups were not measured; %Δ = percent change relative to control mean

- There were increases (some as great as 2-fold) in WBC parameters (total WBCs, lymphocytes, monocytes, and eosinophils) most of which were not statistically significant. The increases followed a similar trend in both "Epoetin Hospira" and Epogen treated dogs.
- There were roughly 10-30% increases (sometimes statistically significant) in APTT for both mid and high dose "Epoetin Hospira" and Epogen treated dogs compared to controls.

Table 14 Comparative Hematology in Female Dogs

Females							
Test article	Vehicle	"Epoetin Hospira"			US-Epogen		
Dose (IU/kg)	0 Mean	150 %Δ	450 %Δ	1500/900 %Δ	150 %Δ	450 %Δ	1500/900 %Δ
RBC (10^{12}/L)							
Week 4	5.72	32↑**	54↑***	70↑***	31↑***	50↑***	75↑***
Week 9	6.28	46↑***	75↑***	83↑***	50↑***	75↑***	84↑***
Week 13	6.28	56↑***	85↑***	94↑***	65↑***	85↑***	91↑***
Recovery	6.58	--	--	40↑	--	--	38↑
HGB (g/L)							
Week 4	131	28↑**	36↑***	47↑***	27↑**	37↑***	45↑***
Week 9	144	37↑*	43↑**	42↑**	38↑*	47↑**	35↑*
Week 13	145	43↑***	41↑***	51↑***	48↑***	47↑***	40↑***
Recovery	155	--	--	5↑	--	--	5↓
HCT (L/L)							
Week 4	0.39	33↑**	49↑***	67↑***	33↑**	49↑***	64↑***
Week 9	0.43	44↑	58↑**	60↑***	47↑	60↑***	56↑***
Week 13	0.43	51↑***	58↑***	72↑***	56↑***	63↑***	65↑***
Recovery	0.46	--	--	15↑	--	--	7↑

Females							
Test article	Vehicle	"Epoetin Hospira"			US-Epogen		
Dose (IU/kg)	0 Mean	150 %Δ	450 %Δ	1500/900 %Δ	150 %Δ	450 %Δ	1500/900 %Δ
PLT(10^9/L)							
Week 4	352	10↓	13↑	14↑	0	6↓	22↑
Week 9	383	24↓	9↓	43↓*	16↓	22↓	36↓*
Week 13	352	16↓	8↓	16↓	23↓	22↓	16↓
Recovery	309	--	--	17↓	--	--	9↓
MCV (fL)							
Week 4	68.9	0	5↑	2↓	0	2↓	7↓
Week 9	68.8	2↓	11↓**	12↓***	3↓	9↓*	15↓***
Week 13	69.2	4↓	16↓***	12↓***	7↓	13↓**	15↓**
Recovery	68.9	--	--	16↓	--	--	22↓
MCH (pg)							
Week 4	23	3↓	12↓***	14↓***	3↓	9↓**	17↓***
Week 9	22.9	6↓	18↓***	22↓***	8↓	16↓***	26↓***
Week 13	23.1	8↓*	24↓***	22↓***	10↓**	20↓***	26↓***
Recovery	23.6	--	--	25↓	--	--	31↓
MCHC (g/L)							
Week 4	333	3↓*	6↓***	8↓***	3↓	7↓***	11↓***
Week 9	333	4↓***	8↓***	11↓***	5↓***	8↓***	13↓***
Week 13	335	4↓	10↓***	22↓***	4↓*	9↓***	14↓***
Recovery	343	--	--	11↓	--	--	12↓
Retic (10^{12}/L)							
Week 4	0.053	32↑	126↑*	200↑***	106↑	142↑	304↑***
Week 9	0.06	60↑	123↑	68↓**	12↑	95↑	70↓**
Week 13	0.048	123↑	150↑	244↑***	83↑	175↑*	331↑***
Recovery	0.032	--	--	13↓	--	--	75↓
BASO (10^9/L)							
Week 4	0.05	43↑**	128↑*	157↑***	120↑*	180↑**	300↑***
Week 9	0.07	186↑**	243↑**	329↑***	129↑*	271↑***	157↑*
Week 13	0.07	271↑***	271↑**	357↑***	271↑***	271↑***	300↑***
Recovery	0.1	--	--	50↑	--	--	10↓
LUC (10^9/L)							
Week 4	0.09	56↑	22↑	78↑	44↑	22↑	122↑*
Week 9	0.1	30↑	20↑	50↑	10↓	20↑	40↑
Week 13	0.07	100↑**	71↑*	100↑**	44↑*	33↑*	157↑***
Recovery	0.09	--	--	22↑	--	--	67↑

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$
Abbreviations: RBC = red blood cells; HGB = hemoglobin; HCT = hematocrit; PLT = platelets; MCV = mean corpuscular volume; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; Retic = reticulocytes; "—" = hematology parameters for low and mid dose recovery groups were not measured; %Δ = percent change relative to control mean

- Hematology results appear less severe for "Epoetin Hospira" treated interim animals on Weeks 2, 4, and 7 (recovery) compared to main study animals and are noted in the Appendix.

Clinical Chemistry

Table 15 Percent Changes in 13-Week Study Dogs Relative to Controls in Clinical Chemistry Parameters – Week 4

(Excerpted from the study report)

"Epoetin Hospira":

Parameter	K		GLUC		AST		GLOB		A/G	
Dose Level (IU/kg)	M	F	M	F	M	F	M	F	M	F
150 IU/kg	13	11	--	--	--	--	--	--	--	--
450 IU/kg	19	19	-28	-14	--	--	--	--	--	--
1500 IU/kg	30	25	-35	-34	65	71	--	+17	--	-18

M= male F= female -- = not applicable

US-Epogen:

Parameter	K		GLUC		AST	
Dose Level (IU/kg)	M	F	M	F	M	F
150 IU/kg	11	13	--	--	--	--
450IU/kg	15	15	-24	-11	--	--
1500 IU/kg	30	26	-30	-36	59	85

M= male F= female -- = not applicable

Table 16 Percent Changes in 13-Week Study Dogs Relative to Controls in Clinical Chemistry Parameters – Week 9

(Excerpted from the study report)

"Epoetin Hospira":

Parameter	K		GLUC	
Dose Level (IU/kg)	M	F	M	F
150 IU/kg	21	15	--	--
450IU/kg	21	26	-38	-41
1500 IU/kg	11	--	-32	-39

M= male F= female -- = not applicable

US-Epogen:

Parameter	K		GLUC	
Dose Level (IU/kg)	M	F	M	F
150 IU/kg	13	20	--	--
450IU/kg	23	17	-45	-25
1500 IU/kg	6	9	-30	-32

M= male F= female -- = not applicable

Table 17 Percent Changes in 13-Week Study Dogs Relative to Controls in Clinical Chemistry Parameters – Week 13

(Excerpted from the study report)

"Epoetin Hospira":

Parameter	K		GLUC		AST		GLOB		A/G	
Dose Level (IU/kg)	M	F	M	F	M	F	M	F	M	F
150 IU/kg	20	15	-27	-30	--	--	--	--	--	--
450IU/kg	30	24	-64	-42	86	71	+29	--	-19	--
1500/900 IU/kg	35	30	-62	-56	103	110	+24	--	-19	--

US-Epogen:

Parameter	K		GLUC		AST	
Dose Level (IU/kg)	M	F	M	F	M	F
150 IU/kg	20	17	-27	-33	--	--
450IU/kg	22	26	-49	-44	--	50
1500/900 IU/kg	30	22	-53	-51	75	24

M= male F= female -- = not applicable

- Similar increases in potassium and decreases in glucose levels observed at Week 4 for "Epoetin Hospira" treated animals in the 13-week study were also observed in interim animals.
- Statistically significant increases in phosphorous, triglycerides, and total protein in "Epoetin Hospira" and US-Epogen treated animals were similar to slightly above values obtained during the pretreatment period and/or claimed by the Sponsor to be within the normal physiological range for beagle dogs. The toxicological significance of these findings is likely minor.
- ALP was elevated in Epogen treated males during Weeks 4 and 9 (2-fold↑).

