

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***

**125545Orig1s000**

**CLINICAL REVIEW(S)**

## CLINICAL REVIEW

|                             |                                                                               |
|-----------------------------|-------------------------------------------------------------------------------|
| Application Type            | 351(k)                                                                        |
| Application Number          | BLA 125545                                                                    |
| Priority or Standard        | Standard                                                                      |
| Submit Date(s)              | Initial 12/16/2014<br>Response to CR 12/22/2016<br>Response to CR 11/17/2017  |
| BsUFA Goal Date             | 5/17/2018                                                                     |
| Division / Office           | Division of Hematology Products<br>Office of Hematology and Oncology Products |
| Reviewer Name(s)            | Lori A. Ehrlich, MD, PhD                                                      |
| Review Completion Date      | 5/3/2018                                                                      |
| Nonproprietary Name         | To be determined (Referred to as "Epoetin Hospira" by the applicant)*         |
| (Proposed) Proprietary Name | Retacrit                                                                      |
| Therapeutic Class           | Proposed Biosimilar to US-licensed Epogen/Procrit                             |
| Applicant                   | Hospira Inc.                                                                  |
| Formulation(s)              | Single-dose vial: 2000, 3000, 4000, 10,000, and 40,000 Units/1 mL             |
| Dosing Regimen              | Same as US-licensed Epogen/Procrit                                            |
| Indication(s)               | All of the indications for which US-licensed Epogen/Procrit is licensed       |

Template Version: March 6, 2009

\* 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 Guidance on Nonproprietary Naming of Biological Products).

# 1. Executive Summary

"Epoetin Hospira" is submitted under Section 351(k) of the Public Health Service Act as a proposed biosimilar to US-licensed Epogen/Procrit. Hospira is seeking licensure for all indications for which US-licensed Epogen/Procrit is currently licensed. The Applicant submitted the initial BLA on 12/16/2014, and the Agency issued a Complete Response (CR) action on 10/16/2015. Hospira submitted a response to CR for "Epoetin Hospira" on 12/22/2016, and the Agency issued a second CR action on 6/21/2017. The current submission is a response to CR submitted on 11/17/2017.

The clinical review of the application was completed during the review of the 12/22/2016 submission. There were no clinical issues in the 6/21/2017 CR Letter. The Agency requested a safety update in the response to CR to include studies performed under their U.S. IND as well as post-marketing experience for EU-approved Retacrit marketed in other countries. The safety update supports the previous finding of no clinically meaningful differences in terms of the safety, purity, and potency of "Epoetin Hospira" compared to US-licensed Epogen/Procrit.

The clinical review team has no issues related to the approvability of this application and recommends approval for "Epoetin Hospira" for all indications for which US-licensed Epogen/Procrit is approved.

## 2. Clinical Safety Update

### 2.1 Safety Update

Study ZIN-EPO-1503 (PIEDA) was the only ongoing clinical study for "Epoetin Hospira" under IND 100685. PIEDA is a randomized, open-label Phase 3b study in patients with chronic kidney disease (CKD) on hemodialysis. The study is now complete. The safety information for PIEDA has not been integrated with the studies previously submitted to support the "Epoetin Hospira" BLA.

In the PIEDA study, 221 patients were enrolled, and 212 patients received "Epoetin Hospira". The rate of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) in PIEDA were lower than the overall safety population for "Epoetin Hospira" in the 12/22/16 BLA safety analysis set. The overall pattern of common TEAEs and SAEs were similar for "Epoetin Hospira" in the PIEDA study compared to the 12/22/16 BLA submission. The study duration in PIEDA was shorter than the studies previously submitted to support the "Epoetin Hospira" BLA with resulting shorter duration of drug exposure.

## **2.2 Post-marketing Safety Report**

The Applicant submitted updated data from the post-marketing safety data from EU-approved Retacrit as supportive safety data to the US application for "Epoetin Hospira". Safety review was completed by the Applicant for EU-approved Retacrit from December 18, 2007 through June 30, 2017, updated from the prior submission which was through May 1, 2016. As noted in the prior clinical review, post-marketing information was provided for EU-approved Retacrit as supportive information only. Bridging information was not provided between the EU-approved Retacrit and "Epoetin Hospira".

No new safety signal was identified regarding the overall safety profile of EU-approved Retacrit including common AEs as well as AEs of special interest. No new confirmed cases of pure red cell aplasia (PRCA) were identified.

## **3. Conclusion**

A clinical safety update was requested in the CR letter issued 6/21/2017. Review of the safety information provided from the PIEDA study and the updated post-marketing safety information did not reveal any new clinical safety concerns. See the prior clinical review for details of the information that supported the finding of no clinically meaningful differences in terms of the safety, purity, and potency of "Epoetin Hospira" compared to US-licensed Epogen/Procrit. The clinical team provided recommendations for the labeling of "Epoetin Hospira" as a biosimilar to US-licensed Epogen/Procrit.

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

LORI A EHRLICH  
05/03/2018

ROMEO A DE CLARO  
05/03/2018

## CLINICAL REVIEW

|                        |                                                                               |
|------------------------|-------------------------------------------------------------------------------|
| Application Type       | 351(k)                                                                        |
| Application Number     | BLA 125545                                                                    |
| Priority or Standard   | Standard                                                                      |
| Submit Date(s)         | Initial 12/16/2014<br>Response to CR 12/22/2016                               |
| Received Date(s)       | Initial 12/16/2014<br>Response to CR 12/22/2016                               |
| BsUFA Goal Date        | 6/22/2017                                                                     |
| Division / Office      | Division of Hematology Products<br>Office of Hematology and Oncology Products |
| Reviewer Name(s)       | Lori A. Ehrlich, MD, PhD                                                      |
| Review Completion Date | 6/1/2017                                                                      |
| Established Name       | To be determined (Referred to as “Epoetin Hospira” by the applicant)*         |
| (Proposed) Trade Name  | Retacrit                                                                      |
| Therapeutic Class      | Proposed Biosimilar to US-licensed Epogen/Procrit**                           |
| Applicant              | Hospira Inc.                                                                  |
| Formulation(s)         | Single-dose vial: 2000, 3000, 4000, 10,000, and 40,000 Units/1 mL             |
| Dosing Regimen         | Same as the reference product, US-licensed Epogen/Procrit                     |
| Indication(s)          | All of the indications for which the reference product is licensed            |

### Template Version: March 6, 2009

\* 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).

\*\* For certain figures and tables in this review, the abbreviation “US-Epogen” or “US-Epogen/Procrit” may be used instead of “US-licensed Epogen/Procrit” due to space limitations.

## Table of Contents

|                                                                                       |           |
|---------------------------------------------------------------------------------------|-----------|
| <b>GLOSSARY .....</b>                                                                 | <b>6</b>  |
| <b>1 RECOMMENDATIONS/RISK BENEFIT ASSESSMENT .....</b>                                | <b>7</b>  |
| 1.1 Recommendation on Regulatory Action .....                                         | 7         |
| 1.2 Risk Benefit Assessment.....                                                      | 7         |
| 1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies ...      | 8         |
| 1.4 Recommendations for Postmarket Requirements and Commitments .....                 | 9         |
| <b>2 INTRODUCTION AND REGULATORY BACKGROUND .....</b>                                 | <b>9</b>  |
| 2.1 Product Information .....                                                         | 9         |
| 2.2 Table of Currently Available Treatments for Proposed Indications.....             | 11        |
| 2.3 Availability of Proposed Active Ingredient in the United States .....             | 12        |
| 2.4 Important Safety Issues With Consideration to Related Drugs.....                  | 12        |
| 2.5 Summary of Presubmission Regulatory Activity Related to Submission .....          | 12        |
| 2.6 Other Relevant Background Information .....                                       | 13        |
| <b>3 ETHICS AND GOOD CLINICAL PRACTICES.....</b>                                      | <b>13</b> |
| 3.1 Submission Quality and Integrity .....                                            | 13        |
| 3.2 Compliance with Good Clinical Practices .....                                     | 14        |
| 3.3 Financial Disclosures.....                                                        | 14        |
| <b>4 SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES .....</b> | <b>14</b> |
| 4.1 Chemistry Manufacturing and Controls .....                                        | 14        |
| 4.2 Clinical Microbiology.....                                                        | 15        |
| 4.3 Preclinical Pharmacology/Toxicology .....                                         | 15        |
| 4.4 Clinical Pharmacology.....                                                        | 15        |
| 4.4.1 Mechanism of Action.....                                                        | 15        |
| 4.4.2 Pharmacodynamics.....                                                           | 15        |
| 4.4.3 Pharmacokinetics.....                                                           | 16        |
| 4.5 Immunogenicity .....                                                              | 16        |
| <b>5 SOURCES OF CLINICAL DATA.....</b>                                                | <b>17</b> |
| 5.1 Tables of Studies/Clinical Trials .....                                           | 17        |
| 5.2 Review Strategy .....                                                             | 17        |
| 5.3 Discussion of Individual Studies/Clinical Trials.....                             | 18        |
| 5.3.1 Study EPOE-10-13.....                                                           | 18        |
| 5.3.2 Study EPOE-10-01.....                                                           | 19        |
| <b>6 REVIEW OF EFFICACY.....</b>                                                      | <b>20</b> |
| Efficacy Summary.....                                                                 | 20        |
| 6.1 Indication .....                                                                  | 20        |
| 6.1.1 Methods .....                                                                   | 21        |

|          |                                                                          |           |
|----------|--------------------------------------------------------------------------|-----------|
| 6.1.2    | Analysis of Primary Endpoint(s) .....                                    | 21        |
| 6.1.3    | Analysis of Clinical Information Relevant to Dosing Recommendations .... | 26        |
| 6.1.4    | Discussion of Persistence of Efficacy and/or Tolerance Effects.....      | 26        |
| <b>7</b> | <b>REVIEW OF SAFETY .....</b>                                            | <b>26</b> |
|          | Safety Summary .....                                                     | 26        |
| 7.1      | Methods.....                                                             | 26        |
| 7.2      | Major Safety Results .....                                               | 27        |
| 7.3      | Additional Submissions / Safety Issues .....                             | 30        |
| <b>8</b> | <b>POSTMARKET EXPERIENCE.....</b>                                        | <b>31</b> |
| <b>9</b> | <b>APPENDICES .....</b>                                                  | <b>33</b> |
| 9.1      | Literature Review/References .....                                       | 33        |
| 9.2      | Labeling Recommendations .....                                           | 33        |
| 9.3      | Advisory Committee Meeting.....                                          | 33        |
| 9.4      | Pediatric Assessment.....                                                | 34        |

## Table of Tables

|                                                                                                    |    |
|----------------------------------------------------------------------------------------------------|----|
| Table 1: "Epoetin Hospira" Product Information .....                                               | 10 |
| Table 2: Current Approved Erythropoietin Stimulating Agents .....                                  | 11 |
| Table 3: Clinical Studies.....                                                                     | 17 |
| Table 4: Sites Closed for GCP non-compliance in Study EPOE-10-13 (SC).....                         | 22 |
| Table 5: Subjects Enrolled in Study EPOE-10-13 (SC).....                                           | 22 |
| Table 6: Primary Efficacy Results in Study EPOE-10-13 (SC).....                                    | 23 |
| Table 7: Sites Closed for GCP non-compliance in Study EPOE-10-01 (IV) .....                        | 24 |
| Table 8: Subjects Enrolled in Study EPOE-10-01 (IV).....                                           | 25 |
| Table 9: Primary Efficacy Results in Study EPOE-10-01 (IV).....                                    | 25 |
| Table 10: Safety populations in Studies EPOE-10-13 (SC) and EPOE-10-01 (IV).....                   | 27 |
| Table 11: Frequency of treatment-emergent adverse events in Study EPOE-10-13 (SC)<br>.....         | 27 |
| Table 12: Frequency of treatment-emergent adverse events in Study EPOE-10-01 (IV)<br>.....         | 28 |
| Table 13: Frequency of common adverse events (≥5% in any group) in Study EPOE-10-<br>13 (SC) ..... | 28 |
| Table 14: Frequency of common adverse events (≥5% in any group) in Study EPOE-10-<br>01 (IV) ..... | 29 |
| Table 15: Adverse events of special interest in Study EPOE-01-13 (SC) .....                        | 30 |
| Table 16: Adverse events of special interest in Study EPOE-01-01 (IV).....                         | 30 |
| Table 17: Approach to Pediatric Assessment for "Epoetin Hospira".....                              | 35 |

## Table of Figures

|                                                 |    |
|-------------------------------------------------|----|
| Figure 1: EPOE-10-13 (SC) Study Schematic.....  | 19 |
| Figure 2: EPOE-10-01 (IV) Study Schematic ..... | 20 |

## Glossary

|                  |                                                      |
|------------------|------------------------------------------------------|
| ADA              | anti-drug antibody                                   |
| AE               | adverse event                                        |
| AESI             | adverse event of special interest                    |
| AUC              | area under curve                                     |
| AUEC             | area under effect curve                              |
| BLA              | biologics license application                        |
| BPCI             | Biologics Price Competition and Innovation Act       |
| BsUFA            | Biosimilar User Fee Act                              |
| CI               | confidence interval                                  |
| CIA              | chemotherapy-induced anemia                          |
| CKD              | chronic kidney disease                               |
| C <sub>max</sub> | maximum concentration                                |
| CR               | complete response                                    |
| CRL              | complete response letter                             |
| DMEPA            | Division of Medication Error Prevention and Analysis |
| E <sub>max</sub> | maximum effect                                       |
| EPO              | erythropoietin                                       |
| ESA              | erythropoietin stimulating agent                     |
| EU               | European Union                                       |
| GCP              | Good Clinical Practice                               |
| Hb               | hemoglobin                                           |
| HIV              | human immunodeficiency virus                         |
| HSA              | human serum albumin                                  |
| IV               | intravenous                                          |
| MOA              | mechanism of action                                  |
| ODAC             | Oncology Drugs Advisory Committee                    |
| OSI              | Office of Scientific Investigation                   |
| PD               | pharmacodynamic                                      |
| PK               | pharmacokinetic                                      |
| PRCA             | pure red cell aplasia                                |
| PREA             | Pediatric Research Equity Act                        |
| PSP              | pediatric study plan                                 |
| RBC              | red blood cell                                       |
| rhEPO            | recombinant human erythropoietin                     |
| SC               | subcutaneous                                         |
| SE               | standard error                                       |
| TEAE             | treatment-emergent adverse event                     |

# **1 Recommendations/Risk Benefit Assessment**

## **1.1 Recommendation on Regulatory Action**

"Epoetin Hospira" is submitted in accordance with Section 351(k) under the Public Health Services act as a biosimilar to US-licensed Epogen/Procrit. Hospira is seeking licensure for all indications for which US-licensed Epogen/Procrit is currently licensed. The Applicant submitted the initial BLA on 12/24/2014, and the Agency issued a Complete Response (CR) action on 10/16/2015. Hospira submitted a response to CR for "Epoetin Hospira" on 12/22/2016.

The clinical issue in the 10/16/2015 CR Letter was regarding the identification of GCP compliance issues with clinical studies EPOE-10-01 and EPOE-10-13. To address the GCP compliance issues, the Agency requested full auditing reports for studies EPOE-10-01 and EPOE-10-13 with descriptions of the GCP compliance issues and sensitivity analyses for efficacy and safety excluding the patients from the sites closed for GCP compliance issues.

The non-CR clinical issue included in the CRL was regarding a case of PRCA seen in the clinical program for EU-approved Retacrit. The Agency requested a root cause analysis of PRCA within the context of the "Epoetin Hospira" development program.

These clinical issues were addressed in the response to CRL submission received 12/22/2016. The clinical review team has no further issues related to approvability of this application and recommends approval for "Epoetin Hospira" for all indications for which US-licensed Epogen/Procrit is approved.

## **1.2 Risk Benefit Assessment**

The clinical studies used to support this BLA for "Epoetin Hospira" as a proposed biosimilar to US-licensed Epogen/Procrit include:

- Study EPOE-10-13: A Therapeutic Equivalence Study Comparing the Efficacy and Safety of Subcutaneous Epoetin Hospira and Epoetin Alfa (Amgen) in Patients with Chronic Renal Failure Requiring Hemodialysis and Receiving Epoetin Maintenance Treatment
- Study EPOE-10-01: A Therapeutic-Equivalence Study Comparing the Efficacy and Safety of Intravenous Epoetin Hospira and Epoetin Alfa (Amgen) in Patients with Chronic Renal Failure Requiring Hemodialysis and Receiving Epoetin Maintenance Treatment

- Two PK/PD studies (EPOE-12-02 and EPOE-14-01): Single dose and multiple dose cross-over studies conducted in healthy subjects.

The two clinical studies EPOE-10-13 and EPOE-10-01 were designed as safety and efficacy comparative studies to the reference product. A sensitivity analysis was conducted removing patients from sites with GCP compliance issues. The sensitivity analyses did not change the overall findings from the original analysis.

The clinical data, including PK, PD, efficacy, safety, and immunogenicity data, supports a demonstration of no clinically meaningful differences in terms of the safety, purity, and potency of the product.

The totality of the analytical data supports a demonstration of highly similar notwithstanding minor differences in clinically inactive components. Residual uncertainties in the analytical data including differences in glycosylation species and trisulfide species were adequately addressed by other data, including clinical data.

Overall, the totality of the evidence supports a demonstration of biosimilarity between "Epoetin Hospira" and US-licensed Epogen/Procrit. Extrapolation to, and approval of "Epoetin Hospira" for all indications for which US-licensed Epogen/Procrit is licensed is supported by the demonstration of biosimilarity and, among other information, the scientific understanding of the mechanism of action across indications.

### **1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies**

At the time of the re-submission of "Epoetin Hospira" BLA, a REMS program was in place for erythropoietin stimulating agents (ESAs) including Epogen/Procrit and Aranesp to ensure their benefits for use as a treatment alternative to RBC transfusion for anemia associated with myelosuppressive chemotherapy, outweigh their risks of shortened overall survival and/or increased risk of tumor progression or recurrence in patients with cancer. The REMS submitted by Hospira is similar to the Epogen/Procrit REMS Program.

On April 13, 2017 the FDA stated that a REMS is no longer necessary to ensure that the benefits of Epogen/Procrit and Aranesp outweigh the risks of shortened overall survival and/or increased risk of tumor progression or recurrence, for the treatment of anemia associated with myelosuppressive chemotherapy. While the REMS for ESAs has been removed, the prescribing information and Medication Guide continue to note an increased risk of tumor progression or recurrence, as well as death, myocardial infarction, stroke, venous thromboembolism, and thrombosis of vascular access.

The risks of approved ESAs, including any biosimilar product(s) (if approved), will continue to be communicated through the product prescribing information and the Medication Guide. The appropriate use of ESAs is supported by the Centers for Medicare & Medicaid Services National Coverage Determination (CMS NCD), the American Society of Clinical Oncology (ASCO) and American Society of Hematology (ASH) clinical guidelines which are evidence-based guidelines intended to provide a basis for the standard of care in clinical oncology.

Routine pharmacovigilance will be conducted by the Applicant.

#### **1.4 Recommendations for Postmarket Requirements and Commitments**

The recommendation for PMRs or PMCs will be made with the next review cycle.

## **2 Introduction and Regulatory Background**

### **2.1 Product Information**

"Epoetin Hospira" product information is summarized in Table 1. "Epoetin Hospira" is a proposed biosimilar product to US-licensed Epogen/Procrit. The proposed proprietary name is Retacrit, and review by Division of Medication Error Prevention and Analysis (DMEPA) has determined the name to be conditionally acceptable. The proposed dosing schedules are the same as the reference product. "Epoetin Hospira" is proposed to be licensed as a single-dose vial provided at 2000, 3000, 4000, 10,000, and 40,000 Units/1 mL. The proposed indications are the same as the reference product: for the treatment of anemia due to chronic kidney disease (CKD) in patients on dialysis and not on dialysis, zidovudine in HIV-infected patients, or the effects of concomitant myelosuppressive chemotherapy, or for the reduction of allogeneic red blood cell transfusions in patients undergoing surgery.

**Table 1: "Epoetin Hospira" Product Information**

|                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|--------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Proposed Trade Name:                 | Retacrit                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Nonproprietary Name<br>Drug Product: | epoetin alfa-xxxx, pending determination of suffix                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Therapeutic Class:                   | Erythropoiesis-stimulating agent (ESA)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Applicant Name:                      | Hospira, Inc.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Strength(s):                         | 2000 Units/mL, 3000 Units/mL, 4000 Units/mL, 10,000 Units/mL, and 40,000 Units/mL                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Route of<br>Administration:          | Intravenous and Subcutaneous                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Dosage Form:                         | Injection                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Proposed Indication(s):              | <ol style="list-style-type: none"> <li>1. For the treatment of anemia due to chronic kidney disease (CKD), including patients on dialysis and not on dialysis to decrease the need for red blood cell (RBC) transfusion</li> <li>2. For the treatment of anemia due to zidovudine administered at <math>\leq 4200</math> mg/week in HIV-infected patients with endogenous serum erythropoietin levels of <math>\leq 500</math> mUnits/mL</li> <li>3. For the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy</li> <li>4. To reduce the need for allogeneic RBC transfusions among patients with perioperative hemoglobin <math>&gt; 10</math> to <math>\leq 13</math> g/dL who are at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery</li> </ol> |

## 2.2 Table of Currently Available Treatments for Proposed Indications

**Table 2: Current Approved Erythropoietin Stimulating Agents**

| Products Name                                      | Relevant Indication                                                                                                                                                                                                                                                                                                                                                                            | Year of Approval                                         | Dosing/ Administration                            | Important Safety and Tolerability Issues                                                                                                                                                               | Other Comments                                                              |
|----------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------|---------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| Epogen/Procrit (epoetin alfa)                      | Treatment of anemia due to:<br>– CKD in patients on dialysis and not on dialysis<br>– zidovudine in HIV-infected patients<br>– the effects of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy<br>Reduction of allogeneic RBC transfusions in patients undergoing elective, noncardiac, nonvascular surgery | 1989 (CKD)<br>1991 (HIV)<br>1993 (CIA)<br>1996 (surgery) | Varies per indication and route of administration | Boxed warning for use in CKD (increased risk of death, cardiovascular reactions, stroke), in CIA (shorted overall survival and/or tumor progression or recurrence), and surgery (deep vein thrombosis) | "Epoetin Hospira" is proposed as a biosimilar to US-licensed Epogen/Procrit |
| Aranesp (darbepoetin alfa)                         | Treatment of anemia due to:<br>– CKD in patients on dialysis and not on dialysis<br>– the effects of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy                                                                                                                                                       | 2001 (CKD)<br>2002 (CIA)                                 | Varies per indication and route of administration | Boxed warning for use in CKD (increased risk of death, cardiovascular reactions, stroke), in CIA (shorted overall survival and/or tumor progression or recurrence)                                     |                                                                             |
| Mircera (methoxy polyethylene glycol-epoetin beta) | Treatment of anemia associated with CKD in adult patients on dialysis and not on dialysis                                                                                                                                                                                                                                                                                                      | 2007                                                     | Varies per indication and route of administration | Boxed warning for use in CKD (increased risk of death, cardiovascular reactions, stroke), in CIA (shorted overall survival and/or tumor progression or recurrence)                                     |                                                                             |

## 2.3 Availability of Proposed Active Ingredient in the United States

### Reference Product:

Epogen was initially licensed in the United States in 1989. Subsequently, three additional indications were approved based on supplements to the BLA. The indications for which Epogen is licensed are:

- For the treatment of anemia due to chronic kidney disease (CKD), including patients on dialysis and not on dialysis to decrease the need for red blood cell (RBC) transfusion.
- For the treatment of anemia due to zidovudine administered at  $\leq 4200$  mg/week in HIV-infected patients with endogenous serum erythropoietin levels of  $\leq 500$  mUnits/mL.
- For the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy.
- To reduce the need for allogeneic RBC transfusions among patients with perioperative hemoglobin (Hb)  $> 10$  to  $\leq 13$  g/dL who are at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery.

## 2.4 Important Safety Issues With Consideration to Related Drugs

Erythropoiesis-stimulating agents (ESAs) include several forms of exogenous erythropoietin which are similar to the endogenous erythropoietin. Erythropoietin is a glycoprotein produced in the kidney that acts on hematopoietic progenitor cells to increase the production of red blood cells. The US-licensed Epogen was the first recombinant human erythropoietin (rhEPO) to be licensed, in 1989.

ESAs have been shown to have class effect with all ESA products containing boxed warnings regarding an increased risk of death, cardiovascular reactions, and strokes in patients with CKD, shortened overall survival and/or tumor progression or recurrence in patients with chemotherapy-induced anemia, and deep vein thrombosis in patients perisurgery. Currently available ESAs are listed in Table 2. The boxed warnings for US-licensed Epogen/Procrit are for the class-effects of ESAs. Immunogenicity is a possibility for all ESAs, but the rate is specific to each product.

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

"Epoetin Hospira" is submitted under the 351(k) pathway as a biosimilar to US-licensed Epogen/Procrit. The Applicant submitted the initial BLA 125545 in the US on 12/24/14. The Agency issued a Complete Response (CR) action on 10/16/2015. Refer to the clinical review of the initial submission of BLA 125545 for summary of the regulatory

activity prior to the initial submission of the BLA and issuance of the 10/16/2015 CR Letter (CRL).

On 2/2/2016, a BPD Type 1 meeting was held between the Applicant and the Agency regarding the Quality and Immunogenicity items identified in the CR letter.

On 7/5/2016, a BPD Type 1 meeting was held between the Applicant and the Agency regarding the Clinical, Statistics, and Clinical Pharmacology items identified in the CR letter.

The Applicant submitted the response to the 10/16/2015 CR in the resubmission of BLA 125545 on 12/22/2016.

## **2.6 Other Relevant Background Information**

The Applicant submitted the initial IND for "Epoetin Hospira" on 12/16/2009 under IND 100685. The development program was initiated prior to enactment of the Biologics Price Competition and Innovation Act (BPCI Act) in the US. "Epoetin Hospira" originated from the development of the Hospira EU-approved Retacrit (epoetin zeta), approved in the EU as a biosimilar to EU-approved Eprex (epoetin alfa). EU-approved Retacrit was approved in the EU in December 18, 2007 and is currently registered in 33 countries. Bridging information was not provided between the EU-approved Retacrit and "Epoetin Hospira."

The Applicant submitted data from the post-marketing safety data from EU-approved Retacrit as supportive safety data to the US application for "Epoetin Hospira". Safety review was completed by the Applicant for EU-approved Retacrit from December 18, 2007 through May 1, 2016. See Section 8 for a summary of the safety findings for EU-approved Retacrit.

## **3 Ethics and Good Clinical Practices**

### **3.1 Submission Quality and Integrity**

BLA 125545 resubmission was received on 12/22/2016 as an electronic submission in CTD format.

### **3.2 Compliance with Good Clinical Practices**

The Sponsor identified sites in studies EPOE-10-13 and EPOE-10-01 that were GCP non-compliant. In study EPOE-10-13, 3 sites were closed during the conduct of the study which impacted 10% of enrolled subjects and 8% of the subjects in the intent-to-treat population. In study 10-01, a total of 7 sites were closed during the conduct of the study and 2 additional sites were identified in a post-study GCP audit and excluded from the final sensitivity analysis, representing 14% of subjects enrolled and 11% of subjects in the ITT population. The Agency conducted sensitivity analyses for both efficacy and safety endpoints excluding the GCP non-compliant sites to confirm the integrity of the initial analysis.

The Applicant submitted a Post-Study GCP Assessment Report which detailed the GCP compliance issues with each site, including the auditing reports and measures taken for the clinical studies to address the GCP compliance issues. The Applicant and clinical sites were not re-inspected by the Office of Compliance. However, the Office of Scientific Investigations (OSI) review of the resubmission found The GCP compliance items and other noncompliance items were addressed adequately in the Post-Study GCP Assessment Report. See prior clinical review and OSI reviews for clinical inspections completed by the Agency.

### **3.3 Financial Disclosures**

See prior clinical review for assessment of financial disclosures submitted for the clinical studies.

## **4 Significant Efficacy/Safety Issues Related to Other Review Disciplines**

### **4.1 Chemistry Manufacturing and Controls**

The Applicant submitted CMC information to support that "Epoetin Hospira" is highly similar to US-licensed Epogen/Procrit, notwithstanding minor differences in clinically inactive components. Analytical data indicate that the primary amino acid sequence is the same between "Epoetin Hospira" and US-licensed Epogen/Procrit. The secondary and tertiary structures and stability of "Epoetin Hospira" and US-licensed Epogen/Procrit are similar.

Minor differences were identified in the glycosylation profile of "Epoetin Hospira" and US-licensed Epogen/Procrit. The product related substances and impurities in "Epoetin

Hospira" were shown to be similar to that of US-licensed Epogen/Procrit, except for the presence of higher levels (4.5%) of a Cys29-Cys33 trisulfide species in "Epoetin Hospira". Clinical data support the conclusion that the differences in glycosylation species and trisulfide species did not impact the biologic activity of "Epoetin Hospira".

The reference product contains human serum albumin (HSA) which is not included in the "Epoetin Hospira" drug product. Removal of HSA in US-Epogen/Procrit was needed for several analytic methods.

Refer to CMC Review for further details.

## **4.2 Clinical Microbiology**

Refer to Microbiology Review.

## **4.3 Preclinical Pharmacology/Toxicology**

Pharmacology and toxicology studies for "Epoetin Hospira" were designed and conducted prior to the Applicant developing their product as a biosimilar to US-licensed Epogen/Procrit. Therefore, the studies were not designed to support a demonstration of biosimilarity. The Applicant submitted the results of Rat and Dog 13-week repeat dose comparative toxicity studies. The rat study showed decreased PD activity and exposure in the US-licensed Epogen/Procrit treatment group that correlated with a high level of anti-drug antibody (ADA) development, possibly due to the presence of HSA in US-licensed Epogen/Procrit. Immunogenicity in animals is not predictive of immunogenicity in humans. In the dog study, animals treated with "Epoetin Hospira" showed lower exposure, but within the range of animal variability. The differences observed in pharmacology/toxicology studies were addressed by subsequent clinical trials. See the pharmacology/toxicology review for details.

## **4.4 Clinical Pharmacology**

### **4.4.1 Mechanism of Action**

The mechanism of action for recombinant erythropoietin (EPO) is the same as for endogenous EPO. EPO binds to the EPO receptor on erythroid progenitor cells. Receptor binding initiates signal transduction that leads to survival, proliferation and differentiation of erythroid progenitor cells into RBCs. Reticulocyte count and hemoglobin levels are pharmacodynamics markers.

### **4.4.2 Pharmacodynamics**

Study EPOE-12-02 was a single-dose PK/PD study in healthy subjects who received subcutaneous study products (100 U/kg) using reticulocyte count as the PD marker. Study EPOE-14-01 was a multiple-dose PD study in healthy subjects who received

subcutaneous study products (100 U/kg, 3 times per week for 4 weeks) using hemoglobin as the PD marker. In both studies, the respective PD markers were within the pre-defined similarity margin of 80-125% for maximum effect ( $E_{\max}$ ) and area under effect curve (AUEC).

#### 4.4.3 Pharmacokinetics

PK assessments were completed in both the single dose and multiple dose clinical pharmacology studies. All PK parameters of maximum concentration ( $C_{\max}$ ) and area under the curve (AUC) were within the pre-defined similarity margin of 80-125%. See the clinical pharmacology review for details of PK/PD findings.

### 4.5 Immunogenicity

Development of anti-drug antibodies (ADA) can impact safety and efficacy of the administered EPO. For EPO therapy immunogenicity is of particular concern because the endogenous counterpart of epoetin alfa is erythropoietin. Erythropoietin is a critical non-redundant growth factor that is required for the development of red blood cells. When neutralizing ADA cross-react with endogenous erythropoietin a life-threatening form of anemia known as pure red cell aplasia (PRCA) can occur. Differences in manufacturing conditions and product quality attributes can cause development of neutralizing ADAs.

Immunogenicity information was obtained in the multiple dose study in healthy subjects (EPOE-14-01, subcutaneous) as well as the two clinical studies in patients with CKD on dialysis (EPOE-10-13, subcutaneous and EPOE-10-01, intravenous). The rates of treatment-induced ADA were similar in subjects treated with "Epoetin Hospira" and US-licensed Epogen/Procrit. No neutralizing antibodies were detected in the submitted clinical trials. See the immunogenicity review for details.

## 5 Sources of Clinical Data

### 5.1 Tables of Studies/Clinical Trials

**Table 3: Clinical Studies**

| Study ID   | Design     | Route        | Number | Subjects                | Dose     | Schedule                   | Primary Endpoint                          |
|------------|------------|--------------|--------|-------------------------|----------|----------------------------|-------------------------------------------|
| EPOE-12-02 | Cross-over | Subcutaneous | 81     | Healthy subjects        | 100 U/kg | Single dose                | PK and PD similarity (reticulocyte count) |
| EPOE-14-01 | Parallel   | Subcutaneous | 129    | Healthy subjects        | 100 U/kg | 3 times / week for 4 weeks | PD similarity (Hb)                        |
| EPOE-10-13 | Parallel   | Subcutaneous | 246    | Patients with CKD on HD | Variable | 1-3 times / week           | Mean weekly Hb<br>Mean weekly dose        |
| EPOE-10-01 | Parallel   | Intravenous  | 612    | Patients with CKD on HD | Variable | 1-3 times / week           | Mean weekly Hb<br>Mean weekly dose        |

### 5.2 Review Strategy

The clinical review of the resubmission application is limited to the clinical issues raised in the CR Letter.

The CR Letter included the following clinical comments:

#### Complete Response Issue

We have identified Good Clinical Practice (GCP) compliance issues with clinical studies EPOE-10-01 and EPOE-10-13. We also note that the BLA submission did not include complete auditing reports for the clinical sites for studies EPOE-10-01 and EPOE-10-13. Hence, the final analysis populations for the assessment of clinically meaningful differences between "Epoetin Hospira" and US-licensed Epogen/Procrit cannot be determined based on the information provided in the BLA submission.

In order to address this deficiency, you will need to submit the following:

- A. Full auditing reports for studies EPOE-10-01 and EPOE-10-13. The reports must include description of the GCP compliance issues that you identified and measures taken to address the GCP compliance issues. For sites closed due to GCP compliance issues, you must include the details of the GCP compliance issues.

- B. Additional sensitivity analyses for efficacy and safety that excludes the patients from sites closed due to GCP compliance issues. You will need to submit amended clinical study reports and datasets for studies EPOE-10-01 and EPOE-10-13.

Additional Comment (non-CR issue to include in CR letter)

We note the reported case of pure red cell aplasia (PRCA) in a patient who was treated with European (EU)-approved Retacrit. The significance of this finding related to your proposed "Epoetin Hospira" product is uncertain. We recommend that you provide a root-cause analysis, and provide additional details regarding the PRCA case within the context of the development program for "Epoetin Hospira".

As such, this review is limited to the sensitivity analyses of the clinical studies excluding GCP non-compliant sites to confirm the integrity of the initial analyses. See prior clinical review for the original analyses and conclusions.

### **5.3 Discussion of Individual Studies/Clinical Trials**

#### **5.3.1 Study EPOE-10-13**

Title: A Therapeutic Equivalence Study Comparing the Efficacy and Safety of Subcutaneous Epoetin Hospira and Epoetin Alfa (Amgen) in Patients with Chronic Renal Failure Requiring Hemodialysis and Receiving Epoetin Maintenance Treatment

See prior clinical review for full assessment of the study design, endpoints, eligibility criteria, treatment plan, schedule of assessments, and statistical analysis plans.

Briefly, EPOE-10-13 was a randomized, double-blind, parallel group phase 3 study in which patients with CKD requiring hemodialysis and receiving EPO maintenance treatment were enrolled. In the titration period of the study, patients who previously received intravenous US-licensed Epogen/Procrit were randomized to subcutaneous "Epoetin Hospira" or US-licensed Epogen/Procrit for 12 to 18 weeks to achieve 4 weeks of stable dosing. Patients who had been on subcutaneous US-licensed Epogen/Procrit were randomized directly into the maintenance period. In the maintenance period, patients were randomized to either "Epoetin Hospira" or US-licensed Epogen/Procrit for 16 weeks. Study schematic is shown in Figure 1.

The co-primary efficacy endpoints were mean weekly hemoglobin (Hb) level during the last 4 weeks of the double-blind Maintenance Period and mean weekly dosage per kg body weight during the last 4 weeks of the double-blind Maintenance Period.

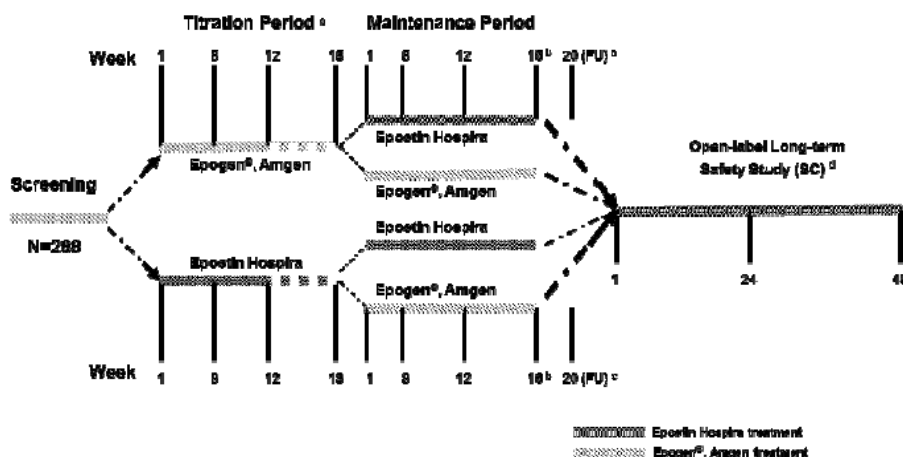


**Figure 1: EPOE-10-13 (SC) Study Schematic**

Source: Applicant Submission, Clinical Study Report

### 5.3.2 Study EPOE-10-01

Title: A Therapeutic-Equivalence Study Comparing the Efficacy and Safety of Intravenous "Epoetin Hospira" and Epoetin Alfa (Amgen) in Patients with Chronic Renal Failure Requiring Hemodialysis and Receiving Epoetin Maintenance Treatment

See prior clinical review for full assessment of the study design, endpoints, eligibility criteria, treatment plan, schedule of assessments, and statistical analysis plan.

