SCIENTIFIC DISCUSSION

1. Introduction

Patients with chronic renal failure (CRF) develop uraemic anaemia as one of the most obvious signs of the disease. This symptom is caused by impeded renal production of erythropoietin (EPO). EPO is produced primarily in the kidneys and stimulates red blood cell counts (RBC) production by promoting survival, proliferation and differentiation of erythroid progenitors in the bone marrow. Epoetin-containing medicinal products are currently indicated for several conditions besides anaemia in patients with chronic renal failure, namely, chemotherapy induced anaemia in cancer patients, for increasing the yield of autologous blood from patients in a pre-donation programme, and for reducing exposure to allogenic blood transfusions in adult non-iron-deficient patients prior to major elective orthopaedic surgery.

The application for SB309 has been submitted as a "similar biological medicinal product" under Article 10(4) of directive 2001/83/EC (as amended), hereafter referred to as biosimilar.

SB309 has been developed as a biosimilar product referring to epoetin alfa, authorised in the EU, e.g. in the UK under the brand name Eprex (Janssen-Cilag Ltd.) and in Germany under the name Erypo (Ortho Biotech, a division of Janssen-Cilag GmbH).

The claimed indications were:

- Treatment of anaemia associated with chronic renal failure in adult and paediatric patients on haemodialysis and adult patients on peritoneal dialysis.
- Treatment of severe anaemia of renal origin accompanied by clinical symptoms in adult patients with renal insufficiency not yet undergoing dialysis.
- Treatment of anaemia and reduction of transfusion requirements in adult patients receiving chemotherapy for solid tumours, malignant lymphoma or multiple myeloma, and at risk of transfusion as assessed by the patient's general status (e.g. cardiovascular status, pre-existing anaemia at the start of chemotherapy).
- SB309 can be used to increase the yield of autologous blood from patients in a predonation programme. Its use in this indication must be balanced against the reported risk of thromboembolic events. Treatment should only be given to patients with moderate anaemia (haemoglobin (Hb) 10-13 g/dl [6.2-8.1 mmol/l], no iron deficiency), if blood saving procedures are not available or insufficient when the scheduled major elective surgery requires a large volume of blood (4 or more units of blood for females or 5 or more units for males).

The claimed indications initially included also reduction of allogeneic blood transfusions in adult non-iron deficient patients prior to major elective orthopaedic surgery. However, during the CHMP scientific assessment it became evident that efficacy and safety of Epoetin zeta have not been demonstrated for the SC route of administration in immunocompetent patients. Therefore, the applicant withdrew all indications using exclusively the SC route of administration in immunocompetent patients. The remainder of this report focuses on the IV route of administration and the SC route in chemotherapy-related anaemia.

About the product

Human erythropoietin is a single chain, monomeric, glycosylated polypeptide of 165 amino acids. Erythropoietin for clinical use is produced by recombinant DNA technology using mammalian cells as expression system. All epoetins in clinical use have an amino acid sequence similar to endogenous erythropoietin but differ in the glycosylation pattern. Glycosylation influences pharmacokinetics and may affect efficacy and safety, particularly immunogenicity.

The active substance in SB309 (Epoetin zeta) is a recombinant human erythropoietin (rhEPO) of identical primary structure produced in Chinese Hamster Ovary (CHO) cells. The molecular weight of the glycosylated protein is 30.6 kDa according to the Ph. Eur. monograph, 40% of which are

carbohydrate structures. The oligosaccharide chains are subject to posttranslational modifications and display heterogeneity to a certain extent.

To support the claim that SB309 is biosimilar to the reference medicinal product Erypo with regard to quality, safety and efficacy, the applicant has submitted a comparability exercise for a similar biological medicinal product versus the reference medicinal product. The main clinical data for the application submitted by the applicant consists of two pharmacokinetic (PK) trials comparing the PK profiles of SB309 and Erypo after single dose administration, and two phase III trials (one correction phase study and one maintenance phase study) comparing efficacy and safety of intravenously (IV) administered SB309 and Erypo in patients with renal anaemia. Two safety trials are still ongoing (interim data have been provided). The applicant received Scientific Advice from the CHMP (Procedures No. EMEA/H/SA/469/1/2004/III, 2004 and EMEA/H/SA/469/1/FU/1/2005/II, 2005).

