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REVIEW

Clinical efficacy and safety of SB309, a biosimilar recombinant human erythropoietin, in the management of anemia

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Abstract: In this second part of a series of three reviews of approved biosimilar erythropoietins, we review the evidence pertaining to the clinical efficacy and safety of SB309 relative to the originator product Eprex®/Erypo®. As in the first review, clinical efficacy is assessed with respect to the therapeutic equivalence of the biosimilar and originator product, while safety is evaluated in terms of immunogenicity, venous thromboembolism, and mortality. Seven studies in chronic renal failure and oncology populations are reviewed. In the renal setting, these include two randomized controlled trials on hemoglobin correction and maintenance in patients receiving long-term hemodialysis; open extension safety studies from both trials analyzed as a pooled database; a post hoc analysis on biosimilar and originator switching; a therapeutic equivalence study of subcutaneously administered SB309 and Eprex/Erypo; and a single-center experience study. In the cancer setting, one open-label non-controlled study is reported. Based on the available therapeutic equivalence and safety data, the clinical and safety outcomes of treatment with SB309 are likely to be similar to those of the originator product Eprex/Erypo. Both products can be considered interchangeable in the management of anemia for the approved indications. Patients transferred from reference product to biosimilar can be expected to show the same efficacy and safety outcomes. There is no evidence of the interchangeability of SB309 with other biosimilar or originator erythropoietins. In keeping with European Medicine Agency guidance regarding traceability, it is recommended that clinicians document the product by its commercial name, especially when switching patients from originator to biosimilar or vice versa.

Keywords: biosimilars, biosimilar pharmaceuticals, efficacy, safety, erythropoietin, recombinant proteins

Introduction

This second paper in a series of three reviews[1] of the clinical efficacy and safety of biosimilar recombinant human erythropoietins approved by the European Medicine Agency (EMA) is focused on SB309, which the EMA approved on October 18, 2007, and is marketed as Retacrit (Hospira, Inc., Lake Forest, IL, USA) but is also known as Silapo®, Eqralys, and Epobel. As detailed further in Table 1, in the renal setting, SB309 is approved for patients with chronic renal failure on hemo- or peritoneal dialysis, or in patients with advanced renal disease not yet on renal replacement therapy. In the cancer setting, SB309 is indicated for patients with solid tumors, or patients with malignant lymphoma or multiple myeloma receiving chemotherapy and at risk for transfusion. The SB309 label also includes patients participating in autologous blood predonation programs so as to increase the yield, as well as in patients undergoing major elective orthopedic surgery to reduce their exposure to allogeneic blood transfu-

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Table 1 Therapeutic indications for SB309

Chronic renal insufficiency	Treatment of symptomatic anemia associated with chronic renal failure in adult and pediatric patients on hemodialysis. Treatment of symptomatic anemia associated with chronic renal failure in adult patients on peritoneal dialysis. Treatment of severe anemia of renal origin accompanied by clinical symptoms in adult patients with renal insufficiency not yet undergoing dialysis.
Cancer	Treatment of anemia and reduction of transfusion requirements in adult patients receiving chemotherapy for solid tumors, malignant lymphoma, or multiple myeloma, and at risk of transfusion as assessed by the patient's general status (eg, cardiovascular status, pre-existing anemia at the start of chemotherapy).
Autologous predonation program	To increase the yield of autologous blood from patients in a predonation program. Use must be balanced against the reported risk of thromboembolic events. Treatments should only be given to non-iron deficient patients with moderate anemia (hemoglobin between 10 g/dL and 13 g/dL), if blood-saving procedures are not available or insufficient when the scheduled major elective surgery requires a large volume of blood (four or more units of blood for females or five or more units for males).
Major elective orthopedic surgery	To reduce exposure to allogeneic blood transfusions in adult noniron deficient patients prior to major elective orthopedic surgery, having a high perceived risk for transfusion complications. Use should be restricted to patients with moderate anemia (hemoglobin between 10 g/dL and 13 g/dL) who do not have an autologous predonation program available and with expected moderate blood loss (900 mL to 1800 mL).

Note: data obtained from the European Medicines Agency (EMA).[2]

sion. Contraindications for SB309, as specified in the EMA label,[2] are listed in Table 2.

Table 2 Contraindications for SB309

Hypersensitivity to the active substance or to any of the excipients.
Patients who develop pure red cell aplasia following treatment with any epoetin.
Uncontrolled hypertension.
Patients who for any reason cannot receive adequate antithrombotic prophylaxis.
In the indication "increasing the yield of autologous blood:" myocardial infarction or stroke in the month preceding treatment, unstable angina pectoris, and increased risk of deep venous thrombosis such as history of venous thromboembolic disease.
In the indication of major elective orthopedic surgery: severe coronary, peripheral arterial, carotid, or cerebral vascular disease, including patients with recent myocardial infarction or cerebral vascular accident.