Briefly, EPOE-10-01 was a randomized, double-blind, parallel group phase 3 study in which patients with CKD requiring hemodialysis and receiving EPO maintenance treatment were enrolled. EPOE-10-01 enrolled the same patient population as in EPOE-10-13 but with only patients on prior IV US-licensed Epogen/Procrit included therefore obviating the need for a titration period. In the maintenance period, patients were randomized to intravenous "Epoetin Hospira" or US-licensed Epogen/Procrit for 24 weeks. Study schematic is shown in Figure 2.

The co-primary efficacy endpoints were mean weekly hemoglobin (Hb) level during the last 4 weeks of the double-blind Treatment Period and mean weekly dosage per kg body weight during the last 4 weeks of the double-blind Treatment Period.

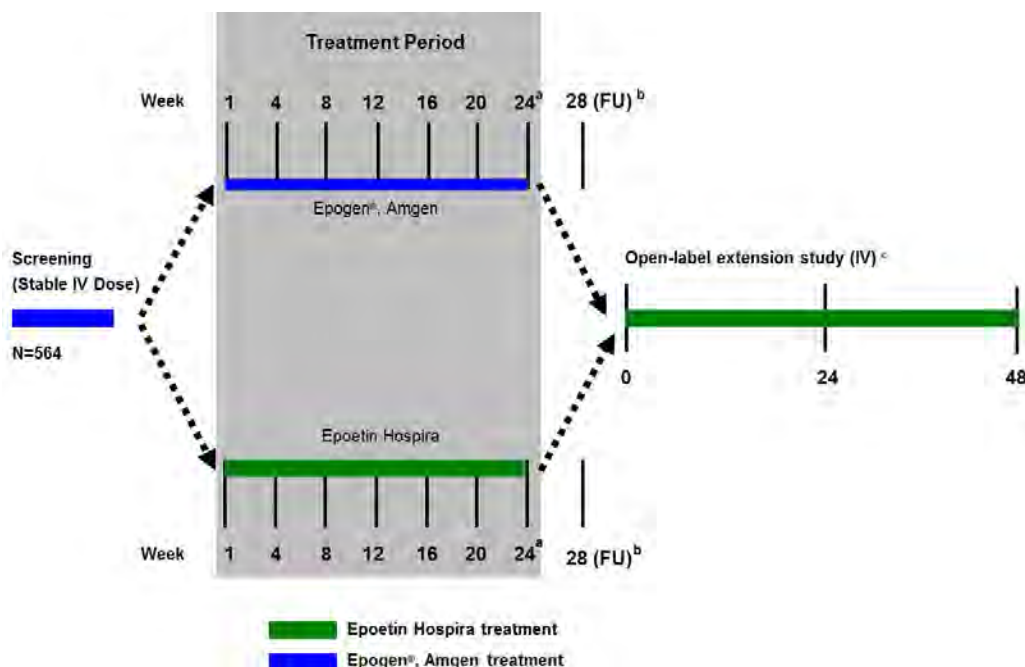


**Figure 2: EPOE-10-01 (IV) Study Schematic**

Source: Applicant Submission, Clinical Study Report

## 6 Review of Efficacy

### Efficacy Summary

Hospira submitted two clinical studies that evaluated efficacy endpoints in support of licensure of "Epoetin Hospira". Both studies were randomized, double-blinded, parallel group studies that enrolled patients with chronic kidney disease on hemodialysis and receiving epoetin maintenance treatment with co-primary endpoints of difference between arms in mean weekly hemoglobin and mean weekly dose. One study (EPOE-10-13) used subcutaneous epoetin, and the other study (EPOE-10-01) used intravenous epoetin. The FDA review of the data from both studies supports the Applicant's conclusion that there are no clinically meaningful differences in efficacy between "Epoetin Hospira" and US-licensed Epogen/Procrit.

### 6.1 Indication

The Applicant proposed indications are the same as those for US-licensed Epogen/Procrit. Clinical studies were performed in subjects with CKD on hemodialysis. See Section 7.3 for information regarding extrapolation to other indications.

#### 6.1.1 Methods

The comparison of "Epoetin Hospira" with US-licensed Epogen with regard to clinical efficacy endpoints for this indication was based on Study EPOE-10-13 (SC) and Study EPOE-10-01 (IV). Sensitivity analyses were performed with removal of subjects from sites with GCP compliance issues. Analyses were limited to the primary endpoint and safety in this review. Analyses of demographics and subject disposition were not performed with removal of subjects from closed sites. See the prior clinical review for information on demographics and subject disposition in the clinical studies. Refer to statistical review for analyses of secondary endpoints and relevant subpopulations. Those sections were removed from this review for brevity.

#### 6.1.2 Analysis of Primary Endpoint(s)

##### Study EPOE-10-13 (SC)

This study was a multicenter, randomized, active-controlled, parallel group, double-blind confirmatory efficacy and safety study in subjects with CKD requiring hemodialysis and receiving epoetin maintenance treatment.

In Study EPOE-10-13, 3 sites were closed during the conduct of the study. The sites and a brief selection of the GCP compliance issues are shown in Table 4.

**Table 4: Sites Closed for GCP non-compliance in Study EPOE-10-13 (SC)**

| Site ID      | Site PI    | Number of subjects enrolled | Number of subjects in ITT | Selected GCP Compliance Issues                                                                                                                                                                                                                                                              |
|--------------|------------|-----------------------------|---------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 21012        | El-Shahawy | 29                          | 14                        | <ul style="list-style-type: none"> <li>• SAEs not fully reported</li> <li>• Insufficient documentation for dosing</li> <li>• Lack of training and follow through on ICH/GCP/ Good Documentation Practices for study personnel</li> <li>• Lack of PI oversight</li> </ul>                    |
| 24020, 24043 | Moustafa   | 17                          | 6                         | <ul style="list-style-type: none"> <li>• SAEs not reported within 24 hours</li> <li>• Multiple protocol deviations</li> <li>• Coordinator incorrectly drawing up IP, incl. not differentiating between 2,000 U and 10,000 U vials</li> <li>• Improper storage temperatures of IP</li> </ul> |
| 21020        | Devidoss   | 7                           | 0                         | <ul style="list-style-type: none"> <li>• ICF discrepancies</li> <li>• Source documentation inconsistencies</li> <li>• Multiple protocol deviations</li> <li>• Lack of PI oversight</li> <li>• ICH/GCP issues, lack of site understanding / background</li> </ul>                            |

Table 5 shows the number of subjects enrolled in the in the study and in the ITT analysis population in the original analysis and after removal of subjects in GCP non-compliant sites.

**Table 5: Subjects Enrolled in Study EPOE-10-13 (SC)**

|          | Original analysis | Closed sites excluded |
|----------|-------------------|-----------------------|
| Enrolled | 556               | 503                   |
| ITT      | 246               | 226                   |

The co-primary efficacy endpoints were the differences between treatments ("Epoetin Hospira" and US-licensed Epogen/Procrit) in mean weekly hemoglobin level and dosage per kg body weight during the last 4 weeks of Maintenance Period. Table 6 shows analysis of the primary endpoint in the original ITT population and after closed sites were excluded.

The equivalence margin proposed by the Applicant for the hemoglobin is  $\pm 0.5$  g/dL. This margin was based on the observed within-subject variability of approximately  $\pm 1$  g/dL obtained from published literature. Half of this observed within-subject variability was

deemed to be not clinically meaningful. The equivalence margin proposed by the Applicant for the dose is  $\pm 45$  U/kg/week, based on published literature. Changes of equal or less than 45 U/kg/week provide no effect on hemoglobin level and higher dose increments were needed to provide a consistent dose-dependent increase in hemoglobin. The Agency had no objection on either of the two equivalence margins proposed. See statistical review for further details and references.

**Table 6: Primary Efficacy Results in Study EPOE-10-13 (SC)**

|                                     | Original ITT                 |                                  | Closed Sites Excluded        |                                  |
|-------------------------------------|------------------------------|----------------------------------|------------------------------|----------------------------------|
|                                     | “Epoetin Hospira”<br>(n=124) | US-<br>Epogen/Procrit<br>(n=122) | “Epoetin Hospira”<br>(n=112) | US-<br>Epogen/Procrit<br>(n=114) |
| Hemoglobin (g/dL)                   |                              |                                  |                              |                                  |
| LS Means (SE)                       | 10.2 (0.07)                  | 10.1 (0.07)                      | 10.2 (0.08)                  | 10.1 (0.08)                      |
| LS Difference                       | 0.04 (0.104)                 |                                  | 0.04 (0.108)                 |                                  |
| 90% CI for Diff.                    | <b>(-0.13, 0.21)</b>         |                                  | <b>(-0.13, 0.22)</b>         |                                  |
| Equivalence Margin                  | (-0.5, 0.5)                  |                                  | (-0.5, 0.5)                  |                                  |
| Dose per Kg Body Weight (U/kg/week) |                              |                                  |                              |                                  |
| LS Means (SE)                       | 79.6 (4.36)                  | 81.9 (4.37)                      | 74.8 (4.15)                  | 74.1 (4.09)                      |
| LS Difference                       | -2.34 (6.175)                |                                  | 0.76 (5.824)                 |                                  |
| 90% CI for Diff.                    | <b>(-12.54, 7.85)</b>        |                                  | <b>(-8.86, 10.38)</b>        |                                  |
| Equivalence Margin                  | (-45, 45)                    |                                  | (-45, 45)                    |                                  |

Source: FDA statistical reviewer

Results of the efficacy analysis during the Maintenance period showed the 90% CIs for the differences between "Epoetin Hospira" and US-licensed Epogen/Procrit in both primary endpoints are within the equivalence margins in study EPOE-10-13. These results were consistent after removal of the subjects from the sites that were closed for GCP non-compliance.

#### Study EPOE-10-01 (IV)

This study was a multicenter, randomized, active-controlled, parallel group, double-blind supportive efficacy and safety study in subjects with CKD requiring hemodialysis and receiving epoetin maintenance treatment.

In Study EPOE-10-01, 7 sites were closed during the conduct of the study, and 2 additional studies were identified in the post-study assessment as having GCP compliance issues and were removed from the final analysis. Three of the 7 sites closed during the conduct of the study also participated in Study EPOE-10-13. The sites and a brief selection of the GCP compliance issues are shown in Table 7.

**Table 7: Sites Closed for GCP non-compliance in Study EPOE-10-01 (IV)**

| Site ID | Site PI           | Number of subjects enrolled | Number of subjects in ITT | Selected GCP Compliance Issues                                                                                                                                                                                                                                                    |
|---------|-------------------|-----------------------------|---------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 14048   | Sakhrani          | 10                          | 5                         | <ul style="list-style-type: none"> <li>• Improper storage temperatures of IP</li> <li>• Lack of PI oversight</li> <li>• Multiple protocol deviations</li> </ul>                                                                                                                   |
| 14015   | Shapiro           | 5                           | 1                         | <ul style="list-style-type: none"> <li>• Source documentation inconsistencies</li> <li>• Lack of PI oversight</li> <li>• Multiple protocol deviations</li> <li>• ICH/GCP issues, lack of site understanding / background</li> <li>• Lack of responsiveness</li> </ul>             |
| 11095   | El-Shahawy        | 9                           | 5                         | <ul style="list-style-type: none"> <li>• As in Table 4</li> </ul>                                                                                                                                                                                                                 |
| 11005   | Espinosa-Melendez | 14                          | 7                         | <ul style="list-style-type: none"> <li>• Lack of PI oversight</li> <li>• SAEs not reported or followed up</li> <li>• Laboratory results not reviewed</li> <li>• Data entry non-compliance</li> <li>• Improper storage temperatures of IP</li> </ul>                               |
| 14028   | Moustafa          | 15                          | 12                        | <ul style="list-style-type: none"> <li>• As in Table 4</li> </ul>                                                                                                                                                                                                                 |
| 11098   | Devidoss          | 15                          | 9                         | <ul style="list-style-type: none"> <li>• As in Table 4</li> </ul>                                                                                                                                                                                                                 |
| 11100   | Baer              | 52                          | 14                        | <ul style="list-style-type: none"> <li>• ICF discrepancies</li> <li>• Source documentation inconsistencies</li> <li>• Multiple protocol deviations</li> <li>• Lack of PI oversight</li> <li>• ICH/GCP issues, lack of site understanding / background</li> </ul>                  |
| 11083*  | Chiang            | 8                           | 5                         | <ul style="list-style-type: none"> <li>• Insufficient documentation to support dosing and reconciliation of study drug</li> </ul>                                                                                                                                                 |
| 11094*  | Liss              | 12                          | 7                         | <ul style="list-style-type: none"> <li>• Source documentation inconsistencies</li> <li>• Multiple protocol deviations</li> <li>• Failure to report SAEs</li> <li>• Lack of PI oversight</li> <li>• Unblinding of all 7 patients</li> <li>• Inadequate informed consent</li> </ul> |

\* Sites identified in the post-study audit

Table 8 shows the number of subjects enrolled in the in the study and in the ITT analysis population in the original analysis and after removal of subjects in GCP non-compliant sites.

**Table 8: Subjects Enrolled in Study EPOE-10-01 (IV)**

|          | <b>Original analysis</b> | <b>Closed sites excluded</b> |
|----------|--------------------------|------------------------------|
| Enrolled | 1017                     | 877                          |
| ITT      | 612                      | 547                          |

The co-primary efficacy endpoints were the differences between treatments ("Epoetin Hospira" and US-licensed Epogen/Procrit) in mean weekly hemoglobin level and dosage per kg body weight during the last 4 weeks of Maintenance Period. Table 9 shows analysis of the primary endpoint in the original ITT population and after closed sites were excluded. Equivalence margins were the same as that in Study EPOE-10-13, as above.

**Table 9: Primary Efficacy Results in Study EPOE-10-01 (IV)**

|                                     | Original ITT                 |                                  | Closed Sites Excluded        |                                  |
|-------------------------------------|------------------------------|----------------------------------|------------------------------|----------------------------------|
|                                     | “Epoetin Hospira”<br>(n=306) | US-<br>Epogen/Procrit<br>(n=306) | “Epoetin Hospira”<br>(n=268) | US-<br>Epogen/Procrit<br>(n=279) |
| Hemoglobin (g/dL)                   |                              |                                  |                              |                                  |
| LS Means (SE)                       | 10.2 (0.05)                  | 10.3 (0.05)                      | 10.2 (0.05)                  | 10.3 (0.05)                      |
| LS Difference                       | -0.12 (0.066)                |                                  | -0.11 (0.070)                |                                  |
| 90% CI for Diff.                    | (-0.22, -0.01)               |                                  | (-0.22, 0.01)                |                                  |
| Equivalence Margin                  | (-0.5, 0.5)                  |                                  | (-0.5, 0.5)                  |                                  |
| Dose per Kg Body Weight (U/kg/week) |                              |                                  |                              |                                  |
| LS Means (SE)                       | 90.2 (3.87)                  | 89.8 (3.88)                      | 87.9 (4.02)                  | 87.6 (3.95)                      |
| LS Difference                       | 0.37 (5.483)                 |                                  | 0.29 (5.637)                 |                                  |
| 90% CI for Diff.                    | (-8.67, 9.40)                |                                  | (-9.00, 9.58)                |                                  |
| Equivalence Margin                  | (-45, 45)                    |                                  | (-45, 45)                    |                                  |

Source: FDA statistical reviewer

Results of the efficacy analysis during the Maintenance period showed the 90% CIs for the differences between "Epoetin Hospira" and US-licensed Epogen/Procrit in both primary endpoints are within the equivalence margins in study EPOE-10-01. These results were consistent after removal of the subjects from the sites that were closed for GCP non-compliance.

Across both clinical efficacy studies, data support a demonstration of no clinically meaningful differences between "Epoetin Hospira" and US-licensed Epogen/Procrit.

#### 6.1.3 Analysis of Clinical Information Relevant to Dosing Recommendations

The dosing regimen used in clinical studies was the same as currently approved for the reference product and no dose finding studies were conducted.

#### 6.1.4 Discussion of Persistence of Efficacy and/or Tolerance Effects

Eligible patients who completed Study EPOE-10-13 and Study EPOE-10-01 had the opportunity to enroll in the open-label 48-week LTSS (studies EPOE-10-13 and EPOE-11-04). See prior clinical review for efficacy findings from those studies.

## 7 Review of Safety

### **Safety Summary**

Hospira submitted two clinical studies that evaluated comparative safety endpoints in support of licensure of "Epoetin Hospira". In both studies, subjects with CKD on hemodialysis were randomized to "Epoetin Hospira" or US-licensed Epogen/Procrit in the double-blinded maintenance period. One study (EPOE-10-13) used subcutaneous epoetin, and the other study (EPOE-10-01) used intravenous epoetin. Sensitivity analyses were conducted removing subjects from sites with GCP non-compliance. Safety outcomes were similar for patients treated with either "Epoetin Hospira" or US-licensed Epogen/Procrit. The FDA review of the data from both studies supports the Applicant's conclusion that there are no clinically meaningful differences in safety between "Epoetin Hospira" and US-licensed Epogen/Procrit.

### **7.1 Methods**

The clinical review of safety endpoints was based on the safety from two comparative Studies EPOE-10-13 (SC) and EPOE-10-01 (IV) conducted in patients with CKD on hemodialysis where subjects were treated with "Epoetin Hospira" or US-licensed Epogen/Procrit. In addition, two open-label long term safety studies EPOE-11-04 (SC) and EPOE-11-03 (IV) conducted in patients with CKD on hemodialysis were used for supporting analyses.

This review is limited to the sensitivity analyses performed with removal of subjects from sites with GCP compliance issues. The sensitivity analyses were limited to the randomized maintenance period of both studies to allow evaluation of the frequency of events between "Epoetin Hospira" and US-licensed Epogen/Procrit. See the prior clinical review for information on categorization of adverse events, adequacy of safety assessments including exposure and dose response, and supportive safety finding such as vital signs and laboratory values in the clinical studies. Those sections were removed from this review for brevity.

Studies EPOE-10-13 (SC) and EPOE-10-01 (IV) used different routes of administration of the study drugs. While a similar safety profile is expected with SC and IV routes of administration, differences in injection site complications and other events are expected. Therefore, safety results were not pooled in the clinical studies. Table 10 shows the number of patients enrolled in each study arm in the original analysis population and after removal of GCP non-compliant sites. The Safety Populations in the randomized phase 3 studies consisted of all subjects who received at least one dose of study drug.

**Table 10: Safety populations in Studies EPOE-10-13 (SC) and EPOE-10-01 (IV)**

|                 | Original Analysis |                   | Closed Sites Excluded |                   |
|-----------------|-------------------|-------------------|-----------------------|-------------------|
|                 | "Epoetin Hospira" | US-Epogen/Procrit | "Epoetin Hospira"     | US-Epogen/Procrit |
| EPOE-10-13 (SC) | 122               | 122               | 110                   | 114               |
| EPOE-10-01 (IV) | 301               | 304               | 264                   | 277               |

## 7.2 Major Safety Results

An overview of the frequency of treatment-emergent adverse events (TEAE) is shown in Table 11 for study EPOE-10-13 and Table 12 for EPOE-10-01, for subcutaneous and intravenous treatment, respectively. No clinically meaningful differences in the frequency of TEAEs were seen in either study.

**Table 11: Frequency of treatment-emergent adverse events in Study EPOE-10-13 (SC)**

|                                                 | Original Analysis                     |                               | Closed Sites Excluded                 |                               |
|-------------------------------------------------|---------------------------------------|-------------------------------|---------------------------------------|-------------------------------|
|                                                 | "Epoetin Hospira"<br>N = 122<br>n (%) | US-Epogen<br>N = 122<br>n (%) | "Epoetin Hospira"<br>N = 110<br>n (%) | US-Epogen<br>N = 114<br>n (%) |
| Subjects Reporting at Least One TEAE            | 85 (70)                               | 86 (71)                       | 79 (72)                               | 79 (69)                       |
| Subjects Reporting at Least One Serious TEAE    | 23 (19)                               | 33 (27)                       | 19 (17)                               | 29 (25)                       |
| Subjects Discontinuing Study Drug due to a TEAE | 4 (3)                                 | 4 (3)                         | 4 (4)                                 | 4 (4)                         |
| Subjects Reporting an TEAE Resulting in Death   | 3 (3)                                 | 2 (2)                         | 3 (3)                                 | 2 (2)                         |

**Table 12: Frequency of treatment-emergent adverse events in Study EPOE-10-01 (IV)**

|                                                 | Original Analysis                     |                                   | Closed Sites Excluded                 |                                   |
|-------------------------------------------------|---------------------------------------|-----------------------------------|---------------------------------------|-----------------------------------|
|                                                 | "Epoetin Hospira"<br>N = 301<br>n (%) | US-<br>Epogen<br>N = 304<br>n (%) | "Epoetin Hospira"<br>N = 264<br>n (%) | US-<br>Epogen<br>N = 277<br>n (%) |
| Subjects Reporting at Least One TEAE            | 232 (77)                              | 229 (75)                          | 207 (78)                              | 210 (76)                          |
| Subjects Reporting at Least One Serious TEAE    | 75 (25)                               | 82 (27)                           | 64 (24)                               | 77 (28)                           |
| Subjects Discontinuing Study Drug due to a TEAE | 9 (3)                                 | 11 (4)                            | 9 (3)                                 | 11 (4)                            |
| Subjects Reporting an TEAE Resulting in Death   | 5 (2)                                 | 6 (2)                             | 3 (1)                                 | 6 (2)                             |

The common adverse events were not considerably different between "Epoetin Hospira" and US-licensed Epogen/Procrit. Common AEs seen in  $\geq 5\%$  of patients in any group are shown in Table 13 for EPOE-01-13 and in Table 14 for EPOE-10-01, including the original analysis and after removal of sites closed for GCP issues.

**Table 13: Frequency of common adverse events ( $\geq 5\%$  in any group) in Study EPOE-10-13 (SC)**

|                                         | Original Analysis                     |                                   | Closed Sites Excluded                 |                                   |
|-----------------------------------------|---------------------------------------|-----------------------------------|---------------------------------------|-----------------------------------|
|                                         | "Epoetin Hospira"<br>N = 122<br>n (%) | US-<br>Epogen<br>N = 122<br>n (%) | "Epoetin Hospira"<br>N = 110<br>n (%) | US-<br>Epogen<br>N = 114<br>n (%) |
| Nausea                                  | 10 (8)                                | 8 (7)                             | 10 (9)                                | 7 (6)                             |
| Fall                                    | 8 (7)                                 | 3 (2)                             | 7 (6)                                 | 3 (3)                             |
| Pyrexia                                 | 8 (7)                                 | 4 (3)                             | 7 (6)                                 | 3 (3)                             |
| Arteriovenous fistula site complication | 6 (5)                                 | 4 (3)                             | 6 (6)                                 | 4 (4)                             |
| Headache                                | 6 (5)                                 | 3 (2)                             | 5 (5)                                 | 2 (2)                             |
| Pain in extremity                       | 6 (5)                                 | 5 (4)                             | 5 (5)                                 | 5 (4)                             |
| Dizziness                               | 3 (2)                                 | 9 (7)                             | 3 (3)                                 | 9 (8)                             |
| Injection site pain                     | 3 (2)                                 | 8 (7)                             | 2 (2)                                 | 6 (5)                             |
| Vomiting                                | 4 (3)                                 | 6 (5)                             | 2 (2)                                 | 6 (5)                             |
| Hyperkalemia                            | 3 (2)                                 | 6 (5)                             | 3 (3)                                 | 5 (4)                             |
| Hypoglycemia                            | 1 (1)                                 | 6 (5)                             | 1 (1)                                 | 6 (5)                             |
| Arthralgia                              | 5 (4)                                 | 4 (3)                             | 5 (5)                                 | 4 (4)                             |
| Urinary tract infection                 | 5 (4)                                 | 4 (3)                             | 5 (5)                                 | 4 (4)                             |

**Table 14: Frequency of common adverse events (≥5% in any group) in Study EPOE-10-01 (IV)**

|                                         | Original Analysis                     |                                   | Closed Sites Excluded                 |                                   |
|-----------------------------------------|---------------------------------------|-----------------------------------|---------------------------------------|-----------------------------------|
|                                         | "Epoetin Hospira"<br>N = 301<br>n (%) | US-<br>Epogen<br>N = 304<br>n (%) | "Epoetin Hospira"<br>N = 264<br>n (%) | US-<br>Epogen<br>N = 277<br>n (%) |
| Nausea                                  | 30 (10)                               | 25 (8)                            | 27 (10)                               | 24 (9)                            |
| Vomiting                                | 28 (9)                                | 15 (5)                            | 26 (10)                               | 14 (5)                            |
| Muscle spasms                           | 27 (9)                                | 24 (8)                            | 27 (10)                               | 19 (7)                            |
| Arteriovenous fistula site complication | 26 (9)                                | 25 (8)                            | 23 (9)                                | 24 (9)                            |
| Headache                                | 23 (8)                                | 16 (5)                            | 23 (9)                                | 14 (5)                            |
| Dyspnea                                 | 22 (7)                                | 21 (7)                            | 22 (8)                                | 20 (7)                            |
| Diarrhea                                | 21 (7)                                | 27 (9)                            | 18 (7)                                | 27 (10)                           |
| Dizziness                               | 20 (7)                                | 15 (5)                            | 17 (6)                                | 14 (5)                            |
| Hypertension                            | 19 (6)                                | 12 (4)                            | 17 (6)                                | 11 (4)                            |
| Cough                                   | 16 (5)                                | 22 (7)                            | 16 (6)                                | 22 (8)                            |
| Hyperkalemia                            | 14 (5)                                | 12 (4)                            | 13 (5)                                | 12 (4)                            |
| Hypotension                             | 14 (5)                                | 23 (8)                            | 9 (3)                                 | 19 (7)                            |
| Pain in extremity                       | 10 (3)                                | 17 (6)                            | 9 (3)                                 | 14 (5)                            |
| Non-cardiac chest pain                  | 7 (2)                                 | 17 (6)                            | 6 (2)                                 | 14 (5)                            |
| Back pain                               | 12 (4)                                | 16 (5)                            | 12 (5)                                | 15 (5)                            |
| Arthralgia                              | 13 (4)                                | 12 (4)                            | 13 (5)                                | 11 (4)                            |
| Fall                                    | 13 (4)                                | 13 (4)                            | 13 (5)                                | 12 (4)                            |
| Anemia                                  | 8 (3)                                 | 13 (4)                            | 8 (3)                                 | 13 (5)                            |
| Constipation                            | 7 (2)                                 | 13 (4)                            | 6 (2)                                 | 13 (5)                            |

The frequency of TEAE, serious events, and events leading to discontinuation of study drug or death was not different between the treatment arms. Major events of interest which are listed as Warnings and Precautions in the prescribing information for US-licensed Epogen/Procrit include myocardial infarction, cerebrovascular events, and thromboembolism. Events in these categories occurred in both studies with no imbalances between treatment arms; see Table 15 and Table 16 for the frequency of these events in studies EPOE-10-13 and EPOE-10-01, respectively. There were no cases of pure red cell aplasia (PRCA) in the randomized studies. A sensitivity analysis excluding non-GCP compliant sites did not change the overall results.

**Table 15: Adverse events of special interest in Study EPOE-01-13 (SC)**

|                        | Original Analysis                     |                                   | Closed Sites Excluded                 |                                   |
|------------------------|---------------------------------------|-----------------------------------|---------------------------------------|-----------------------------------|
|                        | "Epoetin Hospira"<br>N = 122<br>n (%) | US-<br>Epogen<br>N = 122<br>n (%) | "Epoetin Hospira"<br>N = 110<br>n (%) | US-<br>Epogen<br>N = 114<br>n (%) |
| Myocardial infarction  | 0                                     | 1 (1)                             | 0                                     | 1 (1)                             |
| Cerebrovascular events | 0                                     | 2 (2)                             | 0                                     | 2 (2)                             |
| Thromboembolic events  | 4 (3)                                 | 8 (7)                             | 4 (4)                                 | 7 (6)                             |

**Table 16: Adverse events of special interest in Study EPOE-01-01 (IV)**

|                        | Original Analysis                     |                                   | Closed Sites Excluded                 |                                   |
|------------------------|---------------------------------------|-----------------------------------|---------------------------------------|-----------------------------------|
|                        | "Epoetin Hospira"<br>N = 301<br>n (%) | US-<br>Epogen<br>N = 304<br>n (%) | "Epoetin Hospira"<br>N = 264<br>n (%) | US-<br>Epogen<br>N = 277<br>n (%) |
| Myocardial infarction  | 4 (1)                                 | 2 (1)                             | 2 (1)                                 | 2 (1)                             |
| Cerebrovascular events | 4 (1)                                 | 4 (1)                             | 3 (1)                                 | 3 (1)                             |
| Thromboembolic events  | 28 (9)                                | 18 (6)                            | 24 (9)                                | 17 (6)                            |

### 7.3 Additional Submissions / Safety Issues

The Applicant seeks licensure for all indications for which US-licensed Epogen/Procrit is licensed (listed in Introduction Section 2.1 above). The "Epoetin Hospira" clinical program, however, provides clinical efficacy and safety data from a clinical program in patients with chronic kidney disease on hemodialysis.

FDA has determined that it may be appropriate for a biosimilar product to be licensed for one or more conditions of use (e.g., indications) for which the reference product is licensed, based on data from a clinical study(ies) performed in another condition of use. This concept is known as extrapolation.

The scientific justification for extrapolation of data to support a demonstration of biosimilarity in the indications for which the Applicant is seeking licensure includes:

- The primary mode of action (MOA) of EPO is the same as endogenous erythropoietin. EPO binds to the erythropoietin receptor on specific erythrocyte precursor cells, which causes a conformational change in the receptor that brings its intracellular domains into close apposition enabling cross phosphorylation via the binding of JAK2 kinase, the initiation of the signal transduction cascade, and

induction of erythropoiesis. This MOA is independent of the underlying cause of anemia. [Elliot et al. 2008]

- Demonstration that "Epoetin Hospira" is highly similar to US-licensed Epogen/Procrit based on extensive analytical characterization data
- Similar pharmacokinetics/pharmacodynamics (PK/PD) was demonstrated between "Epoetin Hospira" and US-licensed Epogen/Procrit in healthy subjects, and a similar efficacy was demonstrated in patients with CKD on hemodialysis. A similar PK/PD profile would be expected between "Epoetin Hospira" and US-licensed Epogen/Procrit across the other indications for use.
- In the "Epoetin Hospira" clinical program, the frequency of anti-drug antibody formation was low and there were no notable differences between "Epoetin Hospira" and US-licensed Epogen/Procrit in both healthy male subjects and patients with CKD on hemodialysis. Accordingly, similar immunogenicity would be expected between "Epoetin Hospira" and US-licensed Epogen/Procrit in other indications of use.
- Similar clinical safety and efficacy profile was demonstrated between "Epoetin Hospira" and US-licensed Epogen/Procrit in patients with CKD on hemodialysis. As analytical and PK similarity was demonstrated between "Epoetin Hospira" and US-licensed Epogen/Procrit, a similar safety and efficacy profile would be expected in other indications for use.

In aggregate, the evidence indicates that the extrapolation of biosimilarity to the indications for which Hospira is seeking licensure is scientifically justified.

## 8 Postmarket Experience

As noted in Section 2.6, post-marketing information was provided for EU-approved Retacrit as supportive information only. Bridging information was not provided between the EU-approved Retacrit and "Epoetin Hospira".

In a post-marketing study, EPOE-09-11 (PASCO II), one case of PRCA was reported in a 72-year-old woman with CKD receiving subcutaneous EU-approved Retacrit. She became transfusion dependent and tested positive for anti-EPO antibodies confirmed as neutralizing antibodies. She received 3 months of oral steroids with resolution of her transfusion dependence and neutralizing antibodies.

In spontaneous adverse event reporting, 5 reports were assessed for possible PRCA. One event of PRCA was confirmed in a 26-year-old man with CKD on peritoneal dialysis receiving subcutaneous EU-approved Retacrit. He developed transfusion dependence with positive EPO antibodies that were weakly positive for neutralizing antibodies. The case was confounded by the subject receiving prior Mircera with

apparent lack of efficacy. The patient initiated a course of steroids, and the outcome of the PRCA was not recovered as of the cutoff date. The 4 other spontaneous reports of possible PRCA included 2 cases confirmed as not related to events with antibody testing negative, 1 case attributed to an alternative ESA treatment, and 1 case of presumptive pre-existing PRCA.

In the CRL, the Agency requested a root-cause analysis of the occurrence of PRCA in "Epoetin Hospira". The mechanism leading to PRCA in ESAs remains largely unknown with suspected differences in PRCA rates regarding specific products (including different stabilizers, storage containers with possible leachates, protein aggregates, and others), route of administration, and underlying disease. Cases of PRCA tend to occur in subjects receiving subcutaneous ESAs for CKD.

Estimated rate of PRCA with EU-approved Retacrit is 0.03 per 10,000 patient-years of exposure based on the occurrence of one confirmed case and an overall estimated patient exposure of 323,000 patient-years. The rate would be 0.06 per 10,000 patient-years with inclusion of the spontaneously reported case. With the rarity of events, no root cause was identified by the Applicant. The frequency of events is consistent with other ESAs.

## 9 Appendices

### 9.1 Literature Review/References

Elliott, S., E. Pham, and I. C. Macdougall. 2008. "Erythropoietins: a common mechanism of action." *Exp Hematol* 36 (12):1573-84.

### 9.2 Labeling Recommendations

No labeling recommendations were made for this submission. FDA plans to assess the proposed labeling in the next review cycle.

### 9.3 Advisory Committee Meeting

An Oncology Drugs Advisory Committee (ODAC) meeting was held on 5/25/2017. The purpose of the ODAC meeting was to discuss whether the totality of evidence presented support licensure of "Epoetin Hospira" as a biosimilar to US-licensed Epogen/Procrit. This determination requires the following criteria to be met:

- "Epoetin Hospira" is highly similar to US-licensed Epogen/Procrit, notwithstanding minor differences in clinically inactive components, and
- There are no clinically meaningful differences between "Epoetin Hospira" and US-licensed Epogen/Procrit.

Members of the ODAC agreed that the analytical data presented by the Applicant and the Agency supported the criterion that "Epoetin Hospira" is highly similar to US-licensed Epogen/Procrit, despite the differences in glycosylation and trisulfide species.

Regarding no clinically meaningful differences between the products, members of the ODAC discussed that the clinical data presented support that finding within the limitations of data that can be measured in the clinical studies. For example, the occurrence of rare events such as development of neutralizing anti-drug antibodies cannot be estimated in clinical studies of limited duration.

Members of the ODAC expressed residual concerns regarding extrapolation to other indications of use, specifically the lack of data regarding safety and immunogenicity in patients with HIV and cancer.

The ODAC voted 14 yes and 1 no. The no vote was due to that member's concern regarding extrapolation to use in patients with cancer due to the absence of immunogenicity data and in patients with HIV due to the absence of basic safety data.

However, the members of the ODAC generally agreed that the regulatory requirements were met to support licensure of "Epoetin Hospira" as a biosimilar to US-licensed Epogen/Procrit for all indications currently licensed for the reference product.

#### **9.4 Pediatric Assessment**

No pediatric studies have been conducted as part of this clinical program. The Agency agreed with the Applicant's initial pediatric study plan to support the Pediatric Research Equity Act requirement.

Table 17 is from the agreed Pediatric Study Plan (PSP). The Applicant submitted a request for waiver of pediatric studies based on the agreed PSP.

**Table 17: Approach to Pediatric Assessment for "Epoetin Hospira"**

| <b>Adult Indications</b>                                                                                             | <b>Pediatric Information in Package Insert Labeling for Epogen</b>                                                                                                                                                                                                                                                                                                                     | <b>Approach for "Epoetin Hospira" Study Plan</b>                                                                                                                                                                                                                                                    |
|----------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Anemia due to CKD in patients on dialysis and not on dialysis                                                        | Epogen is indicated in pediatric patients, ages 1 month to 16 month years of age, for the treatment of anemia associated with CKD requiring dialysis. Safety and effectiveness in pediatric patients less than 1 month old have not been established. The safety data from these studies are similar to those obtained from the studies of Epogen in adult patients with CKD.          | Extrapolation of the pediatric information from the reference product, Epogen®, to the proposed biosimilar product, Epoetin Hospira, for patients 1 month and older in the context of the proposed biosimilar development program.<br><br>Partial Waiver Requested for Age Group 0 to <1 Month.     |
| Anemia due to concomitant myelosuppressive chemotherapy                                                              | Epogen is indicated in patients 5 to 18 years old for the treatment of anemia due to concomitant myelosuppressive chemotherapy. Safety and effectiveness in pediatric patients less than 5 years of age have not been established. The safety data from these studies are similar to those obtained from the studies of Epogen in adult patients with cancer.                          | Extrapolation of the pediatric information from the reference product, Epogen®, to the proposed biosimilar product, Epoetin Hospira, for patients 5 years and older in the context of the proposed biosimilar development program.<br><br>Partial Waiver Requested for Age Group 0 to <5 Years.     |
| Anemia due to zidovudine in HIV-infected patients                                                                    | Published literature has reported the use of Epogen in 20 zidovudine-treated, anemic, pediatric patients with HIV infection, ages 8 months to 17 years, treated with 50 to 400 Units/kg subcutaneously or intravenously 2 to 3 times per week. Increases in hemoglobin levels and in reticulocyte counts and decreases in or elimination of red blood cell transfusions were observed. | Extrapolation of the pediatric information from the reference product, Epogen®, to the proposed biosimilar product, Epoetin Hospira, for patients 8 months to 17 years in the context of the proposed biosimilar development program.<br><br>Partial Waiver Requested for Age Group 0 to <8 Months. |
| Reduction of allogeneic red blood cell transfusions in patients undergoing elective, noncardiac, nonvascular surgery | No information for pediatric use in the reference product label.                                                                                                                                                                                                                                                                                                                       | Full Waiver Requested for Age Group 0 to 18 Years.                                                                                                                                                                                                                                                  |

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

LORI A EHRLICH  
06/01/2017

ROMEO A DE CLARO  
06/01/2017

## CLINICAL REVIEW

|                      |                                                                                           |
|----------------------|-------------------------------------------------------------------------------------------|
| Application Type     | 351(k)                                                                                    |
| Application Number   | BLA 125545                                                                                |
| Priority or Standard | Standard                                                                                  |
| Submit Date          | 12/16/2014                                                                                |
| Received Date        | 12/16/2014                                                                                |
| BsUFA Goal Date      | 10/16/2015                                                                                |
| Division / Office    | Office of Hematology and Oncology<br>Products/Division of Hematology Products             |
| Reviewer Name        | Saleh Ayache, MD                                                                          |
| Team Leader          | R. Angelo de Claro, MD                                                                    |
| Nonproprietary Name  | To be determined (Referred to as “Epoetin Hospira” by the applicant)*                     |
| Proposed Trade Name  | Retacrit                                                                                  |
| Therapeutic Class    | Proposed Biosimilar to US-licensed<br>Epogen/Procrit, an Erythrocyte Stimulating<br>Agent |
| Applicant            | Hospira                                                                                   |
| Reference Product    | US-licensed Epogen/Procrit                                                                |
| Proposed Formulation | Single-dose vial: 2000, 3000, 4000, 10,000,<br>and 40,000 Units/1 mL                      |
| Dosing Regimen       | Same as the reference product                                                             |
| Proposed Indications | All of the indications for which the<br>reference product is licensed                     |

Template Version: March 6, 2009

\*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).