2. Quality aspects

Product description

SB309 [epoetin zeta (INN)] solution for injection in pre-filled syringes contains recombinant human erythropoietin (rhu-EPO, epoetin) as drug substance and water for injection, sodium monohydrogen phosphate, sodium dihydrogen phosphate, sodium chloride, calcium chloride, polysorbate 20, glycine, leucine, isoleucine, threonine, glutamic acid and phenylalanine as excipients. The syringes (Type I glass) are provided with a fixed steel needle and a plunger stopper with PTFE coating for intravenous (IV) or subcutaneous (SC) injection. Eleven different quantitative sizes of pre-filled syringes of SB309 will be available containing defined amounts of epoetin of 1,000 IU up to 40,000 IU, respectively.

The drug product is presented as a solution for injection in pre-filled syringes in the following strengths: 3,333 IU/ml (presentation of 0.3, 0.6 and 0.9 ml), 10,000 IU/ml (presentations of 0.4, 0.5, 0.6, 0.8 and 1 ml) and 40,000 IU/ml (presentations of 0.5, 0.75 and 1 ml), with all strengths exhibiting the same qualitative composition.

Drug Substance

Manufacture

The drug substance [epoetin zeta (INN)] is manufactured and released by Norbitec GmbH, D-25436 Uetersen, Germany. After a series of sub cultivations, the cells are seeded into the production fermenter. The production is based on a fed-batch process.

The drug substance is recovered from the fermentation broth by a conventional protein purification process comprising orthogonal chromatography steps and a viral filtration step. The manufacturing steps are monitored by process controls that include operational parameters, acceptance criteria and specifications.

The Master Cell Bank (MCB) was established using foetal calf serum (FCS) from a certified source. The Working Cell Bank (WCB) was established without the use of materials from human or animal origin. The cultivation and all subsequent manufacturing steps are also performed without the use of materials from human or animal origin. The cell culture medium is protein-free and does not contain insulin or antibiotics. The selected cell line was analysed with regard to sequence of epoetin cDNA, growth potential, viability, productivity, genetic stability and viral safety.

Process validation data demonstrate that the process steps from thawing the WCB vial, to harvesting the production bioreactor and purification are consistent. All parameters for upstream process (USP) and downstream process (DSP) were maintained within the defined ranges.

Adventitious Agents

The viral safety of the medicinal product Epoetin zeta is assured. This is confirmed by the experimental finding that the CHO cell substrates (MCB, WCB and Post Production Cells (PPC)) show no biological evidence of any productive viral infection. The inherent risk of viral contamination associated with animal-sourced materials (FCS, porcine trypsin) can be excluded, since the cell culture process occurs in serum- and protein-free medium. The data obtained from the comprehensive virus validation studies demonstrate that the purification procedure possesses a reproducibly high and robust capability for virus clearance.

Characterisation

An extensive characterisation programme has been conducted for the drug substance with respect to the protein backbone as well as the carbohydrate moieties.

An orthogonal set of state-of-the-art analytical methods was established to elucidate structural features of the epoetin zeta protein backbone. The primary structure of epoetin zeta was confirmed using peptide mapping using different enzymes and mass spectroscopy. Epoetin zeta has been shown to contain an intact protein structure with correctly linked disulfide bonds, integrity of the C-and N-termini, and minimal degradation caused by oxidation and deamidation. Secondary structure determination using spectroscopic measurements revealed that the alfa helix represents the predominant structure element conforming to the four-helical bundle topology model as predicted for erythropoietin in the literature.