Note: data obtained from the European Medicines Agency (EMA).[2]

Scope and approach

This review includes controlled pre- and post-authorization trials and post-approval observational studies involving patients.

The primary evidence for this review is the EMA's European Public Assessment Report documents for SB309 as posted on the EMA website.[2] As for the prior review,[1] we searched PubMed, OvidSP, Web of Science, and Google Scholar as far back as 2000, for articles published in peer-reviewed journals. Abstracts and posters were excluded because of the inherent limits in the depth of reporting. All European Public Assessment Report and associated documents are publicly available from the EMA website.[2] The manufacturer of SB309 was not approached for information.

Consistent with our prior review,[1] we describe each study in terms of objectives, endpoints, design, and patient populations studied. Efficacy and effectiveness results are reported in detail. Safety data focus on immunogenicity, venous thromboembolism (VTE), and mortality, which are the major clinical safety issues concerning the class of erythropoiesis-stimulating agents (ESA). For other safety concerns, we refer to our recent comprehensive review of the clinical safety of biosimilar erythropoietins.[3] Other methodological information may be found in the HX575[1] paper.

Clinical studies

Overview

The late-stage clinical development program of SB309 submitted to the EMA included one Phase III hemoglobin (Hb) correction study of 609 stage 5 chronic kidney disease (CKD5) patients on hemodialysis with or without prior ESA treatment (study 411-54-04-05-0000, hereafter 04-05)[2,4]; one Phase III Hb maintenance study of 313 CKD5 patients on hemodialysis and prior ESA treatment (411-54-04-04-0000, hereafter 04-04)[5]; open extension safety studies of trials 04-05 and 04-04 involving 745 patients (study 411-54-04-14-0000, hereafter 04-14)[6]; and one study of 462 CKD5 patients evaluating the therapeutic equivalence of SB309 and Eprex®/Erypo® subcutaneous (SC) (Johnson & Johnson, New Brunswick, NJ, USA) for maintenance treatment of renal anemia (study 411-54-07-08-0000, hereafter 07-08).[7] In addition, one article presented a post hoc analysis of switching between Eprex/Erypo and SB309 using data from studies 04-05, 04-04, and 04-14 (study PHS)[8]; and one article reported on a single dialysis center study (study SDC).[9] In the oncology setting, the clinical development program included

an open-label non-controlled study on cancer patients with chemotherapy-induced anemia (study 441-54-04-46-0000, hereafter 04-46).[10] Excluded from our review is a report on two cases of anemia correction in hemodialysis patients with thalassemia minor treated with SB309. This was not a formal study and the indication is at best tangential to the label (Table 1).[11]

Study 04-05: Hb correction in CKD5 patients on hemodialysis and with or without prior ESA treatment

Methods

The primary objective of study 04-05[4] was to evaluate the efficacy and safety of treatment with SB309 compared to Eprex/Erypo, both administered intravenously (IV), in the correction of Hb levels in hemodialysis patients with Hb levels <9 g/dL. The intent was to document the therapeutic equivalence of SB309 IV relative to Eprex/Erypo IV in this population.

The study was designed as a randomized, double-blind, multicenter Phase III trial in which hemodialysis patients were allocated in a 1:1 scheme to SB309 IV or Eprex/Erypo IV and treated for 24 weeks following a run-in period of 6 weeks. Both erythropoietin-naïve patients and patients previously exposed to erythropoietins were eligible.

The primary endpoint of interest to this review was the mean Hb concentration during the last 4 weeks of the trial period. Relevant secondary endpoints were: the increase in Hb levels from baseline to week 24; mean Hb concentration during each 4-week interval; the proportions of patients with Hb >11 g/dL for 2 consecutive weeks (treatment success), with Hb of 11.0±1.0 g/dL for 4 consecutive weeks (maintenance success), or with an increase in Hb >1.0 g/dL for 4 weeks; mean percentage of Hb measurements >10 g/dL; and proportion of patients requiring blood transfusions during the treatment period.

Patients

The sample consisted of male and female adult hemodialysis patients with baseline Hb <9 g/dL, with or without prior erythropoietin treatment, and despite optimal iron supplementation therapy. In addition to common exclusion criteria for studies in erythropoietic therapy involving hemodialysis patients, relevant exclusion criteria were detectable anti-erythropoietin antibodies with clinical symptoms, relative or absolute iron deficiency, or clinically relevant changes to dialysis during the trial period.