## Table of Contents

|          |                                                                                    |           |
|----------|------------------------------------------------------------------------------------|-----------|
| <b>1</b> | <b>RECOMMENDATIONS/RISK BENEFIT ASSESSMENT .....</b>                               | <b>9</b>  |
| 1.1      | Recommendation on Regulatory Action .....                                          | 9         |
| 1.2      | Risk Benefit Assessment .....                                                      | 9         |
| 1.3      | Recommendations for Postmarket Risk Evaluation and Mitigation Strategies .....     | 10        |
| 1.4      | Recommendations for Postmarket Requirements and Commitments .....                  | 10        |
| <b>2</b> | <b>INTRODUCTION AND REGULATORY BACKGROUND .....</b>                                | <b>10</b> |
| 2.1      | Product Information .....                                                          | 10        |
| 2.2      | Tables of Currently Available Treatments for Proposed Indications .....            | 11        |
| 2.3      | Availability of Proposed Active Ingredient in the United States .....              | 12        |
| 2.4      | Important Safety Issues With Consideration to Related Drugs .....                  | 12        |
| 2.5      | Summary of Presubmission Regulatory Activity Related to Submission .....           | 12        |
| 2.6      | Other Relevant Background Information .....                                        | 13        |
| <b>3</b> | <b>ETHICS AND GOOD CLINICAL PRACTICES .....</b>                                    | <b>13</b> |
| 3.1      | Submission Quality and Integrity .....                                             | 13        |
| 3.2      | Compliance with Good Clinical Practices .....                                      | 13        |
| 3.3      | Financial Disclosures .....                                                        | 15        |
| <b>4</b> | <b>SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES.....</b> | <b>15</b> |
| 4.1      | Chemistry Manufacturing and Controls .....                                         | 15        |
| 4.2      | Clinical Microbiology .....                                                        | 16        |
| 4.3      | Preclinical Pharmacology/Toxicology .....                                          | 16        |
| 4.4      | Clinical Pharmacology .....                                                        | 16        |
| 4.4.1    | Mechanism of Action .....                                                          | 16        |
| 4.4.2    | Pharmacodynamics.....                                                              | 16        |
| 4.4.3    | Pharmacokinetics .....                                                             | 17        |
| <b>5</b> | <b>SOURCES OF CLINICAL DATA .....</b>                                              | <b>18</b> |
| 5.1      | Tables of Studies/Clinical Trials .....                                            | 18        |
| 5.2      | Review Strategy .....                                                              | 19        |
| 5.3      | Discussion of Individual Studies/Clinical Trials .....                             | 19        |
| 5.3.1    | Study EPOE-10-13 .....                                                             | 19        |
| 5.3.2    | Study EPOE-10-01 .....                                                             | 26        |
| <b>6</b> | <b>REVIEW OF EFFICACY .....</b>                                                    | <b>33</b> |
|          | Efficacy Summary .....                                                             | 33        |
| 6.1      | Indication.....                                                                    | 36        |
| 6.1.1    | Methods.....                                                                       | 36        |
| 6.1.2    | Demographics.....                                                                  | 36        |
| 6.1.3    | Subject Disposition .....                                                          | 38        |
| 6.1.4    | Analysis of Primary Endpoint(s).....                                               | 42        |

|          |                                                                                        |           |
|----------|----------------------------------------------------------------------------------------|-----------|
| 6.1.5    | Analysis of Secondary Endpoints(s)                                                     | 45        |
| 6.1.6    | Other Endpoints                                                                        | 50        |
| 6.1.7    | Subpopulations                                                                         | 51        |
| 6.1.8    | Analysis of Clinical Information Relevant to Dosing Recommendations                    | 51        |
| 6.1.9    | Discussion of Persistence of Efficacy and/or Tolerance Effects                         | 51        |
| 6.1.10   | Additional Efficacy Issues/Analyses                                                    | 52        |
| <b>7</b> | <b>REVIEW OF SAFETY</b>                                                                | <b>52</b> |
|          | Safety Summary                                                                         | 52        |
| 7.1      | Methods                                                                                | 53        |
| 7.1.1    | Studies/Clinical Trials Used to Evaluate Safety                                        | 54        |
| 7.1.2    | Categorization of Adverse Events                                                       | 54        |
| 7.1.3    | Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence       | 54        |
| 7.2      | Adequacy of Safety Assessments                                                         | 54        |
| 7.2.1    | Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations | 55        |
| 7.2.2    | Explorations for Dose Response                                                         | 56        |
| 7.2.3    | Special Animal and/or In Vitro Testing                                                 | 56        |
| 7.2.4    | Routine Clinical Testing                                                               | 56        |
| 7.2.5    | Metabolic, Clearance, and Interaction Workup                                           | 56        |
| 7.2.6    | Evaluation for Potential Adverse Events for Similar Drugs in Drug Class                | 56        |
| 7.3      | Major Safety Results                                                                   | 56        |
| 7.3.1    | Deaths                                                                                 | 57        |
| 7.3.2    | Nonfatal Serious Adverse Events                                                        | 57        |
| 7.3.3    | Dropouts and/or Discontinuations                                                       | 59        |
| 7.3.4    | Significant Adverse Events                                                             | 59        |
| 7.3.5    | Submission Specific Primary Safety Concerns                                            | 62        |
| 7.4      | Supportive Safety Results                                                              | 65        |
| 7.4.1    | Common Adverse Events                                                                  | 65        |
| 7.4.2    | Laboratory Findings                                                                    | 68        |
| 7.4.3    | Vital Signs                                                                            | 69        |
| 7.4.4    | Electrocardiograms (ECGs)                                                              | 69        |
| 7.4.5    | Special Safety Studies/Clinical Trials                                                 | 69        |
| 7.4.6    | Immunogenicity                                                                         | 70        |
| 7.5      | Other Safety Explorations                                                              | 70        |
| 7.5.1    | Dose Dependency for Adverse Events                                                     | 70        |
| 7.5.2    | Time Dependency for Adverse Events                                                     | 71        |
| 7.5.3    | Drug-Demographic Interactions                                                          | 74        |
| 7.5.4    | Drug-Disease Interactions                                                              | 79        |
| 7.5.5    | Drug-Drug Interactions                                                                 | 79        |
| 7.6      | Additional Safety Evaluations                                                          | 79        |
| 7.6.1    | Human Carcinogenicity                                                                  | 79        |
| 7.6.2    | Human Reproduction and Pregnancy Data                                                  | 79        |
| 7.6.3    | Pediatrics and Assessment of Effects on Growth                                         | 79        |

|          |                                                             |           |
|----------|-------------------------------------------------------------|-----------|
| 7.6.4    | Overdose, Drug Abuse Potential, Withdrawal and Rebound..... | 80        |
| 7.7      | Additional Submissions / Safety Issues.....                 | 81        |
| <b>8</b> | <b>POSTMARKET EXPERIENCE .....</b>                          | <b>81</b> |
| <b>9</b> | <b>APPENDICES.....</b>                                      | <b>82</b> |
| 9.1      | Literature Review/References .....                          | 82        |
| 9.2      | Labeling Recommendations .....                              | 82        |
| 9.3      | Advisory Committee Meeting .....                            | 82        |

## Table of Tables

|                                                                                                                                                                                              |    |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|
| Table 1: Currently Approved Erythropoietin Stimulating Agents (ESA) .....                                                                                                                    | 11 |
| Table 2: Clinical Studies .....                                                                                                                                                              | 18 |
| Table 3: Schedule of Study Activities (EPOE-10-13 Study).....                                                                                                                                | 24 |
| Table 4: Schedule of Study Activities .....                                                                                                                                                  | 32 |
| Table 5: Patients Demographics and Baseline Characteristics, Study EPOE-10-13 (Maintenance Period) .....                                                                                     | 36 |
| Table 6: Patients Demographics and Baseline Characteristics, Study EPOE-10-01 .....                                                                                                          | 37 |
| Table 7: Subject Populations in Maintenance Period (Study EPOE-10-013) .....                                                                                                                 | 39 |
| Table 8: Subject Disposition (Study EPOE-10-13) .....                                                                                                                                        | 40 |
| Table 9: Subject Populations (study EPOE-10-01) .....                                                                                                                                        | 41 |
| Table 10: Subject Disposition (study EPOE-10-01).....                                                                                                                                        | 41 |
| Table 11: Primary Efficacy Endpoint – Mean Weekly Hemoglobin – EPOE-10-13 (SC) .....                                                                                                         | 42 |
| Table 12: Primary Efficacy Endpoint – Mean Weekly Dose per kg - EPOE-10-13 (SC).....                                                                                                         | 42 |
| Table 13: Mean Weekly Hb and Mean Weekly Dose by Body Weight during the Last 4 Weeks of the Maintenance Period (Sensitivity Analyses) .....                                                  | 43 |
| Table 14: Primary Efficacy Endpoint – Mean Weekly Hemoglobin - EPOE-10-01 (IV).....                                                                                                          | 44 |
| Table 15: Primary Efficacy Endpoint – Mean Weekly Dose per kg - EPOE-10-01 (IV) .....                                                                                                        | 44 |
| Table 16: Mean Weekly Hemoglobin (g/dL) and Mean Weekly Dose by Body Weight (U/kg/week) during the Last 4 Weeks of the Treatment Period (Sensitivity Analysis) .....                         | 45 |
| Table 17: Proportion of Subjects with Weekly Mean Hemoglobin Level Within and Outside the Target Range (9.0 to 11.0 g/dL) at Weeks 8 and 16 of the Maintenance Period (ITT Population) ..... | 47 |
| Table 18: Mean Weekly Hemoglobin (g/dL) Every 4 Weeks of Treatment Period (ITT Population) .....                                                                                             | 48 |
| Table 19: Proportion of Subjects with Weekly Mean Hemoglobin Level Within and Outside the Target Range (9.0 to 11.0 g/dL) at Weeks 8 and 16 of the Treatment Period (ITT Population) .....   | 49 |
| Table 20: Drug Exposure during the Maintenance Period (Safety Population, EPOE-10-13 Study) .....                                                                                            | 55 |
| Table 21: Drug Exposure during the Treatment Period (Safety Population, EPOE-10-01 Study).....                                                                                               | 55 |
| Table 22: Treatment-Emergent Serious Adverse Events during the Maintenance Period (Safety Population) .....                                                                                  | 58 |
| Table 23: Treatment-Emergent Serious Adverse Events (Safety Population) .....                                                                                                                | 58 |
| Table 24: Treatment-Emergent Adverse Events with $\geq 2\%$ Incidence in Study EPOE-10-13 by System Organ Class and Preferred Term during the Maintenance Period (Safety Population) .....   | 60 |
| Table 25: Treatment-Emergent Adverse Events with $\geq 2\%$ Incidence in Study EPOE-10-01 by System Organ Class and Preferred Term during the Treatment Period (Safety Population) .....     | 61 |
| Table 26: Treatment-Emergent Adverse Events of Special Interest during the Maintenance Period (EPOE-10-013 Study, SC) .....                                                                  | 63 |

|                                                                                                                                              |    |
|----------------------------------------------------------------------------------------------------------------------------------------------|----|
| Table 27: Treatment-Emergent Adverse Events of Special Interest, Study EPOE-10-01 (Safety Population) .....                                  | 64 |
| Table 28: Incidence of Common Treatment-Emergent Adverse Events in Combined EPOE-11-03 and EPOE-11-04 studies, (Safety Population) .....     | 66 |
| Table 29: Incidence of Positive Hematology Tests (Safety Population) .....                                                                   | 68 |
| Table 30: Incidence of Common TEAEs by Time of Onset for the Combined Randomized Treatment Groups (Weeks 1 to 12) (Safety Population) .....  | 72 |
| Table 31: Incidence of Common TEAEs by Time of Onset for the Combined Randomized Treatment Groups (Weeks 13 to 24) (Safety Population) ..... | 73 |
| Table 32: Incidence of Treatment-Emergent Adverse Events by Sex (Safety Population) .....                                                    | 75 |
| Table 33: Incidence of Treatment-Emergent Adverse Events by Age (Safety Population) .....                                                    | 76 |
| Table 34: Incidence of Treatment-Emergent Adverse Events by Race (Safety Population) .....                                                   | 77 |
| Table 35: Summary of Pediatric Study Plan for “Epoetin Hospira” .....                                                                        | 80 |

## Table of Figures

|                                                                                                                                                                                        |    |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|
| Figure 1: Mean ( $\pm$ SD) Ret% After Single Subcutaneous Administration of 100 U/kg of “Epoetin Hospira” or US-licensed Epogen in Study EPOE-12-02 (Pharmacodynamic Population) ..... | 16 |
| Figure 2: EPOE-10-13 Study Schematic .....                                                                                                                                             | 19 |
| Figure 3: EPOE-10-01 Study Schematic .....                                                                                                                                             | 27 |
| Figure 4: Mean Weekly Hb during the Maintenance Period for EPOE-10-13 (SC) .....                                                                                                       | 45 |
| Figure 5: Mean Weekly dosage during the Maintenance Period for EPOE-10-13 (SC) .....                                                                                                   | 47 |

List of Abbreviations and Definitions of Terms

|            |                                                                                        |
|------------|----------------------------------------------------------------------------------------|
| AE         | adverse event                                                                          |
| anti-rhEPO | anti-recombinant human erythropoietin                                                  |
| APPRISE    | Assisting Providers and cancer Patients with Risk Information for the Safe use of ESAs |
| BLA        | Biologics License Application                                                          |
| BP         | blood pressure                                                                         |
| BPCIA      | Biologics Price Competition and Innovation Act                                         |
| CI         | Confidence interval                                                                    |
| CMC        | Chemistry, Manufacturing, and Controls                                                 |
| CKD        | Chronic Kidney Disease                                                                 |
| CSR        | Clinical Study Report                                                                  |
| GCP        | Good Clinical Practice                                                                 |
| ESA        | Erythropoiesis-stimulating agent                                                       |
| Hb         | Hemoglobin                                                                             |
| Hct        | Hematocrit                                                                             |
| HD         | Hemodialysis                                                                           |
| ITT        | Intent-to-Treat Population                                                             |
| IV         | Intravenous                                                                            |
| LTSS       | Long-term safety study                                                                 |
| mFAS       | Modified Full Analysis Set                                                             |
| NAb        | Neutralizing antibody                                                                  |
| PD         | Pharmacodynamic                                                                        |
| PK         | Pharmacokinetic                                                                        |
| PP         | Per Protocol Population                                                                |
| PRCA       | Pure red cell aplasia                                                                  |
| RBC        | Red Blood Cell                                                                         |
| Ret%       | Reticulocyte count as a percentage of total erythrocytes                               |
| rhEPO      | Recombinant human erythropoietin                                                       |
| SAE        | Serious adverse event                                                                  |
| SAP        | Statistical Analysis Plan                                                              |
| SC         | Subcutaneous                                                                           |
| SoC        | Standard of care                                                                       |
| TEAE       | Treatment-emergent adverse event                                                       |

## 1 Recommendations/Risk Benefit Assessment

### 1.1 Recommendation on Regulatory Action

Hospira submitted Biologics License Application (BLA) 125545 for “Epoetin Hospira” in accordance with Section 351(k) of the Public Health Service Act as a proposed biosimilar to US licensed Epogen/Procrit. “Epoetin Hospira” is a proposed biosimilar to US-licensed Epogen/Procrit, and Hospira is seeking licensure of “Epoetin Hospira” for all indications for which US-licensed Epogen/Procrit is currently licensed.

The clinical review team recommends a Complete Response (CR) action for BLA 125545.

#### Complete Response Issue

We have identified Good Clinical Practice (GCP) compliance issues with clinical studies EPOE-10-01 and EPOE-10-13. We also note that the BLA submission did not include complete auditing reports for the clinical sites for studies EPOE-10-01 and EPOE-10-13. Hence, the final analysis populations for the assessment of clinically meaningful differences between “Epoetin Hospira” and US-licensed Epogen/Procrit cannot be determined based on the information provided in the BLA submission.

In order to address this deficiency, you will need to submit the following:

- A. Full auditing reports for studies EPOE-10-01 and EPOE-10-13. The reports must include description of the GCP compliance issues that you identified and measures taken to address the GCP compliance issues. For sites closed due to GCP compliance issues, you must include the details of the GCP compliance issues.
- B. Additional sensitivity analyses for efficacy and safety that excludes the patients from sites closed due to GCP compliance issues. You will need to submit amended clinical study reports and datasets for studies EPOE-10-01 and EPOE-10-13.

#### Additional Comment (non-CR issue to include in CR letter)

We note the reported case of pure red cell aplasia (PRCA) in a patient who was treated with European (EU)-approved Retacrit. The significance of this finding related to your proposed “Epoetin Hospira” product is uncertain. We recommend that you provide a root-cause analysis, and provide additional details regarding the PRCA case within the context of the development program for “Epoetin Hospira”.

### 1.2 Risk Benefit Assessment

The clinical studies used to support this BLA for “Epoetin Hospira” as a proposed biosimilar to US-licensed Epogen/Procrit include:

- Study EPOE-10-13: A Therapeutic Equivalence Study Comparing the Efficacy and Safety of Subcutaneous “Epoetin Hospira” and Epoetin Alfa (Amgen) in Patients with Chronic Renal Failure Requiring Hemodialysis and Receiving Epoetin Maintenance Treatment
- Study EPOE-10-01: A Therapeutic-Equivalence Study Comparing the Efficacy and Safety of Intravenous “Epoetin Hospira” and Epoetin Alfa (Amgen) in Patients with Chronic Renal Failure Requiring Hemodialysis and Receiving Epoetin Maintenance Treatment
- Two PK/PD studies (EPOE-12-02 and EPOE-14-01): Single dose and multiple dose cross-over studies conducted in healthy volunteers.

The two clinical studies EPOE-10-13 and EPOE-10-01 were designed as safety and efficacy comparative studies to the reference product.

The assessment of no clinically meaningful differences between “Epoetin Hospira” and US-licensed Epogen/Procrit cannot be completed at this time, as the final population for the comparative efficacy and safety analyses has not been finalized.

### **1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies**

The reference drug US-licensed Epogen/Procrit has a Risk Evaluation and Mitigation Strategies (REMS) program to ensure safe use for patients with cancer (oncology indication: for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy). The REMS consist of the following elements:

- Informed decisions between patients and their healthcare providers (HCPs) who are considering treatment with US-licensed Epogen/Procrit (epoetin alfa) by educating them on the risks of US-licensed Epogen/Procrit (epoetin alfa).
- Mitigation of the risk of decreased survival and/or poorer tumor outcomes in patients with cancer, as implemented through the ESA APPRISE (Assisting Providers and cancer Patients with Risk Information for the Safe use of ESAs) Oncology Program.

The Applicant submitted a REMS program. However, the completion of review of the REMS will be done with the next review cycle.

### **1.4 Recommendations for Postmarket Requirements and Commitments**

This will be assessed with the next review cycle.

## **2 Introduction and Regulatory Background**

## 2.1 Product Information

|                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|--------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Proposed Trade Name:     | Retacrit                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Nonproprietary Name:     | Referred to as “Epoetin Hospira” by the Applicant                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Therapeutic Class:       | Erythropoiesis-stimulating agent (ESA)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Applicant Name:          | Hospira, Inc.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Strength(s):             | 2000 Units/mL, 3000 Units/mL, 4000 Units/mL, 10,000 Units/mL, and 40,000 Units/mL                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Route of Administration: | Injection (Intravenous and Subcutaneous)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Dosage Form:             | Injectable                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Proposed Indication(s):  | <ol style="list-style-type: none"> <li>1. For the treatment of anemia due to Chronic Kidney Disease (CKD), including patients on dialysis and not on dialysis to decrease the need for red blood cell (RBC) transfusion</li> <li>2. For the treatment of anemia due to zidovudine administered at <math>\leq 4200</math> mg/week in HIV-infected patients with endogenous serum erythropoietin levels of <math>\leq 500</math> mUnits/mL</li> <li>3. For the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy</li> <li>4. To reduce the need for allogeneic RBC transfusions among patients with perioperative hemoglobin <math>&gt; 10</math> to <math>\leq 13</math> g/dL who are at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery</li> </ol> |

## 2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1: Currently Approved Erythropoietin Stimulating Agents (ESA)

| ESA Agent                                        | Indications                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|--------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Epogen/Procrit<br>(Epoetin Alfa)<br>June 1, 1989 | <ol style="list-style-type: none"> <li>1. For the treatment of anemia due to Chronic Kidney Disease (CKD), including patients on dialysis and not on dialysis to decrease the need for red blood cell (RBC) transfusion</li> <li>2. For the treatment of anemia due to zidovudine administered at <math>\leq 4200</math> mg/week in HIV-infected patients with endogenous serum erythropoietin levels of <math>\leq 500</math> mUnits/mL</li> <li>3. For the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy</li> <li>4. To reduce the need for allogeneic RBC transfusions among patients with perioperative hemoglobin <math>&gt; 10</math> to <math>\leq 13</math> g/dL who are at high risk</li> </ol> |

|                                                                          |                                                                                                                                                                                                                                                                                                                                                                                        |
|--------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                          | for perioperative blood loss from elective, noncardiac, nonvascular surgery                                                                                                                                                                                                                                                                                                            |
| Aranesp<br>Darbepoetin alfa<br>September 17, 2001                        | 1. For the treatment of anemia due to chronic kidney disease (CKD), including patients on dialysis and patients not on dialysis.<br>2. For the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy. |
| Mircera<br>Methoxy polyethylene glycol-epoetin beta<br>November 14, 2007 | 1. For the treatment of anemia associated with chronic kidney disease (CKD in adult patients on dialysis and patients not on dialysis.                                                                                                                                                                                                                                                 |

## 2.3 Availability of Proposed Active Ingredient in the United States

### Reference Product:

Epogen was initially licensed in the United States in 1989. Subsequently, three additional indications were approved based on supplements to the BLA. The indications are:

- For the treatment of anemia due to CKD, including patients on dialysis and not on dialysis to decrease the need for RBC transfusion.
- For the treatment of anemia due to zidovudine administered at  $\leq 4200$  mg/week in human immunodeficiency virus (HIV)-infected patients with endogenous serum erythropoietin levels of  $\leq 500$  mUnits/mL.
- For the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy.
- To reduce the need for allogeneic RBC transfusions among patients with perioperative hemoglobin (Hb)  $>10$  to  $\leq 13$  g/dL who are at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery.

## 2.4 Important Safety Issues With Consideration to Related Drugs

Safety issues to related drugs include adverse events of special interest and immunogenicity.

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

The development program for “Epoetin Hospira” was initiated prior to the Biologics Price Competition and Innovation Act (BPCI Act). The proposed biosimilar originated from the development of the Hospira EU biosimilar, “Epoetin Hospira”. The initial IND 100685 for “Epoetin Hospira” was submitted on 12/16/09. Study EPOE-10-08 (known as the legacy PK study) a PK study in subjects with CKD on HD was initiated under IND 100685 in 2009. Study EPOE-10-08 was conducted with clinical trial material based on an original Drug Product

formulation targeted to match the reference product for in vivo biopotency and supported by an extensive preclinical data package. Following conduct of this study, the manufacturing process was revised to the current proposed commercial process such that the epoetin content is determined based on a target epoetin protein concentration rather than on the basis of in vivo bioactivity.

Several meetings were held to discuss the development plan for “Epoetin Hospira” as a proposed biosimilar product. Hospira submitted protocols (EPOE-10-01 and EPOE-10-13) on 6/20/2011. Hospira submitted the proposed Statistical Analysis Plan (SAPs) for studies EPOE-10-01 and EPOE-10-13 on 8/23/2013. A comparative single dose PK/PD study in healthy volunteers was conducted (Study EPOE-12-02) and multiple dose PD study (EPOE-14-01) on 6/25/2014.

Three meeting was held with the Applicant between May and November 2014 to discuss the planned clinical data package for “Epoetin Hospira” in support of a future 351(k) BLA. The applicant submitted BLA 125545 on December 24, 2014.

## **2.6 Other Relevant Background Information**

Erythropoiesis-stimulating agents (ESAs) include several forms of exogenous erythropoietin which are similar to the endogenous erythropoietin. Erythropoietin is a glycoprotein produced in the kidney that acts on hematopoietic precursor cells to increase the production of red blood cells. The US-licensed Epogen was the first recombinant human erythropoietin (rhEPO) to be licensed in 1989. US-licensed Epogen/Procrit is licensed for the treatment of anemia in several conditions (chronic kidney disease, anemia is due to the effect of concomitant myelosuppressive chemotherapy in patients with non-myeloid malignancies, and due to zidovudine administration in human immunodeficiency virus (HIV)-infected patients) and for reduction of allogeneic red blood cell (RBC) transfusions in patients undergoing elective, noncardiac, nonvascular surgery.

The major benefits of ESA use are the correction of anemia, the mitigation of fatigue, and the reduction or avoidance of blood transfusions.

## **3 Ethics and Good Clinical Practices**

### **3.1 Submission Quality and Integrity**

BLA 125545 was received on 12/16/2014 as an electronic submission in CTD format. Following receipt of missing information provided in response to information requests, the submission was found to be complete and was filed on 2/11/2015.

The preliminary results of the inspection conducted by the Office of Compliance suggested that multiple sites participated in several key studies conducted in support of this application were Good Clinical Practice (GCP) non-compliant. Therefore, the integrity of the data submitted to

support the biosimilar application will require inspection of additional clinical sites to determine the final analysis population to be used in the efficacy and safety analyses.

### 3.2 Compliance with Good Clinical Practices

Informed consent was required from patients in all clinical trials. Independent ethics committees/institutional review boards at all participating centers were required to give permission for these studies.

The following sites were selected for an auditing review to be conducted by the Office of Compliance.

| Site # (Name, Address, Phone number, email, fax#)                                                                                                                                         | Protocol ID                  | Number of Subjects | Indication/Primary endpoint and other endpoints for verification                                                                                          |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------|--------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|
| Site # 24011<br>Zeig, Steven, MD<br>Pines Clinical Research Inc.<br>601 N. Flamingo Road, # 104<br>Pembroke Pines, FL 33028<br>1 (954) 435-5828                                           | EPO-10-13                    | 20                 | Anemia in patients:<br>- CKD on dialysis and not on dialysis<br>- Chemotherapy induced<br>- HIV receiving zidovudine<br>- Reduce the need for transfusion |
| Site # 24005<br>Desai, Anant J., MD<br><br>Site# 14011<br>Ghandhi, Kamal<br><br>Renal Consultants Medical Group<br>16907 Devonshire Street<br>Granada Hills, CA 91344<br>1 (818) 366-4626 | EPOE-10-13<br><br>EPOE-10-01 | 18<br><br>28       | Anemia in patients:<br>- CKD on dialysis and not on dialysis<br>- Chemotherapy induced<br>- HIV receiving zidovudine<br>- Reduce the need for transfusion |
| Site # 11015<br>Lee, Mark C., MD<br>Mark C. Lee, Inc.<br>Santa Fe Springs Dialysis<br>11147 Washington Blvd<br>Whittier, CA 90606<br>1 (562) 413-7736                                     | EPOE-10-01                   | 30                 | Anemia in patients:<br>- CKD on dialysis and not on dialysis<br>- Chemotherapy induced<br>- HIV receiving zidovudine<br>- Reduce the need for transfusion |
| Site # 11003<br>Diamond, Susan Adele, MD<br>San Antonio Kidney Disease Center<br>Physicians Group, PLLC<br>8042 Wurzbach Road, Suite 500                                                  | EPOE-10-01                   | 29                 | Anemia in patients:<br>- CKD on dialysis and not on dialysis<br>- Chemotherapy induced<br>- HIV receiving zidovudine<br>- Reduce the need for             |

|                                           |  |  |             |
|-------------------------------------------|--|--|-------------|
| San Antonio, TX 78229<br>1 (210) 692-7864 |  |  | transfusion |
|-------------------------------------------|--|--|-------------|

Two clinical studies, EPOE-10-01 and EPOE-10-13 were inspected for this BLA. Four domestic clinical study sites covering five clinical investigators (Steven Zeig, M.D., Anant Desai, M.D., Kamal Gandhi, M.D. Mark Lee, M.D., and Susan Diamond, M.D.) were inspected. The Sponsor (Hospira, Inc.) was also audited. The results of inspection noted regulatory violations at three clinical sites covering four clinical investigators. Although initial interim monitoring visits by the Sponsor (and/or CRO) were delayed and did not conform to the clinical management plans for the study, the sponsor monitoring process did result in identification of noncompliant sites and appropriate reporting of protocol deviations to the BLA based upon inspections of a sample of clinical sites. However, additional sites were inspected as for-cause inspection in response to complaints which identified additional violations not previously reported. The preliminary results of the inspection of these sites showed:

- One site inspected enrolled 36 subjects in three protocols (EPOE-10-13, EPOE-10-01, EPOE-11-04 and M11-352). The inspection results classified the inspected site as Official Action Indicated (OAI) because the violation is significant, and the scope and severity of the violation compromises data reliability.
- Two other sites inspected enrolled 16 subjects. The inspection results classified the inspected site as Voluntary Action Indicated (VAI) for failure to conduct the investigation in accordance with investigational plan.

*Reviewer comments: The Office of Scientific Investigations inspection identified GCP compliance issues with the core clinical studies EPOE-10-13 and EPOE-10-01. DHP also noted that the BLA submission did not include complete auditing reports for the clinical sites for studies EPOE-10-01 and EPOE-10-13. Therefore, the final analysis populations for the assessment of clinically meaningful differences between “Epoetin Hospira” and US-licensed Epogen/Procrit cannot be determined based on the information provided in the BLA submission.*

### 3.3 Financial Disclosures

The applicant obtained financial disclosure Forms 3454 from investigators for Studies (EPOE-10-08, EPOE-12-02, EPOE-14-01, EPOE-10-01, EPOE-10-13, EPOE-11-03, EPOE-11-04). None of the investigators in any of the studies was identified as an employee of the applicant, and no disclosable financial interests or arrangements were identified on any of the financial disclosure forms.

## 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

## 4.1 Chemistry Manufacturing and Controls

The applicant proposed to use clinical studies comparing “Epoetin Hospira” to US-licensed Epogen/Procrit to support its claim that “Epoetin Hospira” is highly similar to US-licensed Epogen/Procrit. The Applicant used a comprehensive bioanalytical approach to assess whether “Epoetin Hospira” is highly similar to the US-licensed Epogen®/Procrit® reference product.

Refer to CMC Review for further details.

## 4.2 Clinical Microbiology

Refer to CMC Review.

## 4.3 Preclinical Pharmacology/Toxicology

The pharmacologic activity of “Epoetin Hospira” and the US-licensed Epogen/Procrit were evaluated by *in vitro* (cell-based bioassay functional assays, competitive receptor binding and surface plasmon resonance (SPR) assays) and *in vivo* (normocythemc mouse assay). In addition, evaluation of well-established PD markers for ESAs was incorporated into the two 13-week subchronic comparative toxicity studies. The results obtained using the four different bioassays demonstrate that the potencies of the “Epoetin Hospira” drug product and the US-licensed Epogen product lots representative of all dose strengths are consistent with the designated label claim.

Thirteen week SC administration of “Epoetin Hospira” in rats resulted in increases in RBC counts, Hb, HCT and reticulocytes (RETIC) compared to that of US-licensed Epogen administration at week 13 in all dose groups. Additionally, the 13-week IV administration of “Epoetin Hospira” and US-licensed Epogen in dogs resulted in similar increases in RBC, Hb, HCT, and RETIC at week 13 in all dose groups.

Please refer to Division of Pharmacology Toxicology review for more details.

## 4.4 Clinical Pharmacology

### 4.4.1 Mechanism of Action

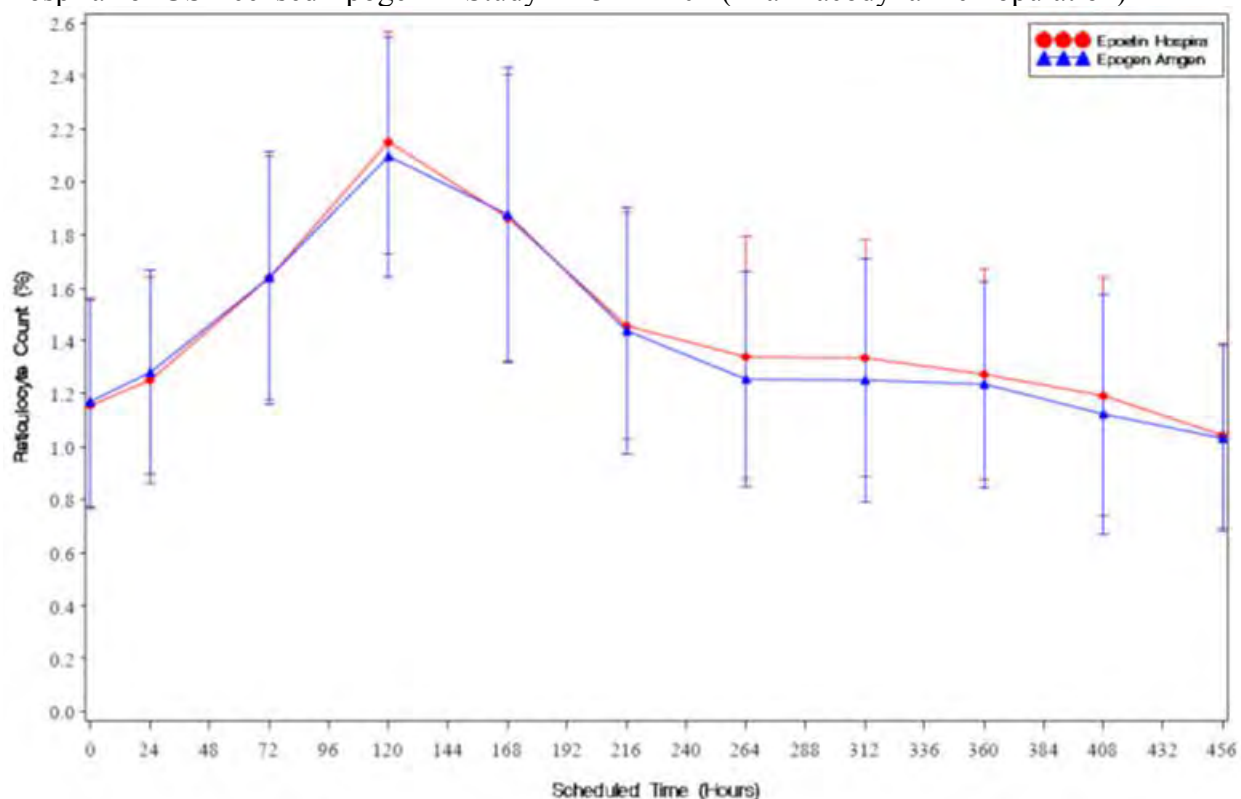
“Epoetin Hospira” is recombinant human erythropoietin (rhEPO) stimulates erythropoiesis by the same mechanism as endogenous erythropoietin.

Both endogenous erythropoietin and exogenous rhEPO can bind to the erythropoietin receptor on specific erythrocyte precursor cells, which causes a conformational change in the receptor that brings its intracellular domains into close apposition enabling cross phosphorylation via the binding of JAK2 kinase, the initiation of the signal transduction cascade, and induction of erythropoiesis.

#### 4.4.2 Pharmacodynamics

In Study EPOE-12-02, following single dose SC administration of 100 U/kg epoetin to healthy male subjects, serial blood samples for reticulocyte count were obtained after dose administration through Day 20 of each study period. Mean Ret% for “Epoetin Hospira” and US-licensed Epogen/Procrit are shown in figure below.

Figure 1: Mean ( $\pm$  SD) Ret% After Single Subcutaneous Administration of 100 U/kg of “Epoetin Hospira” or US-licensed Epogen in Study EPOE-12-02 (Pharmacodynamic Population)



Red circle = “Epoetin Hospira” (N=73); Blue triangle = Epogen (N=73).

Values are shown as mean with bars representing  $\pm$  1 SD.

Dosing at Time 0.

Source: BLA 125545 submission, Module 2.5, Figure 4 P. 24.