The carbohydrate moieties in epoetin zeta were characterised using a complementary panel of analytical methods in order to reveal or to exclude unusual glycan structures with a potentially negative impact on the performance of epoetin zeta. The total glycan pool released from the protein backbone was subjected to fractionation by column chromatography and if necessary further sub-fractionation was performed using a different stationary phase in order to yield sub-fractions of sufficient purity. HPAEC-PAD was used as a major analytical tool to classify the glycans with respect to sialylation and antennarity on each level of sub-fractionation. Further analysis of the sub-fractions by mass spectroscopy enabled the ability to identify and/or exclude unique or unusual structures.

Using NMR-techniques, glycan structures were elucidated with respect to their isomeric nature. Positions of N-acetyllactosamine repeats on antennae, lack of sialylation of antennae, position of fucosylation (in order to identify/exclude certain Lewis-motifs) and presence of O-acetylated groups were confirmed. O-glycans were mainly characterised by mass spectrometrical methods of the de-N-glycosylated protein.

Applying this analytical strategy, the carbohydrate content of epoetin zeta was confirmed to be essentially free of unusual, potentially immunogenic structures.

Specification

Appropriate specifications have been set for analysis of the active substance at release and at the end of shelf life.

Stability

The claimed shelf-life of the active substance is supported by batch data.

Comparability Exercise for Active Substance

Epoetin zeta was compared to epoetin alfa, the drug substance of the selected reference product Eprex/Erypo (Janssen-Cilag GmbH). For the comparability exercise the same set of tests and analytical procedures were applied to the drug substance and the drug product.

In accordance with the Guideline on Similar Biological Medicinal Products containing Biotechnology-derived Proteins as Active Substance: Quality Issues (EMEA/CHMP/BWP/49348/2005), the applicant

isolated active substance from the reference medicinal product in order to perform the comparative analysis at the level of the active substances. Isolation was performed by RP-HPLC.

It was demonstrated that the isolated active substance used in the comparability exercise is representative of the active substance present in the reference medicinal product.

In the comparability study focused on the protein backbone, the data obtained demonstrated equivalence between the two epoetin products.

With respect to the glycan moieties, the overall range of structures was found to be comparable. Even upon sub-fractionation of glycans of both products a very similar profile with respect to antennarity and sialylation was revealed. However, the amount of glycoforms without an O-glycan chain was slightly higher for epoetin zeta as compared to epoetin alfa. On the other hand, the amounts of undesired variants of sialic acid, N-glycolyl neuraminic acid and O-acetyl neuraminic acid were higher in the reference product as compared to epoetin zeta.

Comparison of the purity and in-vivo bioactivity did not reveal any remarkable difference.

In terms of quality, the drug substance comparability between SB309 and Eprex/Erypo is considered demonstrated.

Drug Product

The drug product SB309 is provided as a liquid ready-to-use solution in a single-dose prefilled syringe. It is formulated based on epoetin zeta as active ingredient at concentrations of 3,333 IU/mL, 10,000 IU/mL and 40,000 IU/mL. Eleven dosage strengths are provided from 1,000 IU to 40,000 IU/syringe dependent of different filling volumes (0.3 to 1.0 mL).

Product Development and Manufacture

The drug product contains recombinant human erythropoietin (rhu-EPO, epoetin) as drug substance and water for injection, sodium monohydrogen phosphate, sodium dihydrogen phosphate, sodium chloride, calcium chloride, polysorbate 20, glycine, leucine, isoleucine, threonine, glutamic acid and phenylalanine as excipients. The dosage strengths only differ with respect to drug substance amount. The concentrations of the excipients are identical for all strengths.

The manufacturing process is a conventional process beginning with the dissolution of the excipients followed by addition of the drug substance bulk solution. After mixing, the bulk drug product solution is 0.22 µm filtered, sterile filtered and aseptically filled into syringes. The drug product manufacturing process is validated.

Product Specification

The drug product release specification includes tests for identity, purity and content, as well as pharmaceutical and microbiological tests.

Batch analysis

The batches selected for the batch analysis were considered to be acceptable.