A total of 780 patients were screened, of whom 305 were randomized to the SB309 and 304 to the Eprex/Erypo arm. The per-protocol analysis set included 273 patients in the SB309 arm and 268 patients in the Eprex/Erypo arm. As detailed in Table 3, the two treatment arms were similar in terms of sex, age, weight, time since diagnosis of chronic renal failure, and Hb concentrations at screening/baseline.

Efficacy

Primary and secondary efficacy endpoints are summarized in Table 4. The difference in mean Hb over the last 4 weeks of treatment was –0.02 ($P>0.05$, not significant [ns]). The 95% confidence interval (CI) of –0.25 to 0.20 was within the predefined equivalence range of ±1.0 g/dL. Both treatment arms showed statistically similar increases in Hb levels from baseline to week 24 ($P>0.05$, ns). The proportions of patients in the SB309 and Eprex/Erypo arms with treatment success and maintenance success were statistically similar (both $P>0.05$, ns), as were the proportions of patients showing an increase in Hb exceeding 1 g/dL for 4 weeks ($P>0.05$, ns). The difference in mean percentage of Hb concentrations >10 g/dL was not statistically significant. Similar proportions of patients in both arms received a blood transfusion ($P>0.05$, ns).

Safety

Assays identified eleven patients positive for anti-erythropoietin antibodies, however all these patients were positive at screening and hence a relationship to the study drugs could be excluded. These eleven patients completed the trial. No patients developed neutralizing antibodies during the 24-week trial period. Arteriovenous fistula thrombosis was observed in 2.3% of SB309-treated and 4.6% of Eprex/Erypo-treated patients. Thirteen patients in the SB309 arm died during the study period. Ten of these deaths were not attributed to SB309 treatment, and one death was unlikely, one possibly

Table 3 Patient characteristics in study 04-05

Characteristic	SB309 (n=305)	Eprex®/Erypo®[a] (n=304)
Patients pretreated with epoetin, n (%)	178 (58.4)	180 (59.2)
Male, n (%)	176 (57.7)	177 (58.2)
Age, years (M±SD)	52.3±11.9	53.6±12.7
Weight (kg), median (range)	68.0 (40.0–140.0)	68.0 (40.0–115.0)
Time since end-stage renal failure diagnosis, months	24.0	26.0
Hb, g/dL (M±SD)	8.07±0.79	8.04±0.79

Notes: [a]Johnson & Johnson, New Brunswick, NJ, USA. Data obtained from Krivoshiev et al.[4]

Abbreviations: n, number; M, mean; SD, standard deviation; Hb, hemoglobin.

Table 4 Efficacy endpoints in study 04-05

	SB309 (n=305)	Eprex®/Erypo®[a] (n=304)	*P*
Hb concentration over the last 4 weeks of treatment (g/dL) (M±SD)	11.61±1.27	11.63±1.37	ns
Difference in mean Hb (g/dL)	–0.02		
95% CI	–0.25 to 0.20		
Hb concentration from baseline to week 24 (g/dL) (M±SD)	8.07±0.79 to 11.60±1.37	8.04±0.79 to 11.61±1.44	ns
Proportion of treatment success (%)	84.2	85.8	ns
Proportion of maintenance success (%)	86.4	84.7	ns
M±SD percentage of Hb measurements >10 g/dL	64.3±24.0	65.7±23.7	ns
Blood transfusions	10	9	ns

Notes: [a]Johnson & Johnson, New Brunswick, NJ, USA. Data obtained from Krivoshiev et al.[4]
Abbreviations: n, number; Hb, hemoglobin; M, mean; SD, standard deviation; ns, not significant; CI, confidence interval.

related, and one not assessable. Of the sixteen deaths in the Eprex/Erypo arm, twelve were judged unrelated, three as unlikely to be related, and one as not assessable. These differences were statistically non-significant. Additional safety data have been summarized elsewhere.[3]

Study 04-04: Hb maintenance in CKD5 patients on hemodialysis and with prior ESA treatment

Methods

The primary objective of this Phase III trial[5] was to evaluate the therapeutic efficacy and safety of SB309 IV compared to Eprex/Erypo IV in maintaining target Hb levels in hemodialysis patients with anemia. The secondary objective was to evaluate the safety profile of SB309 IV relative to Eprex/Erypo IV.

The study was designed as a randomized, double-blind, crossover, multiple-dose, international Phase III trial with two phases: an open run-in phase and a double-blind phase. The open run-in phase was included so that patients could be brought to the randomization criterion of a stable Hb in the target range of 10.5–12.5 g/dL. The run-in phase lasted for 12–16 weeks, with the option to extend this time to 18 weeks. In the double-blind phase, patients received either SB309 IV or Eprex/Erypo IV one to three times per week for 12 weeks, then were cross-over to receive the other product for another 12 weeks.