Urinalysis

Unremarkable

Gross Pathology

Table 18 Comparative Macroscopic Findings in the 13-Week Study

Test Article-related findings†		No. of animals affected											
Test Article		"Epoetin Hospira"						US-Epogen					
Dose (IU/kg)		150		450		1500/900		150		450		1500/900	
Sex (M=male; F=female)		M	F	M	F	M	F	M	F	M	F	M	F
Number of animals examined (main/recovery)		4/0	4/0	4/0	4*/0	4/2*	4*/2*	4/0	4/0	4*/0	4*/0	4*/2	4*/2
Bone marrow	Discoloration						0/1*						
Brain	Lesion						1*/0						
Cecum	Discoloration			1/-	1*/-		2*/1*		1/-		2*/-		1/0
Colon	Discoloration			1/-		1/0	2*/1*				2*/-		1/0
Duodenum	Discoloration	2/-	1/-	2/-	2*/-	3/1	2*/1*	3/-	4/-	1/-	4*/-	2/0	3*/0
	Raised area												1*/0

Test Article-related findings†		No. of animals affected											
Test Article		"Epoetin Hospira"						US-Epogen					
Dose (IU/kg)		150		450		1500/900		150		450		1500/900	
Sex (M=male; F=female)		M	F	M	F	M	F	M	F	M	F	M	F
Number of animals examined (main/recovery)		4/0	4/0	4/0	4*/0	4/2*	4*/2*	4/0	4/0	4*/0	4*/0	4*/2	4*/2
Ileum	Discoloration			1/-	1/-		1*/1*				2*/-	1/0	
Jejunum	Discoloration			2/-	2*/-	1/0	1*/1*	1/-	2/-		2*/-	1/0	
Rectum	Discoloration	1/-		1/-	1/-		1*/1*				1/-	1/0	
Heart	Thick						1*/0						
Kidney	Discoloration						1*/1*						1*/0
	Enlarged						0/1*						1*/0
	Dialysis												0/1
Liver	Discoloration												
Pancreas	Discoloration						0/1*				1*/-		1*/0
Pituitary gland	Discoloration						0/1*			1/-		1/0	
Prostate	Small		NA	2/-	NA	1/1*	NA	1/-	NA	2*/-	NA	1/0	NA
Skeletal muscle	Discoloration					0/1*	0/1*						
	Thick					0/1*							
Spinal cord	Lesions						1*/0						
Spleen	Enlarged		2/-		2/-		1/0	1/-			2/-		
	Depressed area							1/-					
	Raised area											0/1	
Stomach	Discoloration	1/-					0/1*				1/-		
Thymus	Discoloration	2/-		4/-	2*/-	3/0	3*/1*	1/-	1/-	2/-	2*/-	1/0	3*/0
	Thick						1*/0						
Thyroid	Discoloration						0/1*				1*/-		1*/0
Urinary bladder	Discoloration						1*/1*						
Uterus	Discoloration	NA		NA		NA	1/1*	NA		NA		NA	
Vagina	Discoloration	NA		NA		NA	1/1*	NA		NA		NA	1*/0

Abbreviations: †=observations were not present in control animals except for enlarged spleen in one control female; empty cell = finding not present (or not assessed, in the case of recovery animals for Groups 2, 3, 5, and 6); "-"= finding present in main study animals was not assessed in recovery animals for Groups 2, 3, 5, and 6; * = finding present in animals with early mortality; NA = organ not present in sex

- Test article-related discoloration in various organs above generally correlated with congestion.
- Discoloration of the dosing site was observed in all groups and correlated microscopically with hemorrhage.
- Discoloration in the lung was also noted in "Epoetin Hospira" treatment and control groups and correlated microscopically with acute inflammation.
- Brain dilation was observed in one 450 IU/kg "Epoetin Hospira" treated interim study female.

Organ Weights

Table 19 Comparative Changes in Organ Weights in the 13-Week Study

		Percent Change Relative to Control Mean											
Test Article		"Epoetin Hospira"						US-Epogen					
Dose (IU/kg)		150		450		1500/900		150		450		1500/900	
Sex(M=male;F=female)		M	F	M	F	M	F	M	F	M	F	M	F
Number of animals examined (main/recovery)		4/0	4/0	4/0	4/0	4/2	4/2	4/0	4/0	4/0	4/0	4/2	4/2
Kidney	Absolute (g)	--	--	24↑	20↑	29↑/19↑	31↑/ 11↑	13↑	10↑	14↑	22↑	21↑/ --	14↑/10↑
	Relative Body weight (%)	--	--	29↑***	20↑	32↑/17↑	29↑/ 11↑	--	11↑	22↑*	19↑	28↑**/--	19↑/26↑
Spleen	Absolute (g)	27↑	77↑	--	70↑	11↓/24↑	29↑/ 45↑	29↑	70↑	--	38↑	--/ --	19↑/--
	Relative Body weight (%)	24↑	67↑*	--	79↑*	10↓/26↑	33↑/ 53↑	23↑	28↑	--	44↑	--/ --	27↑/12↑
Lung	Absolute (g)	--	--	--	--	11↑/--	14↑/ --	--	--	--	--	--/ --	--/19↑
	Relative Body weight (%)	--	--	--	--	11↑/10↓	12↑/ 15↑	--	--	--	--	--/ --	13↑/36↑

Statistically significant: * = p≤0.05; ** = p≤0.01; *** = p≤0.001
"—" = no change or change did not exceed 10% relative to control mean

- Aside from increased spleen and kidney weights, findings were somewhat different at Week 4 in interim animals treated with "Epoetin Hospira". At Week 4, there was a 30% and 13% increase in brain and liver, respectively, relative to body weight in 1500 IU/kg "Epoetin Hospira" treated males compared to controls. There was a 10% and 14% increase in brain and liver relative to body weight, respectively, in 1500 IU/kg "Epoetin Hospira" treated females compared to controls. In recovery females, 21% increases in brain weight relative to body weight were also observed.

Bone Marrow Smears

Table 20 Comparative Bone Marrow Pathology in Dogs in the 13-Week Study

	Number of Animals Affected											
Test Article	"Epoetin Hospira"						US-Epogen					
Dose (IU/kg)	150		450		1500/900		150		450		1500/900	
Sex (M=male;F=female)	M	F	M	F	M	F	M	F	M	F	M	F
Number of animals examined (main/recovery)	4/0	4/0	4/0	4/0	4/2	3/2	4/0	4/0	4/0	4/0	4/2	4/2
Erythroid hyperplasia	**2/-**	**4/-**	**2/-**	**4/-**	**1/1**	**3/2**	**1/-**	**4/-**	**4/-**	**4/-**	**2/2**	**3/2**
mild	0/-	2/-	1/-	2/-	1/1	0/0	0/-	1/-	2/-	1/-	1/0	0/0
moderate	2/-	2/-	1/-	1/-	0/0	2/1	1/-	3/-	2/-	1/-	1/1	2/1
marked	0/-	0/-	0/-	1/-	0/0	1/1	0/-	0/-	0/-	2/-	0/1	1/1
Asynchronous erythroid development	**3/-**	**4/-**	**3/-**	**4/-**	**3/1**	**3/2**	**3/-**	**3/-**	**4/-**	**4/-**	**4/0**	**4/0**
mild	3/-	3/-	3/-	3/-	3/1	3/2	3/-	3/-	3/-	2/-	3/0	2/0
moderate	0/-	1/-	0/-	1/-	0/0	0/0	0/-	0/-	1/-	1/-	1/0	1/0
marked	0/-	0/-	0/-	0/-	0/0	0/0	0/-	0/-	0/-	1/-	0/0	1/0
Asynchronous myeloid development	**0/-**	**0/-**	**0/-**	**1/-**	**4/0**	**1/2**	**2/-**	**1/-**	**2/-**	**3/-**	**0/0**	**3/0**
mild	0/-	0/-	0/-	1/-	4/0	1/2	2/-	0/-	1/-	3/-	0/0	3/0
moderate	0/-	0/-	0/-	0/-	0/0	0/0	0/-	1/-	1/-	0/-	0/0	0/0
Immaturity of megakaryocytes and dysmegakaryocytopoiesis (nuclear hypolobulation); mild	**2/-**	**1/-**	**3/-**	**3/-**	**3/1**	**3/1**	**4/-**	**3/-**	**4/-**	**4/-**	**4/1**	**4/2**
Myelofibrosis	**0/-**	**1/-**	**0/-**	**2/-**	**3/0**	**2/2**	**2/-**	**3/-**	**4/-**	**3/-**	**2/2**	**3/2**
early	0/-	0/-	0/-	0/-	2/0	0/0	2/-	0/-	2/-	0/-	0/0	0/0
mild	0/-	0/-	0/-	0/-	0/0	0/0	0/-	1/-	0/-	3/-	0/2	3/1