*Please refer to Division of Clinical Pharmacology review for more details.*

#### 4.4.3 Pharmacokinetics

The pharmacokinetics of “Epoetin Hospira” were compared to US-licensed Epogen/Procrit in two clinical studies

- EPOE-12-02: A phase I, randomized, single-dose, crossover study evaluating the pharmacokinetics (PK) and pharmacodynamics (PD) of “Epoetin Hospira” compared to

US-licensed Epogen® (Amgen) following subcutaneous (SC) administration to healthy male volunteers

- EPOE-14-01: A randomized, open-label, multiple-dose, parallel group study evaluating the pharmacodynamics and pharmacokinetics of “Epoetin Hospira” compared to US-licensed Epogen® (Amgen) following subcutaneous administration to healthy male volunteers

The PK data from the above studies suggested that there were no differences in the in vivo performance of “Epoetin Hospira” and US-licensed Epogen/Procrit under discerning SC administration single and multiple fixed-dose conditions in healthy male subjects. The PK results from Study EPOE-12-02 and Study EPOE-14-01 will be addressed in the clinical pharmacology review.

*Please refer to Division of Clinical Pharmacology review for more details.*

## 5 Sources of Clinical Data

### 5.1 Tables of Studies/Clinical Trials

Table 2: Clinical Studies

| Study             | Design                                                                                                                                                                                                                                                | Population                  | Primary Endpoint                                                                                                                                                        |
|-------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>EPOE-10-08</b> | A Phase I Study Comparing the Pharmacokinetics of “Epoetin Hospira” and US-licensed Epogen (Amgen) when Administered Intravenously in Patients with Chronic Renal Failure Requiring Hemodialysis and Receiving Epoetin Maintenance Treatment          | 105 Patients with CKD on HD |                                                                                                                                                                         |
| <b>EPOE-12-02</b> | A phase I, randomized, single-dose, crossover study evaluating the pharmacokinetics (PK) and pharmacodynamics (PD) of “Epoetin Hospira” compared to US-licensed Epogen® (Amgen) following subcutaneous (SC) administration to healthy male volunteers | 81 Healthy male volunteers  | PK equivalence of epoetin following single dose SC of “Epoetin Hospira” and US-licensed Epogen® (Amgen) determined from $AUC_{0-\infty}$ or $AUC_{0-t}$ and $C_{max}$ . |
| <b>EPOE-14-01</b> | A randomized, open-label, multiple-dose, parallel group study evaluating the pharmacodynamics and pharmacokinetics of “Epoetin Hospira” compared to US-licensed Epogen® (Amgen) following subcutaneous administration to healthy male volunteers      | 123 Healthy volunteers      |                                                                                                                                                                         |
| <b>EPOE-10-13</b> | A Therapeutic Equivalence Study Comparing the Efficacy and Safety of                                                                                                                                                                                  | 320 Patients with CKD on    | Co-primary efficacy endpoints:<br>• Difference between treatments                                                                                                       |

|                   |                                                                                                                                                                                                                                       |                             |                                                                                                                                                                                                                                                                        |
|-------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                   | Subcutaneous “Epoetin Hospira” and US-licensed Epogen/Procrit (Amgen) in Patients with Chronic Renal Failure Requiring Hemodialysis and Receiving Epoetin Maintenance Treatment                                                       | HD                          | in mean weekly Hb levels during the last 4 weeks of the Maintenance Period<br>• Difference between treatments in mean weekly dosage per kg body weight during the last 4 weeks of the Maintenance Period                                                               |
| <b>EPOE-10-01</b> | A Therapeutic-Equivalence Study Comparing the Efficacy and Safety of Intravenous “Epoetin Hospira” and Epoetin Alfa (Amgen) in Patients with Chronic Renal Failure Requiring Hemodialysis and Receiving Epoetin Maintenance Treatment | 612 Patients with CKD on HD | Co-primary efficacy endpoints:<br>• Difference between treatments in mean weekly Hb levels during the last 4 weeks of the Treatment Period<br>• Difference between treatments in mean weekly dosage per kg body weight during the last 4 weeks of the Treatment Period |

## 5.2 Review Strategy

This review is focused on the comparative safety and efficacy evidences that the applicant provided to support biosimilarity between the “Epoetin Hospira” to the reference drug (US-licensed Epogen) in the proposed indications. The key materials used for the review of the BLA 125545 include:

- Clinical comparative studies
- Relevant published literature
- Relevant information in the public domain

## 5.3 Discussion of Individual Studies/Clinical Trials

### 5.3.1 Study EPOE-10-13

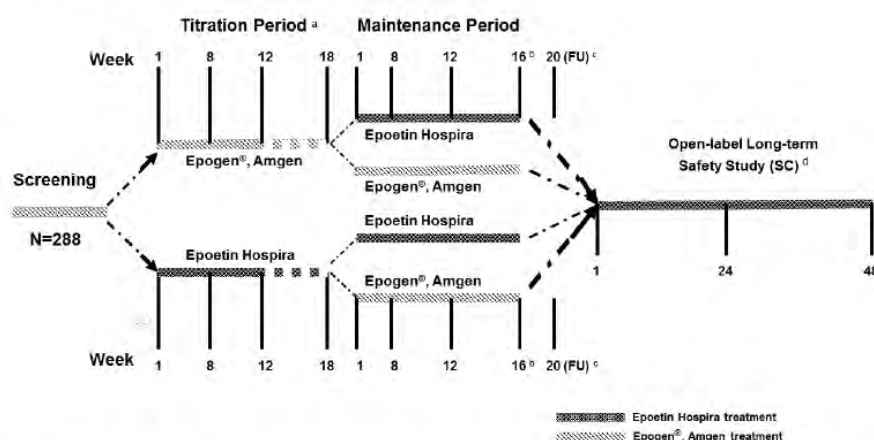
Title: A Therapeutic Equivalence Study Comparing the Efficacy and Safety of Subcutaneous “Epoetin Hospira” and Epoetin Alfa (Amgen) in Patients with Chronic Renal Failure Requiring Hemodialysis and Receiving Epoetin Maintenance Treatment

#### Study Design:

This study was a multicenter, randomized, active-controlled, parallel group, double-blind, confirmatory efficacy and safety study in subjects with CKD requiring hemodialysis and receiving epoetin maintenance treatment. All eligible patients were randomized in 1:1 ratio to receive US-licensed Epogen or “Epoetin Hospira” In the Titration Period, patients were treated (patients who had been on IV US-licensed Epogen received either “Epoetin Hospira” or US-licensed Epogen by SC injection with an initial 20-30% dose reduction from the IV weekly dose) for 12 to 18 weeks to achieve 4 weeks of protocol-defined optimal stable dosing. Patients who were not optimally titrated and stable were excluded from the Maintenance Period and discontinued from the study. Patients who had been on SC US-licensed Epogen treatment at the

time of Screening and had demonstrated protocol-defined optimal stable dosing were randomized by proceeding directly to Maintenance period.

Figure 2: EPOE-10-13 Study Schematic



- Subjects who were already on SC treatment at the time of Screening and demonstrated optimal stable dosing for 4 consecutive weeks were randomized into the Titration Period, received study drug assignment and then proceeded directly to the Maintenance Period if they satisfied all other study criteria for entry into the Maintenance Period. Subjects who did not demonstrate optimal and stable dosing by week 18 of the Titration Period did not continue to the Maintenance Period.
- Subjects who discontinued study drug early during the Maintenance Period received non-study drug SoC ESA treatment until either the Follow-Up Visit or entry into the Long Term Safety Study.
- Subjects who did not enter the Long Term Safety Study underwent a Follow-up Visit, 4 weeks after the end of the Maintenance Period study assessments.
- Subjects had up to 28 days from completion of Week 16 of the Maintenance Period to enter into the Long Term Safety Study and receive Epoetin Hospira study drug by SC administration.

Note: Primary efficacy endpoints were assessed during the last 4 weeks of the Maintenance Period.

Source: BLA submission, Figure 1, P.33.

Subjects who fulfilled the criteria for entry into the Maintenance Period during the last 4 weeks of the Titration Period (Weeks 9-12 to 15-18) or for a period of 4 consecutive weeks if already on SC treatment at the time of Screening and with stable SC epoetin dosage during the same period were randomized to either “Epoetin Hospira” or US-licensed Epogen during the Maintenance Period. Both the Titration Period study drug assignment and study drug dose were used as stratification variables (low < 60 U/kg/week, 60-165 U/kg/week, > 165 U/kg/week) for study drug assignment into the Maintenance Period.

## Endpoints:

### Co-Primary Endpoints:

The following co-primary efficacy endpoints were calculated from Hb levels and dose data collected in the last 4 weeks of the Maintenance Period with each study drug:

- Difference between treatments (“Epoetin Hospira” and US-licensed Epogen) in mean weekly Hb levels during the last 4 weeks of the double-blind Maintenance Period
- Difference between treatments (“Epoetin Hospira” and US-licensed Epogen) in mean weekly dose per kg body weight during the last 4 weeks of the double-blind Maintenance Period

#### Secondary Endpoints:

The following secondary efficacy endpoints were assessed as differences between treatments (“Epoetin Hospira” and US-licensed Epogen):

- Mean weekly Hb levels in 16 weeks of treatment in the Maintenance Period
- Mean weekly dose per kg body weight delivered in 16 weeks of treatment in the Maintenance Period
- The total dose delivered during the 16 weeks of treatment in the Maintenance Period
- The proportion of subjects with a weekly mean Hb level within the target range (9.0-11.0 g/dL) at Week 8 and 16 of the Maintenance Period
- The proportion of subjects requiring permanent dose changes during the Maintenance Period
- The proportion of subjects requiring temporary dose changes during the Maintenance Period
- The proportion of subjects with any transient change of Hb level  $>1.0$  g/dL during the Maintenance Period
- The proportion of subjects with any Hb measurement outside the target range (9.0-11.0 g/dL) during the Maintenance Period
- The proportion of subjects qualifying as optimally titrated and stable at the end of the Titration Period
- Incidence of subjects receiving blood transfusions for each treatment group during the Maintenance Period

#### Safety:

The following safety parameters were calculated for each treatment, and differences between treatments were assessed, as appropriate:

- The proportion of subjects with Hb levels  $<8.0$  g/dL at any time during the Maintenance Period
- The proportion of subjects with Hb levels  $>12.0$  g/dL at any time during the Maintenance Period
- The incidence of treatment-emergent adverse events (TEAEs), including the nature, frequency, severity, relationship to study drug treatment, and outcome at all visits
- Adverse Events of Special Interest
- The incidence of hypersensitivity adverse events (AEs)
- Concomitant medications
- Vital signs and weight, including change from baseline
- Clinical laboratory parameters, including change from baseline
- Physical examination, including change from baseline
- Electrocardiogram (ECG), including change from baseline

#### Eligibility Criteria

##### Inclusion Criteria

1. Adults patients on hemodialysis with chronic renal failure and renal anemia currently on stable US-licensed Epogen dose administered IV or SC, 1 to 3 times per week, for whom the following applied:

- a. A change in US-licensed Epogen dosing of no more than 10% from the mean
  - b. Mean Hb between 9.0 and 11.0 g/dL
  - c. No more than one Hb result outside of range from 9.0-11.0 g/dL
  - d. No Hb result more than  $\pm 1.0$  g/dL from the mean Hb level
2. Subject had been on stable, adequate dialysis for at least 12 weeks prior to randomization, defined as no clinically relevant changes of dialysis regimen and/or dialyzer
3. Subject had adequate iron stores, defined as plasma ferritin  $>100$  mcg/L and TSAT  $>20\%$ , prior to randomization
4. Female subject must have been either postmenopausal for at least 1 year prior to randomization, surgically sterile (bilateral tubal ligation, bilateral oophorectomy, or hysterectomy), or practicing at least 1 of the following methods of birth control:
  - a. hormonal contraceptives (oral, parenteral, or transdermal) for at least 3 months prior to randomization
  - b. intrauterine device (IUD)
  - c. double-barrier method (condoms, contraceptive sponge, diaphragm, or vaginal ring with spermicidal jellies or cream)

Exclusion:

1. Subject's maintenance Epoetin dosage was  $>600$  U/kg per week (1-3 times per week)
2. Subject received treatment with long-acting epoetin analogues such as Aranesp® within 12 weeks prior to randomization
3. Subject experienced any of the following within 3 months prior to randomization:
  - a. Myocardial infarction
  - b. Stroke (cerebrovascular accident)/cerebrovascular insult (minor stroke) or transient ischemic attack/intracerebral bleeding/cerebral infarction
  - c. Severe/unstable angina
  - d. Coronary angioplasty, bypass surgery, or peripheral artery bypass graft
  - e. Decompensated congestive heart failure (New York Heart Association [NYHA] class IV)
  - f. Pulmonary embolism
  - g. Deep vein thrombosis or other thromboembolic event
  - h. Receipt of live or attenuated vaccination (except flu vaccination)
4. Subject had uncontrolled hypertension within the 4 weeks prior to randomization, defined as more than 10% of post-dialysis blood pressures (BPs)  $>170$  mmHg systolic and/or  $>110$  mmHg diastolic, based on BP readings obtained when the subject's post-dialysis body weight was not more than 0.5 kg above the subject's listed dry weight
5. Subject had known, clinically manifested deficiency of folic acid and/or vitamin B12 (irrespective of whether currently treated or not)
6. Subject had any active, uncontrolled systemic, inflammatory or malignant disease that in the Investigator's opinion might have been significant to exclude the subject from participation in the study, including but not limited to demyelinating diseases such as multiple sclerosis, microbial, viral, or fungal infection or mental disease
7. Subject had a contraindication for the test drug or had been previously treated with “Epoetin Hospira”
8. Subject had relative or absolute iron deficiency at the end of the Titration Period

9. Subject had a platelet count below  $100 \times 10^9/L$
10. Subject had a clinically relevant increase of CRP ( $> 10 \text{ mg/dL}$ ) for at least 2 weeks
11. Subject had a significant drug sensitivity or a significant allergic reaction to any drug, as well as known hypersensitivity or idiosyncratic reaction to epoetin (or its excipients, including albumin) or any other related drugs that in the judgment of the Investigator was exclusionary for the study participation
12. Subject had a history of any of the following:
  - a. Detectable anti-rhEPO antibodies
  - b. Clinically relevant malnutrition
  - c. Confirmed aluminum intoxication
  - d. Myelodysplastic syndrome
  - e. Known bone marrow fibrosis (osteitis fibrosa cystica)
  - f. Known seizure disorder
  - g. Liver cirrhosis with clinical evidence of complications (portal hypertension, splenomegaly, ascites)
13. Subject was a female who was pregnant, lactating or planning a pregnancy during the study
14. Subject had a history of drug abuse or alcohol abuse within 2 years prior to randomization, as determined by the Investigator
15. Subject was currently participating or had participated in a drug or other investigational research study within 30 days prior to randomization
16. Subject may not have been able to comply with the requirements of this clinical study, communicate effectively with study personnel, or was considered by the Investigator, for any reason, to be an unsuitable candidate for the study
17. Subject had donated or lost  $>475 \text{ mL}$  (i.e., 1 pint) blood volume (including plasmapheresis) or had a transfusion of any blood product within 3 months prior to randomization
18. Subject, in the Investigator's opinion, had any clinically significant abnormal laboratory evaluations, including liver function taken at the Screening Visit
19. Subject had a positive laboratory test for human immunodeficiency virus (HIV) or hepatitis B surface antigen (HBsAg)

#### Treatment Plan

All subjects in the study were administered study drug (“Epoetin Hospira” or US-licensed Epogen) by SC injection as per current US-licensed Epogen/Procrit Package Insert 1 to 3 times per week on dialysis treatment days. Dose, frequency, and timing of administration of study drug in relation to the hemodialysis were kept the same as per local practice during the 4 weeks prior to randomization for each subject. All injections were to be administered at least 30 – 60 minutes prior to the end of dialysis treatment.

The dose of study drug could be adjusted every 4 weeks period to maintain the Hb value within a target range of 9.0 to 11.0 g/dL. Changes in dosing while Hb is within the target range were generally avoided. The intervals for dosing adjustment were:

- The dose was not to be increased more frequently than once every 4 weeks

- The dose could be decreased more frequently
- Frequent dose adjustments were to be avoided

For Hb increases, the following criteria were used:

- If the Hb increased rapidly (e.g., more than 1.0 g/dL in any 2-week period), the dose was to be reduced by 25% or more as needed to reduce rapid responses
- If the Hb level exceeded 11.0 g/dL, the dose of epoetin was reduced or interrupted

For subjects who did not respond adequately, changes to dose were made according to the following criteria:

- If the Hb had not increased by more than 1.0 g/dL after 4 weeks of therapy, the dose was increased by 25%
- If the response was not adequate over a 12-week escalation period, increasing the dose further was considered unlikely to improve response and may have increased risks. The lowest dose that maintained a Hb level sufficient to reduce the need for RBC transfusions was recommended. Other causes of anemia were evaluated. Epoetin was discontinued if responsiveness did not improve.

Prior and Concomitant Therapy: Concomitant medication was allowed for the duration of the study, if considered to be necessary for the subject’s welfare.

Subjects enrolled under the original protocol through Amendments #2 who received short acting non-study drug SoC ESA were allowed to return to randomized study drug. Subjects enrolled under Amendment #3 who received short-acting non-study drug SoC ESA were not allowed to return to randomized study drug. Subjects receiving long-acting ESAs were withdrawn from the study.

Rescue Therapy: If any rescue therapy was indicated, subjects may have received SoC treatment including ESA (non-study drug), blood transfusions or other therapies as judged appropriate by the treating physician. In such situations, subjects enrolled under the original protocol through Amendments #2 were allowed to remain in the study; subjects enrolled under Amendment #3 and #4, if they received non-study drug SoC ESA rescue therapy were discontinued from study drug. However, if the subject was in the Maintenance Period, the subject was allowed to remain in the study, continued to receive short-acting non-study drug SoC ESA and was followed per the protocol’s Schedule of Study Activities for up to 16 weeks.

#### *Schedule of Assessments*

For the assessment of the co-primary endpoint, measurement of Hb levels (g/dL) by central laboratory performed weekly and the dose required to maintain Hb in a target range of 9.0 to 11.0 g/dL was recorded following randomization and throughout the duration of the study, and at the Follow-up visit.

Table 3: Schedule of Study Activities (EPOE-10-13 Study)

| Evaluation                                          | Screening <sup>a</sup> | Titration Period               |   |   |   |                                               |                                  |    |    |    |    |    |                |   |   |   |   | Maintenance Period |    |    |    |   |   |   |  | FU <sup>c</sup> |
|-----------------------------------------------------|------------------------|--------------------------------|---|---|---|-----------------------------------------------|----------------------------------|----|----|----|----|----|----------------|---|---|---|---|--------------------|----|----|----|---|---|---|--|-----------------|
|                                                     |                        |                                |   |   |   | 4 Stable Weeks Assessment Period <sup>b</sup> |                                  |    |    |    |    |    |                |   |   |   |   |                    |    |    |    |   |   |   |  |                 |
| Study Week                                          | up to -4               | 1                              | 2 | 4 | 6 | 8                                             | 9                                | 10 | 12 | 14 | 16 | 18 | 1 <sup>d</sup> | 2 | 4 | 6 | 8 | 10                 | 12 | 14 | 16 | 4 |   |   |  |                 |
| Clinical Assessments/Activities                     |                        |                                |   |   |   |                                               |                                  |    |    |    |    |    |                |   |   |   |   |                    |    |    |    |   |   |   |  |                 |
| Written Informed Consent                            | X                      |                                |   |   |   |                                               |                                  |    |    |    |    |    |                |   |   |   |   |                    |    |    |    |   |   |   |  |                 |
| Inclusion / Exclusion Criteria                      | X                      |                                |   |   |   |                                               |                                  |    |    |    |    |    |                |   |   |   |   |                    |    |    |    |   |   |   |  |                 |
| Demographics & Medical History                      | X                      |                                |   |   |   |                                               |                                  |    |    |    |    |    |                |   |   |   |   |                    |    |    |    |   |   |   |  |                 |
| Physical Examination <sup>e</sup>                   | X                      |                                |   |   |   |                                               | completed at the last assessment |    |    |    |    |    |                |   |   |   |   |                    |    |    | X  | X |   |   |  |                 |
| Vital Signs <sup>e,f</sup>                          | X                      | assessed every visit at dosing |   |   |   |                                               |                                  |    |    |    |    |    |                |   |   |   |   |                    |    |    |    |   | → | X |  |                 |
| Tolerability                                        |                        | assessed every visit at dosing |   |   |   |                                               |                                  |    |    |    |    |    |                |   |   |   |   |                    |    |    |    |   | → |   |  |                 |
| 12-lead Electrocardiogram <sup>e,g</sup>            | X                      |                                |   |   |   |                                               | completed at the last assessment |    |    |    |    |    |                |   |   |   |   |                    |    |    | X  | X |   |   |  |                 |
| Randomization                                       |                        | X                              |   |   |   |                                               |                                  |    |    |    |    |    |                |   |   |   |   |                    |    |    |    |   |   |   |  |                 |
| Study Drug Assignment                               |                        | X                              |   |   |   |                                               |                                  |    |    |    |    |    |                | X |   |   |   |                    |    |    |    |   |   |   |  |                 |
| Prior & Concomitant Medications                     | X                      |                                |   |   |   |                                               |                                  |    |    |    |    |    |                |   |   |   |   |                    |    |    |    |   | → | X |  |                 |
| Adverse Events                                      | X                      |                                |   |   |   |                                               |                                  |    |    |    |    |    |                |   |   |   |   |                    |    |    |    |   | → | X |  |                 |
| Laboratory Assessments <sup>e</sup>                 |                        |                                |   |   |   |                                               |                                  |    |    |    |    |    |                |   |   |   |   |                    |    |    |    |   |   |   |  |                 |
| Serum Pregnancy Test <sup>h</sup>                   | X                      |                                |   |   |   |                                               |                                  |    |    |    |    |    |                |   |   |   |   |                    |    |    |    | X |   |   |  |                 |
| Clinical Chemistry                                  | X                      | X                              |   | X |   | X                                             |                                  |    | X  |    | X  |    | X              | X |   | X |   | X                  |    | X  |    | X |   |   |  |                 |
| C-reactive protein                                  | X                      | X                              |   |   |   |                                               |                                  |    | X  |    | X  |    |                |   |   |   |   |                    |    |    |    | X |   |   |  |                 |
| Hematology & Coagulation Panel                      | X                      | X                              |   | X |   | X                                             |                                  |    | X  |    | X  |    | X              | X |   | X |   | X                  |    | X  |    | X |   |   |  |                 |
| Hb and Hct <sup>i</sup>                             | X                      | weekly Hb and Hct assessments  |   |   |   |                                               |                                  |    |    |    |    |    |                |   |   |   |   |                    |    |    |    |   | → | X |  |                 |
| Iron Status (Plasma ferritin, TSAT)                 | X                      | X                              |   | X |   | X                                             |                                  |    | X  |    | X  |    | X              | X |   | X |   | X                  |    | X  |    | X |   |   |  |                 |
| Vitamin B <sub>12</sub> and folic acid <sup>j</sup> | X                      |                                |   |   |   |                                               |                                  |    |    |    |    |    |                |   |   |   |   |                    |    |    |    |   |   |   |  |                 |
| Serology (HBsAg, anti-HCV Abs, anti-HIV Abs)        | X                      |                                |   |   |   |                                               |                                  |    |    |    |    |    |                |   |   |   |   |                    |    |    |    |   |   |   |  |                 |
| stdK <sub>d</sub> /V <sup>k</sup>                   | X                      | X                              |   | X |   | X                                             |                                  |    | X  |    | X  |    | X              | X |   | X |   | X                  |    | X  |    | X |   |   |  |                 |
| Anti-rhEPO Abs <sup>l</sup>                         |                        | X                              |   |   |   |                                               | completed at the last assessment |    |    |    |    |    | X              |   |   |   |   |                    |    |    | X  | X |   |   |  |                 |
| Treatment                                           |                        |                                |   |   |   |                                               |                                  |    |    |    |    |    |                |   |   |   |   |                    |    |    |    |   |   |   |  |                 |
| Study Drug Administration <sup>m</sup>              |                        |                                |   |   |   |                                               |                                  |    |    |    |    |    |                |   |   |   |   |                    |    |    |    |   | → |   |  |                 |

a Subjects who completed the screening criteria and met all other enrollment criteria including optimal stable dosing were randomized into the Titration Period (within a period of 4 weeks). The first study assessment (study drug dosing or lab draw) began on Day1/Week 1.

b Subjects were treated for 12-18 weeks in the Titration Period, the length of which was determined by the time it took to achieve 4 weeks of optimal titration and stable dosing following the first 8 weeks of the period, with a minimum of 12 weeks and an upper limit of 18 total weeks for achieving this aim. Subjects who had been on stable SC Epogen for 4 consecutive weeks and met all other entry criteria at the time of Screening including optimal stable dosing, were randomized into the Titration Period, received study drug assignment and then were assigned study drug treatment into the Maintenance Period. All subjects must have demonstrated optimal stable dosing to qualify for entry into the Titration and Maintenance Periods.

c Subjects who elected to enroll into the Long Term Safety Study did not need to perform the Follow-up Visit.

d Subjects received their dose(s) of blinded study drug for the last week of the Titration Period stable assessment and were then assigned study drug treatment to begin the Maintenance Period (i.e., at Week 1 of the Maintenance Period).

e Physical examination, vital signs, ECG, and laboratory assessments at Week 16 of the Maintenance Period were performed after the last dose of study drug. Blood samples, except for those required to calculate stdK<sub>d</sub>/V were drawn prior to dialysis.

f (Vital signs) temperature, BP, and heart rate were collected within 1 hour before and 1 hour after dialysis on dosing days whether or not the subject received randomized study drug, while weight was only checked after dialysis. Blood Samples, except for those required to calculate stdK<sub>d</sub>/V were to be drawn prior to dialysis.

g ECG assessments were performed before the first dose of randomized study drug, at the last day of stable assessment of the Titration Period, at Week 16 of the Maintenance Period and at the Follow-up Visit.

h For females of childbearing potential only.

i Hemoglobin and Hct levels were assessed at Screening and weekly after randomization, throughout the duration of the study.

j Only subjects with macrocytosis (increased MCV) were assessed for vitamin B<sub>12</sub> and folic acid at screening.

k stdK<sub>d</sub>/V was calculated during the study and at the last visit for stable assessment evaluation.

l Samples for anti-rhEPO testing were collected at Week 1 of the Titration Period (prior to the first dose of study drug in the Titration Period), prior to the last dose of the Titration Period, at Week 1 of the Maintenance Period (prior to the first dose of study drug in the Maintenance Period), at Week 16 of the Maintenance Period (prior to the first dose of Follow-up treatment) and at the Follow-up Visit.

m Dose of study drug was to be evaluated for adjustment regularly (i.e., at least every week); however, subjects must have had a stable dose during the last 4 weeks of the Titration Period (e.g., no dose change for 4 consecutive weeks between Weeks 12 and 18) to enter the Maintenance Period.

Source: BLA 125545, Module 3.5.1.5, Table 4, P. 58.

### Statistical Analysis Plan

The co-primary efficacy endpoints were the difference between treatments (“Epoetin Hospira” and US-licensed Epogen/Procrit) in mean weekly Hb level and the mean weekly dosage per kg body weight during the last 4 weeks of the double-blind Maintenance Period.

A hierarchical test strategy was used in this study, whether there is a clinically meaningful difference in the mean Hb level during the last 4 weeks of the Maintenance Period. If no clinically meaningful difference in Hb levels was concluded based on Hb results (95% 2-sided CI within the  $\pm 0.5$  g/dL acceptance limits), the difference in mean weekly dose during the last 4 weeks of treatment was tested.

**Intent-to-Treat (ITT) Population:** The ITT Population consisted of all subjects who were randomized into the Maintenance Period. The ITT Population was used for the analysis of the primary variables.

**Safety Population:** The Safety Population included all subjects who received at least one dose of study drug treatment.

**Modified Safety Population:** The modified Safety Population included all subjects who received at least one dose of study drug and no non-study drug SoC ESA during the Maintenance Period.

**Full Analysis Set (FAS) Population:** The Full Analysis Set (FAS) Population included all randomized subjects who: (1) received study drug treatment during the Maintenance Period; (2) had both Hb and dose data for Weeks 13-16 of treatment in the Maintenance Period although they may have had the dose held during the last week; and (3) had not discontinued study drug during Weeks 13-16. The FAS Population was used in sensitivity analyses.

**Modified Full Analysis Set (mFAS) Population:** The modified Full Analysis Set (mFAS) Population included all subjects randomized to study drug in the Maintenance Period who received at least one dose of study drug treatment during the Maintenance Period and must have had both Hb and dose data for at least two consecutive weeks of treatment with study drug in the Maintenance Period. The mFAS Population was used in sensitivity analyses.

**Per Protocol (PP) Population:** The Per Protocol (PP) Population was a subset of the ITT subjects who met the following criteria:

- Had at least 4 weeks of treatment with study drug in the Maintenance Period
- Had at least 4 weeks of Hb data collected while on study drug during the Maintenance Period
- Had at least 4 weeks of study drug administration data collected while on study drug during the Maintenance Period (note that held dosing for a week would meet this criterion and the subject would be included)
- Had no important protocol deviation
- Had no use of other ESAs during the last 4 weeks of study drug administration
- Had received no packed red blood cells or whole blood transfusions during study conduct

Sensitivity analyses for the co-primary endpoint analyses were conducted on the PP, FAS, mFAS, and RET Populations, and on the ITT Population using alternative data imputation methodologies.

### 5.3.2 Study EPOE-10-01

**Title:** A Therapeutic-Equivalence Study Comparing the Efficacy and Safety of Intravenous “Epoetin Hospira” and Epoetin Alfa (Amgen) in Patients with Chronic Renal Failure Requiring Hemodialysis and Receiving Epoetin Maintenance Treatment

**Study Design:**

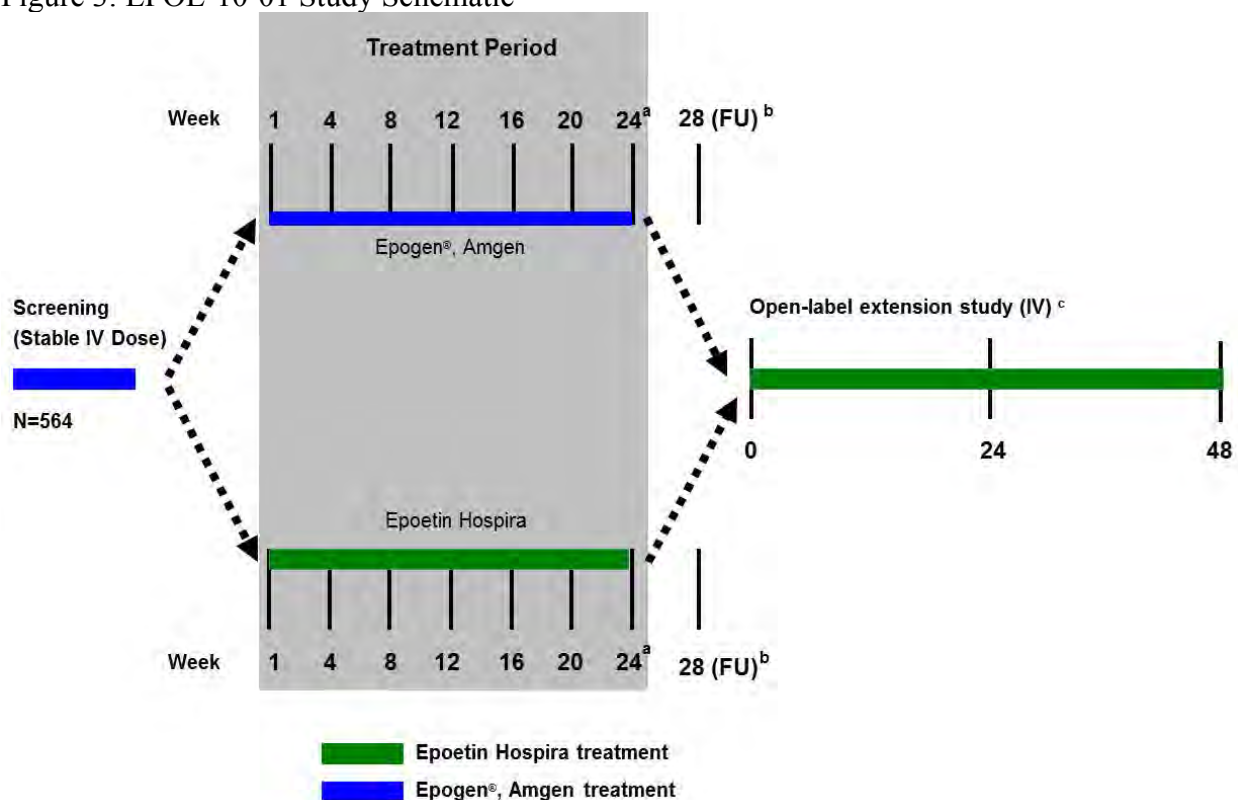
This study was a multicenter, randomized, active-controlled, parallel group, double-blind, Phase III study evaluating the efficacy and safety of IV administered “Epoetin Hospira” (1 to 3 times per week) in male and female subjects aged 18 to 80 years treated for anemia associated with CKD on stable US-licensed Epogen treatment for 4 weeks and stable, adequate hemodialysis for at least

12 weeks prior to randomization. Subjects who fulfilled the study criteria were randomized to 1 of 2 treatment groups (randomization ratio of 1:1). Subjects were treated for up to 24 weeks in the Treatment Period. Data for the co-primary efficacy endpoints were collected during the last 4 weeks of the Treatment Period.

After completing the Treatment Period, all subjects had the opportunity to enter an open label Long-Term Safety Study (LTSS) under a separate protocol, EPOE-11-03, and be treated with “Epoetin Hospira” for up to an additional 48 weeks. Subjects who discontinued from the randomized study drug during the Treatment Period were also eligible to enter the LTSS after completion of treatment with standard of care (SoC) erythropoiesis-stimulating agent (ESA) and study activity assessments for the remaining length of the Treatment Period. Subjects not entering the LTSS continued to be treated per SoC treatment and had a Follow up Visit, 4 weeks after the end of the Treatment Period, at Week 28.

During the Treatment Period, the dose of study drug was adjusted to maintain the Hb value within the target range of 9.0 to 11.0 g/dL. Adjustments to dose for study treatment were allowed in concordance with the US-licensed Epogen/Procrit Package Insert or as per current standard practice at the dialysis center.

Figure 3: EPOE-10-01 Study Schematic



a Subjects who discontinued early from the randomized study drug received non-study drug SoC ESA until either the Follow-Up Visit or entry into the open-label LTSS.

b Subjects who completed the Treatment Period and who did not enter the LTSS underwent a Follow-Up (FU) Visit at Week 28, 4 weeks after the end of Week 24 Study Activity Assessments.

c Subjects had up to 28 days from completion of the Week 24 visit to enter into the LTSS to receive “Epoetin Hospira” study drug by IV administration.

Source: BLA 125545 submission, Module 5.3.5.1, Figure 1, P.30.

## Endpoints:

### Co-Primary Endpoints:

The following co-primary efficacy endpoints were calculated from Hb levels and dose data collected in the last 4 weeks of the treatment with each study drug:

- Difference between treatments (“Epoetin Hospira” and US-licensed Epogen) in mean weekly Hb levels during the last 4 weeks of the double-blind Treatment Period
- Difference between treatments (“Epoetin Hospira” and US-licensed Epogen) in mean weekly dosage per kg body weight during the last 4 weeks of the double-blind Treatment Period

### Secondary Efficacy:

The following secondary efficacy endpoints were assessed as differences between treatments:

- Mean weekly Hb level in 24 weeks of treatment
- Mean weekly dosage per kg body weight delivered in 24 weeks of treatment

- The total dose delivered during the 24 weeks of treatment in the Treatment Period
- The proportion of subjects with a weekly mean Hb level within the target range (9.0 - 11.0 g/dL) at Weeks 12 and 24 of the Treatment Period
- The proportion of subjects requiring permanent dose changes during the Treatment Period
- The proportion of subjects requiring temporary dose changes during the Treatment Period
- The proportion of subjects with any transient change of Hb level >1.0 g/dL during the Treatment Period
- The proportion of subjects with any Hb measurement outside the target range during the Treatment Period
- Incidence of subjects receiving blood transfusions for each treatment group

## **Eligibility Criteria**

### **Inclusion Criteria**

- Subject was able to provide written informed consent after risks and benefits of the study had been explained prior to any study related activities
- Subject was a hemodialysis patient with chronic renal failure and renal anemia currently on stable US-licensed Epogen treatment for at least 4 weeks prior to randomization, for whom the following applied (during the Screening Period):
  - a. US-licensed Epogen dose had been administered IV 1 to 3 times per week with no more than a 10% dose change from the mean for at least 4 weeks prior to randomization
  - b. Subject had a stable Hb, defined as meeting all of the following:
    - i. Mean Hb during the 4 weeks prior to randomization was between 9.0 and 11.0 g/dL
    - ii. No more than one Hb was outside the range of 9.0-11.0 g/dL during the 4 weeks prior to randomization
    - iii. No Hb result more than  $\pm 1.0$  g/dL from the mean Hb level was observed during the 4-week period prior to randomization
- Subject had been on stable, adequate dialysis for at least 12 weeks prior to randomization, defined as no clinically relevant changes of dialysis regimen and/or dialyzer
- Subject had adequate iron stores, defined as ferritin >100 mcg/L and TSAT >20%, prior to randomization
- Subject was male or female aged 18 to 80 years (both inclusive)
- If female, subject must have been either postmenopausal for at least 1 year prior to randomization, surgically sterile (bilateral tubal ligation, bilateral oophorectomy, or hysterectomy), or using at least 1 of the following methods of birth control:
  - a. hormonal contraceptives (oral, parenteral, or transdermal) for at least 3 months prior to randomization
  - b. intrauterine device (IUD)
  - c. double-barrier method (condoms, contraceptive sponge, diaphragm, or vaginal ring with spermicidal jellies or cream)

### **Exclusion Criteria:**

1. Subject’s maintenance Epoetin dosage was >600 U/kg per week
2. Subject received treatment with long-acting epoetin analogues such as Aranesp® within 3 months prior to randomization
3. Subject experienced any of the following within 3 months prior to randomization:
  - i. Myocardial infarction
  - ii. Stroke (cerebrovascular accident)/cerebrovascular insult (minor stroke) or transient ischemic attack/intracerebral bleeding/cerebral infarction
  - iii. Severe/unstable angina
  - iv. Coronary angioplasty, bypass surgery, or peripheral artery bypass graft
  - v. Decompensated congestive heart failure (New York Heart Association [NYHA] class IV)
  - vi. Pulmonary embolism
  - vii. Deep vein thrombosis or other thromboembolic event
  - viii. Receipt of live or attenuated vaccination (except flu vaccination)
4. Subject had uncontrolled hypertension within the 4 weeks prior to randomization, defined as more than 10% of post-dialysis blood pressures (BPs) >170 mmHg systolic and/or >110 mmHg diastolic, based on BP readings obtained when the subject’s post-dialysis body weight was not more than 0.5 kg above the subject’s listed dry weight
5. Subject had known, clinically manifested deficiency of folic acid and/or vitamin B12 (irrespective of whether currently treated or not)
6. Subject had any active, uncontrolled systemic, inflammatory or malignant disease (including demyelinating diseases such as multiple sclerosis) that in the Investigator’s opinion might have been significant to exclude the subject from participation in the study, including but not limited to microbial, viral, or fungal infection or mental disease
7. Subject had a contraindication for the test drug or had been previously treated with “Epoetin Hospira”
8. Subject had relative or absolute iron deficiency prior to randomization
9. Subject had a platelet count below 100 x 10<sup>9</sup>/L
10. Subject had a clinically relevant increase of CRP (>10 mg/dL) for at least 2 weeks
11. Subject had a significant drug sensitivity or a significant allergic reaction to any drug, as well as known hypersensitivity or idiosyncratic reaction to epoetin (or its excipients, including albumin) or any other related drugs that in the judgment of the Investigator were exclusionary for the study participation
12. Subject had a history of any of the following:
  - i. Detectable anti-rhEPO antibodies
  - ii. Clinically relevant malnutrition
  - iii. Confirmed aluminum intoxication
  - iv. Myelodysplastic syndrome
  - v. Known bone marrow fibrosis (osteitis fibrosa cystica)
  - vi. Known seizure disorder
  - vii. Liver cirrhosis with clinical evidence of complications (portal hypertension, splenomegaly, ascites)
13. Subject was a female who was pregnant, lactating, or planning a pregnancy during the study

14. Subject had a history of drug abuse or alcohol abuse within 2 years prior to randomization as determined by the Investigator
15. Subject was currently participating or had participated within 30 days prior to randomization in a drug or other investigational research study
16. Subject may not have been able to comply with the requirements of this clinical study, communicate effectively with study personnel, or was considered by the Investigator, for any reason, to be an unsuitable candidate for the study
17. Subject had donated or lost >475 mL (i.e., 1 pint) blood volume (including plasmapheresis) or had a transfusion of any blood product within 3 months prior to randomization
18. Subject, in the Investigator’s opinion, had any clinically significant abnormal laboratory evaluations, including liver function taken at the Screening Visit
19. Subject had a positive laboratory test for human immunodeficiency virus (HIV) or hepatitis B surface antigen (HBsAg)

#### Treatment Plan

All subjects in the study were administered study drug (“Epoetin Hospira” or US-licensed Epogen) by IV bolus as per current US-licensed Epogen/Procrit Package Insert 1 to 3 times per week on dialysis treatment days. Dose, frequency, and timing of administration of study drug in relation to the hemodialysis were kept the same as per local practice during the 4 weeks prior to randomization for each subject.