The primary efficacy endpoint of relevance to this review was the difference in mean absolute change in Hb levels, with the equivalence margin set as the 95% CI falling within ±0.60 g/dL. The secondary endpoints of relevance were the proportion of patients with any permanent or transient changes in Hb levels of more than 1 g/dL, the proportion of patients with one or more Hb measurements outside the target range, and the number of blood transfusions.

Patients

The sample included male and female adult hemodialysis patients with renal anemia who had been treated with epoetin for at least 3 months prior to randomization. In addition to common exclusion criteria for studies on erythropoietic therapy involving hemodialysis patients, relevant exclusion criteria were detectable neutralizing anti-erythropoietin antibodies, known hypersensitivity or known lack of response to erythropoietin, and relative or absolute iron deficiency.

Of the 407 patients screened, 313 were randomized and constituted the safety population. Of the 155 patients allocated to each study arm, 121 in the SB309 and 118 in the Eprex/Erypo arm completed treatment without major protocol violations. As detailed in Table 5, the two treatment arms were similar in terms of sex, age, height, weight, time since diagnosis of chronic renal failure, and Hb concentrations at screening/baseline.

Efficacy

As shown in Table 6, the difference in mean Hb over the double-blind phase was 0.19 g/dL ($P>0.05$, ns), which was within the predefined equivalence range of ±0.60 g/dL. The proportions of patients in the SB309 and Eprex/Erypo arms with permanent and transient Hb >1 g/dL changes were

Table 5 Patient characteristics in study 04-04

Characteristic	SB309–Eprex®/Erypo®[a] (n=121)	Eprex®/Erypo®[a]–SB309 (n=118)
Male, n (%)	53 (34.2)	72 (45.6)
Age (years), median (range)	57.0 (23.0–76.0)	57.0 (20.0–77.0)
Height (cm), median (range)	169.0 (100.0–196.0)	168.0 (130.0–202.0)
Weight (kg), median (range)	75.5 (45.0–145.0)	72.7 (44.3–110.5)
Time since CKD stage five diagnosis (months), median (range)	37.0 (3.0–347.0)	36.0 (3.0–307.0)
Hemoglobin (g/dL), M (range)	11.6 (8.70–13.40)	11.7 (9.80–13.60)

Notes: [a]Johnson & Johnson, New Brunswick, NJ, USA. Data obtained from Wizemann et al.[5]
Abbreviations: n, number; M, mean; CKD, chronic kidney disease.

Table 6 Efficacy endpoints in study 04-04

	SB309–Eprex®/Erypo®[a] (n=121)	Eprex®/Erypo®[a]–SB309 (n=118)	*P*
Mean Hb levels (g/dL) (range)	11.35 (8.96–14.22)	11.54 (8.74–13.84)	ns
Difference in mean Hb (g/dL) 95% CI	0.19 0.09 to 0.28		
Permanent changes in Hb levels of >1 g/dL (%)	10.5	11.3	ns
Transient changes in Hb levels of >1 g/dL (%)	55.2	56.1	ns
Blood transfusions	3	2	ns

Notes: [a]Johnson & Johnson, New Brunswick, NJ, USA. Data obtained from Wizemann et al.[5]
Abbreviations: n, number; Hb, hemoglobin; CI, confidence interval; ns, not significant.

statistically similar (both $P>0.05$, ns). Similar numbers of patients in both arms received a blood transfusion ($P>0.05$, ns).

Safety

Three patients had positive assays for anti-erythropoietin antibodies, however all these patients were positive at screening and hence a relationship to the study drugs could be excluded. These three patients completed the trial. No patients developed neutralizing antibodies during the trial period. No VTEs were observed. Of the nine recorded deaths, five occurred during the run-in period and one in the month following completion of the study protocol. Of the three patients who died during the double-blind period, two were receiving SB309 and one Eprex/Erypo. These deaths were judged to be unlikely to be related to study medication. Additional safety data have been summarized elsewhere.[3]

Study 04-14: open extension safety studies of 04-05 and 04-04

Methods

Patients enrolled in studies 04-05 and 04-04 were invited to participate in an open extension study in which all patients were treated with SB309[6] IV, including those previously randomized to the Eprex/Erypo IV arm. The duration was 56 weeks for all patients; patients in the Bulgarian centers were followed for 108 weeks. The primary objective was to assess the long-term safety of SB309 IV. The secondary objective was to further evaluate the efficacy of SB309 IV.