	Number of Animals Affected											
Test Article	"Epoetin Hospira"						US-Epogen					
Dose (IU/kg)	150		450		1500/900		150		450		1500/900	
Sex (M=male;F=female)	M	F	M	F	M	F	M	F	M	F	M	F
Number of animals examined (main/recovery)	4/0	4/0	4/0	4/0	4/2	3/2	4/0	4/0	4/0	4/0	4/2	4/2
moderate	0/-	1/-	0/-	2/-	0/0	2/2	0/-	2/-	2/-	0/-	2/0	0/1
well-advanced	0/-	0/-	0/-	0/-	1/0	0/0	0/-	0/-	0/-	0/-	0/0	0/0
Mean M/E (myeloid/erythroid) ratio	0.84	0.69	0.91	0.66	1.39/ 0.79	0.57/ 0.53	1.02	1.23	0.65	0.52	0.87/ 2.98	0.60/ 2.99
Reticuloendothelial hyperplasia	**2/-**	**1/-**	**0/-**	**1/-**	**3/0**	**2/2**	**2/-**	**3/-**	**4/-**	**3/-**	**1/2**	**3/2**
mild	2/-	1/-	0/-	1/-	3/0	2/1	2/-	3/-	4/-	3/-	1/2	3/0
moderate	0/-	0/-	0/-	0/-	0/0	0/1	0/-	0/-	0/-	0/-	0/0	0/2
Scattered clusters of osteoblasts, scattered erythroblastic islands	**0/-**	**0/-**	**0/-**	**1/-**	**0/-**	**0/1**	**0/-**	**0/-**	**0/-**	**0/-**	**1/2**	**1/0**
Occasional binucleated rubricytes	**0/-**	**0/-**	**0/-**	**0/-**	**0/1**	**0/0**	**0/-**	**0/-**	**0/-**	**0/-**	**0/0**	**0/0**
Bone marrow hypoplasia	**0/-**	**0/-**	**0/-**	**0/-**	**0/1**	**0/0**	**0/-**	**0/-**	**0/-**	**0/-**	**0/0**	**0/1**
Increased amounts of storage iron consistent with decreased erythroid production	**0/-**	**0/-**	**0/-**	**0/-**	**0/1**	**0/0**	**0/-**	**0/-**	**0/-**	**0/-**	**0/0**	**0/1**

Mean M/E ratio for control males = 1.27/1.15 (main study/recovery) and for control females = 1.29/1.23; Controls were not positive for most findings (except one control female who had occasional bone marrow spicules showing early myelofibrosis and mild reticuloendotheliosis), so are not included in the table; bold = total number of animals in group with finding, regardless of severity.

Interim Study Animals:

- Dose-related findings included erythroid hyperplasia and myelofibrosis. Mild erythroid hyperplasia was noted in 1/4 males and 1/4 females, while 2/4 females had evidence for myelofibrosis at 450 IU/kg.
- At 1500 IU/kg, erythroid hyperplasia was noted in 3/4 females and evidence of myelofibrosis was noted in 4/4 females.
- No changes were observed in the marrows of the 1500 IU/kg treated male dogs.
- Erythroid hyperplasia was reversible and some control animals and test article treated recovery animals showed evidence of myelofibrosis. Fifty percent of 1500 IU/kg recovery females showed evidence for myelofibrosis, reticulodendothelial hyperplasia and clusters of osteoblasts.

Histopathology

Adequate Battery Yes

Peer Review No

Histological Findings

Table 21 Comparative Microscopic Findings in Male Dogs in the 13-Week Study - Day 92

(Excerpted from the study report)

Tissue/Dose Level IU/kg	0	150	450	1500/900	150 RA	450 RA	1500/900 RA
Bone Marrow, Femur/No. Ex.	4	4	4	3	4	3	4
Within normal limits	4	0	0	0	0	0	0
Hypercellularity, minimal	0	2	0	0	0	0	0
Hypercellularity, mild	0	2	0	0	4	1	2
Hypercellularity, moderate	0	0	4	3	0	2	0
Fibrosis, minimal	0	0	0	1	0	0	2
Fibrosis, mild	0	0	0	0	0	0	1
Fibrosis, moderate	0	0	0	0	0	0	1
Bone Marrow, Sternum /No. Ex.	4	4	4	3	4	3	4
Within normal limits	4	0	0	0	0	0	0
Hypercellularity, minimal	0	0	0	0	1	0	2
Hypercellularity, mild	0	4	4	1	3	2	0
Hypercellularity, moderate	0	0	0	2	0	1	0
Fibrosis, minimal	0	0	0	1	0	0	1
Fibrosis, mild	0	0	0	1	0	0	2
Fibrosis, moderate	0	0	0	0	0	0	1
Kidney /No. Ex	4	4	4	3	4	3	4
Within normal limits	0	0	0	0	0	0	0
Inflammation, chronic, cortical, focal, minimal	1	0	0	0	0	0	0
Inflammation, chronic, cortical, multifocal, minimal	0	0	3	1	0	0	1
Regeneration, tubular, multifocal, minimal	0	0	1	1	0	0	2
Regeneration, tubular, multifocal, mild	0	0	3	0	0	1	0
Regeneration, tubular, multifocal, moderate	0	0	0	1	0	1	0
Liver /No. Ex	4	4	4	3	4	3	4
Within normal limits	0	0	0	0	0	0	0
Congestion, centrilobular, minimal	0	4	4	2	2	0	1
Congestion, centrilobular, mild	0	0	0	1	2	3	3
Pigmentation, hepatocellular, centrilobular, minimal	0	2	2	0	3	0	3
Pigmentation, hepatocellular, centrilobular, mild	0	1	2	1	0	2	1
Nerve, Sciatic	4	4	4	3	4	3	3
Within normal limits	4	4	1	1	4	1	3
Degeneration, axonal, focal, minimal	0	0	0	0	0	1	0
Degeneration, axonal, multifocal, minimal	0	0	2	2	0	0	0
Degeneration, axonal, multifocal, mild	0	0	1	0	0	1	0
Spleen /No. Ex	4	4	4	3	4	3	4
Within normal limits	4	4	2	0	4	2	0
Erythropoiesis, minimal	0	0	2	2	0	1	1
Erythropoiesis, mild	0	0	0	1	0	0	3
Dosing Site/No. Ex.	4	4	4	3	4	3	4