During the Treatment Period, the dose of study drug was evaluated for adjustment on a regular basis (i.e., at least every week), to maintain the Hb value within a range of 9.0 to 11.0 g/dL. Dose adjustments were allowed in line with the US-licensed Epogen/Procrit Package Insert, after evaluation of Hb measures over the previous 4-week period. For subjects who demonstrated Hb levels below the target range of 9.0 to 11.0 g/dL, the dose was increased by 25% if Hb had not increased by >1.0 g/dL after 4 weeks of therapy. The dose was reduced by 25% when Hb exceeded 11.0 g/dL or when Hb increased >1.0 g/dL in any 2-week period. Changes in dosing while Hb was within the target range were generally avoided. Dose selection and dose adjustment and/or titration were at the discretion of the Investigator. Subjects were treated with study drug for up to 24 weeks.

Prior and Concomitant Therapy: concomitant medication was allowed for the duration of the study, if considered to be necessary for the subject’s welfare. Subjects enrolled under the original protocol through Amendment #2 who received short acting non-study drug SoC ESA were allowed to return to randomized study drug. Subjects enrolled under Amendments #3-5 who received short-acting non-study drug SoC ESA were not allowed to return to randomized study drug. Subjects receiving long-acting ESAs were to be withdrawn from the study.

Rescue Therapy: If any rescue therapy was indicated, subjects may have received SoC treatment including ESA (non-study drug), blood transfusions or other therapies as judged appropriate by the treating physician. In such situations, subjects enrolled under the original protocol through

Amendment #2 were allowed to remain in the study; subjects enrolled under Amendments #3-5, if they received non-study drug ESA rescue therapy were not to receive any additional study drug.

### Schedule of Assessment

For the assessment of the co-primary endpoint, measurement of Hb levels (g/dL) by central laboratory performed weekly and the dose required to maintain Hb in a target range of 9.0 to 11.0 g/dL was recorded following randomization and throughout the duration of the study, and at the Follow-up visit.

Table 4: Schedule of Study Activities

| Evaluation                                                                                                                                                                                                                                                                         | Screening <sup>a</sup> | Treatment Period                         |   |   |   |   |    |    |    |    |    |    |    |    |    | FU <sup>e</sup> |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|------------------------------------------|---|---|---|---|----|----|----|----|----|----|----|----|----|-----------------|
| Study Week                                                                                                                                                                                                                                                                         | Up to -4               | 1                                        | 2 | 4 | 6 | 8 | 10 | 12 | 14 | 16 | 18 | 20 | 22 | 24 | 28 |                 |
| Clinical Assessments/Activities                                                                                                                                                                                                                                                    |                        |                                          |   |   |   |   |    |    |    |    |    |    |    |    |    |                 |
| Written Informed Consent                                                                                                                                                                                                                                                           | X                      |                                          |   |   |   |   |    |    |    |    |    |    |    |    |    |                 |
| Inclusion / Exclusion Criteria                                                                                                                                                                                                                                                     | X                      |                                          |   |   |   |   |    |    |    |    |    |    |    |    |    |                 |
| Demographics & Medical History (including History/Information on Renal Failure and Hemodialysis)                                                                                                                                                                                   | X                      |                                          |   |   |   |   |    |    |    |    |    |    |    |    |    |                 |
| Physical Examination <sup>c</sup>                                                                                                                                                                                                                                                  | X                      |                                          |   |   |   |   |    |    |    |    |    |    |    | X  | X  |                 |
| Vital Signs <sup>c,d,e</sup>                                                                                                                                                                                                                                                       | X                      | -----→                                   |   |   |   |   |    |    |    |    |    |    |    |    |    | X               |
| 12-lead Electrocardiogram <sup>c,e</sup>                                                                                                                                                                                                                                           | X                      |                                          |   |   |   |   |    |    |    |    |    |    |    | X  | X  |                 |
| Randomization                                                                                                                                                                                                                                                                      |                        | X                                        |   |   |   |   |    |    |    |    |    |    |    |    |    |                 |
| Prior/Concomitant Medications                                                                                                                                                                                                                                                      | X                      | -----→                                   |   |   |   |   |    |    |    |    |    |    |    |    |    | X               |
| Adverse Events                                                                                                                                                                                                                                                                     | X                      | -----→                                   |   |   |   |   |    |    |    |    |    |    |    |    |    | X               |
| Laboratory Assessments <sup>a</sup>                                                                                                                                                                                                                                                |                        |                                          |   |   |   |   |    |    |    |    |    |    |    |    |    |                 |
| Serum Pregnancy Test <sup>f</sup>                                                                                                                                                                                                                                                  | X                      |                                          |   |   |   |   |    |    |    |    |    |    |    | X  |    |                 |
| Clinical Chemistry                                                                                                                                                                                                                                                                 | X                      | X                                        |   | X |   | X |    | X  |    | X  |    | X  |    | X  | X  |                 |
| C-reactive protein                                                                                                                                                                                                                                                                 | X                      | X                                        |   |   |   |   |    |    |    |    |    |    |    | X  |    |                 |
| Hematology & Coagulation Panel                                                                                                                                                                                                                                                     | X                      | X                                        |   | X |   | X |    | X  |    | X  |    | X  |    | X  | X  |                 |
| -----Hb and Hct <sup>g</sup>                                                                                                                                                                                                                                                       | X                      | -----Weekly Hb and Hct assessments-----→ |   |   |   |   |    |    |    |    |    |    |    |    |    | X               |
| Iron Status (Plasma ferritin, TSAT)                                                                                                                                                                                                                                                | X                      | X                                        |   | X |   | X |    | X  |    | X  |    | X  |    | X  |    |                 |
| Vitamin B <sub>12</sub> and folic acid <sup>h</sup>                                                                                                                                                                                                                                | X                      |                                          |   |   |   |   |    |    |    |    |    |    |    |    |    |                 |
| Serology (HBsAg, anti-HCV Abs, anti-HIV Abs)                                                                                                                                                                                                                                       | X                      |                                          |   |   |   |   |    |    |    |    |    |    |    |    |    |                 |
| stdK <sub>dt</sub> /V                                                                                                                                                                                                                                                              | X                      | X                                        |   | X |   | X |    | X  |    | X  |    | X  |    | X  | X  |                 |
| Anti-rhEPO Abs <sup>i</sup>                                                                                                                                                                                                                                                        |                        | X                                        |   |   |   |   |    | X  |    |    |    |    |    | X  | X  |                 |
| Treatment                                                                                                                                                                                                                                                                          |                        |                                          |   |   |   |   |    |    |    |    |    |    |    |    |    |                 |
| Study Drug Administration <sup>j</sup>                                                                                                                                                                                                                                             |                        | -----→                                   |   |   |   |   |    |    |    |    |    |    |    |    |    |                 |
| a Subjects who completed the screening criteria and met all other enrollment criteria were randomized into the Treatment Period (within a period of 4 weeks). The first study assessment (study drug dosing or lab draw) began Day 1/Week 1.                                       |                        |                                          |   |   |   |   |    |    |    |    |    |    |    |    |    |                 |
| b Subjects who elected to enroll into the LTSS (under a separate protocol) did not need to perform a Follow-up Visit.                                                                                                                                                              |                        |                                          |   |   |   |   |    |    |    |    |    |    |    |    |    |                 |
| c Physical examination, vital signs, and ECG at Week 24 of the Treatment Period were performed after the last dose of study drug: study drug was given during dialysis. Blood samples, except for those required to calculate stdK <sub>dt</sub> /V, were drawn prior to dialysis. |                        |                                          |   |   |   |   |    |    |    |    |    |    |    |    |    |                 |
| d Temperature, BP, and heart rate were collected within 1 hour before and after dialysis on dosing days while weight was checked only after dialysis on dosing days.                                                                                                               |                        |                                          |   |   |   |   |    |    |    |    |    |    |    |    |    |                 |
| e Vital signs at Week 1 of the Treatment Period were captured before the first dose of randomized study drug. ECG assessments were performed at Screening before the first dose of randomized study drug.                                                                          |                        |                                          |   |   |   |   |    |    |    |    |    |    |    |    |    |                 |
| f For females of childbearing potential only.                                                                                                                                                                                                                                      |                        |                                          |   |   |   |   |    |    |    |    |    |    |    |    |    |                 |
| g Hemoglobin and hematocrit levels were assessed at Screening and assessed weekly following randomization and throughout the duration of the study.                                                                                                                                |                        |                                          |   |   |   |   |    |    |    |    |    |    |    |    |    |                 |
| h Only subjects with macrocytosis (increased MCV) were assessed for vitamin B <sub>12</sub> and folic acid at Screening.                                                                                                                                                           |                        |                                          |   |   |   |   |    |    |    |    |    |    |    |    |    |                 |
| i Sample for anti-rhEPO antibody tests were collected at Week 1, Week 12, and Week 24 of the Treatment Period and Follow-up. Sample collection for antibody testing at Week 1 was to be done prior to the first dose of study drug in the Treatment Period.                        |                        |                                          |   |   |   |   |    |    |    |    |    |    |    |    |    |                 |
| j Dose of study drug was to be evaluated for adjustment regularly (i.e., at least every week).                                                                                                                                                                                     |                        |                                          |   |   |   |   |    |    |    |    |    |    |    |    |    |                 |

Source: BLA 125545 submission, Module 5.3.5.1, Table 3. P. 51.

### Protocol Amendments:

The original protocol dated June 30, 2011 was amended five times.

Amendment #1 dated December 01, 2011:

1. Change the target level of Hb to 9.0 to 11.0 g/dL in accordance with new FDA requirements

2. Change of length of time a subject needs to be on stable treatment prior to randomization from 12 weeks to 4 weeks.
3. Addition of definition of the re-screening period
4. Addition of section to describe Non-Screen Failed (NSF) Population
5. Addition of new reference concerning new FDA requirements for US-licensed Epogen
6. Deletion of section entitled Assessment of Blood Target Parameters
7. Clarification of sample size and significance level
8. Substitute 2008 version of Declaration of Helsinki for 2004 version
9. Other administrative changes and clarifications.

## 6 Review of Efficacy

### Efficacy Summary

**Disclaimer: The efficacy analyses should be re-analyzed based on the issues identified in Section 3, which noted multiple sites that were GCP non-compliant. The results below should be interpreted with caution. As such, conclusions regarding the comparative assessment of efficacy between the proposed biosimilar and the reference product cannot be made at this time.**

**Note: The efficacy analyses below are based on the ITT population that included patients from GCP non-compliant sites.**

The comparison of “Epoetin Hospira” with US-licensed Epogen with regard to efficacy endpoints in an intended population was based on Studies EPOE-10-13 (SC) and EPOE-10-01 (IV). The studies were randomized, double-blind comparative studies comparing “Epoetin Hospira” and the US-licensed Epogen for treatment of anemia in patients with CKD on hemodialysis receiving US-licensed Epogen as maintenance therapy. The study drug was administered as SC in study EPOE-10-13 and IV in study EPOE-10-01. The co-primary endpoints for efficacy were mean weekly Hb and mean weekly dose per body weight in the last 4 weeks of the studies period. The study drug was administered at starting dose and the dose was adjusted to maintain the hemoglobin level between 10 – 11 g/dL according to the US-licensed Epogen/Procrit label.

### Study EPOE-10-13 (SC)

This study was a multicenter, randomized, active-controlled, parallel group, double-blind confirmatory efficacy and safety study in subjects with CKD requiring hemodialysis and receiving epoetin maintenance treatment. A total of 320 patients were treated for 12 to 18 weeks in the Titration Period to achieve a 4 weeks of protocol-defined optimal stable dosing. Eligible Patients who had been on IV US-licensed Epogen received either “Epoetin Hospira” or US-licensed Epogen by SC injection with an initial 20-30% dose reduction. Patients were treated for 12 to 18 weeks in the Titration Period to achieve 4 weeks of protocol-defined optimal stable dosing. Patients who were not optimally titrated and stable were excluded from the Maintenance

Period and discontinued from the study. Patients who had been on SC treatment at the time of Screening and had demonstrated protocol-defined optimal stable dosing were randomized into the Titration Period, received study drug assignment but did not receive treatment in the Titration Period, and then proceeded directly to randomization into the Maintenance Period for Maintenance Period study drug assignment. A total 246 patients (ITT Population) were stratified based on the titration period study dose (low (<60 U/kg/week), medium (60-165 U/kg/week) or high (>165 U/kg/week)) and randomized in Maintenance Period in 1:1 ratio to receive “Epoetin Hospira” (124 patients) or US-licensed Epogen (122 patients). Subjects were treated for up to 16 weeks in the Maintenance Period.

The co-primary efficacy endpoints were the differences between treatments (“Epoetin Hospira” and US-licensed Epogen) in mean weekly hemoglobin level and dosage per kg body weight during the last 4 weeks of Maintenance Period.

The key secondary endpoints include, the mean weekly Hb levels in 16 weeks of treatment in the Maintenance Period, the mean weekly dose per kg body weight delivered in 16 weeks of treatment in the Maintenance Period, the total dose delivered during the 16 weeks of treatment in the Maintenance Period, and the proportion of subjects with a weekly mean Hb level within the target range (9.0-11.0 g/dL) at Week 8 and 16 of the Maintenance Period.

Results of the efficacy analyses on during the Maintenance Period showed the following:

- The co-primary endpoints of both mean weekly Hb and the mean weekly dose per kg body weight met the pre-specified acceptance limits. There were no clinically meaningful difference between “Epoetin Hospira” and the US-licensed Epogen product.
  - The analysis for the ITT Population for mean weekly Hb levels showed that the least square (LS) mean for the difference between the “Epoetin Hospira” group and the US-licensed Epogen group in weekly Hb during the last 4 weeks of the Maintenance Period was 0.04 g/dL, with a 95% CI of -0.17 to 0.24 g/dL. This result of 95% CI is within the pre-specified acceptance limits of -0.5 to 0.5 g/dL.
  - The analysis for the ITT Population for the mean dose per kg body weight showed that the LS mean for the difference between the “Epoetin Hospira” group and the US-licensed Epogen group in weekly epoetin dose per kg body weight during the last 4 weeks of the Treatment Period was -2.34 U/kg/week, with a 95% CI of -14.51 to 9.82 U/kg/week. This CI was contained within the pre-specified acceptance limits of -45 to 45 U/kg/week.
- Sensitivity analyses from different population (PP, FAS, mFAS, RET) showed that the difference between two treatment arms and its 95% CI are within the equivalence limits.
  - The LS means of the difference in mean weekly Hb during the last 4 weeks of the Maintenance Period for all these different population ranged from 0.00 to 0.13 g/dL. These 95% CIs were within the acceptance limits of -0.5 and 0.5 g/dL.
  - The LS means of the difference in weekly epoetin dose by body weight during the last 4 weeks of the Treatment Period ranged from -2.73 to 1.63 U/kg/week. These 95% CIs were within the acceptance limits of -45 to 45 U/kg/week.
- Results of the analyses of the key secondary endpoints revealed:

- The mean weekly Hb and the mean weekly dose per kg body weight for each 4 weeks interval in 16 weeks of treatment in the maintenance period revealed no clinically meaningful difference between the treatment groups.
- The incidence of red blood cell transfusion was similar between the two groups. There was no statistical significant difference observed between treatment groups.

#### Study EPOE-10-01 (IV)

This study was a multicenter, randomized, active-controlled, parallel group, double-blind supportive efficacy and safety study in subjects with CKD requiring hemodialysis and receiving epoetin maintenance treatment. A total of 612 of eligible patients were randomized in 1:1 ratio to “Epoetin Hospira” (n=306) or US-licensed Epogen (n=306). Patients received study drug by IV bolus injection administered 1 to 3 times per week at the same stable weekly dose that the subject received during the last week of the Screening Period. During the Treatment Period patients were treated up to 24 weeks, the dose of study drug was evaluated for adjustment on a regular basis (i.e., at least every week), to maintain the Hb value within a range of 9.0 to 11.0 g/dL. The dose of study drug was adjusted in line with the US-licensed Epogen/Procrit Package Insert. For patients who demonstrated Hb levels below the target range of 9.0 to 11.0 g/dL, the dose was increased by 25% if Hb had not increased by >1.0 g/dL after 4 weeks of therapy. The dose was reduced by 25% when Hb exceeded 11.0 g/dL or when Hb increased >1.0 g/dL in any 2-week period.

The co-primary efficacy endpoints were the differences between treatments (“Epoetin Hospira” and US-licensed Epogen) in mean weekly hemoglobin level and dosage per kg body weight during the last 4 weeks of Treatment Period.

The key secondary endpoints included, the mean weekly Hb levels in 24 weeks of treatment, the mean weekly dosage per kg body weight delivered in 24 weeks of treatment, and the incidence of subjects receiving blood transfusions for each treatment group during the Maintenance Period.

Results of the efficacy analyses on during the Treatment Period showed the following:

- The co-primary endpoints of both mean weekly Hb and the mean weekly dose per kg body weight met the pre-specified acceptance limits. There were no clinically meaningful difference between “Epoetin Hospira” and the US-licensed Epogen product.
  - The least square (LS) mean for the difference between the “Epoetin Hospira” group and the US-licensed Epogen group in weekly Hb during the last 4 weeks of the Treatment Period was -0.12 g/dL, with a 95% CI of -0.25 to 0.01 g/dL. This result of 95% CI is within the pre-specified acceptance limits of -0.5 to 0.5 g/dL.
  - The LS mean for the difference between the “Epoetin Hospira” group and the US-licensed Epogen group in weekly epoetin dose per kg body weight during the last 4 weeks of the Treatment Period was 0.37 U/kg/week, with a 95% CI of -10.40 to 11.13 U/kg/week. This CI was contained within the pre-specified acceptance limits of -45 to 45 U/kg/week.
- Results of sensitivity analyses performed on different populations (PP, FAS, m FAS, and RET, ITT-AE, ITT- ≥ 4 weeks population) showed that the difference between two

treatment arms, for mean Hb and mean dose, and its 95% CI are within the equivalence limits.

- The LS means of the difference in mean weekly Hb during the last 4 weeks of the Treatment Period for all these different population ranged from - 0.13 to - 0.10 g/dL. These 95% CIs were within the acceptance limits of -0.5 and 0.5 g/dL.
- For these same populations, the LS means of the difference in weekly epoetin dose by body weight during the last 4 weeks of the Treatment Period ranged from - 6.48 to 0.57 U/kg/week. These 95% CIs were within the acceptance limits of -45 to 45 U/kg/week.

## 6.1 Indication

The Applicant proposed indications are the same as those of the US-licensed Epogen/Procrit:

- For the treatment of anemia due to Chronic Kidney Disease (CKD), including patients on dialysis and not on dialysis to decrease the need for red blood cell (RBC) transfusion
- For the treatment of anemia due to zidovudine administered at < 4200 mg/week in HIV-infected patients with endogenous serum erythropoietin levels of < 500 mUnits/mL
- For the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy
- To reduce the need for allogeneic RBC transfusions among patients with perioperative hemoglobin > 10 to < 13 g/dL who are at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery.

### 6.1.1 Methods

The comparison of “Epoetin Hospira” with US-licensed Epogen with regard to clinical efficacy endpoints for this indication was based on Study EPOE-10-13 and Study EPOE-10-01.

### 6.1.2 Demographics

#### 6.1.2.1 Study EPOE-10-13

The gender distributions were comparable between the two groups. Female patients constituted 48% of patients of “Epoetin Hospira” group and 52% of the US-licensed Epogen group. The majority of patients were white of non-Hispanic race. The median age was 59.5 years in “Epoetin Hospira” arm and 58.5 years in the US-licensed Epogen arm. Diabetes and hypertension were the main cause for CKD in both arms. The median baseline hemoglobin was similar between the two groups.

Table 5: Patients Demographics and Baseline Characteristics, Study EPOE-10-13 (Maintenance Period)

|                                                                                      | “Epoetin Hospira”<br>(N = 122) | US-licensed<br>Epogen<br>(N = 122) |
|--------------------------------------------------------------------------------------|--------------------------------|------------------------------------|
| Sex, n (%)                                                                           |                                |                                    |
| Female                                                                               | 59 (48)                        | 67 (55)                            |
| Male                                                                                 | 63 (52)                        | 55 (45)                            |
| Race, n (%)                                                                          |                                |                                    |
| White                                                                                | 69 (57)                        | 58 (48)                            |
| Black or African-American                                                            | 48 (39)                        | 60 (49)                            |
| Other                                                                                | 5 (4)                          | 4 (3)                              |
| Ethnicity [n (%)]                                                                    |                                |                                    |
| Hispanic or Latino                                                                   | 34 (28)                        | 31 (25)                            |
| Not Hispanic or Latino                                                               | 88 (72)                        | 91 (75)                            |
| Age (years)                                                                          |                                |                                    |
| Median (Min, Max)                                                                    | 59.5 (25, 80)                  | 56.5 (24, 79)                      |
| Primary Cause of Chronic Kidney Disease, n (%)                                       |                                |                                    |
| Diabetes                                                                             | 56 (45)                        | 41 (34)                            |
| Hypertension                                                                         | 43 (35)                        | 58 (48)                            |
| Nephropathies                                                                        | 13 (11)                        | 16 (13)                            |
| Median Baseline Hemoglobin (Min, Max) (g/dL)                                         | 10.3 (8.2, 12.8)               | 10.4 (7.4, 12.1)                   |
| Median Time from First Diagnosis of Chronic Kidney Disease to Randomization (months) | 57.5 (3, 351)                  | 63.5 (-1.0, 335)                   |
| Median Baseline Weekly Dose by Body Weight (U/kg/week)                               | 56.8 (3.2, 645)                | 53.0 (4.9, 383)                    |
| Medical History of Hypertension at Baseline, n (%)                                   | 116 (95)                       | 118 (97)                           |

Source: BLA 125545 submission, Module 5.3.5.1, Table 10-13. P. 92-97.

#### 6.1.2.2 Study EPOE-10-01

There were more male patients enrolled in the US-licensed Epogen group 57% than that in the “Epoetin Hospira” group 52%. The two groups were balanced for race and ethnicity. The median age was 57 (21, 78) years for “Epoetin Hospira” group compared to 58 (25, 80) years in the US-licensed Epogen group. Diabetes and hypertension were the primary cause of CKD in both treatment groups. The median hemoglobin at baseline was similar between the two groups. The majority of patients > 95% had hypertension at baseline with similar incidence between the two groups.

Table 6: Patients Demographics and Baseline Characteristics, Study EPOE-10-01

|                                                                                      | “Epoetin Hospira”<br>(N = 301) | US-licensed<br>Epogen<br>(N = 304) |
|--------------------------------------------------------------------------------------|--------------------------------|------------------------------------|
| Sex, n (%)                                                                           |                                |                                    |
| Female                                                                               | 145 (48)                       | 129 (42)                           |
| Male                                                                                 | 156 (52)                       | 175 (58)                           |
| Race, n (%)                                                                          |                                |                                    |
| White                                                                                | 141 (47)                       | 150 (49)                           |
| Black or African-American                                                            | 146 (49)                       | 125 (41)                           |
| Other                                                                                | 14 (4)                         | 29 (10)                            |
| Ethnicity [n (%)]                                                                    |                                |                                    |
| Hispanic or Latino                                                                   | 94 (31)                        | 99 (33)                            |
| Not Hispanic or Latino                                                               | 207 (69)                       | 204 (67)                           |
| Age (years)                                                                          |                                |                                    |
| Median (Min, Max)                                                                    | 57 (21, 78)                    | 58 (25, 80)                        |
| Primary Cause of Chronic Kidney Disease, n (%)                                       |                                |                                    |
| Diabetes                                                                             | 145 (47)                       | 151 (49)                           |
| Hypertension                                                                         | 105 (34)                       | 85 (28)                            |
| Nephropathies                                                                        | 36 (12)                        | 44 (14)                            |
| Others                                                                               | 15 (7)                         | 24 (10)                            |
| Median Baseline Hemoglobin (Min, Max) (g/dL)                                         | 10.4 (8.3, 13.6)               | 10.5 (8.6, 12.6)                   |
| Median Time from First Diagnosis of Chronic Kidney Disease to Randomization (months) | 48.5 (4, 434)                  | 48.0 (4, 514)                      |
| Median Baseline Weekly Dose by Body Weight (U/kg/week)                               | 74 (2.6, 583)                  | 76.7 (1.3, 676)                    |
| Medical History of Hypertension at Baseline, n (%)                                   | 295 (96)                       | 298 (97)                           |

Source: BLA 125545 submission, Module 5.3.5.1, Tables 8-10. P. 80-4.

### 6.1.3 Subject Disposition

#### 6.1.3.1 Study EPOE-10-13

A total of 556 subjects were enrolled in this study of which 320 subjects were randomized into the Titration Period, 160 subjects to “Epoetin Hospira” and 160 subjects to the US-licensed Epogen. A total of 246 subjects constituting the ITT Population were randomized into the Maintenance Period, 124 subjects to “Epoetin Hospira” and 122 subjects to the US-licensed Epogen.

Of the 124 subjects randomized to “Epoetin Hospira” in the Maintenance Period, one subject received no treatment in the Maintenance Period and three subjects were actually treated with the US-licensed Epogen in the Maintenance Period and received the US-licensed Epogen throughout the entire Maintenance Period.

Of the 122 subjects randomized to the US-licensed Epogen in the Maintenance Period, one subject received no treatment in the Maintenance Period, and two subjects were actually treated with “Epoetin Hospira” in the Maintenance Period and received “Epoetin Hospira” throughout the entire Maintenance Period.

The FAS Population was a subset of the ITT Population which had both Hb and dose data in Weeks 13-16 of the Maintenance Period (though dosing may have been held during the last week) and had not discontinued study drug during Weeks 13-16. For the FAS Population, 71 subjects (57.3%) were in the “Epoetin Hospira” group and 78 subjects (63.9%) were in the US-licensed Epogen group.

The PP Population was a subset of the ITT Population which had at least 4 weeks of treatment with study drug in the Maintenance Period, at least 4 weeks of Hb data and study drug administration data collected while on study drug during the Maintenance Period. In addition, patients should not have had no important protocol deviations, no use of non-study drug ESAs during the last 4 weeks of study drug administration, and had received no red blood cells or whole blood transfusions during study conduct. For the PP Population, 86 subjects (69.4%) were in the “Epoetin Hospira” group and 92 subjects (75.4%) were in the US-licensed Epogen group.

Table 7 summarizes the study population in the study EPOE-10-013.

Table 7: Subject Populations in Maintenance Period (Study EPOE-10-013)

|                                                        | “Epoetin Hospira”<br>(N = 124) | US-licensed Epogen<br>(N = 122) |
|--------------------------------------------------------|--------------------------------|---------------------------------|
| Intent-to-Treat (ITT) <sup>a</sup> , n (%)             | 124 (100)                      | 122 (100)                       |
| Full Analysis Set (FAS) <sup>b</sup> , n (%)           | 71 (57)                        | 78 (64)                         |
| Modified Full Analysis Set (mFAS) <sup>c</sup> , n (%) | 122 (98)                       | 118 (97)                        |
| Safety Population <sup>d</sup> , n (%)                 | 122 (98)                       | 122 (100)                       |
| Modified Safety Population <sup>e</sup> , n (%)        | 108 (87)                       | 102 (84)                        |
| Per Protocol (PP) Population <sup>f</sup> , n (%)      | 86 (69)                        | 92 (75)                         |

a The ITT Population consists of all subjects randomized into the Maintenance Period.

b The FAS Population consists of all subjects randomized to study drug in the Maintenance Period who received study drug treatment during the Maintenance Period and had both Hb and dose data in Weeks 13-16 of treatment in the Maintenance Period and who did not discontinue study drug during Weeks 13-16.

c The mFAS Population consists of all randomized to study drug in the Maintenance Period who received at least 1 dose of study drug treatment during the Maintenance Period and who had both Hb and dose data for at least the same 2 consecutive weeks of treatment with study drug in the Maintenance Period.

d The Safety Population consists of all subjects who received at least one dose of study drug.

e The Modified Safety Population consists of all subjects who received at least one dose of study drug and no ESA standard of care during Maintenance Period.

f The PP Population consists of all ITT subjects who did not have important protocol violations that could affect efficacy.

Of the 124 subjects randomized in the Maintenance Period to receive “Epoetin Hospira”, 74 (59.7%) subjects had not been treated in the Titration Period, and 26 (21.0%) subjects and 24 (19.4%) subjects had been treated with “Epoetin Hospira” and the US-licensed Epogen, respectively, in the Titration Period. Of the 122 subjects randomized in the Maintenance Period to receive the US-licensed Epogen, 76 (62.3%) subjects had not been treated in the Titration Period, and 20 (16.4%) subjects and 26 subjects (21.3) had been treated with “Epoetin Hospira” and the US-licensed Epogen, respectively, in the Titration Period.

Subject disposition in study EPOE-10-13 is summarized Table 8.

Table 8: Subject Disposition (Study EPOE-10-13)

|                                                     | “Epoetin Hospira”<br>N = 124 | US-licensed Epogen<br>N = 122 |
|-----------------------------------------------------|------------------------------|-------------------------------|
| Subjects Received Wrong Treatment Assignment, n (%) | 4 (3.2)                      | 3 (2.5)                       |
| Never treated in Treatment Period, n (%)            | 1 (0.8)                      | 1 (0.8)                       |
| Completed on Study Drug, n (%)                      | 100 (80.6)                   | 99 (80.9)                     |
| Discontinued during Maintenance Period, n (%)       | 8 (6.5)                      | 7 (5.7)                       |
| Discontinued during Follow-Up, n (%)                | 10 (8.1)                     | 10 (8.2)                      |
| Reason for Discontinuation                          |                              |                               |
| Withdrawal Of Consent                               | 3 (2.4)                      | 6 (4.9)                       |
| Adverse Event                                       | 3 (2.4)                      | 2 (1.6)                       |
| Lost To Follow-Up                                   | 0                            | 2 (1.6)                       |
| Physician Decision                                  | 1 (0.8)                      | 2 (1.6)                       |
| Did Not Meet Criteria For Maintenance Period        | 0                            | 1 (0.8)                       |
| Other                                               | 11 (8.9)                     | 4 (3.3)                       |

Source: BLA 125545 submission, Module 5.3.5.1, Tables 9, P. 86.

#### 6.1.3.2 Study EPOE-10-01

A total of 1017 subjects were enrolled in this study. Six hundred twelve subjects were randomized in 1:1 to ratio into “Epoetin Hospira” or the US-licensed Epogen. Three hundred six subjects were randomized to “Epoetin Hospira” and 306 subjects were randomized to the US-licensed Epogen.

Of the 306 subjects randomized to “Epoetin Hospira”, five subjects were never treated, one subject was treated with the US-licensed Epogen and received the US-licensed Epogen throughout the entire Treatment Period (i.e., never received “Epoetin Hospira”); and one subject was administered non-study drug SoC ESA during Week 1 and then had study drug dose held for the remainder of the study due to increased Hb, so never received study drug.

Of the 306 subjects randomized to the US-licensed Epogen, one subject was never treated and two subjects were treated with “Epoetin Hospira” and received “Epoetin Hospira” throughout the entire Treatment Period.

Table 9 summarizes the study population in the study EPOE-10-01.

Table 9: Subject Populations (study EPOE-10-01)

|                                                        | “Epoetin Hospira”<br>(N = 306) | US-licensed Epogen<br>(N = 306) |
|--------------------------------------------------------|--------------------------------|---------------------------------|
| Intent-to-Treat (ITT) <sup>a</sup> , n (%)             | 306 (100)                      | 306 (100)                       |
| Full Analysis Set (FAS) <sup>b</sup> , n (%)           | 161 (53)                       | 153 (50)                        |
| Modified Full Analysis Set (mFAS) <sup>c</sup> , n (%) | 295 (96)                       | 300 (98)                        |
| Safety Population <sup>d</sup> , n (%)                 | 301 (98)                       | 304 (99)                        |
| Modified Safety Population <sup>e</sup> , n (%)        | 233 (76)                       | 231 (76)                        |
| Per Protocol (PP) <sup>f</sup> , n (%)                 | 204 (67)                       | 192 (63)                        |

a The ITT Population consists of all subjects randomized into the Treatment Period.

b The FAS Population consists of all randomized subjects who started therapy and had both Hb and dose data in Weeks 21-24 (dose may have been held during the last week) and did not discontinue study drug during Weeks 21-24.

c The mFAS Population consists of all randomized subjects who had both Hb and dose data for at least 2 consecutive weeks of treatment with study drug.

d The Safety Population consists of all subjects who received at least one dose of study drug.

e The Modified Safety Population consists of all subjects who received at least one dose of study drug and no ESA standard of care during Treatment Period.

f The PP Population consists of all ITT subjects who did not have important protocol violations that could affect efficacy.

For the ITT Population, 300 subjects (98.0%) in the “Epoetin Hospira” group and 305 subjects (99.7%) in the US-licensed Epogen group received treatment. A comparable percentage in each group (approximately 70%) completed the Treatment Period Week 24 on study drug. Forty-six subjects (15.0%) in the “Epoetin Hospira” group and 54 (17.6%) subjects in the US-licensed Epogen group discontinued study drug but remained in the study. The majority of subjects (76.5%) in each group never received non-study drug SoC ESA. Fifty-four (17.6%) subjects in the “Epoetin Hospira” group and 47(15.4%) subjects in the US-licensed Epogen group discontinued the study, 8 (2.6%) subjects in each group discontinued the study due to an AE.

Table 10 summarizes the subject disposition in the study EPOE-10-01.

Table 10: Subject Disposition (study EPOE-10-01)

|                                                | “Epoetin Hospira” | US-licensed Epogen |
|------------------------------------------------|-------------------|--------------------|
| Subjects Received Wrong or no Treatment, n (%) | 6 (2)             | 3 (1)              |
| Completed on Study Drug, n (%)                 | 214 (70)          | 213 (70)           |
| Discontinued Study Drug, n (%)                 | 54 (18)           | 47 (15)            |
| Reason for Discontinuation                     |                   |                    |
| Withdrawal Of Consent                          | 4 (1)             | 7 (2)              |
| Adverse Event                                  | 8 (3)             | 8 (3)              |
| Lost To Follow-Up                              | 4 (1)             | 2 (1)              |
| Physician Decision                             | 1 (<1)            | 4 (1)              |
| Randomization Error                            | 3 (1)             | 1 (<1)             |
| Other                                          | 34 (11)           | 25 (8)             |

Source: BLA 125545 submission, Module 5.3.5.1, Table 7, P. 76.

#### 6.1.4 Analysis of Primary Endpoint(s)

##### 6.1.4.1 Study EPOE-10-13

The co-primary efficacy endpoints of differences between treatments (“Epoetin Hospira” and US-licensed Epogen) in mean weekly Hb levels and in mean weekly doses per kg body weight were calculated from Hb levels and dose data collected in the last 4 weeks of the Maintenance Period with each study drug.