The primary endpoint of interest to this review was the assessment of adverse events and the occurrence of anti-erythropoietin antibodies. Relevant secondary endpoints were mean Hb levels, the proportions of patients with any permanent or transient changes in Hb levels of >1 g/dL, proportion of patients with any Hb measurement outside the target range, and the number of blood transfusions.

Patients

The sample consisted of male and female hemodialysis patients who had completed the double-blind treatment period of studies 04-05 and 04-04.[4,5] Of the 745 patients who enrolled in the study, 532 patients completed 56 weeks and 123 also completed 108 weeks of treatment. Characteristics of patients enrolled in study 04-14 were not stated.

Effectiveness

Primary and secondary endpoints are summarized in Table 7. Mean Hb values remained stable over 56 and 108 weeks (both $P>0.05$, ns). The majority of patients experienced permanent (70.9%) and/or transient changes (88.6%) in Hb levels exceeding 1 g/dL, and Hb titers outside the target range of 10.5–12.5 g/dL (90.2%). Forty-eight patients required a blood transfusion.

Safety

Assays identified two patients positive for anti-erythropoietin antibodies, however these patients were positive at screening for the prior trials and hence a relationship to the study drugs could be excluded. No patients developed neutralizing antibodies during the trial period. The incidence of vascular access thrombosis was 0.7%.

A total of 73 patients died during the course of the trial. Death was not attributed to SB309 treatment in 68 patients. The relationship of SAEs to SB309 treatment was assessed as possible in only four cases. One death was not assessable in terms of its relationship to SB309. Four deaths were considered possibly related to SB309 therapy. Additional safety data have been summarized elsewhere.[3]

Table 7 Efficacy endpoints in study 04-14

	56 weeks (n=745)	108 weeks (n=164)	*P*
Hb level (g/dL) (range)	11.3–11.6	11.1–11.6	ns
Permanent changes in Hb levels of >1 g/dL (%)	70.9		
Transient changes in Hb levels of >1 g/dL (%)	88.6		
Hb measurements outside the target range (10.5–12.5 g/dL) (%)	90.2		
Blood transfusions	48		

Note: data obtained from Baldamus et al.[6]
Abbreviations: n, number; Hb, hemoglobin; ns, not significant.

Study PHS: post hoc analysis of 04-05, 04-04, and 04-14 focused on switching between Eprex/Erypo and SB309

Methods

The primary objective of this post hoc analysis[8] was to evaluate the impact on Hb concentration and patient safety of switching hemodialysis patients from Eprex/Erypo IV to SB309 IV, or vice versa. The aim was to document the therapeutic equivalence of SB309 IV relative to Eprex/Erypo IV in this population.

This was a retrospective analysis of the data of randomized trials 04-05 and 04-04 and their open extension study 04-14.[4–6] Patients were classified into four groups. Switch group 1 (n=118) were 04-04 patients who had received Eprex/Erypo IV during the first 12 weeks of the trial and were then switched to SB309 IV for the final 12 weeks. Switch group 2 (n=121) comprised 04-04 patients treated for 12 weeks with SB309 IV and subsequently for 12 weeks with Eprex/Erypo IV. Switch group 3 (n=101) included 04-04 patients on Eprex/Erypo IV during the last 12 weeks of the trial, then switched to SB309 IV in the open extension study, and completing 12 weeks of follow-up period without major protocol violations. Switch group 4 (n=242) consisted of patients in the Eprex/Erypo IV arm of 04–05 and switched to SB309 IV in the open extension study and completing 12 weeks of follow-up without major protocol violations.

The primary endpoint of interest to this review was Hb concentration change and patient safety when switching patients from Eprex/Erypo IV to SB309 IV, or vice versa. The secondary endpoint was to assess the therapeutic equivalence of the two study drugs pre- and post-switch. Hb levels were determined for each group in the 4-week treatment period immediately preceding the switch in study medication and in the last 4 weeks of the 12-week post-switch period. They were considered equivalent if the 95% CI fell within ±1 g/dL.

Patients

Table 8 details patient demographics. There were no statistically significant differences between groups in sex, age, weight, and height.

Effectiveness

Mean Hb levels for all four groups were within the Hb target range of 10.5–12.5 g/dL throughout the time period of interest. As summarized in Table 9, the 95% CI for mean change in Hb concentrations was within the predefined equivalence range of ±1.0 g/dL.

Table 8 Patient characteristics in PHS

Characteristic	Switch group 1 (n=118)	Switch group 2 (n=121)	Switch group 3 (n=101)	Switch group 4 (n=242)
Male, n (%)	64 (54.2)	77 (63.6)	66 (65.3)	142 (58.7)
Age (years), median	57.5	57.0	56.0	54.0
Weight (kg), median	72.8	76.0	74.5	68.0
Height (cm), median	168.0	170.0	170.0	168.0

Note: data obtained from Więcek et al.[8]
Abbreviations: PHS, post hoc study; n, number.