Within normal limits	2	0	2	0	1	1	1
Hemorrhage, subcutaneous, multifocal, minimal	1	0	1	0	0	1	0
Hemorrhage, subcutaneous, multifocal, mild	1	1	0	2	3	1	1
Hemorrhage, subcutaneous, multifocal, moderate	0	3	1	0	0	0	2
Hemorrhage, subcutaneous, multifocal, marked	0	0	0	1	0	0	0
Inflammation, chronic, focal, minimal	0	1	0	0	0	2	3
Inflammation, chronic, focal, mild	0	1	1	0	1	0	0
Cecum/No. Ex.	4	4	4	3	4	3	4
Within normal limits	4	4	0	0	1	2	1
Congestion (diffuse, focal, or multifocal), minimal	0	0	3	3	3	1	3
Congestion (diffuse, focal, or multifocal), mild	0	0	1	0	0	0	0
Colon/No. Ex.	4	4	4	3	4	3	4
Within normal limits	4	4	1	1	1	1	0
Congestion (diffuse, focal, or multifocal), minimal	0	0	3	2	3	2	4
Duodenum/No. Ex	4	4	4	3	4	3	4
Within normal limits	4	3	1	0	1	1	0
Congestion (diffuse, focal, or multifocal), minimal	0	0	2	2	3	2	3
Congestion (diffuse, focal, or multifocal), mild	0	1	1	1	0	0	1
Ileum/No. Ex	4	4	4	3	4	3	4
Within normal limits	4	3	4	0	3	1	2
Congestion (diffuse or multifocal), minimal	0	2	0	3	1	2	1
Congestion (diffuse or multifocal), mild	0	0	0	0	0	0	1
Jejunum/No. Ex	4	4	4	3	4	3	4
Within normal limits	4	3	0	0	0	0	1
Congestion (diffuse, focal, or multifocal), minimal	0	1	4	3	4	3	3
Rectum/No. Ex	4	4	4	3	4	3	4
Within normal limits	4	3	3	2	2	2	1
Congestion (diffuse, focal, or multifocal), minimal	0	1	1	1	2	1	3
Lung/No. Ex	4	4	4	3	4	3	4
Within normal limits	2	1	0	1	1	2	1
Hemorrhage, focal, minimal	0	0	0	0	0	0	1
Inflammation, chronic, peribronchial, multifocal, minimal	0	2	1	1	2	0	2
Inflammation, chronic, peribronchial, multifocal, mild	0	0	1	0	0	0	1
Lymph Node (Mediastinal)/No. Ex	0	0	0	1	0	0	0
Within normal limits	0	0	0	0	0	0	0

Infiltration, erythrocytic, sinusoid, moderate	0	0	0	1	0	0	0
Lymph Node (Mesenteric)/No. Ex	3	4	4	3	4	3	4
Within normal limits	0	0	2	0	0	0	0
Infiltration, erythrocytic, sinusoid, minimal	0	2	0	2	1	0	1
Pituitary Gland/No. Ex	4	4	4	3	4	3	4
Within normal limits	3	3	2	3	3	2	1
Congestion, minimal	0	0	0	0	0	1	1
Spinal Cord, Thoracic/No. Ex	4	4	4	3	4	3	4
Within normal limits	4	4	2	1	4	0	3
Hemorrhage, acute, multifocal, minimal	0	0	1	2	0	2	1
Stomach/No. Ex	4	4	4	3	4	3	4
Within normal limits	0	0	0	0	0	0	0
Accumulation, lymphocytic, mucosa, multifocal, minimal	0	0	0	2	1	0	1
Accumulation, lymphocytic, mucosa, multifocal, mild	3	3	2	0	2	1	1
Accumulation, lymphocytic, mucosa, multifocal, moderate	1	1	2	1	1	2	2
Thymus/No. Ex	4	4	4	3	4	3	4
Within normal limits	2	1	0	0	0	1	0
Congestion, minimal	0	0	1	0	0	0	0
Congestion, mild	0	0	1	1	1	1	1
Hemorrhage, multifocal, minimal	0	0	1	0	1	1	1
Hemorrhage, multifocal, mild	0	0	1	1	0	0	0
Hemorrhage, multifocal, moderate	0	0	0	1	0	0	0

Table 22 Comparative Microscopic Findings in Female Dogs in the 13-Week Study - Day 92

(Excerpted from the study report)

Tissue/Dose Level IU/kg	0	150	450	1500/900	150 RA	450 RA	1500/900 RA
Bone Marrow, Femur/No. Ex.	4	4	3	3	4	3	3
Within normal limits	4	0	0	0	0	0	0
Hypercellularity, minimal	0	1	0	0	0	0	0
Hypercellularity, mild	0	3	1	0	2	0	1
Hypercellularity, moderate	0	0	2	3	2	3	2
Fibrosis, minimal	0	0	0	1	0	1	1
Fibrosis, mild	0	0	0	0	0	0	2
Bone Marrow, Sternum /No. Ex.	4	4	3	3	4	3	3
Within normal limits	4	0	0	0	0	0	0
Hypercellularity, minimal	0	1	0	0	0	0	1
Hypercellularity, mild	0	3	3	3	2	2	2
Hypercellularity, moderate	0	0	0	0	2	1	0
Fibrosis, minimal	0	0	0	2	0	0	1
Fibrosis, mild	0	0	0	0	0	0	2
Kidney /No. Ex	4	4	3	3	4	3	3
Within normal limits	0	0	0	0	0	0	0
Inflammation, chronic, cortical, focal, minimal	0	0	0	0	0	1	0
Inflammation, chronic, cortical, multifocal, minimal	0	0	0	1	0	1	0
Regeneration, tubular, multifocal, minimal	0	0	0	2	0	0	1
Regeneration, tubular, multifocal, mild	0	0	0	1	0	1	1
Liver /No. Ex	4	4	3	3	4	3	3
Within normal limits	0	0	0	0	0	0	0
Congestion, centrilobular, minimal	0	4	3	1	4	2	3
Congestion, centrilobular, mild	0	0	0	2	0	1	0
Pigmentation, hepatocellular, centrilobular, minimal	0	4	3	2	4	3	3
Pigmentation, hepatocellular, centrilobular, mild	0	0	0	1	0	0	0
Nerve, Sciatic	4	4	3	3	4	3	3
Within normal limits	4	4	3	2	4	2	2
Degeneration, axonal, multifocal, minimal	0	0	0	1	0	0	1
Degeneration, axonal, multifocal, mild	0	0	0	0	0	1	0
Spleen /No. Ex	4	4	3	3	4	3	3
Within normal limits	4	4	2	0	3	0	0
Erythropoiesis, minimal	0	0	1	2	1	0	3
Erythropoiesis, mild	0	0	0	1	0	1	0
Dosing Site/No. Ex.	4	4	3	3	4	3	3
Within normal limits	1	0	0	0	0	0	0
Hemorrhage, subcutaneous, multifocal, minimal	0	0	0	0	1	0	0
Hemorrhage, subcutaneous, multifocal, mild	2	3	2	2	2	2	1

Hemorrhage, subcutaneous, multifocal, moderate	0	0	1	1	1	1	2
Hemorrhage, subcutaneous, multifocal, marked	0	1	0	0	0	0	0
Inflammation, chronic, focal, minimal	1	2	0	2	1	0	1
Inflammation, chronic, focal, mild	0	1	1	1	2	0	1
Cecum/No. Ex.	4	4	3	3	4	3	3
Within normal limits	4	2	0	0	0	1	0
Congestion (diffuse, focal, or multifocal), minimal	0	2	3	3	4	2	3
Colon/No. Ex.	4	4	3	3	4	3	3
Within normal limits	3	0	0	2	1	0	0
Congestion (diffuse, focal, or multifocal), minimal	1	4	3	1	3	3	3
Duodenum/No. Ex	4	4	3	3	4	3	3
Within normal limits	3	2	2	2	0	1	0
Congestion (diffuse, focal, or multifocal), minimal	0	2	1	1	4	1	3
Congestion (diffuse, focal, or multifocal), mild	0	0	0	0	0	1	0
Ileum/No. Ex	4	4	3	3	4	3	3
Within normal limits	4	3	1	2	3	2	1
Congestion (diffuse, focal, or multifocal), minimal	0	1	1	1	1	1	2
Congestion (diffuse, focal, or multifocal), mild	0	0	1	0	0	0	0
Jejunum/No. Ex	4	4	3	3	4	3	3
Within normal limits	4	3	0	1	0	1	2
Congestion (diffuse, focal, or multifocal), minimal	0	1	3	2	4	2	1
Rectum/No. Ex	4	4	3	3	4	3	3
Within normal limits	4	3	0	1	1	1	1
Congestion (diffuse, focal, or multifocal), minimal	0	1	3	2	3	2	2
Kidney/No. Ex	4	4	3	3	4	3	3
Within normal limits	0	0	0	0	0	0	0
Congestion, mild	0	0	0	1	0	0	0
Lung/No. Ex	4	4	3	3	4	3	3
Within normal limits	2	3	1	1	2	0	1
Atelectasis, focal, mild	0	0	0	1	0	0	0
Accumulation, macrophage, multifocal, mild	0	0	0	0	0	0	1
Inflammation, chronic, interstitium, focal, minimal	0	0	0	1	0	0	0
Inflammation, chronic, peribronchial, multifocal, minimal	1	0	0	1	1	1	0
Inflammation, chronic, peribronchial, multifocal, mild	1	0	0	0	0	0	0
Lymph Node (Mediastinal) /No. Ex	0	0	1	0	1	0	0