The analysis for the ITT Population for mean weekly Hb levels showed that the least square (LS) mean for the difference between the “Epoetin Hospira” group and the US-licensed Epogen group in weekly Hb during the last 4 weeks of the Maintenance Period was 0.04 g/dL, with a 95% CI of -0.17 to 0.24 g/dL. This result of 95% CI is within the pre-specified acceptance limits of -0.5 to 0.5 g/dL.

Table 11: Primary Efficacy Endpoint – Mean Weekly Hemoglobin – EPOE-10-13 (SC)

|                          | <b>“Epoetin Hospira”<br/>(n=124)</b> | <b>US-licensed Epogen<br/>(n=122)</b> | <b>Difference</b>   |
|--------------------------|--------------------------------------|---------------------------------------|---------------------|
| n                        | 124                                  | 122                                   |                     |
| Mean (SD)                | 10.17 (0.821)                        | 10.11 (0.838)                         | 0.06                |
| Median                   | 10.20                                | 10.15                                 |                     |
| Min, Max                 | 8.1, 13.4                            | 8.1, 12.0                             |                     |
| LS Means (SE)            | 10.16 (0.073)                        | 10.12 (0.074)                         | <b>0.04 (0.104)</b> |
| 95% CI for LS Mean Diff. |                                      |                                       | (-0.17, 0.24)       |
| 90% CI for LS Mean Diff. |                                      |                                       | (-0.13, 0.21)       |

The analysis for the ITT Population for the mean dose per kg body weight showed that the LS mean for the difference between the “Epoetin Hospira” group and the US-licensed Epogen group in weekly epoetin dose per kg body weight during the last 4 weeks of the Treatment Period was -2.34 U/kg/week, with a 95% CI of -14.51 to 9.82 U/kg/week. This CI was contained within the pre-specified acceptance limits of -45 to 45 U/kg/week.

Table 12: Primary Efficacy Endpoint – Mean Weekly Dose per kg - EPOE-10-13 (SC)

|                          | <b>“Epoetin Hospira”<br/>(n=124)</b> | <b>US-licensed Epogen<br/>(n=122)</b> | <b>Difference</b>    |
|--------------------------|--------------------------------------|---------------------------------------|----------------------|
| n                        | 124                                  | 122                                   |                      |
| Mean (SD)                | 82.07 (95.517)                       | 79.14 (82.264)                        | 2.93                 |
| Median                   | 52.20                                | 46.65                                 |                      |
| Min, Max                 | 0.0, 611.8                           | 0.0, 399.1                            |                      |
| LS Means (SE)            | 79.57 (4.356)                        | 81.91 (4.373)                         | <b>-2.34 (6.175)</b> |
| 95% CI for LS Mean Diff. |                                      |                                       | (-14.51, 9.82)       |
| 90% CI for LS Mean Diff. |                                      |                                       | (-12.54, 7.85)       |

### Sensitivity Analyses:

Results of sensitivity analyses performed on different populations (PP, FAS, m FAS, and RET, ITT-AE, and ITT-  $\geq 4$  weeks population) showed that the difference between two treatment arms, for mean Hb and mean dose, and its 95%CI are within the equivalence limits. The LS means of the difference in mean weekly Hb during the last 4 weeks of the Maintenance Period for all these different population ranged from 0.00 to 0.13 g/dL. These 95% CIs were within the acceptance limits of -0.5 and 0.5 g/dL. For these same populations, the LS means of the difference in weekly epoetin dose by body weight during the last 4 weeks of the Treatment Period ranged from -2.73 to 1.63 U/kg/week. These 95% CIs were within the acceptance limits of -45 to 45 U/kg/week.

Table 13: Mean Weekly Hb and Mean Weekly Dose by Body Weight during the Last 4 Weeks of the Maintenance Period (Sensitivity Analyses)

| Analysis Population        | Mean Weekly Hemoglobin (g/dL) Level during the Last 4 Weeks of the Maintenance Period |               | Mean Weekly Epoetin Dose (U/kg/Week) during Last 4 Weeks of the Maintenance Period |               |
|----------------------------|---------------------------------------------------------------------------------------|---------------|------------------------------------------------------------------------------------|---------------|
|                            | Estimate of Difference LS Mean (SE)                                                   | 95% CI        | Estimate of Difference LS Mean (SE)                                                | 95% CI        |
| Per Protocol               | 0.00 (0.118)                                                                          | (-0.23, 0.23) | 1.63 (7.15)                                                                        | (-12.5, 15.8) |
| Full Analysis Set          | 0.12 (0.124)                                                                          | (-0.12, 0.37) | -1.26 (8.08)                                                                       | (-17.2, 14.7) |
| Modified Full Analysis Set | 0.07 (0.106)                                                                          | (-0.14, 0.27) | -1.91 (6.28)                                                                       | (-14.3, 10.5) |
| Retained Set               | 0.13 (0.111)                                                                          | (-0.09, 0.35) | -2.38 (6.86)                                                                       | (-15.9, 11.2) |
| ITT - AE                   | 0.04 (0.104)                                                                          | (-0.17, 0.24) | -2.73 (6.18)                                                                       | (-14.9, 9.5)  |
| ITT - $\geq 4$ weeks       | 0.04 (0.104)                                                                          | (-0.17, 0.24) | -2.34 (6.17)                                                                       | (-14.5, 9.8)  |

Source: BLA 125545 submission, Module 5.3.5.1, Table 15, P. 102.

*Reviewer comments: Results of the analysis of the co-primary endpoints of both mean weekly Hb and the mean weekly dose per kg body weight met the pre-specified acceptance limits. There were no clinically meaningful difference between “Epoetin Hospira” and the US-licensed Epogen. Sensitivity analyses support the conclusion no meaningful differences in efficacy between the two treatment groups.*

#### 6.1.4.2 Study EPOE-10-01

The co-primary efficacy endpoints of differences between treatments (“Epoetin Hospira” and US-licensed Epogen) in mean weekly Hb levels and in mean weekly doses per kg body weight were calculated from Hb levels and dose data collected in the last 4 weeks of the Treatment Period with each study drug.

The analysis for the ITT Population, for mean weekly Hb levels showed that the least square (LS) mean for the difference between the “Epoetin Hospira” group and the US-licensed Epogen group in weekly Hb during the last 4 weeks of the Treatment Period was -0.12 g/dL, with a 95% CI of -0.25 to 0.01 g/dL. This result of 95% CI is within the pre-specified acceptance limits of -0.5 to 0.5 g/dL.

Table 14: Primary Efficacy Endpoint – Mean Weekly Hemoglobin - EPOE-10-01 (IV)

|                          | <b>“Epoetin Hospira”<br/>(n=306)</b> | <b>US-licensed Epogen<br/>(n=306)</b> | <b>Difference</b>    |
|--------------------------|--------------------------------------|---------------------------------------|----------------------|
| n                        | 306                                  | 306                                   |                      |
| Mean (SD)                | 10.17 (0.847)                        | 10.28 (0.839)                         | -0.11                |
| Median                   | 10.10                                | 10.30                                 |                      |
| Min, Max                 | 7.6, 12.6                            | 8.1, 13.7                             |                      |
| LS Means (SE)            | 10.17 (0.047)                        | 10.28 (0.047)                         | <b>-0.12 (0.066)</b> |
| 95% CI for LS Mean Diff. |                                      |                                       | (-0.25, 0.01)        |
| 90% CI for LS Mean Diff. |                                      |                                       | (-0.22, -0.01)       |

The analysis for the ITT Population for the mean dose per kg body weight showed that the LS mean for the difference between the “Epoetin Hospira” group and the US-licensed Epogen group in weekly epoetin dose per kg body weight during the last 4 weeks of the Treatment Period was 0.37 U/kg/week, with a 95% CI of -10.40 to 11.13 U/kg/week. This CI was contained within the pre-specified acceptance limits of -45 to 45 U/kg/week.

Table 15: Primary Efficacy Endpoint – Mean Weekly Dose per kg - EPOE-10-01 (IV)

|                          | <b>“Epoetin Hospira”<br/>(n=306)</b> | <b>US-licensed Epogen<br/>(n=306)</b> | <b>Difference</b>   |
|--------------------------|--------------------------------------|---------------------------------------|---------------------|
| n                        | 305                                  | 305                                   |                     |
| Mean (SD)                | 89.61 (99.824)                       | 90.37 (88.492)                        | -0.76               |
| Median                   | 56.20                                | 64.90                                 |                     |
| Min, Max                 | 0.0, 532.7                           | 0.0, 766.9                            |                     |
| LS Means (SE)            | 90.16(3.874)                         | 89.79 (3.880)                         | <b>0.37 (5.483)</b> |
| 95% CI for LS Mean Diff. |                                      |                                       | (-10.40, 11.13)     |
| 90% CI for LS Mean Diff. |                                      |                                       | (-8.67, 9.40)       |

### Sensitivity Analyses:

Results of sensitivity analyses performed on different populations (PP, FAS, m FAS, and RET, ITT-AE, ITT-  $\geq 4$  weeks population) showed that the difference between two treatment arms, for mean Hb and mean dose, and its 95% CI are within the equivalence limits. The LS means of the

difference in mean weekly Hb during the last 4 weeks of the Treatment Period for all these different population ranged from -0.13 to -0.10 g/dL. These 95% CIs were within the acceptance limits of -0.5 and 0.5 g/dL. For these same populations, the LS means of the difference in weekly epoetin dose by body weight during the last 4 weeks of the Treatment Period ranged from - 6.48 to 0.57 U/kg/week. These 95% CIs were within the acceptance limits of -45 to 45 U/kg/week.

Table 16: Mean Weekly Hemoglobin (g/dL) and Mean Weekly Dose by Body Weight (U/kg/week) during the Last 4 Weeks of the Treatment Period (Sensitivity Analysis)

| Analysis Population        | Mean Weekly Hemoglobin (g/dL) Level during Last 4 Weeks of the Treatment Period |               | Mean Weekly Epoetin Dose (U/kg/Week) during Last 4 Weeks of the Treatment Period |               |
|----------------------------|---------------------------------------------------------------------------------|---------------|----------------------------------------------------------------------------------|---------------|
|                            | Estimate of Difference LS Mean (SE)                                             | 95% CI        | Estimate of Difference LS Mean (SE)                                              | 95% CI        |
| Per Protocol               | -0.10 (0.08)                                                                    | (-0.27, 0.06) | -2.41 (6.79)                                                                     | (-15.8, 10.9) |
| Full Analysis Set          | -0.12 (0.08)                                                                    | (-0.29, 0.04) | -6.48 (7.73)                                                                     | (-21.7, 8.7)  |
| Modified Full Analysis Set | -0.13 (0.07)                                                                    | (-0.26, 0.01) | -0.17 (5.60)                                                                     | (-11.2, 10.8) |
| Retained Set               | -0.11 (0.07)                                                                    | (-0.24, 0.03) | -5.37 (6.88)                                                                     | (-18.9, 8.1)  |
| ITT - AE                   | -0.12 (0.07)                                                                    | (-0.25, 0.01) | -0.57 (5.48)                                                                     | (-10.2, 11.4) |
| ITT - $\geq 4$ weeks       | -0.12 (0.07)                                                                    | (-0.25, 0.01) | -0.37 (5.48)                                                                     | (-10.4, 11.1) |

Source: BLA 125545 submission, Module 5.3.5.1, Table 13, P. 89.

*Reviewer comments: Results of the analysis of the co-primary endpoints of both mean weekly Hb and the mean weekly dose per kg body weight met the pre-specified acceptance limit. Sensitivity analyses also show that the co-primary endpoints of both mean weekly Hb and the mean weekly dose per kg body weight met the pre-specified acceptance limit.*

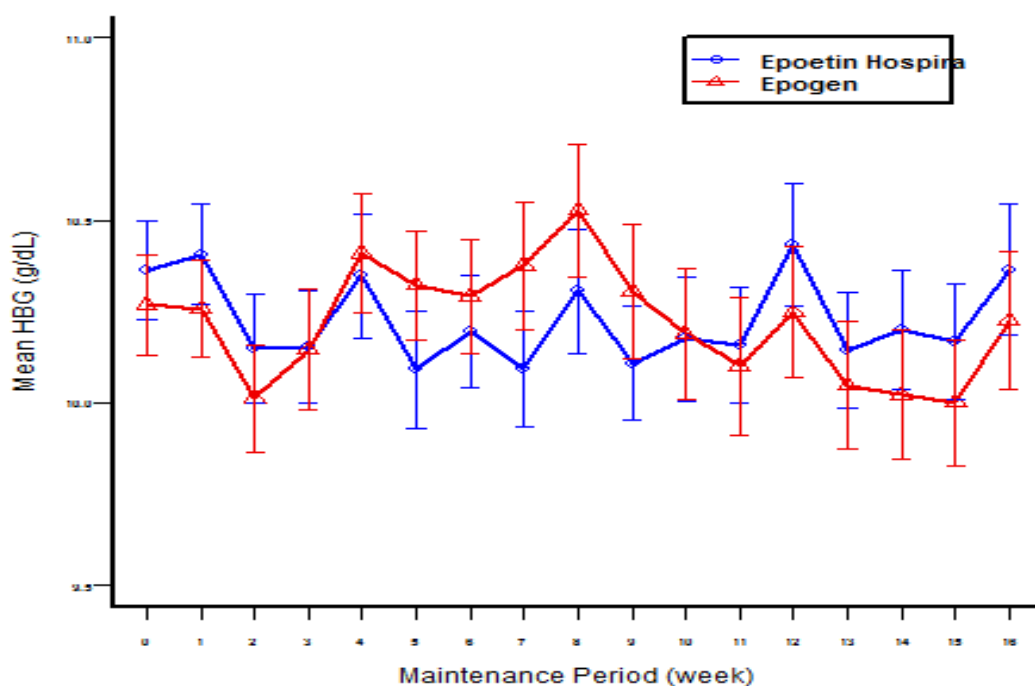
## 6.1.5 Analysis of Secondary Endpoints(s)

### 6.1.5.1 Study EPOE-10-13

#### Mean Weekly Hemoglobin Levels for Each 4-Week Interval during Maintenance Period

The secondary endpoint of mean weekly Hb level for each 4-week interval during the 16-week Maintenance Period for the ITT Population was ranged between 10.18 and 10.27 g/dL in the “Epoetin Hospira” group and 10.08 and 10.36 g/dL in the US-licensed Epogen group. The difference between the two treatment groups in the mean weekly Hb for each 4-week interval ranged from -0.18 to 0.12 g/dL.

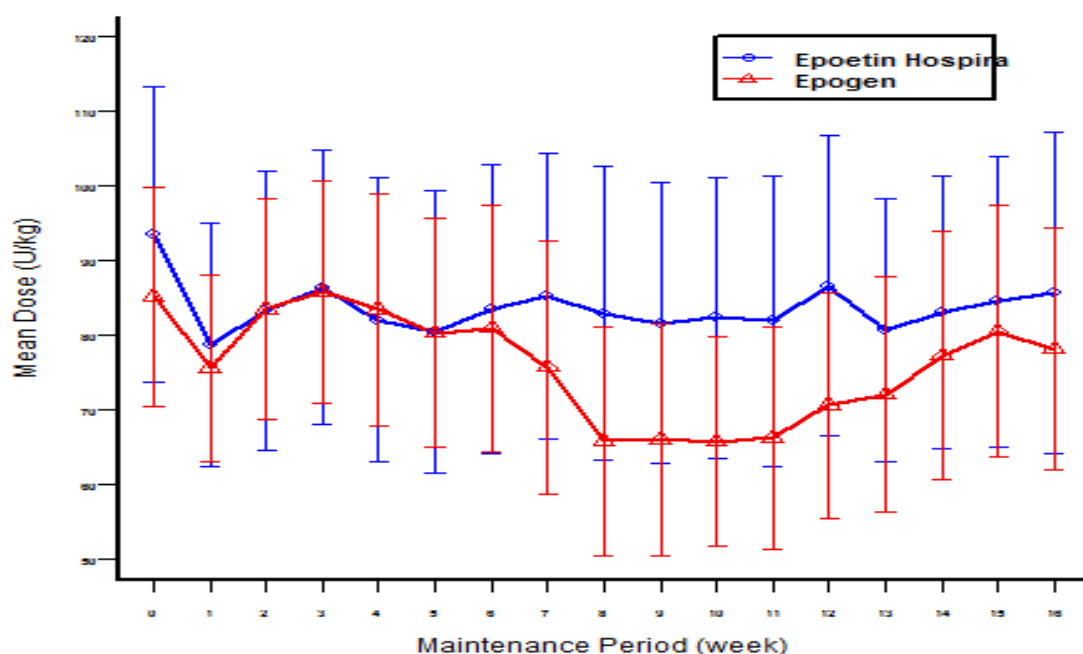
Figure 4: Mean Weekly Hb during the Maintenance Period for EPOE-10-13 (SC)



#### Mean Weekly Epoetin Dosage by Body Weight for Each 4-Week Interval during Maintenance Period

The secondary endpoint of mean weekly dose per kg for each 4-week interval during the 16-week Maintenance Period for the ITT Population was ranged between 81.81 and 84.43 U/kg/week in the “Epoetin Hospira” group and 67.66 and 81.03 U/kg/week in the US-licensed Epogen group. The difference between the two treatment groups in the mean weekly dose per kg for each 4 week interval ranged from 0.83 to 14.15 U/kg/week.

Figure 5: Mean Weekly dosage during the Maintenance Period for EPOE-10-13 (SC)



Proportion of Subjects with Weekly Mean Hemoglobin Within and Outside the Target Range at Weeks 8 and 16 of the Maintenance Period

The rates of patients with weekly mean hemoglobin level within the range of 9 – 11 g/dL at week 8 and week 16 were higher in the Eptein Hospira (74% and 80%, respectively) than that in the US-licensed Epogen group (61% and 74%, respectively). The rate of patients with weekly mean hemoglobin level < 9 g/dL at week 8 was similar between the two groups at 8%. However the rate of patients with weekly mean hemoglobin <9 g/dL at week 16 was lower in the Eptein Hospira (4%) than that in the US-licensed Epogen group (9%).

The proportion of subjects with mean weekly Hb level within and outside the target range of 9.0 to 11.0 g/dL at Weeks 8 and 16 of the Maintenance Period for the ITT Population is summarized in Table 17.

Table 17: Proportion of Subjects with Weekly Mean Hemoglobin Level Within and Outside the Target Range (9.0 to 11.0 g/dL) at Weeks 8 and 16 of the Maintenance Period (ITT Population)

| Week                | Number of Observations <sup>a</sup> | “Epoetin Hospira” (N = 124) | US-licensed Epogen (N = 122) | p-value <sup>b</sup> |
|---------------------|-------------------------------------|-----------------------------|------------------------------|----------------------|
| Week 8              | 223                                 |                             |                              |                      |
| Within Target Range |                                     | 83 (73.5)                   | 67 (60.9)                    | 0.0632               |
| Out of Target Range |                                     | 30 (26.5)                   | 43 (39.1)                    |                      |
| Hb < 9.0 g/dL       |                                     | 9 (8.0)                     | 9 (8.2)                      |                      |

|                     |     |           |           |        |
|---------------------|-----|-----------|-----------|--------|
| Hb > 11.0 g/dL      |     | 21 (18.6) | 34 (30.9) |        |
| Week 16             | 208 |           |           |        |
| Within Target Range |     | 83 (79.8) | 77 (74.0) | 0.4108 |
| Out of Target Range |     | 21 (20.2) | 27 (26.0) |        |
| Hb < 9.0 g/dL       |     | 4 (3.8)   | 9 (8.7)   |        |
| Hb > 11.0 g/dL      |     | 17 (16.3) | 18 (17.3) |        |

a Number of subjects with a valid Hb value at the given week.

b p-value from a Fisher's Exact Test.

Note: Percentages are calculated using the number of observations within a treatment group at each visit as the denominator.

Source: BLA 125545 submission, Module 5.3.5.1, Table 18, P. 110.

### Incidence of Transfusion During Maintenance Period

During the maintenance period (16 weeks), 10 (4%) patients (5 patients (4%) in each group) received red blood cell transfusion. One patient in each arm received a blood transfusion in the first 4 weeks of maintenance period. In the weeks 5-8 of maintenance period one patients in the US-licensed Epogen group and none from the “Epoetin Hospira” received a blood transfusion. For the weeks 9-12 and weeks 13-16, two patients in each group received blood transfusion in each 4 weeks intervals.

*Reviewer comments: Results of the analyses of the key secondary endpoints in the ITT population revealed:*

- The mean weekly Hb and the mean weekly dose per kg body weight for each 4 weeks interval in 16 weeks of treatment in the maintenance period showed no clinically meaningful difference between the treatment groups.
- There were no statistically significant difference between the treatment groups in proportion of subjects within and outside the target range at Week 8 and Week 16.
- The incidence of red blood cell transfusion was similar between the two groups with no statistical significant difference observed between treatment groups.

### 6.1.5.2 Study EPOE-10-01

#### Mean Weekly Hemoglobin Levels for Each 4-Week Interval during Treatment Period

The secondary endpoint of mean weekly Hb level for each 4-week interval during the 24-week Treatment Period for the ITT Population was ranged between 10.15 and 10.39 g/dL in the “Epoetin Hospira” group and 10.22 and 10.38 g/dL in the US-licensed Epogen group. The difference between the two treatment groups in the mean weekly Hb for each 4-week interval ranged from -0.13 to 0.08 g/dL.

Table 18: Mean Weekly Hemoglobin (g/dL) Every 4 Weeks of Treatment Period (ITT Population)

| Mean Weekly Hemoglobin (g/dL) Level during Each 4 Weeks of the Treatment Period | “Epoetin Hospira” (N = 306) | US-licensed Epogen (N = 306) | Difference (“Epoetin Hospira” – US-licensed Epogen) |
|---------------------------------------------------------------------------------|-----------------------------|------------------------------|-----------------------------------------------------|
| Weeks 1-4, n                                                                    | 302                         | 305                          |                                                     |
| Mean (SD)                                                                       | 10.39 (0.73)                | 10.38 (0.73)                 | 0.01                                                |
| Median (Min, Max)                                                               | 10.4 (8.4, 13.0)            | 10.4 (8.3, 12.5)             |                                                     |
| Weeks 5-8, n                                                                    | 295                         | 296                          |                                                     |
| Mean (SD)                                                                       | 10.35 (0.80)                | 10.27 (0.91)                 | 0.08                                                |
| Median (Min, Max)                                                               | 10.3 (7.9, 13.0)            | 10.4 (6.7, 12.6)             |                                                     |
| Weeks 9-12, n                                                                   | 289                         | 291                          |                                                     |
| Mean (SD)                                                                       | 10.20 (0.74)                | 10.22 (0.90)                 | -0.02                                               |
| Median (Min, Max)                                                               | 10.2 (8.1, 13.3)            | 10.2 (7.7, 12.9)             |                                                     |
| Weeks 13-16, n                                                                  | 282                         | 281                          |                                                     |
| Mean (SD)                                                                       | 10.18 (0.73)                | 10.22 (0.79)                 | -0.04                                               |
| Median (Min, Max)                                                               | 10.2 (7.4, 13.3)            | 10.2 (7.4, 12.7)             |                                                     |
| Weeks 17-20, n                                                                  | 273                         | 274                          |                                                     |
| Mean (SD)                                                                       | 10.15 (0.84)                | 10.26 (0.75)                 | -0.11                                               |
| Median (Min, Max)                                                               | 10.2 (7.4, 13.1)            | 10.2 (8.2, 12.8)             |                                                     |
| Weeks 21-24, n                                                                  | 270                         | 267                          |                                                     |
| Mean (SD)                                                                       | 10.16 (0.86)                | 10.29 (0.84)                 | -0.13                                               |
| Median (Min, Max)                                                               | 10.1 (7.6, 12.6)            | 10.2 (8.1, 13.8)             |                                                     |

Source: BLA 125545 submission, Module 5.3.5.1, Table 14, P. 92.

#### Mean Weekly Epoetin Dosage by Body Weight for Each 4-Week Interval during Treatment Period

The secondary endpoint of mean weekly dose per kg for each 4-week interval during the 24-week Treatment Period for the ITT Population was ranged between approximately 84 and 91 U/kg/week for the “Epoetin Hospira” group, and between approximately 87 and 94 U/kg/week for the US-licensed Epogen group. The difference between the two treatment groups in the mean weekly dose per kg for each 4-week interval ranged from -6.97 to -2.25 U/kg/week.

Proportion of Subjects with Weekly Mean Hemoglobin Within and Outside the Target Range at Weeks 12 and 24 of the Treatment Period

The rates of patients with weekly mean hemoglobin level within the range of 9 – 11 g/dL at week 12 and week 24 were higher in the Epoetin Hospira (81% and 73%, respectively) than that in the US-licensed Epogen group (73% and 71%, respectively).

The proportion of subjects with mean weekly Hb level within and outside the target range of 9.0 to 11.0 g/dL at Weeks 12 and 24 of the Treatment Period for the ITT Population is summarized in Table 19.

Table 19: Proportion of Subjects with Weekly Mean Hemoglobin Level Within and Outside the Target Range (9.0 to 11.0 g/dL) at Weeks 8 and 16 of the Treatment Period (ITT Population)

| Week                | Number of Observations <sup>a</sup> | “Epoetin Hospira” (N = 306) | US-licensed Epogen (N = 306) | p-value <sup>b</sup> |
|---------------------|-------------------------------------|-----------------------------|------------------------------|----------------------|
| Week 12             | 545                                 |                             |                              |                      |
| Within Target Range |                                     | 221 (81.0)                  | 199 (73.2)                   | 0.032                |
| Out of Target Range |                                     | 52 (19.0)                   | 73 (26.8)                    |                      |
| Hb < 9.0 g/dL       |                                     | 14 (5.1)                    | 19 (7.0)                     |                      |
| Hb > 11.0 g/dL      |                                     | 38 (13.9)                   | 54 (19.9)                    |                      |
| Week 24             | 516                                 |                             |                              |                      |
| Within Target Range |                                     | 188 (73.2)                  | 185 (71.4)                   | 0.694                |
| Out of Target Range |                                     | 69 (26.8)                   | 74 (28.6)                    |                      |
| Hb < 9.0 g/dL       |                                     | 14 (5.4)                    | 19 (7.3)                     |                      |
| Hb > 11.0 g/dL      |                                     | 55 (21.4)                   | 55 (21.2)                    |                      |

a Number of subjects with a valid Hb value at the given week.

b p-value from a Fisher’s Exact Test.

Note: Percentages are calculated using the number of observations within a treatment group at each visit as the denominator.

Source: BLA 125545 submission, Module 5.3.5.1, Table 16, P. 98.

Incidence of Transfusion During Treatment Period

During the treatment period (24 weeks), 37 (6%) patients (19 patients in Epoetin Hospira group and 18 in the US-licensed Epogen group) received red blood cell transfusion. There was no statistically significant difference between the two treatment groups.

*Reviewer comments: Results of the analyses of the key secondary endpoints in the ITT population showed:*

- *The mean weekly Hb and the mean weekly dose per kg body weight for each 4-weeks interval during 24 weeks of treatment revealed no clinically meaningful difference between the treatment groups.*

- *There was higher rate of patients within the Hb target range (9-11 g/dL) at Week 12 in the “Epoetin Hospira” than that in the US-licensed Epogen group. The difference was statistically significant.*
- *There was no statistically significant difference between the treatment groups in proportion of patients within and outside the target range at Week 24.*

#### 6.1.6 Other Endpoints

Assessment of rate of rise of hemoglobin on co-primary efficacy endpoint was performed by the Applicant using the ITT population. The results of the analyses of rate of rise of Hb on mean weekly dose by body weight during the treatment period for the ITT Population for SC and IV administration suggested that the dose by body weight was similar between “Epoetin Hospira” and US-licensed Epogen treatment groups when examined by categorical baseline Hb and by rate of change of Hb.

#### 6.1.7 Subpopulations

The Applicant provided subgroup analyses conducted to evaluate the impact of subgroup factors such as sex (female, male), race (White, Black/African American, Other), and age ( $\leq 65$  years or  $>65$  years) on the co-primary efficacy endpoints using the ITT population.

The results of the subgroup analysis showed:

- No effect of sex or age on the co-primary efficacy of mean weekly Hb and mean weekly dose by body weight between the treatment groups for both SC and IV administration.
- No effect of race on the co-primary efficacy of mean weekly Hb and mean weekly dose by body weight between the treatment groups for SC administration. There was no effect of race on the co-primary efficacy of mean weekly dose by body weight between the treatment groups for IV administration. Although there were a statistically significant effect of race on mean weekly Hb for IV administration, the findings were confounded due to small number of subjects in the Other Race category precluded informative analysis for that category.

#### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The dosing regimen recommendation used in clinical studies was the same as those currently approved for the reference product and no dose finding studies were conducted.

#### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Eligible patients who completed Study EPOE-10-13 and Study EPOE-10-01 had the opportunity to enroll in the open-label 48-week LTSS (studies EPOE-10-13 and EPOE-11-04). A total of 78 patients enrolled in EPOE-11-04 (SC) and 118 patients enrolled in EPOE-11-03 (IV). The data from the LTSS was evaluated for the persistence of effect and lack of tolerance to effect.

Results:

For study EPOE-11-04:

The mean weekly dose of “Epoetin Hospira” by body weight for Weeks 1-4 in study EPOE-10-13 was 94.50 (111.9) U/kg/week compared to 86.15 (92.2) U/kg/week in EPOE-1104 study. The mean weekly dose of “Epoetin Hospira” by body weight for Weeks 13-16 in study EPOE-10-13 was 90.67 (106.6) U/kg/week compared to 80.78 (84.9) U/kg/week in EPOE-1104. The mean weekly dose of “Epoetin Hospira” by body weight for the final 4 weeks in study EPOE-10-13 was 86.35 (101.9) U/kg/week compared to 90.16 (114.8) U/kg/week in EPOE-1104 study.

These results show that the mean weekly “Epoetin Hospira” dose by body weight remained within the same ranges for patients who received “Epoetin Hospira” in EPOE-10-13 and then in EPOE-11-04, over a period of up to 64 weeks.

For study EPOE-11-03:

The mean weekly dose of “Epoetin Hospira” by body weight for Weeks 1-4 in study EPOE-10-01 was 87.67 (74.3) U/kg/week compared to 94.51 (93.9) U/kg/week in EPOE-11-03 study. The mean weekly dose of “Epoetin Hospira” by body weight for Weeks 21-24 in study EPOE-10-01 was 73.76 (61.6) U/kg/week compared to 90.18 (71.2) U/kg/week in EPOE-11-03. The mean weekly dose of “Epoetin Hospira” by body weight for the final 4 weeks in study EPOE-10-01 was 73.22 (61.4) U/kg/week compared to 99.09 (95.9) U/kg/week in EPOE-11-03 study.

These results show that the mean weekly “Epoetin Hospira” dose by body weight remained within the same ranges for patients who received “Epoetin Hospira” in EPOE-10-01 and then in EPOE-11-03, over a period of up to 72 weeks.

*Reviewer comments: The results from the LTSS of SC and IV suggested that the effect of “Epoetin Hospira” continue over a period of up to 72 weeks with significant tolerance devolved which consistent with that of the reference drug.*

#### 6.1.10 Additional Efficacy Issues/Analyses

No additional efficacy analyses performed.

## 7 Review of Safety

### Safety Summary

**Disclaimer:** The safety analyses should be re-analyzed based on the issues identified in Section 3, which noted multiple sites that were GCP non-compliant. The results below should be interpreted with caution. As such, conclusions regarding the comparative assessment of safety between the proposed biosimilar and the reference product cannot be made at this time.

**Note: The safety analyses below are based on the safety population that included patients from GCP non-compliant sites.**

A detailed analysis of the safety outcomes for “Epoetin Hospira” was conducted using data from studies EPOE-10-13, EPOE-10-01, EPOE-11-03, and EPOE-11-04. Studies EPOE-10-13 (SC) and EPOE-10-01 (IV) were randomized, double-blind studies conducted in 859 patients (423 “Epoetin Hospira” and 426 US-licensed Epogen) on dialysis and comparing “Epoetin Hospira” to the US-licensed Epogen for the treatment of anemia due to Chronic Kidney Disease (CKD) to decrease the need for red blood cell (RBC) transfusion. Supportive safety data from two open-label long term safety studies EPOE-11-04 (SC) and EPOE-11-03 (IV) conducted in 189 subjects with CKD on HD. These four studies constitute the combined clinical development program were randomized and received treatment with either the US-licensed Epogen or “Epoetin Hospira” administered either IV or SC. The study drug regimen was consistent with the proposed dose-schedule and according to the reference drug label for the treatment of anemia in patients with CKD. The mean duration of study drug exposure was approximately 18 weeks.

Analysis of the safety data for Studies EPOE-10-13 (SC) and EPOE-10-01 (IV) showed:

- Deaths: There were a total of 17 patients (2%), 9 patients (2%) in the “Epoetin Hospira” group and 8 patients (2%) in the US-licensed Epogen group, in the combined randomized treatment groups experienced a TEAE resulting in death. For the combined LTSS, 18 patients (10%) experienced a TEAE resulting in death.
- Serious Adverse Events (SAEs): The rate of patients who experienced at least one SAE in the randomized studies was 24 % in the “Epoetin Hospira” group compared to 27% in the US-licensed Epogen group. The most common SAEs in the both groups were pneumonia, non-cardiac chest pain, dyspnea, cellulitis, fluid overload, and vascular access thrombosis, with similar incidences between the two treatment groups. In the combined LTSS, 38% of subjects reported at least one SAE. The most common SAEs were pneumonia, cardiorespiratory arrest, hyperkalemia, and cardiac failure congestive.
- Adverse Events of Special Interest: In general the rates of adverse events of Special Interest in the randomized studies were similar between the two treatment groups.
  - Hypertension was reported in 6% of patients in the “Epoetin Hospira” and 5% in the Epogen group reported.
  - The rates of myocardial infarction and the cerebrovascular events were similar between the treatments groups and reported in 1% of patients.
  - Seizure reported in 1 patient in the US-licensed Epogen with no event in the “Epoetin Hospira”.
  - The rate of thromboembolic events was 8% in the “Epoetin Hospira” compared to 6% in the US-licensed Epogen group. Vascular access thrombosis was the most common thromboembolic event with incidence of 6% in the US-licensed Epogen group compared to 4% in the US-licensed Epogen group.
  - Allergic reaction was reported in 2% of patients in the “Epoetin Hospira” compared to 1% in the US-licensed Epogen group.

- There were no reported events of pure red cell aplasia (PRCA) reported in the clinical studies. However, a case report of pure red cell aplasia (PRCA) reported in a patient who was enrolled in a long-term, non-interventional, observational post approval study (PASCO II) with European (EU)-approved Retacrit.
- The rates of treatment-emergent adverse event (TEAE) were approximately 75% of patients in the randomized studies (10-13 and 10-01) and approximately 80% of patients in the 48-week open-label LTSS studies.
- Adverse Events Leading to Study Drug Discontinuation: The incidences of TEAEs leading to study drug discontinuation were comparable between the “Epoetin Hospira” (3%) and US-licensed Epogen (4%) treatment groups. In the combined LTSS, 9% of patients experienced an adverse event (AE) leading to study drug discontinuation.

In summary, safety outcomes were similar for patients treated with either “Epoetin Hospira” or US-licensed Epogen.

## 7.1 Methods

### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The main clinical review of safety endpoints for this BLA was based on the safety from two comparative Studies EPOE-10-13 (SC) and EPOE-10-01 (IV) conducted in patients with CKD on HD where a US-licensed Epogen was used as the control. In addition, two open-label long term safety studies EPOE-11-04 (SC) and EPOE-11-03 (IV) conducted in patients with CKD on HD were used for supporting analyses.

### 7.1.2 Categorization of Adverse Events

Safety assessments from clinical studies included adverse events, laboratory test results, ECG findings, and physical examination findings. The AEs were categorized as follow:

- Treatment-emergent Adverse Events (TEAEs) defined as any new event where the onset was after the first dose of study drug or an existing condition or event that worsened in either intensity or frequency. TEAEs were categorized by severity (mild, moderate, or severity) and by its relationship to study drug (definitely related, probably related, possibly related, probably not related, not related).
- Serious Adverse Event: Any event within 24 hours of occurrences resulted in death; was life threatening; required in-patient hospitalization or prolongation of existing hospitalization; resulted in persistent or significant disability/incapacity or a congenital anomaly/birth defect; or was considered an important medical event (i.e., jeopardized the health of the subject).
- Adverse Events of Special Interest: Adverse Events of Special Interest have been identified based on the safety information of the US-licensed Epogen reference product, as described in the US-licensed Epogen Package Insert.

### 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Data across clinical studies were pooled based on the route of administration of the study drug (IV, SC). Data from patients in EPOE-10-13 and EPOE-11-04 were integrated to create an SC administration group and patients in EPOE-10-01 and EPOE-11-03 were integrated to create an IV administration group. Data were also pooled across route of administration from subjects who participated in the Maintenance Period of EPOE-10-13 and the Treatment Period of EPOE-10-01 to create a combined randomized US-licensed Epogen treatment group and a combined randomized “Epoetin Hospira” treatment group

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

#### 7.2.1.1 Study EPOE-10-13 Drug Exposure:

For the safety population in study 10-13, during the Maintenance Period, the mean duration of exposure was approximately 14 weeks in each group. The median duration of study drug exposure for both treatment groups was approximately 15 weeks. The mean weekly dose of epoetin was 7500 U/week for “Epoetin Hospira” and 6792 U/week for the US-licensed Epogen. The median dose was 4699 U/week for “Epoetin Hospira” and 4686 U/week for the US-licensed Epogen. The mean weekly dose per kg body weight of epoetin over the 16-week Maintenance Period was  $82 \pm 93.8$  U/kg/week for “Epoetin Hospira” and  $75 \pm 72.2$  U/kg/week for the US-licensed Epogen.