Safety

Safety issues of interest are summarized above in the reviews of the three constituent studies.

Study 07-08: therapeutic equivalence of SB309 SC and Eprex/Erypo SC in anemia maintenance treatment in hemodialysis patients

Methods

The primary objective of this Phase III trial[7] was to examine the therapeutic equivalence of a subcutaneous (SC) formulation of SB309 to Eprex/Erypo SC when maintaining the Hb concentrations in hemodialysis patients. The secondary objective concerned the safety of these formulations with special consideration of immunogenicity issues.

The study was designed as a randomized parallel groups controlled trial of patients undergoing 28 weeks of subcutaneous epoetin treatment one to three times weekly. Following an open run-in period of 12–16 weeks of SB309 SC therapy to achieve stable Hb patients were randomized to either the SB309 SC or Eprex/Erypo SC arms. Following completion of the trial, patients were invited to participate in a 54 weeks open-label observational safety extension study in which all patients received SB309 SC.

The primary endpoints of interest to this review were mean Hb level and the difference in mean change in Hb levels.

Table 9 Efficacy endpoints in PHS

	Switch group 1 (n=118)	Switch group 2 (n=121)	Switch group 3 (n=101)	Switch group 4 (n=242)
Hb levels (g/dL) (M±SD)	0.01±1.00	–0.06±0.96	–0.08±1.16	–0.35±1.66
95% CI	–0.19 to 0.17	–0.77 to –0.43	–0.31 to 0.15	–0.56 to –0.14

Note: data obtained from Więcek et al.[8]
Abbreviations: PHS, post hoc study; n, number; Hb, hemoglobin; M, mean; SD, standard deviation; CI, confidence interval.

The equivalence margin for the latter was set as the 95% CI falling within ±0.5 g/dL. The relevant secondary endpoints of relevance to this review were the proportions of patients with any permanent or transient Hb changes of >1 g/dL, the proportion with Hb measurements outside the target range of 10–12 g/dL, and the number of blood transfusions.

Patients

The sample included male and female adult hemodialysis patients on epoetin treatment for at least 3 months prior randomization. Relevant exclusion criteria were detectable anti-erythropoietin antibodies with clinical symptoms and relative or absolute iron deficiency.

Of the 707 patients screened; 679 were entered into the open run-in phase with SB309; 462 patients were subsequently randomized to either the SB309 (n=232) or Eprex/Erypo (n=230) study arms; and, of these, respectively 121 and 118 patients completed the study without major protocol violations. As detailed in Table 10, the two treatment arms were similar in terms of sex, age, height, weight, time since diagnosis of chronic renal failure, and Hb concentrations at screening/baseline.

Efficacy

Table 11 presents the results for the primary and secondary endpoints. There were no statistically significant differences between groups in mean Hb levels, the proportions of patients with transient or permanent changes in Hb levels and Hb measurements outside the 10–12 g/dL target range, and the number of blood transfusions administered. The 95% CI for the difference in mean absolute Hb change between both arms was within the predefined range.

Safety

No patients developed significant anti-erythropoietin antibodies. VTE rates were 4.4% in the SB309 and 2.0% in the Eprex/Erypo. Thirty-four patients died during the study, including 11 in the run-in period and 23 in the randomized phase. The deaths in the run-in period were assessed as having no relationship to study drug administration. Of the remaining 23 deaths, only two were regarded as having any relationship to the study drugs; one in each group. Additional safety data have been summarized elsewhere.[3]

Table 10 Patient characteristics in study 07-08

Characteristic	SB309 (n=232)	Eprex®/Erypo®[a] (n=230)
Male, n (%)	138 (59.5)	134 (58.3)
Age, years (M±SD)	55.6±12.47	55.2±12.58
Height, cm (M±SD)	167.9±8.77	167.0±9.50
Weight, kg (M±SD)	70.5±15.11	70.8±15.84
Time since end-stage renal failure diagnosis, months (median)	37.0	36.5
Hb, g/dL (M±SD)	10.56±1.35	10.40±1.43

Notes: [a]Johnson & Johnson, New Brunswick, NJ, USA. Data obtained from Więcek et al.[8]
Abbreviations: n, number; M, mean; SD, standard deviation; Hb, hemoglobin.