Within normal limits	0	0	0	0	0	0	0
Infiltration, erythrocytic, sinusoid, moderate	0	0	1	0	1	0	0
Lymph Node (Mesenteric)/No. Ex	4	4	3	3	4	3	3
Within normal limits	0	0	0	0	0	0	0
Infiltration, erythrocytic, sinusoid, minimal	0	1	1	1	1	1	1
Infiltration, erythrocytic, sinusoid, mild	0	0	0	1	0	0	0
Spinal Cord, Thoracic/No. Ex	4	4	3	3	4	3	3
Within normal limits	3	4	1	2	4	3	1
Hemorrhage, acute, multifocal, minimal	1	0	0	1	0	0	2
Stomach/No. Ex	4	4	3	3	4	3	3
Within normal limits	0	0	0	0	0	0	0
Accumulation, lymphocytic, mucosa, multifocal, minimal	0	2	0	1	0	0	0
Accumulation, lymphocytic, mucosa, multifocal, mild	3	1	1	0	3	1	3
Accumulation, lymphocytic, mucosa, multifocal, moderate	1	1	2	2	1	2	0
Thymus/No. Ex	4	4	3	3	4	3	3
Within normal limits	0	0	1	0	0	0	0
Congestion, mild	0	0	1	2	1	0	1
Hemorrhage, multifocal, minimal	0	0	0	0	0	1	1
Uterus/No. Ex	4	4	3	3	4	3	3
Within normal limits	4	4	3	2	4	3	3
Congestion, mild	0	0	0	1	0	0	0
Vagina/No. Ex	4	4	3	3	4	3	3
Within normal limits	4	4	3	2	4	3	3
Congestion, mild	0	0	0	1	0	0	0

- Fibrosis in the bone marrow, findings in the kidney, liver and sciatic nerve and spinal cord were not noted at 4 weeks in interim animals (see Appendix).

Table 23 Comparative Microscopic Findings in Dogs in the 13-Week Study - Day 120

(Excerpted from the study report)

Tissue	Males			Females		
Dose Level IU/kg	0	1500/900	RA 1500/900	0	1500/900	RA 1500/900
Bone Marrow, Femur/No. Ex.	2	1	2	2	1	2
Within normal limits	2	0	0	2	1	1
Fibrosis, minimal	0	0	0	0	0	1
Fibrosis, mild	0	0	1	0	0	0
Hypocellularity, minimal	0	0	1	0	0	0
Hypocellularity, mild	0	1	1	0	0	1
Bone Marrow, Sternum /No. Ex.	2	1	2	2	1	2
Within normal limits	2	0	0	2	1	2
Hypocellularity, minimal	0	0	2	0	0	0
Hypocellularity, mild	0	1	0	0	0	0
Sciatic Nerve/No. Ex.	2	1	2	2	1	2
Within normal limits	2	1	2	2	1	1
Degeneration, axonal, multifocal, minimal	0	0	0	0	0	1
Kidney/No. Ex.	2	1	2	2	1	2
Within normal limits	0	0	0	0	0	0
Hydronephrosis, mild	0	0	0	0	0	1
Lymph Node (Mediastinal) /No. Ex	1	0	0	0	0	1
Within normal limits	0	0	0	0	0	0
Infiltration, erythrocytic, sinusoid, mild	0	0	0	0	0	1
Infiltration, erythrocytic, sinusoid, moderate	1	0	0	0	0	0

Special Evaluation

Immunogenicity

Table 24 Summary of Immunogenicity Results in Dogs

(Excerpted from the study report)

Immunogenicity Results					
Group	Sex	Animal Number	Time point (Week)	ADA Results	NAb Results
4 [Epoetin Hospira 1500/900 IU/kg]	Female	4501A	4	Positive	Positive
5 [Epogen 150 IU/kg]	Female	5503G	4	Positive	Positive
6 [Epogen 450 IU/kg]	Female	6501E	9,11, and 13	Positive	Positive
7 [Epogen 1500/900 IU/kg]	Male	7003G	6, 9, and 13	Positive	Positive
			11	Positive	Negative
	Female	7501E	6	Positive	Positive
			9, 11, and 13	Positive	Negative
ADA: Binding antibody determination; NAb: Neutralizing antibody determination					

- In all cases, the serum erythropoietin concentrations of the individual animals on the appropriate PK sampling day (Animal Nos. 4501 and 5503 on Day 26 and Animal Nos. 6501, 7003 and 7501 on Day 89) are within one standard deviation or close thereof of the group mean serum concentrations. Similarly, the pharmacokinetic parameters of the ADA positive animals are close to the mean PK parameter values. These observations suggest that antibody production does not impact the pharmacokinetic behavior of erythropoietin.

Table 25 Comparison of Onset of Anti-Drug Antibodies for "Epoetin Hospira" and US-Epogen in the Rat and Dog

Test Item	Sex	Rat		Dog	
		Onset	No.+ (%) at Onset	Onset	No.+ (%) at Onset
EH 150	M	Week 15	1/6 (17%)	--	--
	F	Week 4	2/6 (33%)	--	--
EH 450	M	Week 13	1/5 (20%)	--	--
	F	Week 6	1/6 (17%)	--	--
EH 1500/900	M	Week 4	1/6 (17%)	--	--
	F	Week 4	2/6 (33%)	Week 4*	1/12 (8%)
RP 150	M	Week 4	2/6 (33%)	--	--
	F	Week 4	3/6 (50%)	Week 4	1/6 (17%)
RP 450	M	Week 4	3/6 (50%)	--	--
	F	Week 4	4/6 (67%)	Week 9	1/6 (17%)
RP 1500/900	M	Week 4	6/6 (100%)	Week 6	1/6 (17%)
	F	Week 4	1/6 (17%)	Week 6	1/6 (17%)

Timepoints evaluated were pretreatment, Weeks 2, 4, 6, 9, 11, 13, 15, and 17
Abbreviations: No.+ = number of animals testing positive for ADA; % = (number of animals that test positive/total number of animals evaluated at onset at a given timepoint) x 100; EH = "Epoetin Hospira"; RP = reference product (US-Epogen); * = last time point of evaluation was 4 weeks for 4/10 "Epoetin Hospira" treated dogs; "—" = no ADA observed

Toxicokinetics

- Mean exposure (C_{max} and AUC_{0-t}) values increased with increasing dose with generally dose proportional increases for C_{max} and greater than dose proportional increases for AUC (except for Day 89 when increases in AUC were less than dose proportional between the mid and high doses).
- Mean exposures were slightly lower following administration for "Epoetin Hospira" compared to US-Epogen, but fell within the range of individual animal variability when taking into account standard deviation.
- AUC exposures tended to decrease with repeat-dosing, which could be related to an increase in clearance rates with repeat dosing.
- T_{max} was reached within an hour for both test articles.
- Half-lives ($t_{1/2}$) were similar ranging from 6 to 12 h on Day 1, from 5 to 6 h on Day 26 and from 5 to 7 h on Day 89 for "Epoetin Hospira" and 7 to 11 h on Day 1 and from 5 to 6 h on Days 26 and 89.
- Mean clearance rates were similar on Days 1 and 26 - ranging from ~7 to 13 mL/h/kg on Day 1 and ~11 to 17 mL/h/kg on Day 26 for "Epoetin Hospira" and ~6 to 11 mL/h/kg on Day 1 and ~9 to 16 mL/h/kg on Day 26 for US-Epogen. Mean clearance was faster for "Epoetin Hospira" on Day 89 compared to US-Epogen – ranging from ~16 to 30 mL/h/kg verses ~13 to 18 mL/h/kg, respectively. However, differences in clearance rates generally fell within the range of individual animal variability when taking into account the range of minimum and maximum rates for each dose level.
- There were no apparent gender related differences.