Table 20: Drug Exposure during the Maintenance Period (Safety Population, EPOE-10-13 Study)

|                                                     | <b>“Epoetin Hospira”<br/>(N = 122)</b> | <b>US-licensed<br/>Epogen<br/>(N = 122)</b> |
|-----------------------------------------------------|----------------------------------------|---------------------------------------------|
| Mean Duration of Exposure (SD), Weeks               | 13.9 (3.4)                             | 13.7 (3.6)                                  |
| Median Duration of Exposure (Min, Max), Weeks       | 15.1 (0.1, 17.1)                       | 15.1 (0.1, 15.9)                            |
| Mean Weekly Dose Exposure (SD), U/Week              | 7500 (9603)                            | 6792 (6108)                                 |
| Median Weekly Dose Exposure (Min, Max), U/Week      | 4699 (143, 57325)                      | 4686 (517, 30000)                           |
| Mean Weekly Dose per kg body weight (SD), U/kg/Week | 82 (93.8)                              | 75 (72.2)                                   |

#### 7.2.1.2 Study EPOE-10-01 Drug Exposure:

For the Safety Population, the mean duration of study drug exposure was similar between the two groups, approximately 20 weeks. The median duration of study drug exposure for both treatment groups was approximately 23 weeks. The mean weekly study drug dose was 7621 U/week for “Epoetin Hospira” and 8296 U/week for the US-licensed Epogen. The median dose was 5042 U/week for “Epoetin Hospira” and 6024 U/week for the US-licensed Epogen. The mean weekly drug dose exposure per kg body weight during the overall Treatment Period was  $88 \pm 86.4$  U/kg/week for “Epoetin Hospira” group and  $91 \pm 80.6$  U/kg/week for the US-licensed Epogen group.

Table 21: Drug Exposure during the Treatment Period (Safety Population, EPOE-10-01 Study)

|                                                     | <b>“Epoetin Hospira”<br/>(N = 301)</b> | <b>US-licensed<br/>Epogen<br/>(N = 304)</b> |
|-----------------------------------------------------|----------------------------------------|---------------------------------------------|
| Mean Duration of Exposure (SD), Weeks               | 19.9 (6.5)                             | 19.5 (7.1)                                  |
| Median Duration of Exposure (Min, Max), Weeks       | 23.1 (0.1, 24.9)                       | 23.1 (0.1, 25.4)                            |
| Mean Weekly Dose Exposure (SD), U/Week              | 7621 (7471)                            | 8296 (8856)                                 |
| Median Weekly Dose Exposure (Min, Max), U/Week      | 5042 (209, 47473)                      | 6024 (30, 98000)                            |
| Mean Weekly Dose per kg body weight (SD), U/kg/Week | 88 (86.4)                              | 91 (80.6)                                   |

#### 7.2.2 Explorations for Dose Response

In Study EPOE-10-13 (SC), weekly dose by weight of “Epoetin Hospira” and US-licensed Epogen, and weekly Hb level were evaluated in this study. Per the current US-licensed Epogen Package Insert, epoetin is administered to patients with CKD on hemodialysis at a starting dose of 50-100 U/kg TIW with dosing to be individualized to maintain Hb between 9.0-and 11.0 g/dL.

#### 7.2.3 Special Animal and/or In Vitro Testing

N/A

#### 7.2.4 Routine Clinical Testing

The schedule of safety evaluations is described in section 5.3 above. The frequency of monitoring dictated by the protocols was considered adequate to assess the safety profile.

### 7.2.5 Metabolic, Clearance, and Interaction Workup

Relevant results from the pharmacology studies are discussed in Section 4.4. There were no findings in the pharmacology studies that warranted additional clinical safety testing.

### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Adverse Events of Special Interest were informed based on the known safety profile of ESAs drug class. The safety evaluation of “Epoetin Hospira” was included AEs of Special Interest (myocardial infarction, cerebrovascular events, thromboembolic events, hypertension, seizures, PRCA, potential allergic reactions).

## 7.3 Major Safety Results

### 7.3.1 Deaths

#### 7.3.1.1 Study EPOE-10-13

There were a total of ten patients died during treatment, 4 patients during titration period and 6 patients during maintenance period.

Form the 4 patients died during titration period 3 in the “Epoetin Hospira” group and one in the US-licensed Epogen group. The three deaths in subjects receiving “Epoetin Hospira” were the result of cardiac arrest, multifactorial functional decline, and sepsis (1 subject each). The one death which occurred in a subject receiving the US-licensed Epogen was the result of acute myocardial infarction.

From the 5 patients died during maintenance period 3 patients received “Epoetin Hospira” and 2 received the US-licensed Epogen. The three deaths in subjects receiving “Epoetin Hospira” were the result of cardiac arrest, gastrointestinal bleed, and azotemia (1 subject each). The two deaths in subjects receiving the US-licensed Epogen were the result of arrhythmia and aortic stenosis (1 subject each).

A total of 8 patients the deaths were reported by the investigators as not related to the study drug and 2 deaths occurred in the maintenance period and both received the US-licensed Epogen were reported as probably not related to the study drug.

*Reviewer comments: Almost half of the deaths in this study were as result of cardiovascular disease which could be due to co-morbidities of CKD patients on hemodialysis.*

#### 7.3.1.2 Study EPOE-10-01

There were a total of eleven deaths during the study, five subjects (1.7%) in the “Epoetin Hospira” group and six subjects (2.0%) in the US-licensed Epogen group. The five deaths in subjects receiving “Epoetin Hospira” were the result of azotemia (2 subjects), and sudden death of unknown cause, sepsis, and metabolic encephalopathy (1 subject each). The six deaths in

subjects receiving the US-licensed Epogen were the result of cardiac arrest (3 subjects), cardio-respiratory arrest (2 subjects), and metastatic lung cancer (1 subject).

*Reviewer comments: The number of deaths was similar between the two groups.*

## 7.3.2 Nonfatal Serious Adverse Events

### 7.3.2.1 Study EPOE-10-13

For the Safety Population, 23 (19%) patients in the “Epoetin Hospira” group and 33 (27.0%) patients in the US-licensed Epogen group experienced an SAE during the Maintenance Period. Infections, gastrointestinal disorders and vascular access thrombosis were the most common.

Table 22 summarizes the serious AEs reported during maintenance period in the study EPOE-10-13.

Table 22: Treatment-Emergent Serious Adverse Events during the Maintenance Period (Safety Population)

|                                                       | <b>“Epoetin Hospira”<br/>(N = 122)</b> | <b>US-licensed Epogen<br/>(N = 122)</b> |
|-------------------------------------------------------|----------------------------------------|-----------------------------------------|
| Treatment-Emergent Serious Adverse Events, n (%)      | 23 (19)                                | 33 (27)                                 |
| Infections and Infestations, n (%)                    | 8 (7)                                  | 5 (4)                                   |
| Pneumonia                                             | 3 (3)                                  | 2 (2)                                   |
| Gastrointestinal Disorders, n (%)                     | 5 (4)                                  | 7 (6)                                   |
| Cardiac Disorder, n (%)                               | 3 (3)                                  | 8 (7)                                   |
| Injury, Poisoning And Procedural Complications, n (%) | 3 (3)                                  | 3 (3)                                   |
| Vascular Graft or Fistula Thrombosis                  | 0 (0)                                  | 3 (3)                                   |

*Reviewer comments: Although there were a numerical increased number of SAEs in the US-licensed Epogen group compared to “Epoetin Hospira”, the incidence of pneumonia and cardiac adverse events were similar between the two groups.*

### 7.3.2.2 Study EPOE-10-01

For the Safety Population, the rate of serious adverse events were similar between the two groups with 75 (25%) patients in the “Epoetin Hospira” group and 82 (27%) patients in the US-licensed Epogen group experienced at least one SAE.

Table 23 summarizes the serious AEs reported during treatment period in the study EPOE-10-01.

Table 23: Treatment-Emergent Serious Adverse Events (Safety Population)

|  | <b>“Epoetin Hospira”<br/>(N = 301)</b> | <b>US-licensed Epogen<br/>(N = 304)</b> |
|--|----------------------------------------|-----------------------------------------|
|  |                                        |                                         |

|                                                             |         |         |
|-------------------------------------------------------------|---------|---------|
| Treatment-Emergent Serious Adverse Events, n (%)            | 75 (25) | 82 (27) |
| Infections and Infestations, n (%)                          | 20 (7)  | 30 (10) |
| Abdominal Abscess                                           | 0 (0)   | 2 (1)   |
| Pneumonia                                                   | 4 (1)   | 9 (3)   |
| Cellulitis                                                  | 0 (0)   | 6 (2)   |
| Sepsis                                                      | 3 (1)   | 3 (1)   |
| Gastrointestinal Disorders, n (%)                           | 8 (3)   | 10 (3)  |
| Gastritis                                                   | 0 (0)   | 2 (1)   |
| Gastrointestinal hemorrhage                                 | 1 (<1)  | 2 (1)   |
| Gangrene                                                    | 0 (0)   | 3 (1)   |
| General disorders and administration site conditions, n (%) | 8 (3)   | 10 (3)  |
| Non-cardiac chest pain                                      | 4 (1)   | 7 (2)   |
| Pyrexia                                                     | 0 (0)   | 2 (1)   |
| Cardiac Disorder, n (%)                                     | 15 (5)  | 19 (6)  |
| Acute myocardial infarction                                 | 2 (1)   | 2 (1)   |
| Atrial fibrillation                                         | 2 (1)   | 1 (<1)  |
| Cardiac bradycardia                                         | 3 (1)   | 1 (<1)  |
| Cardiac failure congestive                                  | 4 (1)   | 4 (1)   |
| Cardiac arrest                                              | 0 (0)   | 3 (1)   |
| Tachycardia                                                 | 2 (1)   | 0 (0)   |
| Injury, Poisoning And Procedural Complications, n (%)       | 12 (4)  | 10 (3)  |
| Arteriovenous fistula thrombosis                            | 3 (1)   | 2 (1)   |
| Metabolism and nutrition disorders, n (%)                   | 7 (2)   | 13 (4)  |
| Fluid overload                                              | 1 (<1)  | 6 (2)   |
| Hyperkalemia                                                | 2 (1)   | 4 (1)   |
| Hypoglycemia                                                | 2 (1)   | 0 (0)   |
| Nervous system disorders, n (%)                             | 8 (3)   | 9 (3)   |
| Syncope                                                     | 2 (1)   | 1 (<1)  |
| Respiratory, thoracic and mediastinal disorders, n (%)      | 15 (5)  | 14 (5)  |
| Respiratory failure                                         | 4 (1)   | 2 (1)   |
| Chronic obstructive pulmonary disease                       | 3 (1)   | 0 (0)   |
| Dyspnea                                                     | 3 (1)   | 8 (3)   |
| Vascular disorders, n (%)                                   | 8 (3)   | 10 (3)  |
| Hypertension                                                | 3 (1)   | 4 (1)   |

*Reviewer comments: The rate of SAEs occurred during treatment were similar between the two arms.*

### 7.3.3 Dropouts and/or Discontinuations

In study EPOE-10-13 (SC) there were a total 35 patients who discontinued the study. Eighteen patients discontinued the study drug due to AEs in titration period (7 in “Epoetin Hospira”, 11 in

the US-licensed Epogen). Thirteen patients discontinued study drug in maintenance period (7 in “Epoetin Hospira”, 6 in the US-licensed Epogen).

### 7.3.4 Significant Adverse Events

#### 7.3.4.1 Study EPOE-10-13

For the Safety Population, 85 (70%) patients in the “Epoetin Hospira” group and 86 (71%) patients in the US-licensed Epogen group reported at least one TEAE during the Maintenance Period.

Table 24 summarizes the TEAEs with  $\geq 2\%$  Incidence reported during maintenance period.

Table 24: Treatment-Emergent Adverse Events with  $\geq 2\%$  Incidence in Study EPOE-10-13 by System Organ Class and Preferred Term during the Maintenance Period (Safety Population)

| <b>System Organ Class<br/>Preferred Term</b>         | <b>“Epoetin<br/>Hospira”<br/>(N = 122)<br/>n (%)</b> | <b>US-licensed<br/>Epogen<br/>(N = 122)<br/>n (%)</b> |
|------------------------------------------------------|------------------------------------------------------|-------------------------------------------------------|
| Any Treatment-Emergent Adverse Event                 | 85 (70)                                              | 86 (71)                                               |
| Blood And Lymphatic System Disorders                 | 4 (3)                                                | 6 (5)                                                 |
| Anemia                                               | 3 (3)                                                | 1 (1)                                                 |
| Cardiac Disorders                                    | 10 (8)                                               | 16 (13)                                               |
| Atrial Fibrillation                                  | 2 (2)                                                | 3 (3)                                                 |
| Cardiac Failure Congestive                           | 0 (0)                                                | 3 (3)                                                 |
| Tachycardia                                          | 3 (3)                                                | 3 (3)                                                 |
| Gastrointestinal Disorders                           | 31 (25)                                              | 25 (21)                                               |
| Abdominal Pain                                       | 5 (4)                                                | 2 (2)                                                 |
| Diarrhea                                             | 4 (3)                                                | 5 (4)                                                 |
| Nausea                                               | 10 (8)                                               | 8 (7)                                                 |
| Vomiting                                             | 4 (3)                                                | 6 (5)                                                 |
| General Disorders And Administration Site Conditions | 23 (19)                                              | 24 (20)                                               |
| Asthenia                                             | 2 (2)                                                | 5 (4)                                                 |
| Chills                                               | 4 (3)                                                | 1 (1)                                                 |
| Pyrexia                                              | 8 (7)                                                | 4 (3)                                                 |
| Injection Site Pain                                  | 3 (3)                                                | 8 (7)                                                 |
| Edema Peripheral                                     | 0 (0)                                                | 5 (4)                                                 |
| Infections And Infestations                          | 32 (26)                                              | 28 (23)                                               |
| Pneumonia                                            | 3 (3)                                                | 3 (3)                                                 |
| Upper Respiratory Tract Infection                    | 9 (8)                                                | 9 (8)                                                 |
| Injury, Poisoning And Procedural Complications       | 26 (21)                                              | 32 (26)                                               |
| Arteriovenous fistula or graft thrombosis            | 4 (3)                                                | 4 (3)                                                 |
| Procedural Hypotension                               | 3 (3)                                                | 5 (4)                                                 |
| Fall                                                 | 8 (7)                                                | 3 (3)                                                 |

|                                                 |         |         |
|-------------------------------------------------|---------|---------|
| Metabolism And Nutrition Disorders              | 13 (11) | 16 (13) |
| Hyperkalemia                                    | 3 (3)   | 6 (5)   |
| Hypoglycemia                                    | 1 (1)   | 6 (5)   |
| Musculoskeletal And Connective Tissue Disorders | 20 (16) | 17 (14) |
| Arthralgia                                      | 5 (4)   | 4 (3)   |
| Muscle Spasms                                   | 4 (3)   | 3 (3)   |
| Pain In Extremity                               | 6 (5)   | 5 (4)   |
| Nervous System Disorders                        | 9 (7)   | 21 (17) |
| Dizziness                                       | 3 (3)   | 9 (7)   |
| Headache                                        | 6 (5)   | 3 (3)   |
| Respiratory, Thoracic And Mediastinal Disorders | 14 (12) | 16 (13) |
| Cough                                           | 4 (3)   | 3 (3)   |
| Dyspnea                                         | 4 (3)   | 6 (5)   |
| Vascular Disorders                              | 6 (5)   | 16 (13) |
| Hypertension                                    | 3 (3)   | 4 (3)   |
| Hypotension                                     | 0 (0)   | 5 (4)   |

Source: BLA 125545 submission, Module 5.3.5.1, Table 14.3.1.2.2.1.2, P. 653.

*Reviewer comments: The incidences of TEAEs in general were similar between the two groups and comparable with that reported in the US-licensed Epogen label.*

#### 7.3.4.2 Study EPOE-10-01

For the Safety Population, 232 (77%) patients in the “Epoetin Hospira” group and 229 (75%) patients in the US-licensed Epogen group reported at least one TEAE during the Treatment Period.

Table 25 summarizes the TEAEs with  $\geq 2\%$  Incidence reported during maintenance period.

Table 25: Treatment-Emergent Adverse Events with  $\geq 2\%$  Incidence in Study EPOE-10-01 by System Organ Class and Preferred Term during the Treatment Period (Safety Population)

| <b>System Organ Class<br/>Preferred Term</b> | <b>“Epoetin<br/>Hospira”<br/>(N = 301)<br/>n (%)</b> | <b>US-licensed<br/>Epogen<br/>(N = 304)<br/>n (%)</b> |
|----------------------------------------------|------------------------------------------------------|-------------------------------------------------------|
| Any Treatment-Emergent Adverse Event         | 232 (77)                                             | 229 (75)                                              |
| Blood And Lymphatic System Disorders         | 17 (6)                                               | 18 (6)                                                |
| Anemia                                       | 8 (3)                                                | 13 (4)                                                |
| Cardiac Disorders                            | 29 (10)                                              | 33 (11)                                               |
| Angina                                       | 3 (1)                                                | 6 (2)                                                 |
| Cardiac Failure                              | 5 (2)                                                | 4 (1)                                                 |
| Gastrointestinal Disorders                   | 80 (27)                                              | 88 (29)                                               |
| Abdominal Pain                               | 15 (5)                                               | 12 (4)                                                |
| Constipation                                 | 7 (2)                                                | 13 (4)                                                |

|                                                      |         |         |
|------------------------------------------------------|---------|---------|
| Diarrhea                                             | 21 (7)  | 27 (9)  |
| Nausea                                               | 30 (10) | 25 (8)  |
| Vomiting                                             | 28 (9)  | 15 (5)  |
| General Disorders And Administration Site Conditions | 60 (20) | 55 (18) |
| Fatigue or asthenia                                  | 13 (4)  | 5 (2)   |
| Non-cardiac chest pain                               | 7 (2)   | 17 (6)  |
| Pyrexia                                              | 8 (7)   | 4 (3)   |
| Injection Site Pain                                  | 3 (3)   | 8 (7)   |
| Edema Peripheral                                     | 11 (4)  | 4 (1)   |
| Infections And Infestations                          | 71 (24) | 77 (25) |
| Cellulitis                                           | 1 (<1)  | 9 (3)   |
| Pneumonia                                            | 9 (3)   | 11 (4)  |
| Upper Respiratory Tract Infection                    | 19 (6)  | 26 (9)  |
| Injury, Poisoning And Procedural Complications       | 83 (28) | 76 (25) |
| Arteriovenous fistula site complication              | 26 (9)  | 25 (8)  |
| Arteriovenous fistula or graft thrombosis            | 15 (5)  | 8 (3)   |
| Procedural Hypotension                               | 6 (2)   | 7 (2)   |
| Fall                                                 | 13 (4)  | 13 (4)  |
| Metabolism And Nutrition Disorders                   | 37 (12) | 42 (14) |
| Hyperkalemia                                         | 14 (5)  | 12 (4)  |
| Musculoskeletal And Connective Tissue Disorders      | 72 (24) | 77 (25) |
| Arthralgia                                           | 13 (4)  | 12 (4)  |
| Muscle Weakness                                      | 27 (9)  | 24 (8)  |
| Pain In Extremity                                    | 10 (3)  | 17 (6)  |
| Nervous System Disorders                             | 51 (17) | 49 (16) |
| Dizziness                                            | 20 (7)  | 15 (5)  |
| Headache                                             | 23 (8)  | 16 (5)  |
| Respiratory, Thoracic And Mediastinal Disorders      | 62 (21) | 69 (22) |
| Cough                                                | 16 (5)  | 22 (7)  |
| Dyspnea                                              | 24 (8)  | 22 (7)  |
| Psychiatric Disorders                                | 21 (7)  | 21 (7)  |
| Anxiety                                              | 9 (3)   | 9 (3)   |
| Insomnia                                             | 11 (4)  | 5 (2)   |
| Vascular Disorders                                   | 38 (13) | 53 (17) |
| Hypertension                                         | 20 (7)  | 15 (5)  |
| Hypotension                                          | 14 (5)  | 25 (8)  |

Source: BLA 125545 submission, Module 5.3.5.1, Table 14.3.1.2.2.1, P. 510.

*Reviewer comments: The incidences of TEAEs in general were similar between the two groups and comparable with that reported in the US-licensed Epogen label.*

### 7.3.5 Submission Specific Primary Safety Concerns

Adverse Events of Special Interest: Adverse Events of Special Interest have been identified based on the safety information of the US-licensed Epogen reference product, as described in the US-licensed Epogen Package Insert. These pre-defined categories included myocardial infarction, cerebrovascular events, thromboembolic events, hypertension, seizures, pure red cell aplasia (PRCA), and potential allergic reactions (pre-defined as combination of angioedema and anaphylactic reactions).

#### 7.3.5.1 Study EPOE-10-13

For the Safety Population during the Maintenance Period, 9 (7%) patients in the “Epoetin Hospira” and 12 (10%) patients in the US-licensed Epogen reported at least one TEAE of special interest. One patient in the US-licensed Epogen group experienced two events of thromboembolic myocardial infarction. There was one cerebrovascular event reported in each group (Transient ischemic attack in “Epoetin Hospira” and thrombotic cerebrovascular event in US-licensed Epogen). Four patients (3%) in the “Epoetin Hospira” group and eight patients (7%) in the US-licensed Epogen group experienced a TEAE in the category of thromboembolic events. Three patients in the “Epoetin Hospira” and 4 patients in the US-licensed Epogen group reported an adverse event of hypertension. There were no cases of cardiac failure or seizure reported in any patient in either treatment group during the Maintenance Period. There were no events of PRCA in either treatment group. There were two patients in “Epoetin Hospira” and 3 patients in US-licensed Epogen group experienced an allergic reaction during the maintenance period.

Table 26: Treatment-Emergent Adverse Events of Special Interest during the Maintenance Period (EPOE-10-013 Study, SC)

|                                                            | <b>“Epoetin Hospira”<br/>(N =122)</b> | <b>US-licensed Epogen<br/>(N = 122)</b> |
|------------------------------------------------------------|---------------------------------------|-----------------------------------------|
| Patients with at least one TEAE of Special Interest, n (%) | 9 (7)                                 | 12 (10)                                 |
| Myocardial Infarction, n (%)                               | 0 (0)                                 | 1 (1)                                   |
| Cardia failure, n (%)                                      | 0 (0)                                 | 0 (0)                                   |
| Cerebrovascular Events, n (%)                              | 1 (1)                                 | 1 (1)                                   |
| Thromboembolic Events, n (%)                               | 4 (3)                                 | 8 (7)                                   |
| Arteriovenous fistula or graft thrombosis                  | 4 (3)                                 | 5 (4)                                   |
| Vena cava thrombosis                                       | 0 (0)                                 | 2 (2)                                   |
| Hypertension, n (%)                                        | 3 (3)                                 | 4 (3)                                   |
| Seizure, n (%)                                             | 0 (0)                                 | 0 (0)                                   |
| Pure Red Cell Aplasia, n (%)                               | 0 (0)                                 | 0 (0)                                   |
| Allergic Reaction, n (%)                                   | 2 (2)                                 | 3 (3)                                   |

*Reviewer comments: There were no differences in the incidence of TEAEs or special interest AEs between “Epoetin Hospira” and US-licensed Epogen treated patients.*

### 7.3.5.2 Study EPOE-10-01

For the Safety Population, 51 (17%) patients in the “Epoetin Hospira” and 36 (12%) patients in the US-licensed Epogen reported at least one TEAE of special interest. Four patients in the “Epoetin Hospira” and two patients in the US-licensed Epogen group experienced myocardial infarction. No cases of cardiac failure reported in the study. There were four patients in each group experienced cerebrovascular event (1 Carotid artery stenosis, 1 hemorrhagic stroke, 2 thromboembolic strokes in “Epoetin Hospira” and 1 carotid arteriosclerosis, 2 CVA accident and 1 thromboembolic transient ischemic attack in the US-licensed Epogen). A total of 46 patients, 28 (9%) patients in the “Epoetin Hospira” group and 18 (6%) patients in the US-licensed Epogen group experienced thromboembolic events. Hypertension adverse events were reported in 22 (7%) of patients in the “Epoetin Hospira” group compared to 13 (4%) in the US-licensed Epogen group. Seizures were reported in no patient in the “Epoetin Hospira” group and one patient in the US-licensed Epogen group. There were no reported events of PRCA in either treatment group. Allergic reaction adverse events were reported in 7 (2%) patients in the “Epoetin Hospira” compared to 4 (1%) patients in the US-licensed Epogen group.

Table 27: Treatment-Emergent Adverse Events of Special Interest, Study EPOE-10-01 (Safety Population)

|                                                            | <b>“Epoetin Hospira”<br/>(N =301)</b> | <b>US-licensed Epogen<br/>(N = 304)</b> |
|------------------------------------------------------------|---------------------------------------|-----------------------------------------|
| Patients with at least one TEAE of Special Interest, n (%) | 51 (17)                               | 36 (12)                                 |
| Myocardial Infarction, n (%)                               | 4 (1)                                 | 2 (1)                                   |
| Cardia failure, n (%)                                      | 0 (0)                                 | 0 (0)                                   |
| Cerebrovascular Events, n (%)                              | 4 (1)                                 | 4 (1)                                   |
| Thromboembolic Events, n (%)                               | 28 (9)                                | 18 (6)                                  |
| Myocardial Infarction                                      | 4 (1)                                 | 2 (1)                                   |
| Arteriovenous fistula or graft thrombosis                  | 21 (7)                                | 8 (3)                                   |
| Deep venous thrombosis                                     | 1 (<1)                                | 3 (1)                                   |
| Cerebrovascular accident/Stoke                             | 2 (1)                                 | 2 (1)                                   |
| Hypertension, n (%)                                        | 22 (7)                                | 13 (4)                                  |
| Seizure, n (%)                                             | 0 (0)                                 | 1 (<1)                                  |
| Pure Red Cell Aplasia, n (%)                               | 0 (0)                                 | 0 (0)                                   |
| Allergic Reaction, n (%)                                   | 7 (2)                                 | 4 (1)                                   |

*Reviewer comments:*

- The incidences of special interest AE such as MI, cerebrovascular, seizure and allergic reaction events were similar between the two groups.
- There were a numerically higher number of patients experienced thromboembolic events in “Epoetin Hospira” group compared to that in the US-licensed Epogen group 28 (9%) patients vs 18 (3%) patients.
- The vascular access thrombosis account for most of the differences between the two groups with 21 (7%) events in “Epoetin Hospira” compared to 8 (3%) events in the US-licensed Epogen group. The percentage of adverse events of vascular access thrombosis reported in “Epoetin Hospira” treated patients was comparable to that reported in the US-licensed Epogen/Procrit label 8%.
- Although the rate of hypertension events reported among patients treated with “Epoetin Hospira” (7%) was higher than that reported among patients treated with US-licensed Epogen 4%, this rate of hypertensive events were lower than that reported in the US-licensed Epogen label (28%). In addition, the majority of patients >90% had hypertension at baseline.

## 7.4 Supportive Safety Results

Supportive clinical studies consist of the following:

1. Study EPOE-11-04 was a supportive open-label, long-term safety extension study for EPOE-10-13 during which “Epoetin Hospira” was administered to all subjects for up to an additional 48 weeks. During EPOE-11-04, “Epoetin Hospira” was administered SC continuing the route of administration the subject had received in EPOE-10-13.
2. Study EPOE-11-03 was a supportive open-label, long-term safety extension study for EPOE-10-01 during which “Epoetin Hospira” was administered to all subjects for up to an additional 48 weeks. During EPOE-11-03, “Epoetin Hospira” was administered IV continuing the route of administration the subject had received in EPOE-10-01.
3. Two PK/PD trials were conducted in healthy male subjects (EPOE-12-02 and EPOE-14-01), and one legacy PK trial was conducted in subjects with CKD on HD with the legacy formulation of “Epoetin Hospira” (EPOE-10-08).
  - a. Study EPOE-12-02, the definitive PK/PD study, was a single-center, open-label, randomized, two-period crossover, PK equivalence study in healthy male volunteers, in which a single dose of “Epoetin Hospira” or US-licensed Epogen was administered SC at 100 U/kg. There were two study periods, with a 28-day washout period between the doses of “Epoetin Hospira” and US-licensed Epogen.
  - b. Study EPOE-14-01, the definitive comparative multiple dose PD study, was a single center, open-label, randomized, parallel arm, PD equivalence study in healthy male volunteers who received epoetin as 12 fixed SC doses, administered at 100 U/kg three times a week (TIW) for 4 weeks

#### 7.4.1 Common Adverse Events

##### Studies EPOE-11-03 and EPOE-11-04

The safety populations (who enrolled and received at least one dose of “Epoetin Hospira” study drug) consist of 114 patients in study EPOE-11-03 and 75 patients in study EPOE-11-04, totaling 189 patients.

For the Safety Population, in the combined 48-week open-label LTSS, EPOE-11-04 and EPOE-11-03, the mean duration of study drug exposure and overall mean weekly study drug dose by body weight were approximately 33 weeks, and 84.9 U/kg/week, respectively. Approximately 72% of subjects did not miss any weeks of study drug administration, and the mean number of weeks missed was 0.5 weeks.

For the combined LTSS, 152 (80%) patients experienced at least one TEAE. Treatment-emergent adverse events were responsible for discontinuation of study drug and discontinuation of the study by 9% and 11% of subjects, respectively. Eighteen (10%) patients experienced a TEAE resulting in death. A total of 72 (38%) patients reported at least one SAE. Thirty three (18%) patients experienced at least one AE of Special Interest.

Table 28: Incidence of Common Treatment-Emergent Adverse Events in Combined EPOE-11-03 and EPOE-11-04 studies, (Safety Population)

| <b>System Organ Class<br/>Preferred Term</b>                | <b>“Epoetin Hospira”<br/>Open-Label<br/>(N = 189)</b> |
|-------------------------------------------------------------|-------------------------------------------------------|
| Patient with any Treatment-Emergent AE, n (%)               | 152 (80)                                              |
| Patient with at Least One SAE, n (%)                        | 72 (38)                                               |
| Patient with at Least One AE Resulted in Death, n (%)       | 18 (10)                                               |
| Patients with at Least One AE of Special Interest, n (%)    | 33 (18)                                               |
| Blood and Lymphatic System Disorders, n (%)                 | 11 (6)                                                |
| Anemia                                                      | 8 (4)                                                 |
| Cardiac Disorders, n (%)                                    | 27 (14)                                               |
| Cardiac Failure                                             | 4 (2)                                                 |
| Tachycardia                                                 | 4 (2)                                                 |
| Gastrointestinal Disorders, n (%)                           | 60 (32)                                               |
| Abdominal Pain                                              | 10 (5)                                                |
| Diarrhea                                                    | 16 (9)                                                |
| Nausea                                                      | 16 (9)                                                |
| Vomiting                                                    | 15 (8)                                                |
| General Disorders and Administration Site Conditions, n (%) | 48 (25)                                               |

|                                                        |         |
|--------------------------------------------------------|---------|
| Asthenia or Fatigue                                    | 11 (6)  |
| Pyrexia                                                | 9 (5)   |
| Infections and Infestations, n (%)                     | 67 (35) |
| Pneumonia                                              | 14 (7)  |
| Upper Respiratory Tract Infection                      | 19 (10) |
| Urinary Tract Infection                                | 8 (4)   |
| Injury, Poisoning, and Procedural Complication, n (%)  | 50 (27) |
| Arteriovenous Fistula or Graft Site Complication       | 15 (8)  |
| Arteriovenous Fistula or Graft Thrombosis              | 11 (6)  |
| Fall                                                   | 4 (2)   |
| Musculoskeletal and Connective Tissue Disorder, n (%)  | 59 (31) |
| Arthralgia                                             | 8 (4)   |
| Back Pain                                              | 10 (5)  |
| Muscle Spasm                                           | 32 (17) |
| Pain in extremity                                      | 10 (5)  |
| Nervous System Disorders, n (%)                        | 50 (27) |
| Dizziness                                              | 16 (9)  |
| Headache                                               | 18 (10) |
| Psychiatric Disorders                                  | 9 (5)   |
| Anxiety                                                | 5 (3)   |
| Respiratory, Thoracic and Mediastinal Disorders, n (%) | 49 (26) |
| Cough                                                  | 13 (7)  |
| Dyspnea                                                | 17 (9)  |
| Skin and Subcutaneous Tissue Disorders, n (%)          | 22 (12) |
| Pruritus                                               | 10 (5)  |
| Skin Ulcer                                             | 6 (3)   |
| Vascular Disorders, n (%)                              | 28 (15) |
| Hypertension                                           | 8 (4)   |
| Hypotension                                            | 12 (6)  |

#### Study EPOE-12-02

The Safety Population consists of 81 subjects who received at least one dose of study drug (41 in the “Epoetin Hospira” group; 40 in the US-licensed Epogen group). During the treatment period the rate of treatment emergent adverse events (TEAEs) was similar between the “Epoetin Hospira” treated subjects (12%) and the US-licensed Epogen treated subjects (14%).

The TEAEs occurring in more than one subject in each treatment group were headache reported in 3 subjects (4%) and presyncope reported in 2 subjects (3%) in the “Epoetin Hospira” group and oropharyngeal pain reported in 2 subjects (3%) in the US-licensed Epogen group.

#### Study EPOE-14-01

The Safety Population consists of 129 subjects who received at least one dose of study drug (66 in the “Epoetin Hospira” group; 63 in the US-licensed Epogen group). During the treatment period 14 subjects (21%) in the “Epoetin Hospira” group and 15 subjects (24%) in the US-licensed Epogen group experienced at least one TEAE. The most common TEAEs were seen with the following incidences in the “Epoetin Hospira” and US-licensed Epogen groups were, respectively: constipation (6% and 3%), diarrhea (3% and 3%), upper respiratory tract infection (2% and 5%), headache (2% and 3%), dizziness (3% and 0%), vomiting (0% and 3%), and dyspnea (0% and 3%). There were no severe and no serious TEAEs reported in EPOE-14-01.

There were no AEs of Special Interest reported in Study EPOE-14-01.

*Reviewer comments: The safety analyses of supportive studies showed that the rates of the TEAEs were generally similar between “Epoetin Hospira” and US-licensed Epogen treated groups. In addition, the incidences of TEAEs were also comparable to that described in the US-licensed Epogen label.*

#### 7.4.2 Laboratory Findings

Assessment of clinical laboratory of hematology and clinical chemistry safety signals were evaluate during the studies included:

- Hb <8.0 g/dL or >12.0 g/dL with  $\pm 2.0$  g/dL change in Hb from baseline
- RBC <1.5 x 10<sup>6</sup>/mm<sup>3</sup> and reticulocyte percentage of total erythrocytes <0.5%
- Alanine transaminase (ALT) >3x upper limit of normal (ULN) or aspartate transaminase (AST) >3x ULN and total bilirubin >1.5x ULN
- Absolute neutrophil count <1000/mm<sup>3</sup>, and
- Platelet count <100,000/mm<sup>3</sup> and International Normalized Ratio (INR) >3.5

The incidences of positive hematology signals were similar between the treatment groups for the combined randomized core studies and stable over the course of combined LTSS.

Table 29: Incidence of Positive Hematology Tests (Safety Population)

|                                                                                                            | US-licensed<br>Epogen   | “Epoetin Hospira”       |                         |                    |
|------------------------------------------------------------------------------------------------------------|-------------------------|-------------------------|-------------------------|--------------------|
|                                                                                                            | Randomized<br>(N = 426) | Randomized<br>(N = 423) | Open-Label<br>(N = 189) | Total<br>(N = 516) |
| Hb <8.0 g/dL or >12.0 g/dL with $\pm$ 2.0 g/dL change in Hb, n/N (%)                                       | 61/426 (14)             | 44/423 (10)             | 24/187 (13)             | 63/516 (12)        |
| RBC <1.5x10 <sup>6</sup> /mm <sup>3</sup> and reticulocyte percentage of total erythrocytes <0.5%, n/N (%) | 0/424 (0)               | 0/423 (0)               | 0/183 (0)               | 0/515 (0)          |
| Absolute neutrophil count <1000/mm <sup>3</sup> , n/N (%)                                                  | 17/424 (4)              | 23/423 (5)              | 13/183 (7)              | 34/515 (7)         |
| Platelet count <100,000/mm <sup>3</sup> and INR >3.5, n/N (%)                                              | 0/425 (0)               | 2/423 (1)               | 0/183 (0)               | 2/515 (<1)         |

Two patients received epoetin in study EPOE-10-13 reported an incidence of decreased in platelets count associate with increased INR.

24011-0250: Platelet count 78,000/ mm<sup>3</sup> and INR= 4.2, patient had a medical history of clotting/bleeding disorders. Platelet count was 106,000 mm<sup>3</sup>/ and INR was 1.2

24035-0143: Platelet count 46,000/ mm<sup>3</sup> and INR = >10.0, patient had a medical history of Hepatitis C and liver transplant. Platelet count at baseline was 53,000/ mm<sup>3</sup> and INR was 1.3.

No patients in the combined randomized core studies or in the combined LTSS met the criteria for Hy's Law.

### 7.4.3 Vital Signs

#### Blood Pressure (BP):

More than 98% of patients in the combined clinical studies had hypertension at baseline. For the Safety Population, for the combined core studies (EPOE-10-13 and EPOE-10-01), the changes from baseline in blood pressure were generally unremarkable. The mean change in systolic BP from baseline to Week 24 showed a decrease of -5.65 (27.68) mmHg in the “Epoetin Hospira” group and of -3.79 (24.42) mmHg in the US-licensed Epogen group. The mean change in diastolic BP from baseline to Week 24 showed a decrease of -3.17 (17.14) mmHg in the “Epoetin Hospira” group and of -2.70 (13.7) mmHg in the US-licensed Epogen group.

#### Heart Rate:

For the Safety Population, for the combined core studies (EPOE-10-13 and EPOE-10-01), the mean change in heart rate from baseline to Week 24 showed an increase of 1.86 (12.4) beats/minute in the “Epoetin Hospira” group and a decrease of -0.22 (11.88) beats/ minute in the US-licensed Epogen group.

#### Temperature:

For the Safety Population, for the combined core studies (EPOE-10-13 and EPOE-10-01), the mean change in temperature from baseline to Week 24 showed an increase of 0.05 (0.47) °C in the “Epoetin Hospira” group and an increase of 0.03 (0.53) °C in the US-licensed Epogen group.