Table 11 Efficacy endpoints in study 07-08

	SB309 (n=232)	Eprex®/Erypo®[a] (n=230)	P
Mean Hb levels (g/dL) (M±SD)	10.94±0.84	11.02±0.94	ns
Difference in mean Hb (g/dL)	0.08		
95% CI	–0.28 to 0.12		
Permanent changes in Hb levels of >1 g/dL (%)	42.9	35.8	ns
Transient changes in Hb levels of >1 g/dL (%)	85.1	89.7	ns
Hb measurements outside the target range (10.0–12.0 g/dL) (%)	87.0	86.7	ns
Blood transfusions	2	1	ns

Notes: [a]Johnson & Johnson, New Brunswick, NJ, USA. Data obtained from Krivoshiev et al.[7]
Abbreviations: n, number; M, mean; SD, standard deviation; CI, confidence interval; Hb, hemoglobin; ns, not significant.

Study SDC: single-center experience with SB309 IV in hemodialysis patients

Methods

This single-center report[9] describes the outcomes of renal anemia management with SB309 IV in 18 hemodialysis patients. Following a 2-month run-in period, patients were treated for 6 months with SB309 IV. Hb concentrations were measured monthly.

Patients

Eighteen patients were recruited into the study. Seventeen were on ESA therapy at the time of enrollment and one was ESA-naïve.

Efficacy

Mean Hb concentration was 11.72±0.64 g/dL at the start and 11.62±0.70 g/dL (P=0.74) at the end of the 6-month period (P>0.05, ns). One patient required a blood transfusion.

Safety

No immunogenicity issues, VTEs, or deaths were observed.

Study 04-46: management of chemotherapy-induced anemia in cancer patients with SB309 SC

Methods

The study's[10] primary objective of interest was to evaluate the safety and efficacy of SB309 SC in cancer patients with chemotherapy-induced anemia. Designed as an open, non-controlled, multicenter study of SB309 SC one to three times per week, the study included two periods: a fixed 12-week treatment in patients on a chemotherapy regiment of at least 8 weeks; and a follow-on period of 13–36 weeks of treatment for patients on longer chemotherapy regiments. Endpoints of interest were the incidence of clinically significant thrombotic events, change in Hb level, hematopoietic response, and blood transfusion.

Patients

Eligible were male or female adult patients with a solid tumor, malignant lymphoma, or multiple myeloma; a life expectancy of at least 12 weeks; and a planned or actual cyclic chemotherapy regimen of at least 8 weeks. Relevant exclusion criteria ESA therapy or blood transfusion in the 4 weeks prior to the first dose of SB309; uncontrolled hypertension; known hypersensitivity to epoetin or any of the inactive components of SB309; anti-erythropoietin antibodies; inadequate iron supplementation; high VTE risk; and chronic renal failure.

Of the 261 patients screened, 216 were enrolled (safety population) and 100 patients (per-protocol population) completed at least 11 weeks of SB309 therapy. The number of patients completing at least 11 weeks per-protocol, was 100/216 (46.3%). As detailed in Table 12, the two treatment groups were similar in terms of sex, age, time since cancer diagnosis, tumor type, baseline Hb concentration, and proportion having previously been treated with chemotherapy.

Effectiveness

Table 13 summarizes the results for the endpoints of interest. Though increases in both groups were statistically significant, the per-protocol population had a higher mean increase in Hb than the safety population over the 12-week period, (all $P<0.0001$). Proportionately more patients in the per-protocol population achieved the various markers of hematopoietic response.

Safety

No patients developed anti-erythropoietin antibodies during the study. Eleven patients experienced a clinically significant thrombotic event; nine in the first and two in the second treatment period. Within the first treatment period with SB309, nine patients experienced a clinically significant thrombotic event. Three events were fatal, all occurring in the first treatment period. Additional safety data have been summarized elsewhere.[3]

Comments

The studies included here provide adequate evidence about the therapeutic equivalence of IV and SC formulations of SB309 relative to originator Eprex/Erypo. This therapeutic equivalence was demonstrated in the renal (hemodialysis) and oncology (chemotherapy-induced anemia) settings. The target Hb ranges reflected standard clinical practice at the time the studies were conceived. In the more recent studies, the upper boundary of the target Hb range was 12.0 g/dL, in keeping with the revised label for ESAs.

In hemodialysis, the comparative trial design of studies 04-05, 04-04, and 07-08 permitted direct inferences about the therapeutic equivalence of SB309 relative to both the Hb

Table 12 Patient characteristics in study 04-46

Characteristic	Safety population (n=216)	Per-protocol population (n=100)	*P*
Male, n (%)	103 (47.7)	47 (47.0)	ns
Mean age, years (range)	60.02 (18.0–83.0)	60.41 (26–79)	ns
Mean time since cancer diagnosis, months (range)	23.8 (0–212)	24.0 (0–130)	ns
Tumor type			
Solid tumor	115 (53.2)	51 (51.0)	
Malignant lymphoma	71 (32.9)	32 (32.0)	
Multiple myeloma	30 (13.9)	17 (17.0)	
Mean hemoglobin level, g/dL (range)	8.7 (5.6–10.3)	8.6 (6.8–9.9)	ns
Previous chemotherapy	107 (49.5)	53 (53.0)	ns

Note: data obtained from Tzekova et al.[10]
Abbreviations: n, number; ns, not significant.