Table 26 Comparative Toxicokinetics in Dogs

(Excerpted from the Toxicology Tabulated Summary)

Day 1:

Daily Dose	150 IU/Kg				450 IU/Kg				1500 IU/Kg			
Number of Animals	Male (4 + 4)		Female (4 + 4)		Male (4 + 4)		Female (4 + 4)		Male (4 + 4)		Female (4 + 4)	
Test Item	Epoetin Hospira	Epogen	Epoetin Hospira	Epogen	Epoetin Hospira	Epogen	Epoetin Hospira	Epogen	Epoetin Hospira	Epogen	Epoetin Hospira	Epogen
C_{max} (mIU/mL) (Mean ± SD)	2287.43 ± 565.12	2516.14 ± 320.80	2470.11 ± 319.49	2725.54 ± 678.18	8782.49 ± 2227.06	7147.43 ± 1416.79	7534.84 ± 550.29	6422.88 ± 2937.08	23040.08 ± 4253.29	29680.39 ± 5942.56	22025.63 ± 6396.69	27884.91 ± 5948.90
AUC_{0-24} (mIU hour/mL) (Mean ± SD)	-	-	-	-	-	-	-	-	-	-	-	-
AUC_{last} (mIU hour/mL) (Mean ± SD)	13071.58 ± 1759.39	12304.36 ± 1184.71	11265.56 ± 1467.43	14536.01 ± 2206.74	40756.95 ± 6212.35	48019.62 ± 6538.79	43859.67 ± 5469.56	42304.27 ± 6157.45	159513.74 ± 16736.16	196993.56 ± 23792.55	160904.55 ± 24883.87	198483.17 ± 17135.60
AUC_{0-t} (mIU hour/mL) (Mean ± SD)	13071.58 ± 1759.39	12304.36 ± 1184.71	11265.56 ± 1467.43	14536.01 ± 2206.74	40756.95 ± 6212.35	48019.62 ± 6538.79	43859.67 ± 5469.56	42304.27 ± 6157.45	159513.74 ± 16736.16	196993.56 ± 23792.55	160904.55 ± 24883.87	198483.17 ± 17135.60
t_{max} (hours) (Mean ± SD)	0.121 ± 0.082	0.146 ± 0.080	0.108 ± 0.068	0.146 ± 0.080	0.244 ± 0.175	0.237 ± 0.199	0.242 ± 0.173	1.071 ± 1.954	0.197 ± 0.131	0.364 ± 0.343	0.218 ± 0.101	0.153 ± 0.170
$t_{1/2}$ (hours) (Mean ± SD)	7.48 ± 1.28	7.96 ± 1.67	6.03 ± 0.77	7.43 ± 0.51	10.08 ± 1.38	10.24 ± 0.70	9.41 ± 1.83	11.41 ± 3.58	11.88 ± 2.83	9.86 ± 2.71	11.30 ± 3.18	10.94 ± 3.46

Day 26:

Daily Dose	150 IU/Kg				450 IU/Kg				1500 IU/Kg			
Number of Animals	Male (4 + 4)		Female (4 + 4)		Male (4 + 4)		Female (4 + 4)		Male (4 + 4)		Female (4 + 4)	
Test Item	Epoetin Hospira	Epogen	Epoetin Hospira	Epogen	Epoetin Hospira	Epogen	Epoetin Hospira	Epogen	Epoetin Hospira	Epogen	Epoetin Hospira	Epogen
C_{max} (mIU/mL) (Mean ± SD)	2305.68 ± 196.29	2202.98 ± 980.16	2659.58 ± 452.88	2194.40 ± 493.75	6720.19 ± 2234.10	9193.73 ± 1566.46	7411.63 ± 667.34	9668.70 ± 2035.37	27145.53 ± 3207.19	28654.92 ± 3900.92	28219.42 ± 3370.55	31751.09 ± 1740.84
AUC_{0-24} (mIU hour/mL) (Mean ± SD)	8469.82 ± 889.33	9456.14 ± 1976.89	8617.45 ± 1031.29	9191.36 ± 2058.59	28756.38 ± 4479.26	38107.64 ± 5697.02	30394.49 ± 2477.94	37359.29 ± 5044.98	126051.35 ± 16027.60	151362.75 ± 17250.24	131891.50 ± 15869.77	168955.65 ± 19889.60
AUC_{last} (mIU hour/mL) (Mean ± SD)	-	-	-	-	-	-	-	-	-	-	-	-
AUC_{0-t} (mIU hour/mL) (Mean ± SD)	8469.95 ± 889.44	9456.14 ± 1976.89	8617.57 ± 1031.29	9191.36 ± 2058.59	28758.14 ± 4479.55	38107.64 ± 5697.02	30395.75 ± 2478.78	37359.29 ± 5044.98	126086.31 ± 16068.40	151362.75 ± 17250.24	131892.37 ± 15869.84	168969.47 ± 19919.95
t_{max} (hours) (Mean ± SD)	0.083 ± 0.000	0.058 ± 0.029	0.077 ± 0.046	0.071 ± 0.025	0.692 ± 1.344	0.083 ± 0.000	0.150 ± 0.076	0.058 ± 0.029	0.210 ± 0.127	0.255 ± 0.209	0.242 ± 0.184	0.158 ± 0.080
$t_{1/2}$ (hours) (Mean ± SD)	5.40 ± 0.48	6.21 ± 1.88	5.10 ± 0.29	5.59 ± 1.27	5.90 ± 1.03	5.35 ± 0.65	5.42 ± 0.66	5.90 ± 1.00	6.06 ± 0.86	6.36 ± 0.83	5.51 ± 0.69	5.45 ± 0.53

Day 89:

Daily Dose	150 IU/Kg				450 IU/Kg				1500 IU/Kg			
Number of Animals	Male (4 + 4)		Female (4 + 4)		Male (4 + 4)		Female (4 + 4)		Male (4 + 4)		Female (4 + 4)	
Test Item	Epoetin Hospira	Epogen	Epoetin Hospira	Epogen	Epoetin Hospira	Epogen	Epoetin Hospira	Epogen	Epoetin Hospira	Epogen	Epoetin Hospira	Epogen
C_{max} (mIU/mL) (Mean ± SD)	2481.80 ± 344.20	3536.70 ± 984.53	2253.21 ± 231.47	3026.27 ± 652.78	9923.32 ± 588.35	10209.89 ± 3986.20	5325.79 ± 2394.21	8820.60 ± 1403.03	17266.87 ± 554.87	21333.66 ± 3498.35	17527.97 ± 1345.49	21410.29 ± 3189.04
AUC_{0-24} (mIU hour/mL) (Mean ± SD)	7499.83 ± 886.26	10297.47 ± 1192.85	8133.61 ± 1431.20	9888.18 ± 2432.84	28515.22 ± 2338.21	32924.61 ± 8680.50	24333.00 ± 4016.99	33033.51 ± 5682.96	64244.03 ± 6162.26	89897.34 ± 19972.21	50849.07 ± 13657.11	80793.01 ± 8658.01
AUC_{last} (mIU hour/mL) (Mean ± SD)	-	-	-	-	-	-	-	-	-	-	-	-
AUC_{0-t} (mIU hour/mL) (Mean ± SD)	7499.83 ± 886.26	10297.68 ± 1193.27	8133.61 ± 1431.20	9888.34 ± 2432.72	28515.22 ± 2338.21	32925.27 ± 8680.05	24334.41 ± 4014.61	33033.51 ± 5682.96	64244.03 ± 6162.26	89897.34 ± 19972.21	50850.04 ± 13657.76	80793.01 ± 8658.01
t_{max} (hours) (Mean ± SD)	0.050 ± 0.024	0.067 ± 0.067	0.104 ± 0.073	0.092 ± 0.056	0.104 ± 0.042	0.105 ± 0.125	0.444 ± 0.488	0.072 ± 0.019	0.300 ± 0.237	0.125 ± 0.084	0.208 ± 0.084	0.143 ± 0.079
$t_{1/2}$ (hours) (Mean ± SD)	5.15 ± 0.34	5.13 ± 0.38	5.73 ± 0.61	5.59 ± 0.16	5.24 ± 0.47	5.59 ± 0.91	6.43 ± 1.52	6.12 ± 0.86	5.68 ± 1.19	5.54 ± 0.53	6.53 ± 1.45	5.62 ± 0.82

Dosing Solution Analysis

Based on the Applicant's summary, the analysis of the concentration of "Epoetin Hospira" and US-Epogen in the dose formulations administered on Day 1 and Weeks 4, 9 and 13 were performed using a validated Enzyme Linked Immunosorbent Assay Detection (ELISA)/Photometric Method. The analysis demonstrated that all concentrations ranged from 92% to 120% of the nominal concentration and were, therefore, within the study protocol's acceptable range of 100 ± 20% of nominal concentrations. In addition, the analysis of the control/vehicle samples confirmed the absence of the test and reference articles in the control/vehicle article formulation.