*Reviewer comments: The mean changes in vital signs from baseline to Week 24 between the two treatment group were minimal and clinically insignificant.*

#### 7.4.4 Electrocardiograms (ECGs)

In the clinical study EPOE-10-13, three patients in the “Epoetin Hospira” group and four patients in the US-licensed Epogen group had clinically significant electrocardiograms (ECG) changes from baseline during maintenance period. In the clinical study EPOE-10-01, there were four patients in the “Epoetin Hospira” group and two patients in the US-licensed Epogen group had clinically significant ECG changes from baseline during the treatment period.

The incidence of abnormal clinically significant ECG ranged between 2- 3% with similar incidence between the combined randomized “Epoetin Hospira” and combined randomized US-licensed Epogen groups.

#### 7.4.5 Special Safety Studies/Clinical Trials

There were no special studies for similarity of safety endpoints submitted for review.

#### 7.4.6 Immunogenicity

According to the Applicant, the results from the immunogenicity evaluation revealed no patient in any studies developed anti-rhEPO neutralizing antibodies or pure red cell aplasia (PRCA) at the time of BLA submission (24 December 2014).

There were a total of 5 subjects tested positive to anti-rhEPO by radioimmunoprecipitation (RIP) assay and none of the subject developed neutralizing antibody (NAb).

- 1) One patient in Study EPOE-10-13 (SC) tested positive for anti-rhEPO antibody (RIP) but NAb negative prior to receive study drug and remained positive for anti-rhEPO antibodies by RIP assay with stable titers throughout the EPOE-10-13 core study and the EPOE-11-04 LTSS, during both of which study drug was administered SC.
- 2) One patient in study EPOE-10-01 (IV) who tested positive for anti-rhEPO antibodies by RIP assay and was negative prior to receive study drug.
- 3) One subject in study EPOE-12-02 tested positive for anti-rhEPO antibodies by the RIP assay and negative for NAb prior to study drug administration with stable post-dosing titers and no evidence of clinical deterioration.
- 4) Two subjects in Study EPOE-14-01 tested positive for anti-rhEPO antibodies by the RIP assay and negative for NAb prior to study drug administration with stable post-dosing titers and no evidence of clinical deterioration.

For further information refer to the Clinical pharmacology and OBP Immunogenicity review.

On 07 July 2015, the Applicant notified the Agency of a case of PRCA that reported within a long-term, non-interventional, observational post approval study with European (EU) approved Retacrit™, PASCO II. This is the first confirmed report of PRCA associated with EU Retacrit.

Case Report: A 73 year-old Caucasian female patient from Italy was treated with EU Retacrit for anemia associated with renal failure not undergoing dialysis starting June 2014. Her hemoglobin concentrations dropped and failed to improve despite increasing frequency of ESA administrations. She presented to the emergency room (ER) in February 21, 2015 with Hb of 3.9 g/dL. Test results for immunogenicity testing from several samples collected on May 29, June 17 and July 1, 2015, were received 17 July 2015 confirming neutralizing antibodies against erythropoietin in all three samples.

## **7.5 Other Safety Explorations**

### **7.5.1 Dose Dependency for Adverse Events**

No dose dependency for adverse events analysis performed since the dose of the study drug was adjusted based on hemoglobin level.

### **7.5.2 Time Dependency for Adverse Events**

Time dependency of AEs: The time to onset by 4-week intervals for common TEAEs and by treatment group for the combined randomized treatment groups by route of administrations (SC vs IV) was analyzed using the safety population.

Table 30 and Table 31 summarize the time to onset by 4-week intervals for common TEAEs for all treatment groups (Studies EPOE-10-13 and EPOE-10-01) during treatment period.

Table 30: Incidence of Common TEAEs by Time of Onset for the Combined Randomized Treatment Groups (Weeks 1 to 12) (Safety Population)

| System Organ Class<br>Preferred Term    | Weeks 1-4                        |                                  | Weeks 5-8                        |                                  | Weeks 9-12                       |                                  |
|-----------------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|
|                                         | US-licensed<br>Epogen            | “Epoetin<br>Hospira”             | US-licensed<br>Epogen            | “Epoetin<br>Hospira”             | US-licensed<br>Epogen            | “Epoetin<br>Hospira”             |
|                                         | Randomized<br>(N = 426)<br>n (%) | Randomized<br>(N = 423)<br>n (%) | Randomized<br>(N = 399)<br>n (%) | Randomized<br>(N = 409)<br>n (%) | Randomized<br>(N = 382)<br>n (%) | Randomized<br>(N = 387)<br>n (%) |
| Subjects with At Least One Event        | 134 (32)                         | 154 (36)                         | 148 (37)                         | 144 (35)                         | 131 (34)                         | 114 (30)                         |
| Diarrhea                                | 9 (2)                            | 5 (1)                            | 6 (2)                            | 6 (2)                            | 8 (2)                            | 4 (1)                            |
| Nausea                                  | 7 (2)                            | 11 (2)                           | 7 (2)                            | 14 (3)                           | 7 (2)                            | 3 (1)                            |
| Vomiting                                | 9 (2)                            | 8 (2)                            | 0                                | 6 (2)                            | 7 (2)                            | 4 (1)                            |
| Pyrexia                                 | 3 (1)                            | 6 (1)                            | 5 (1)                            | 5 (1)                            | 2 (1)                            | 4 (1)                            |
| Pneumonia                               | 0                                | 3 (1)                            | 3 (1)                            | 3 (1)                            | 0                                | 2 (<1)                           |
| Upper Respiratory Tract Infection       | 1 (<1)                           | 2 (1)                            | 2 (1)                            | 4 (1)                            | 1 (<1)                           | 1 (<1)                           |
| Arteriovenous Fistula Site Complication | 9 (2)                            | 5 (1)                            | 8 (2)                            | 5 (1)                            | 5 (1)                            | 9 (2)                            |
| Fall                                    | 2 (1)                            | 6 (1)                            | 6 (2)                            | 6 (2)                            | 5 (1)                            | 1 (<1)                           |
| Back Pain                               | 3 (1)                            | 5 (1)                            | 6 (2)                            | 3 (1)                            | 6 (2)                            | 1 (<1)                           |
| Muscle Spasms                           | 6 (1)                            | 11 (3)                           | 5 (1)                            | 11 (3)                           | 11 (3)                           | 7 (2)                            |
| Pain In Extremity                       | 4 (1)                            | 9 (2)                            | 6 (2)                            | 2 (1)                            | 5 (1)                            | 2 (1)                            |
| Dizziness                               | 11 (3)                           | 3 (1)                            | 4 (1)                            | 7 (2)                            | 5 (1)                            | 6 (2)                            |
| Headache                                | 2 (1)                            | 4 (1)                            | 7 (2)                            | 6 (2)                            | 2 (1)                            | 6 (2)                            |
| Cough                                   | 5 (1)                            | 5 (1)                            | 7 (2)                            | 3 (1)                            | 5 (1)                            | 4 (1)                            |
| Dyspnea                                 | 5 (1)                            | 3 (1)                            | 8 (2)                            | 6 (2)                            | 8 (2)                            | 4 (1)                            |
| Pruritus                                | 0                                | 1 (<1)                           | 4 (1)                            | 1 (<1)                           | 2 (1)                            | 1 (<1)                           |
| Hypertension                            | 4 (1)                            | 11 (3)                           | 5 (1)                            | 4 (1)                            | 5 (1)                            | 5 (1)                            |
| Hypotension                             | 6 (1)                            | 2 (1)                            | 12 (3)                           | 5 (1)                            | 7 (2)                            | 6 (2)                            |

Table 31: Incidence of Common TEAEs by Time of Onset for the Combined Randomized Treatment Groups (Weeks 13 to 24) (Safety Population)

| System Organ Class<br>Preferred Term    | Weeks 13-16                      |                                  | Weeks 17-20                      |                                  | Weeks 21-24                      |                                  |
|-----------------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|
|                                         | US-licensed<br>Epogen            | “Epoetin<br>Hospira”             | US-licensed<br>Epogen            | “Epoetin<br>Hospira”             | US-licensed<br>Epogen            | “Epoetin<br>Hospira”             |
|                                         | Randomized<br>(N = 360)<br>n (%) | Randomized<br>(N = 366)<br>n (%) | Randomized<br>(N = 243)<br>n (%) | Randomized<br>(N = 244)<br>n (%) | Randomized<br>(N = 227)<br>n (%) | Randomized<br>(N = 229)<br>n (%) |
| Subjects with At Least One Event        | 116 (32)                         | 120 (33)                         | 61 (25)                          | 75 (31)                          | 85 (37)                          | 59 (26)                          |
| Diarrhea                                | 8 (2)                            | 4 (1)                            | 3 (1)                            | 5 (2)                            | 3 (1)                            | 3 (1)                            |
| Nausea                                  | 4 (1)                            | 7 (2)                            | 6 (3)                            | 5 (2)                            | 3 (1)                            | 4 (2)                            |
| Vomiting                                | 3 (1)                            | 6 (2)                            | 3 (1)                            | 6 (3)                            | 1 (<1)                           | 4 (2)                            |
| Pyrexia                                 | 2 (1)                            | 5 (1)                            | 2 (1)                            | 1 (<1)                           | 1 (<1)                           | 1 (<1)                           |
| Pneumonia                               | 6 (2)                            | 0                                | 2 (1)                            | 1 (<1)                           | 1 (<1)                           | 2 (1)                            |
| Upper Respiratory Tract Infection       | 5 (1)                            | 0                                | 0                                | 2 (1)                            | 5 (2)                            | 1 (<1)                           |
| Arteriovenous Fistula Site Complication | 5 (1)                            | 6 (2)                            | 2 (1)                            | 5 (2)                            | 5 (2)                            | 6 (3)                            |
| Fall                                    | 3 (1)                            | 6 (2)                            | 0                                | 1 (<1)                           | 2 (1)                            | 4 (2)                            |
| Back Pain                               | 3 (1)                            | 2 (1)                            | 0                                | 1 (<1)                           | 1 (<1)                           | 3 (1)                            |
| Muscle Spasms                           | 7 (2)                            | 8 (2)                            | 3 (1)                            | 5 (2)                            | 4 (2)                            | 2 (1)                            |
| Pain In Extremity                       | 5 (1)                            | 2 (1)                            | 1 (<1)                           | 2 (1)                            | 3 (1)                            | 0                                |
| Dizziness                               | 3 (1)                            | 4 (1)                            | 2 (1)                            | 6 (3)                            | 2 (1)                            | 0                                |
| Headache                                | 4 (1)                            | 6 (2)                            | 1 (<1)                           | 1 (<1)                           | 4 (2)                            | 7 (3)                            |
| Cough                                   | 4 (1)                            | 4 (1)                            | 3 (1)                            | 2 (1)                            | 2 (1)                            | 2 (1)                            |
| Dyspnea                                 | 6 (2)                            | 6 (2)                            | 3 (1)                            | 3 (1)                            | 4 (2)                            | 5 (2)                            |
| Pruritus                                | 2 (1)                            | 1 (<1)                           | 1 (<1)                           | 2 (1)                            | 2 (1)                            | 2 (1)                            |
| Hypertension                            | 3 (1)                            | 1 (<1)                           | 3 (1)                            | 3 (1)                            | 3 (1)                            | 2 (1)                            |
| Hypotension                             | 5 (1)                            | 3 (1)                            | 2 (1)                            | 2 (1)                            | 3 (1)                            | 0                                |

*Reviewer comments: The rates of TEAEs were comparable throughout the time on the study.*

### 7.5.3 Drug-Demographic Interactions

The incidences of at least one TEAE in all “Epoetin Hospira” treatment groups (randomized controlled 10-13, 10-03 and open label LLS 12-02, 14-01) were higher for female subjects (80% - 85%) than for male subjects (71% – 76%). Within treatment groups, the incidences of common TEAEs and AEs of Special Interest were similar between males and females.

The incidences of common TEAEs and AEs of special interest by sex are summarized in Table 32.

Table 32: Incidence of Treatment-Emergent Adverse Events by Sex (Safety Population)

| System Organ Class or Grouping Preferred Term of Group | Female                        |                               |                              |                          | Male                          |                               |                              |                          |
|--------------------------------------------------------|-------------------------------|-------------------------------|------------------------------|--------------------------|-------------------------------|-------------------------------|------------------------------|--------------------------|
|                                                        | US-licensed Epogen            | “Epoetin Hospira”             |                              |                          | US-licensed Epogen            | “Epoetin Hospira”             |                              |                          |
|                                                        | Randomized (N = 196)<br>n (%) | Randomized (N = 204)<br>n (%) | Open-Label (N = 98)<br>n (%) | Total (N = 252)<br>n (%) | Randomized (N = 230)<br>n (%) | Randomized (N = 219)<br>n (%) | Open-Label (N = 91)<br>n (%) | Total (N = 264)<br>n (%) |
| Number of Events                                       | 723                           | 693                           | 514                          | 1207                     | 813                           | 704                           | 406                          | 1110                     |
| Subjects with At Least One Event                       | 142 (72)                      | 163 (80)                      | 83 (85)                      | 212 (84)                 | 174 (76)                      | 155 (71)                      | 69 (76)                      | 195 (74)                 |
| Diarrhea                                               | 16 (8)                        | 11 (5)                        | 7 (7)                        | 18 (7)                   | 16 (7)                        | 14 (6)                        | 9 (10)                       | 22 (8)                   |
| Nausea                                                 | 14 (7)                        | 24 (12)                       | 8 (8)                        | 31 (12)                  | 19 (8)                        | 16 (7)                        | 8 (9)                        | 22 (8)                   |
| Vomiting                                               | 9 (5)                         | 20 (10)                       | 10 (10)                      | 27 (11)                  | 12 (5)                        | 12 (6)                        | 5 (6)                        | 16 (6)                   |
| Pyrexia                                                | 9 (5)                         | 5 (3)                         | 4 (4)                        | 8 (3)                    | 6 (3)                         | 14 (6)                        | 5 (6)                        | 19 (7)                   |
| Pneumonia                                              | 7 (4)                         | 3 (2)                         | 10 (10)                      | 13 (5)                   | 5 (2)                         | 8 (4)                         | 2 (2)                        | 10 (4)                   |
| Upper Respiratory Tract Infection                      | 7 (4)                         | 6 (3)                         | 8 (8)                        | 14 (6)                   | 5 (2)                         | 4 (2)                         | 5 (6)                        | 9 (3)                    |
| Arteriovenous Fistula Site Complication                | 13 (7)                        | 18 (9)                        | 2 (2)                        | 20 (8)                   | 16 (7)                        | 14 (6)                        | 5 (6)                        | 18 (7)                   |
| Fall                                                   | 9 (5)                         | 11 (5)                        | 2 (2)                        | 13 (5)                   | 7 (3)                         | 10 (5)                        | 2 (2)                        | 11 (4)                   |
| Back Pain                                              | 7 (4)                         | 12 (6)                        | 7 (7)                        | 19 (8)                   | 12 (5)                        | 3 (1)                         | 3 (3)                        | 6 (2)                    |
| Muscle Spasms                                          | 8 (4)                         | 15 (7)                        | 19 (19)                      | 33 (13)                  | 19 (8)                        | 16 (7)                        | 13 (14)                      | 29 (11)                  |
| Pain In Extremity                                      | 12 (6)                        | 9 (4)                         | 8 (8)                        | 17 (7)                   | 10 (4)                        | 7 (3)                         | 2 (2)                        | 9 (3)                    |
| Dizziness                                              | 14 (7)                        | 8 (4)                         | 7 (7)                        | 15 (6)                   | 10 (4)                        | 15 (7)                        | 9 (10)                       | 22 (8)                   |
| Headache                                               | 8 (4)                         | 11 (5)                        | 8 (8)                        | 17 (7)                   | 11 (5)                        | 18 (8)                        | 10 (11)                      | 27 (10)                  |
| Cough                                                  | 13 (7)                        | 11 (5)                        | 10 (10)                      | 20 (8)                   | 12 (5)                        | 9 (4)                         | 3 (3)                        | 12 (5)                   |
| Dyspnea                                                | 16 (8)                        | 9 (4)                         | 8 (8)                        | 17 (7)                   | 10 (4)                        | 16 (7)                        | 9 (10)                       | 24 (9)                   |
| Pruritus                                               | 5 (3)                         | 5 (3)                         | 5 (5)                        | 10 (4)                   | 5 (2)                         | 3 (1)                         | 5 (6)                        | 8 (3)                    |
| Hypertension                                           | 9 (5)                         | 11 (5)                        | 5 (5)                        | 16 (6)                   | 9 (4)                         | 13 (6)                        | 3 (3)                        | 16 (6)                   |
| Hypotension                                            | 15 (8)                        | 8 (4)                         | 6 (6)                        | 13 (5)                   | 13 (6)                        | 6 (3)                         | 6 (7)                        | 12 (5)                   |
| <b>Adverse Events of Special Interest</b>              |                               |                               |                              |                          |                               |                               |                              |                          |
| Hypertension                                           | 10 (5)                        | 14 (7)                        | 5 (5)                        | 19 (8)                   | 9 (4)                         | 13 (6)                        | 3 (3)                        | 16 (6)                   |
| Cerebrovascular Events                                 | 4 (2)                         | 2 (1)                         | 2 (2)                        | 4 (2)                    | 2 (1)                         | 2 (1)                         | 3 (3)                        | 5 (2)                    |
| Myocardial Infarction                                  | 1 (1)                         | 4 (2)                         | 1 (1)                        | 5 (2)                    | 2 (1)                         | 0                             | 2 (2)                        | 2 (1)                    |
| Potential Allergic Reactions                           | 4 (2)                         | 3 (2)                         | 4 (4)                        | 7 (3)                    | 2 (1)                         | 7 (3)                         | 2 (2)                        | 9 (4)                    |
| Pure Red Cell Aplasia                                  | 0                             | 0                             | 0                            | 0                        | 0                             | 0                             | 0                            | 0                        |
| Seizures                                               | 1 (1)                         | 0                             | 0                            | 0                        | 0                             | 0                             | 0                            | 0                        |
| Thromboembolic Events                                  | 14 (7)                        | 17 (8)                        | 10 (10)                      | 27 (11)                  | 12 (5)                        | 15 (7)                        | 9 (10)                       | 23 (9)                   |

|                               |       |        |       |        |       |        |       |        |
|-------------------------------|-------|--------|-------|--------|-------|--------|-------|--------|
| Thrombosis of Vascular Access | 9 (5) | 13 (6) | 8 (8) | 21 (8) | 9 (4) | 14 (6) | 6 (7) | 19 (7) |
|-------------------------------|-------|--------|-------|--------|-------|--------|-------|--------|

Source: BLA submission, Module 2.7.4, Table 61, P. 177.

Age:

The incidences of TEAEs across treatment groups were similar in patients  $\leq 65$  years of age (ranged 74% – 80%) compared to that in patients  $> 65$  years of age (ranged 76% - 83%).

The incidences of common TEAEs and AEs of special interest by age are summarized in Table 33.

Table 33: Incidence of Treatment-Emergent Adverse Events by Age (Safety Population)

| System Organ Class or Grouping Preferred Term of Group | 65 Years of Age and Under     |                               |                               |                          | Over 65 Years of Age          |                               |                              |                          |
|--------------------------------------------------------|-------------------------------|-------------------------------|-------------------------------|--------------------------|-------------------------------|-------------------------------|------------------------------|--------------------------|
|                                                        | US-licensed Epogen            | “Epoetin Hospira”             |                               |                          | US-licensed Epogen            | “Epoetin Hospira”             |                              |                          |
|                                                        | Randomized (N = 309)<br>n (%) | Randomized (N = 318)<br>n (%) | Open-Label (N = 142)<br>n (%) | Total (N = 385)<br>n (%) | Randomized (N = 117)<br>n (%) | Randomized (N = 105)<br>n (%) | Open-Label (N = 47)<br>n (%) | Total (N = 131)<br>n (%) |
| Number of Events                                       | 1055                          | 985                           | 649                           | 1634                     | 481                           | 412                           | 271                          | 683                      |
| Subjects with At Least One Event                       | 227 (74)                      | 236 (74)                      | 113 (80)                      | 229 (78)                 | 89 (76)                       | 82 (78)                       | 39 (83)                      | 108 (82)                 |
| Diarrhea                                               | 23 (7)                        | 18 (6)                        | 10 (7)                        | 27 (7)                   | 9 (8)                         | 7 (7)                         | 6 (13)                       | 13 (10)                  |
| Nausea                                                 | 22 (7)                        | 31 (10)                       | 14 (10)                       | 42 (11)                  | 11 (9)                        | 9 (9)                         | 2 (4)                        | 11 (8)                   |
| Vomiting                                               | 19 (6)                        | 24 (8)                        | 12 (9)                        | 34 (9)                   | 2 (2)                         | 8 (8)                         | 3 (6)                        | 9 (7)                    |
| Pyrexia                                                | 11 (4)                        | 15 (5)                        | 8 (6)                         | 22 (6)                   | 4 (3)                         | 4 (4)                         | 1 (2)                        | 5 (4)                    |
| Pneumonia                                              | 9 (3)                         | 6 (2)                         | 11 (8)                        | 17 (4)                   | 3 (3)                         | 5 (5)                         | 1 (2)                        | 6 (5)                    |
| Upper Respiratory Tract Infection                      | 11 (4)                        | 9 (3)                         | 10 (7)                        | 19 (5)                   | 1 (1)                         | 1 (1)                         | 3 (6)                        | 4 (3)                    |
| Arteriovenous Fistula Site Complication                | 16 (5)                        | 23 (7)                        | 4 (3)                         | 26 (7)                   | 13 (11)                       | 9 (9)                         | 3 (6)                        | 12 (9)                   |
| Fall                                                   | 10 (3)                        | 12 (4)                        | 2 (1)                         | 14 (4)                   | 6 (5)                         | 9 (9)                         | 2 (4)                        | 11 (8)                   |
| Back Pain                                              | 12 (3)                        | 10 (3)                        | 8 (6)                         | 18 (5)                   | 7 (6)                         | 5 (5)                         | 2 (4)                        | 7 (5)                    |
| Muscle Spasms                                          | 20 (7)                        | 21 (7)                        | 26 (18)                       | 46 (12)                  | 7 (6)                         | 10 (10)                       | 6 (13)                       | 16 (12)                  |
| Pain In Extremity                                      | 14 (5)                        | 9 (3)                         | 7 (5)                         | 16 (4)                   | 8 (7)                         | 7 (7)                         | 3 (6)                        | 10 (8)                   |
| Dizziness                                              | 21 (7)                        | 16 (5)                        | 12 (9)                        | 27 (7)                   | 3 (3)                         | 7 (7)                         | 4 (9)                        | 11 (8)                   |
| Headache                                               | 14 (5)                        | 26 (8)                        | 16 (11)                       | 39 (10)                  | 5 (4)                         | 3 (3)                         | 2 (4)                        | 5 (4)                    |
| Cough                                                  | 15 (5)                        | 17 (5)                        | 9 (6)                         | 25 (7)                   | 10 (9)                        | 3 (3)                         | 4 (9)                        | 7 (5)                    |
| Dyspnea                                                | 17 (6)                        | 21 (7)                        | 13 (9)                        | 33 (9)                   | 9 (8)                         | 4 (4)                         | 4 (9)                        | 8 (6)                    |

Clinical Review  
BLA 125545  
“Epoetin Hospira”

|                                           |        |        |         |         |       |       |        |        |
|-------------------------------------------|--------|--------|---------|---------|-------|-------|--------|--------|
| Pruritus                                  | 9 (3)  | 6 (2)  | 7 (5)   | 13 (3)  | 1 (1) | 2 (2) | 3 (6)  | 5 (4)  |
| Hypertension                              | 16 (5) | 18 (6) | 8 (6)   | 26 (7)  | 2 (2) | 6 (6) | 0 (0)  | 6 (5)  |
| Hypotension                               | 19 (6) | 9 (3)  | 7 (5)   | 16 (4)  | 9 (8) | 5 (5) | 5 (11) | 9 (7)  |
| <b>Adverse Events of Special Interest</b> |        |        |         |         |       |       |        |        |
| Hypertension                              | 17 (6) | 21 (7) | 8 (6)   | 29 (8)  | 2 (2) | 6 (6) | 0 (0)  | 6 (5)  |
| Cerebrovascular Events                    | 3 (1)  | 3 (1)  | 3 (2)   | 6 (2)   | 3 (3) | 1 (1) | 2 (4)  | 3 (2)  |
| Myocardial Infarction                     | 2 (1)  | 3 (1)  | 3 (2)   | 6 (2)   | 1 (1) | 1 (1) | 0 (0)  | 1 (1)  |
| Potential Allergic Reactions              | 4 (1)  | 9 (3)  | 5 (4)   | 14 (4)  | 2 (2) | 1 (1) | 1 (2)  | 2 (2)  |
| Pure Red Cell Aplasia                     | 0      | 0      | 0       | 0       | 0     | 0     | 0      | 0      |
| Seizures                                  | 1 (<1) | 0      | 0       | 0       | 0     | 0     | 0      | 0      |
| Thromboembolic Events                     | 19 (6) | 26 (8) | 14 (10) | 39 (10) | 7 (6) | 6 (6) | 5 (11) | 11 (8) |
| Thrombosis of Vascular Access             | 14 (5) | 22 (7) | 10 (7)  | 31 (8)  | 4 (3) | 5 (5) | 4 (9)  | 9 (7)  |

Source: BLA submission, Module 2.7.4, Table 62, P. 181.

Race:

The rates of TEAEs across treatment groups were slightly higher among White patients (76% - 83%) than that among Black/African-American patients (72% - 79%).

The incidences of common TEAEs and AEs of special interest by race are summarized in Table 34.

Table 34: Incidence of Treatment-Emergent Adverse Events by Race (Safety Population)

| System Organ Class or Grouping<br>Preferred Term of Group | White                            |                                  |                            |                             | Black or African-American        |                                  |                            |                             |
|-----------------------------------------------------------|----------------------------------|----------------------------------|----------------------------|-----------------------------|----------------------------------|----------------------------------|----------------------------|-----------------------------|
|                                                           | US-licensed<br>Epogen            | “Epoetin Hospira”                |                            |                             | US-licensed<br>Epogen            | “Epoetin Hospira”                |                            |                             |
|                                                           | Randomized<br>(N = 208)<br>n (%) | Randomized<br>(N = 210)<br>n (%) | Open-<br>Label<br>(N = 89) | Total<br>(N = 257)<br>n (%) | Randomized<br>(N = 185)<br>n (%) | Randomized<br>(N = 194)<br>n (%) | Open-<br>Label<br>(N = 89) | Total<br>(N = 234)<br>n (%) |
| Number of Events                                          | 928                              | 851                              | 549                        | 1400                        | 530                              | 526                              | 345                        | 871                         |
| Subjects with At Least One Event                          | 158 (76)                         | 168 (80)                         | 73 (82)                    | 213 (83)                    | 139 (75)                         | 140 (72)                         | 70 (79)                    | 176 (75)                    |
| Diarrhea                                                  | 23 (11)                          | 14 (7)                           | 10 (11)                    | 23 (9)                      | 6 (3)                            | 11 (6)                           | 6 (7)                      | 17 (7)                      |
| Nausea                                                    | 24 (12)                          | 25 (12)                          | 9 (10)                     | 33 (13)                     | 9 (5)                            | 15 (8)                           | 6 (7)                      | 19 (8)                      |
| Vomiting                                                  | 12 (6)                           | 18 (9)                           | 8 (9)                      | 24 (9)                      | 9 (5)                            | 14 (7)                           | 7 (8)                      | 19 (8)                      |
| Pyrexia                                                   | 6 (3)                            | 12 (6)                           | 4 (5)                      | 16 (6)                      | 9 (5)                            | 7 (4)                            | 5 (6)                      | 11 (5)                      |
| Pneumonia                                                 | 7 (3)                            | 4 (2)                            | 3 (3)                      | 7 (3)                       | 5 (3)                            | 7 (4)                            | 8 (9)                      | 15 (6)                      |

Clinical Review  
BLA 125545  
“Epoetin Hospira”

|                                         |         |         |         |         |        |         |         |         |
|-----------------------------------------|---------|---------|---------|---------|--------|---------|---------|---------|
| Upper Respiratory Tract Infection       | 7 (3)   | 4 (2)   | 7 (8)   | 11 (4)  | 5 (3)  | 5 (3)   | 6 (7)   | 11 (5)  |
| Arteriovenous Fistula Site Complication | 11 (5)  | 12 (6)  | 4 (5)   | 16 (6)  | 17 (9) | 19 (10) | 2 (2)   | 20 (9)  |
| Fall                                    | 8 (4)   | 17 (8)  | 1 (1)   | 17 (7)  | 7 (4)  | 4 (2)   | 1 (1)   | 5 (2)   |
| Back Pain                               | 10 (5)  | 9 (4)   | 4 (5)   | 13 (5)  | 7 (4)  | 6 (3)   | 5 (6)   | 11 (5)  |
| Muscle Spasms                           | 16 (8)  | 21 (10) | 21 (24) | 41 (16) | 10 (5) | 9 (5)   | 11 (12) | 20 (9)  |
| Pain In Extremity                       | 11 (5)  | 8 (4)   | 7 (8)   | 15 (6)  | 11 (6) | 8 (4)   | 3 (4)   | 11 (5)  |
| Dizziness                               | 20 (10) | 17 (8)  | 9 (10)  | 25 (10) | 4 (2)  | 5 (3)   | 5 (6)   | 9 (4)   |
| Headache                                | 15 (7)  | 17 (8)  | 12 (14) | 26 (10) | 3 (2)  | 12 (6)  | 4 (5)   | 16 (7)  |
| Cough                                   | 14 (7)  | 11 (5)  | 9 (10)  | 19 (7)  | 8 (4)  | 9 (5)   | 3 (4)   | 12 (5)  |
| Dyspnea                                 | 16 (8)  | 12 (6)  | 8 (9)   | 20 (8)  | 6 (3)  | 12 (6)  | 8 (9)   | 19 (8)  |
| Pruritus                                | 9 (4)   | 6 (3)   | 6 (7)   | 12 (5)  | 1 (1)  | 2 (1)   | 4 (5)   | 6 (3)   |
| Hypertension                            | 10 (5)  | 11 (5)  | 3 (4)   | 14 (5)  | 6 (3)  | 12 (6)  | 5 (6)   | 17 (7)  |
| Hypotension                             | 18 (9)  | 6 (3)   | 5 (6)   | 10 (4)  | 8 (4)  | 6 (3)   | 7 (8)   | 13 (6)  |
| Adverse Events of Special Interest      |         |         |         |         |        |         |         |         |
| Hypertension                            | 10 (5)  | 13 (6)  | 3 (4)   | 16 (6)  | 7 (4)  | 13 (7)  | 5 (6)   | 18 (8)  |
| Cerebrovascular Events                  | 3 (1)   | 4 (2)   | 1 (1)   | 5 (2)   | 3 (2)  | 0       | 3 (4)   | 3 (1)   |
| Myocardial Infarction                   | 3 (1)   | 3 (1)   | 1 (1)   | 4 (2)   | 0      | 1 (1)   | 2 (2)   | 3 (1)   |
| Potential Allergic Reactions            | 2 (1)   | 6 (3)   | 2 (2)   | 8 (3)   | 4 (2)  | 4 (2)   | 4 (5)   | 8 (4)   |
| Pure Red Cell Aplasia                   | 0       | 0       | 0       | 0       | 0      | 0       | 0       | 0       |
| Seizures                                | 0       | 0       | 0       | 0       | 1 (1)  | 0       | 0       | 0       |
| Thromboembolic Events                   | 13 (6)  | 17 (8)  | 9 (10)  | 26 (10) | 13 (7) | 15 (8)  | 9 (10)  | 23 (10) |
| Thrombosis of Vascular Access           | 9 (4)   | 13 (6)  | 7 (8)   | 20 (8)  | 9 (5)  | 14 (7)  | 6 (7)   | 19 (8)  |

Source: BLA submission, Module 2.7.4, Table 63, P. 184.

*Reviewer comments: The safety analysis of demographic effect on rate of TEAEs suggested that a higher incidence of TEAEs in female or white patients compared to those reported in male or black patients. However, no difference in TEAEs observed based on patient age (65 years or older vs over 65 years).*

#### 7.5.4 Drug-Disease Interactions

The analysis of effect of presence of diabetes at baseline on the overall incidence of TEAEs showed that the rate of TEAEs across treatment groups in patients with diabetes at baseline (75% - 81%) was comparable to that in subjects without diabetes at baseline (69% - 81%). In addition the rate of special interest AEs were generally similar between patients with and without diabetes at baseline.

The analysis of effect of history of thromboembolic events at baseline on the overall incidence of TEAEs showed that the rate of TEAEs across treatment groups in patients with history of thromboembolic events at baseline (77% - 85%) was higher than that in subjects without history of thromboembolic events at baseline (71% - 78%). In addition the rate of special interest AEs were generally similar between patients with and without history of thromboembolic events at baseline.

#### 7.5.5 Drug-Drug Interactions

No specific drug-drug interaction studies were conducted as part of the “Epoetin Hospira” clinical development program.

### 7.6 Additional Safety Evaluations

#### 7.6.1 Human Carcinogenicity

N/A

#### 7.6.2 Human Reproduction and Pregnancy Data

No events of pregnancy were reported by subjects who participated in the clinical program. Per the US-licensed Epogen US Package Insert, the US-licensed Epogen reference product is Pregnancy Category C.

#### 7.6.3 Pediatrics and Assessment of Effects on Growth

No pediatric studies have been conducted as part of this clinical program. An agreement has been reach on the Applicant’s initial pediatric study plan to support the Pediatric Research Equity Act requirement.

Table 35 summarizes the agreed upon initial Pediatric Study Plan for “Epoetin Hospira.”

Table 35: Summary of Pediatric Study Plan for “Epoetin Hospira”

| <b>Adult Indications</b>                                                                                             | <b>Pediatric Information in Package Insert Labeling for US-licensed Epogen</b>                                                                                                                                                                                                                                                                                                                         | <b>Approach for “Epoetin Hospira” Study Plan</b>                                                                                                                                                                                                                                                        |
|----------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Anemia due to CKD in patients on dialysis and not on dialysis                                                        | US-licensed Epogen is indicated in pediatric patients, ages 1 month to 16 month years of age, for the treatment of anemia associated with CKD requiring dialysis. Safety and effectiveness in pediatric patients less than 1 month old have not been established. The safety data from these studies are similar to those obtained from the studies of Epogen in adult patients with CKD.              | Extrapolation of the pediatric information from the US-licensed Epogen <sup>®</sup> , to the proposed biosimilar product, “Epoetin Hospira”, for patients 1 month and older in the context of the proposed biosimilar development program.<br>Partial Waiver Requested for Age Group 0 to <1 Month.     |
| Anemia due to concomitant Myelosuppressive chemotherapy                                                              | US-licensed Epogen is indicated in patients 5 to 18 years old for the treatment of anemia due to concomitant myelosuppressive chemotherapy. Safety and effectiveness in pediatric patients less than 5 years of age have not been established. The safety data from these studies are similar to those obtained from the studies of Epogen in adult patients with cancer.                              | Extrapolation of the pediatric information from the US-licensed Epogen <sup>®</sup> , to the proposed biosimilar product, “Epoetin Hospira”, for patients 5 years and older in the context of the proposed biosimilar development program.<br>Partial Waiver Requested for Age Group 0 to <5 Years.     |
| Anemia due to Zidovudine in HIV-infected patients                                                                    | Published literature has reported the use of the US-licensed Epogen in 20 zidovudine-treated, anemic, pediatric patients with HIV infection, ages 8 months to 17 years, treated with 50 to 400 Units/kg subcutaneously or intravenously 2 to 3 times per week. Increases in hemoglobin levels and in reticulocyte counts and decreases in or elimination of red blood cell transfusions were observed. | Extrapolation of the pediatric information from the US-licensed Epogen <sup>®</sup> , to the proposed biosimilar product, “Epoetin Hospira”, for patients 8 months to 17 years in the context of the proposed biosimilar development program.<br>Partial Waiver Requested for Age Group 0 to <8 Months. |
| Reduction of allogeneic red blood cell transfusions in patients undergoing elective, noncardiac, nonvascular surgery | No information for pediatric use in the reference product label.                                                                                                                                                                                                                                                                                                                                       | Full Waiver Requested for Age Group 0 to 18 Years.                                                                                                                                                                                                                                                      |

#### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were no adverse event of overdose with “Epoetin Hospira” or US-licensed Epogen reported in the clinical program. Cases of severe hypertension have been observed following overdose with ESAs. Withdrawal of ESAs may lead to decrease in Hb and hematocrit.

## **7.7 Additional Submissions / Safety Issues**

Analyses of adverse events of special interest were discussed in Section 7.3.5.

## **8 Postmarket Experience**

The Applicant provided post marketing experiences from the Hospira’s biosimilar European approved Retacrit. However, the information was not reviewed due to manufacturing differences between the EU-approved Retacrit and the “Epoetin Hospira” manufactured in US.

## **9 Appendices**

### **9.1 Literature Review/References**

- 1- Kausz AT, Khan SS, Abichandani R, et al. Management of patients with chronic renal insufficiency in the Northeastern United States. J Am Soc Nephrol 2001 Jul; 12(7):1501-1507.
- 2- Nassif ME, Patel JS, Shuster JE, et al. Clinical outcomes with use of erythropoiesis stimulating agents in patients with the Heart Mate II left ventricular assist device. JACC Heart Fail. 2015 Feb; 3(2):146-53.
- 3- United States Renal Data System; 2012. Annual Data Report. Vol 2, Chapter 11. Costs of ESRD. Available at: [http://www.usrds.org/2012/view/v2\\_11.aspx](http://www.usrds.org/2012/view/v2_11.aspx).

### **9.2 Labeling Recommendations**

No labeling recommendations were made for this application.

### **9.3 Advisory Committee Meeting**

An advisory committee meeting was not held due to the complete response issue discussed in Section 1.1.

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

SALEH AYACHE  
09/11/2015

ROMEO A DE CLARO  
09/11/2015