Table 13 Endpoints in study 04-46

	Safety population (n=216)	Per-protocol population (n=100)	*P*
Increase in Hb level (g/dL) (M±SD) during the first treatment period	1.8±2.04	2.3±1.75	<0.0001
Hb response >11.5 g/dL	48.1	65.0	0.002
Hb response >1 g/dL or reticulocytes counts >40,000 cells/μL			
By week 4 (%)	71.8	80.0	0.033
By week 8 (%)	81.5	96.0	<0.0001
Hb response >2 g/dL or reticulocytes counts >40,000 cells/μL			
By week 8 (%)	70.8	82.0	0.012
Blood transfusions	36	33	ns

Note: data obtained from Tzekova et al.[10]
Abbreviations: n, number; M, mean; SD, standard deviation; CI, confidence interval; Hb, hemoglobin; ns, not significant.

correction (04-05) and Hb maintenance phases (04-04 and 07-08) of anemia management. The PHS further documented the equivalence by examining specific scenarios of switching between treatment with SB309 IV and Eprex/Erypo IV. Together, these studies showed that Hb levels did not differ significantly between SB309- and Eprex/Erypo-treated patients and did not shift significantly when therapy would be changed from one agent to the other.

For chemotherapy-induced anemia, study 04-46 showed the relative therapeutic equivalence of SB309 SC relative to Eprex/Erypo SC in patients with solid tumors, malignant lymphoma, and myeloma. The inference of therapeutic equivalence is indirect as 04-46 was not designed as a comparative study.

The available data indicate that the clinical and safety outcomes of treatment with SB309 can be expected to be similar to those of the originator product Eprex/Erypo in routine clinical practice. Both products can be considered interchangeable; patients transferred from reference product to the biosimilar can be expected to show the same efficacy and safety results.

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References

1. Abraham I, MacDonald K. Clinical efficacy and safety of HX575, a biosimilar recombinant human erythropoietin, in the management of anemia. *Biosimilars*. 2012;2:13–25.
2. European Medicines Agency. Retacrit – summary of the European public assessment report. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000872/human_med_001031.jsp&mid=WC0b01ac058001d124. Updated: October 18, 2011. Accessed October 9, 2012.
3. Abraham I, MacDonald K. Clinical safety of biosimilar recombinant human erythropoietins. *Expert Opin Drug Saf*. 2012;11(5):819–840.
4. Krivoshiev S, Todorov VV, Manitius J, et al. Comparison of the therapeutic effects of epoetin zeta and epoetin alfa in the correction of renal anaemia. *Curr Med Res Opin.* 2008;24:1407–1415.
5. Wizemann V, Rutkowski B, Baldamus C, et al. Comparison of the therapeutic effects of epoetin zeta and epoetin alfa in the maintenance phase of renal anaemia treatment. *Curr Med Res Opin*. 2008;24:625–637.
6. Baldamus C, Krivoshiev S, Wolf-Pflugmann, et al. Long-term safety and tolerability of epoetin zeta, administered intravenously, for maintenance treatment of renal anemia. *Adv Ther.* 2008;25:1215–1228.
7. Krivoshiev S, Wizemann V, Czekalski S, et al. Therapeutic equivalence of epoetin zeta and alfa, administered subcutaneously, for maintenance treatment of renal anemia. *Adv Ther.* 2010;27:105–117.
8. Więcek A, Ahmed I, Scigalla P, Koytchev R. Switching epoetin alfa and epoetin zeta in patients with renal anemia on dialysis: posthoc analysis. *Adv Ther.* 2010;27:941–952.
9. Lonnemann G, Wrenger E. Biosimilar epoetin zeta in nephrology – a single dialysis center experience. *Clin Nephrol.* 2011;75:59–62.
10. Tzekova V, Mihaylov G, Elezovic I, et al. Therapeutic effects of epoetin zeta in the treatment of chemotherapy-induced anaemia. *Curr Med Res Opin.* 2009;25:1689–1697.
11. Kumvhev E, Koytchev R, Dimitrakov D, et al. Effect of epoetin zeta for correction of renal anemia in hemodialysis patients with thalassemia minor. *Adv Ther.* 2008;25:1375–1378.