Original Research

Pharmacokinetic and Pharmacodynamic Equivalence of Epoetin Hospira and Epogen After Single Subcutaneous Doses to Healthy Male Subjects

Dennis Stalker, PhD; Susan Reid, MEd, PMP; Atulkumar Ramaiya, PhD; Wayne A. Wisemandle, MA; and Nancy E. Martin, PharmD, MD

Global Clinical Development, Hospira, Inc, Lake Forest, Illinois

ABSTRACT

Purpose: The purpose of this study was to evaluate the pharmacokinetic (PK) and pharmacodynamic (PD) equivalence of single 100 U/kg subcutaneous doses of Epoetin Hospira and Epogen in healthy male subjects as part of an overall program to demonstrate biosimilarity of Epoetin Hospira to the reference product Epogen.

Methods: This single-center, open-label, randomized, 2-period, crossover study was conducted in 81 healthy male subjects. Subjects were randomized to Sequence 1, in which they received 100 U/kg of Epoetin Hospira or to sequence 2, in which they received 100 U/kg Epogen subcutaneously in the first study period and the alternative treatment in the second study period. Blood was collected for determination of baseline-adjusted epoetin concentrations (BAECs) for pharmacokinetics and for determination of reticulocyte percentage of total erythrocytes for pharmacodynamics throughout both study periods. The primary PK end points were the geometric mean ratios (GMRs) of the 2 treatments for AUC_{0-t} and C_{max} based on the BAEC, and the primary PD end points were the GMRs of the 2 treatments for AUC_{0-t} and C_{max} for reticulocyte percentage.

Findings: The GMRs of Epoetin Hospira to Epogen for the BAEC-derived PK parameters were 1.05 for AUC_{0-t} with a 90% CI of 1.01 to 1.11, and 1.09 for C_{max} with a 90% CI of 1.01 to 1.18, with both 90% CIs contained within the prespecified equivalence margin of 0.80 to 1.25. The GMRs (Epoetin Hospira/Epogen) for the reticulocyte percentage–derived PD parameters were 1.01 for AUC_{0-t} with a 95% CI of 0.98 to 1.05, and 1.02 for C_{max} with a 95% CI of 0.98 to 1.06, with both 95% CIs contained within the prespecified equivalence margin of 0.80 to 1.25. Overall, the adverse events were of similar frequency (11.7% and 13.9% for Epoetin Hospira and Epogen, respectively) and severity between treatments. One subject had a positive anti– recombinant human erythropoietin antibody result by radioimmunoprecipitation assay before dosing and throughout the conduct of the study with negative neutralizing antibodies and with no evidence of clinical deterioration or impact on the pharmacokinetics, pharmacodynamics, or safety.

Implications: The results of this study established the PK and PD equivalence of single 100 U/kg subcutaneous doses of the proposed biosimilar Epoetin Hospira to the reference product Epogen in healthy male subjects and support the overall demonstration of biosimilarity of Epoetin Hospira and Epogen. (*Clin Ther.* 2016;38:1778–1788) © 2016 Published by Elsevier HS Journals, Inc.

Key words: biosimilar, epoetin alfa, equivalence, erythropoietin, pharmacokinetics, pharmacodynamics.

INTRODUCTION

Erythropoietin is an essential growth factor required for the production of red blood cells. The oxygen content of blood delivered to the renal interstitial cells is believed to be the stimulus for erythropoietin production. When the peritubular renal cells are functioning correctly, low hemoglobin concentrations

Accepted for publication June 10, 2016.
http://dx.doi.org/10.1016/j.clinthera.2016.06.010
0149-2918/$ - see front matter

will increase production of erythropoietin, resulting in increased red blood cell production.[1–3]

Epogen® (epoetin alfa Amgen) is a recombinant human erythropoietin approved for intravenous or subcutaneous administration for the treatment of anemia due to chronic kidney disease in adult and pediatric patients, anemia due to zidovudine therapy in human HIV–infected patients, and anemia due to concomitantly administered chemotherapy in adult and pediatric patients with nonmyeloid malignancies. It is also approved for the reduction of allogeneic red blood cell transfusions in patients undergoing elective noncardiac, nonvascular surgery.[4]

The passage of the Biologics Price Competition and Innovation Act of 2009 creating a licensure pathway for biosimilar biological products,[5] and issuance of US Food and Drug Administration Guidance for demonstration of biosimilarity[6] prompted development of biosimilars as alternatives to the originator molecules, with the potential to increase access treatment.[7] In Europe, specific guidance for biosimilar approval was developed in 2005[8] by the European Medicines Agency.

Epoetin Hospira (epoetin alfa Hospira) was developed as a biosimilar product for the same indications, dose, and administration as the reference product, Epogen. Epoetin Hospira consists of a single-chain, monomeric, glycosylated polypeptide of 165 amino acids with an apparent molecular weight of 30,400 Da, identical in amino acid sequence and comparable in carbohydrate composition to that of Epogen.

Unlike small molecule drugs, whose homogeneous structure can usually be well defined at the molecular level, large-molecule protein therapeutics, particularly glycosylated proteins, are typically more complex heterogeneous mixtures and are unlikely to be shown to be structurally identical to a reference product. Many potential differences in these glycoprotein structures can arise. Because even minor structural differences (including certain changes in glycosylation patterns) may affect a protein's PK and PD properties, safety, purity, and/or potency, it is important to evaluate any potential differences.[6]

In this context, it is important to note that every biological drug displays a certain degree of variability ("microheterogeneity"), even between different batches of the same product, due to the inherent variability of the biological expression system and the manufacturing process.[9] Because biosimilars are produced by their own independent manufacturing process, the resulting biosimilar and the respective originator product (the reference product) can technically never be entirely "identical."[9] However, the analytical variability of the biosimilar is not expected to be greater than that of the reference product[9,10] or to result in clinically meaningful differences. Therefore, biosimilar products must have efficacy and safety similar to those of the originator product.

For these reasons, the requirements for approval for biosimilar products are more stringent than those for small-molecule generic products in which PK equivalence is generally all that is required to demonstrate equivalence of a generic small molecule to the originator small molecule for regulatory approval purposes.[11] Biosimilarity to a reference product must be demonstrated by analytical characterization, animal studies, clinical PK and PD studies, and, if required, comparative clinical studies in a relevant target patient population.[6]

The purpose of this study was to evaluate the PK and PD equivalence of single doses of Epoetin Hospira and Epogen when administered subcutaneously to healthy male volunteers. The comparative safety and tolerability of Epoetin Hospira and Epogen were also assessed.

MATERIALS AND METHODS

Study Population

The study included healthy nonsmoking male volunteers 18 to 55 years of age who provided written informed consent and who, before randomization, had a body mass index between 18.5 and 32.0 kg/m^2; weighed <100 kg; had hemoglobin values in the range of 13.5 to 15.5 g/dL, a reticulocyte count of $\leq 3\%$, erythropoietin concentration of ≤ 30 mIU/mL, a ferritin level >20 ng/mL, transferrin saturation of 20% to 50%, and a creatinine level of ≤ 1.3 mg/dL; and agreed to abstain from alcohol consumption for the duration of the study. Subjects with active, systemic, or immunologic disease; a history of bleeding abnormalities or clinically significant abnormal laboratory evaluations; or who had donated or lost ≥ 475 mL of blood within 3 months before study drug administration were excluded. This study was conducted using a crossover design in healthy male volunteers and using the most sensitive design and population to detect any meaningful differences in PK and PD should they exist. Female subjects were excluded to eliminate any heterogeneity that could