Samples collected from the top, middle and bottom of the "Epoetin Hospira" dose formulation (1500 IU/mL) intended for use during Week 1 were analyzed using a validated HPLC method. The analysis of these samples demonstrated that the test article concentrations at different layers of the formulation ranged from 93% to 98% of the nominal concentration, and were therefore within the study protocol's acceptance criteria of 100 ± 15%, confirming that the formulations were homogeneous.

The stability of "Epoetin Hospira" formulations under the conditions of use and/or storage on the study including sufficient room temperature stability to cover the period of dosing was performed at ITR using a validated HPLC analytical method (Study No. 40312). The results of these stability analyses demonstrated that the 1500 IU/mL "Epoetin Hospira" dose formulation was stable for 24 hours when stored at room temperature. The concentration of the "Epoetin Hospira" formulation at 24 hours post preparation was 97% of the nominal concentration obtained at time zero, and was therefore within the study protocol's acceptance criteria of 100 ± 15%.

10 Special Toxicology Studies

None were submitted.

11 Integrated Summary and Safety Evaluation

Two GLP-compliant 13-week comparative toxicology studies were submitted to support the similarity of "Epoetin Hospira" to US-Epogen using the IV (in the Beagle dog) and SC (in the Sprague-Dawley rat) routes of administration 3x/week, which is consistent with the currently approved labeling of the US-licensed Epogen reference product.

The 13-week SC injection comparative toxicology study with a 4-week recovery period (Study No. 70882) was conducted in Sprague-Dawley rats administered 150, 450 or 1500/900 IU/kg "Epoetin Hospira" or US-Epogen. Mortality was observed at doses as low as 150 IU/kg in rats, which represents approximately the human starting dose (based on the US-licensed Epogen package insert). A high incidence of ADA to US-Epogen (generally at or in excess of 50% of rats/group) was observed at all doses, which correlated with reduced PD endpoints, including RBC, HGB, HCT, and absolute reticulocytes compared to "Epoetin Hospira" treated rats. This also correlated with > 50% reduced exposure (AUC_{0-t}) by Day 89 of US-Epogen compared to "Epoetin

Hospira", except in females treated with 150 IU/kg. Therefore, conclusions regarding the similarity of "Epoetin Hospira" to US-Epogen could not be made for SC injection in rats.

The 13-week IV comparative toxicology study with a 4-week recovery period (Study No. 60486) was conducted in Beagle dogs administered 150, 450 or 1500/900 IU/kg "Epoetin Hospira" or US-Epogen. There was mortality at doses ≥ 450 IU/kg, with more total deaths in "Epoetin Hospira" treated dogs, but more death in US-Epogen treated dogs at lower doses. Similar increases in PD endpoints between "Epoetin Hospira" and US-Epogen were observed at all doses. The specific microscopic findings were not identical between "Epoetin Hospira" and US-Epogen treated animals, but the target organs were overall similar: hematopoietic system (fibrosis and hypercellularity of the bone marrow, erythropoiesis of the spleen, lymph node hyperplasia, thymus atrophy and necrosis); inflammation/regeneration of the kidneys; axonal degeneration of the sciatic nerve and hemorrhage of the spinal cord; hemorrhage/inflammation of the dosing site; and, inflammation/congestion of multiple organs (gastrointestinal tract (stomach, small and large intestines, rectum), pancreas, pituitary gland, lung, and liver). Overall, "Epoetin Hospira" and US-Epogen displayed similar trends in reversibility of toxicity.

Results from the dog study suggest more toxicity to the brain, heart, eye, and skeletal muscle with "Epoetin Hospira". Hemorrhage, dilation, ↑ brain weights and lower heart rates were observed in "Epoetin Hospira" treated dogs that were not observed in dogs with the reference product. However, in rats, despite neutralizing ADA development and lower exposures to US-Epogen, toxicities to the heart and brain were noted in US-Epogen treated rats. Findings deemed non adverse by the ophthalmologist of more pronounced vascular retinal pattern (size) and tortuosity of the eye were observed in "Epoetin Hospira" compared to US-Epogen treated dogs and there was a qualitative increase of the red color of the retinal and uveal vascular pattern (red reflex) observed in "Epoetin Hospira" interim rats at Week 4. The study reports note these findings may be due to the increase in RBC counts. Findings of marked skeletal muscle infarction in one male high dose "Epoetin Hospira" treated rat and moderate edema in one high dose "Epoetin Hospira" treated dog with early mortality were not observed in US-Epogen treated animals. These difference are likely not translatable to humans since they are cardiovascular in nature and cardiovascular toxicity is noted in the WARNINGS AND PRECAUTIONS section of the US-Epogen package insert.

Five dogs developed neutralizing ADA: one US-Epogen treated female at each dose, one US-Epogen treated male at 1500/900 IU/kg, and one "Epoetin Hospira" treated female at 1500/900 IU/kg. Unlike in rats, the development of ADA in dogs did not appear to correlate with reduced exposures. The incidence of ADA was also lower in the dog study; however, the onset was similar (somewhere between 2 and 4 weeks following the first administered dose).

Exposures to erythropoietin were measured at several timepoints throughout the 13-week studies in rats and dogs and, based on the results, there are some differences between "Epoetin Hospira" and US-Epogen. Mean toxicokinetic parameters (C_{max} and

AUC_{0-t}) for "Epoetin Hospira" were slightly lower on all assessment days (1, 26, and 89) and at all doses (up to 40% on Day 89) in dogs and in rats on Day 1. In dogs, clearance was faster for "Epoetin Hospira" on Day 89 compared to US-Epogen – ranging from approximately 16 to 30 mL/h/kg verses 13 to 18 mL/h/kg, respectively. However, differences in mean exposures and clearance rates were generally within the range of individual animal variability.

In conclusion, the nonclinical evidence supports similarity of "Epoetin Hospira" to US-Epogen administered intravenously, based on similar pharmacodynamics and organs of toxicity in dogs. Pharmacodynamics and toxicokinetics for US-Epogen were much lower (>50%) than "Epoetin Hospira" when administered subcutaneously in rats. This could be related to the development of neutralizing anti-drug antibodies, which has been observed previously with long-term repeat SC dosing of recombinant human erythropoietin in rats[2]. Therefore, considering the differences observed with subcutaneous administration, there are discipline-specific uncertainties regarding the overall similarity of "Epoetin Hospira" to US-Epogen from the Pharmacology/Toxicology perspective.

12 Appendix/Attachments

Below is a summary of interim findings (at 4 weeks and following a 2 week recovery period) in "Epoetin Hospira" treated dogs that were not included in the main review of Study No. 60486):

The following clinical signs for main study interim animals treated with "Epoetin Hospira" appeared at higher incidence in treated vs. controls:

- Cage side observations - material (dry, liquid, frothy or mucoid), undigested food, discolored feces, salivation, and thin
- Detailed observations - liquid or loose feces, material liquid, and thin
- Timed observations (1-2 hours postdose) - liquid or loose feces and material (liquid, loose, or mucoid); also, no feces or salivation were observed in a recovery Group 4 female and one Group 4 male on Days 5 and Day 1, respectively.

Table 27 Tabulated Mean Body Weight and Body Weight Gain Changes after 4 Weeks "Epoetin Hospira" Treatment and 2-Week Recovery – Interim Dog Study

Changes in mean body weight (BW) compared to control (Days 28/42)

Dose EH (IU/kg)	Males		Females	
	BW (kg)	%Δ control	BW (kg)	%Δ control
150	6.9	8%↓	6.5	2%↓
450	7.5	0%	6.3	5%↓
1500	6.3/7.2	16%↓/1%↑	5.6/5.9	15%↓/19%↓

%Δ control = percent change compared to the control mean (main study/recovery means for males = 7.5 kg/7.1 kg; females = 6.6 kg/7.3 kg); EH="Epoetin Hospira"

[2] Tillmann, HC, Kuhn B, Kränzlin B, Sadick M, Gross J, Gretz N, Pill J, 2006, Efficacy and immunogenicity of novel erythropoietic agents and conventional rhEPO in rats with renal insufficiency, Kidney International, 69(1):60-7.

Changes in body weight (BW) gain compared to control (Days -1 to 28/42)

Dose EH (IU/kg)	Males		Females	
	BW gain (kg)	%Δ control	BW gain (kg)	%Δ control
150	-0.1	ND	-0.2	ND
450	-0.2	ND	0	ND
1500	-0.4/-0.3	ND/25%↑	-0.4/-0.1	ND/108%↓

%Δ control = percent change compared to the control mean (main study/recovery means for males = 0 kg/-0.4 kg; females = 0 kg/1.3 kg); ND = not determined because BW changes in controls are zero; EH="Epoetin Hospira"

Table 28 Summary of Hematology Changes in Interim Study with "Epoetin Hospira" in Dogs

"Epoetin Hospira" – Interim Animals								
Sex	Males				Females			
Dose (IU/kg)	0 Mean	150 %Δ	450 %Δ	1500 %Δ	0 Mean	150 %Δ	450 %Δ	1500 %Δ
RBC (10^{12}/L)								
Week 2	5.93	14↑**	23↑***	31↑***	6.15	10↑*	14↑***	27↑***
Week 4	5.94	22↑**	43↑***	59↑***	6.08	21↑*	36↑***	57↑***
Recovery	6.18	--	--	47↑	6.14	--	--	46↑
HGB (g/L)								
Week 2	139	12↑**	19↑***	21↑***	141	10↑*	15↑***	21↑***
Week 4	136	18↑	33↑***	34↑***	138	17↑*	33↑***	40↑***
Recovery	143	--	--	16↑	137	--	--	20↑
HCT (L/L)								
Week 2	0.41	15↑**	24↑***	27↑***	0.42	10↑*	19↑***	29↑***
Week 4	0.42	19↑**	38↑***	45↑***	0.42	19↑*	43↑***	50↑***
Recovery	0.43	--	--	28↑	0.42	--	--	22↑
PLT (10^{9}/L)								
Week 2	316	33↑	21↑	28↑	304	33↑	41↑	31↑
Week 4	324	16↑	1↑	23↑	296	27↑	18↑	45↑
Recovery	424	--	--		232	--	--	25↑
MCV (fL)								
Week 2	68.7	1↑	0	2↓	67.8	0	4↑	1↑
Week 4	69.5	0	2↓	8↓*	69.1	1↓	4↑	5↓
Recovery	69.8	--	--	13↓	67.6	--	--	11↓
MCH (pg)								
Week 2	23.5			8↓**	22.9	0	0	4↓
Week 4	23		7↓*	16↓***	22.7	4↓	2↓	14↓***
Recovery	23.2	--	--	21↓	22.3	--	--	18↓
MCHC (g/dL)								
Week 2	341		4↓*	6↓***	338	0	3↓*	5↓***
Week 4	331	3↓**	6↓***	9↓***	329	3↓	6↓***	9↓***
Recovery	332	--	--	9↓	330	--	--	9↓
Retic (10^{12}/L)								
Week 2	0.064	150↑**	147↑*	238↑***	0.049	102↑***	349↑***	424↑***
Week 4	0.063	64↑	98↑*	186↑***	0.055	73↑	244↑***	295↑***
Recovery	0.094	--	--	88↓	0.064	--	--	84↓

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Abbreviations: RBC = red blood cells; HGB = hemoglobin; HCT = hematocrit; PLT = platelets; MCV = mean corpuscular volume; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; Retic.= reticulocytes; "—" = hematology parameters for low and mid dose recovery groups were not measured; %Δ = percent change relative to control mean

Table 29 Treatment-Related Microscopic Findings in Main Study Dogs in Interim Study - Day 29

(Excerpted from the study report)

Tissue	Males				Females			
Dose Level IU/kg	0	150	450	1500	0	150	450	1500
Bone Marrow, Femur/No. Ex.	4	4	4	4	4	4	4	4
Within normal limits	4	0	0	0	3	0	0	0
Hypercellularity, minimal	0	3	0	0	1	4	0	0
Hypercellularity, mild	0	1	4	0	0	0	4	1
Hypercellularity, moderate	0	0	0	4	0	0	0	3
Bone Marrow, Sternum /No. Ex.	4	4	4	4	4	4	4	4
Within normal limits	4	2	0	0	4	2	0	0
Hypercellularity, minimal	0	1	0	0	0	2	0	0
Hypercellularity, mild	0	1	4	3	0	0	4	4
Hypercellularity, moderate	0	0	0	1	0	0	0	0
Spleen /No. Ex	4	4	4	4	4	4	4	4
Within normal limits	4	4	0	0	4	4	1	0
Erythropoiesis, minimal	0	0	4	0	0	0	3	1
Erythropoiesis, mild	0	0	0	4	0	0	0	3
Dosing Site/No. Ex.	4	4	4	4	4	4	4	4
Hemorrhage, subcutaneous, multifocal, minimal	1	0	2	1	0	0	3	1
Hemorrhage, subcutaneous, multifocal, mild	3	4	2	3	4	3	0	2
Hemorrhage, subcutaneous, multifocal, moderate	0	0	0	0	0	0	0	1
Cecum/No. Ex.	4	4	4	4	4	4	4	4
Congestion (diffuse, focal, or multifocal), minimal	0	0	0	2	1	3		2
Colon/No. Ex.	4	4	4	4	4	4	4	4
Congestion (diffuse, focal, or multifocal), minimal	1	0	0	1	2	3	4	3
Duodenum/No. Ex	4	4	4	4	4	4	4	4
Congestion (diffuse, focal, or multifocal), minimal	0	0	0	1	0	0	1	2
Necrosis (crypt; multifocal), mild	0	0	0	1	0	0	0	0
Ileum/No. Ex	4	4	4	4	4	4	4	4
Congestion (diffuse or focal), minimal	0	0	0	0	1	0	1	1
Congestion (diffuse or focal), minimal, mild	0	0	0	1	0	0	0	0
Jejunum/No. Ex	4	4	4	4	4	4	4	4
Congestion (diffuse), minimal	0	0	0	1	0	0	1	0
Rectum/No. Ex	4	4	4	4	4	4	4	4
Congestion (diffuse), minimal	0	0	0	1	0	0	0	1
Lymph Node (Iliac) /No. Ex	4	4	4	4	4	4	4	4
Hyperplasia, follicular, mild	0	0	0	0	0	0	0	1

Thymus/No. Ex	4	4	4	4	4	4	4	4
Hemorrhage, multifocal, minimal	0	0	0	0	0	0	0	1
Hemorrhage, multifocal, mild	0	0	0	0	0	0	0	1

Table 30 Treatment-Related Microscopic Findings in Recovery Dogs in Interim Study - Day 43

(Excerpted from the study report)

Tissue	Males				Females			
Dose Level IU/kg	0	150	450	1500	0	150	450	1500
Bone Marrow, Femur/No. Ex.	2	0	0	2	2	0	0	2
Within normal limits	2	0	0	0	2	0	0	0
Hypercellularity, minimal	0	0	0	2	0	0	0	2

No. Ex. = Number Examined

- Also, minimal multifocal, mucosal congestion of the colon and duodenum was present in one high dose female and one high dose male, respectively on Day 43.

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/s/

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