Stability of the Product

A shelf life of 24 months for the dosage strengths 1,000 IU, 2,000 IU and 3,000 IU and 18 months for the dosage strengths 4,000 IU, 5,000 IU, 6,000 IU, 8,000 IU, 10,000 IU, 20,000 IU, 30,000 IU and 40,000 IU is demonstrated when stored at 2-8 °C.

Comparability Exercise for Drug Product

SB309 drug product batches were compared to Eprex/Erypo drug product batches.

All batches were found to be similar with regard to protein backbone as well as carbohydrate moieties and hence the overall comparability of SB309 and Eprex/Erypo is considered demonstrated.

Discussion on chemical, pharmaceutical and biological aspects

In general, the dossier for SB309 is of good quality. The two major concerns as well as the minor deficiencies that had been identified and summarised in the Day 120 LoQ, have been appropriately addressed by the applicant.

Very extensive, high quality studies were performed to compare SB309 to the reference product Eprex/Erypo at both the drug substance and the drug product level. Likewise the characterisation of the drug substance and the comparability studies to compare drug substance from different scale manufacturing process is considered high quality with an extreme level of detail applying state-of-the-art analytical methods.

Comparability studies confirmed that the protein backbone of epoetin zeta is comparable to epoetin alfa. Regarding the overall range of glycan structures a high level of similarity between SB309 and Eprex/Erypo was demonstrated. Minor differences were noted at the level of particular structural elements. These reflect the foreseen variability of glycoproteins derived from different manufacturing processes.

The identified minor differences in glycostructures are not of concern and particularly the lower levels of undesired glycostructures such as N-glycolyl neuraminic acids and O-acetylated neuraminic acids in SB309 as compared to the reference product are not considered to pose any safety issues.

3. Non-clinical aspects

Introduction

Toxicity studies were in compliance with Good Laboratory Practice with the exception that bioanalytical and toxicokinetic elements of these two studies did not include independent Quality Assurance inspection or audit of reports. In mid 2006, CHMP issued guidance[1] on the development of similar medicinal products containing recombinant erythropoietin and the non-clinical testing of epoetin zeta is therefore judged against this guidance, which requires that the applicant shall demonstrate the 'comparability of the product applied for to a reference product authorised in the EU'. The applicant sought scientific advice from the CHMP in early 2004, including on the necessity of any preclinical studies. The dossier that was submitted includes the recommended studies. Testing comprised comparative *in vitro* and *in vivo* pharmacodynamics and comparative repeated dose toxicity studies in rats and dogs. Local tolerance by a number of routes was also tested. In accordance with CHMP guidance, no studies on safety pharmacology, reproductive toxicology, mutagenicity or carcinogenicity were conducted.

[1] Annex to guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. Guidance on similar medicinal products containing recombinant erythropoietins. (EMEA/CHMP/BMWP/94526/2005).

Pharmacology

Primary pharmacodynamics

Pharmacodynamic biosimilarity of two batches of SB309 and Erypo was tested in three in-vitro studies measuring receptor binding, proliferation and second messenger activation in cultured cells, and in one in-vivo study (normocythaemic mouse assay according to Ph. Eur.). There was a different slope of the displacement curve and a different EC50 value for SB309 as compared to Erypo in the receptor binding, study # 176. A possible reason could be that SB309 and the reference product Erypo were not compared directly in the same experiments but investigated in consecutive experimental setups.. There were initial problems (e.g. high variability of the results) with the functional in-vitro assays in study #177 intended to measure burst- and colony forming activity in erythrocyte precursors. The Applicant repeated these experiments with fresh cell material and thereby obtained reliable results. The effects of Retacrit and Erypo were highly similar. In the third in-vitro study, direct comparison of SB309 and Erypo was performed as desirable at the level of receptor binding as well as in functional assays although the relevance of the results was somewhat limited by the low number of replicates.
An *in vivo* comparison of the potency of SB309 and of Erypo over the dosage range 3.3 to 90 IU/ml in normocythaemic mice was undertaken using methodology described in the European Pharmacopoeia (01/2005: 1316 corrected, method B). EPO-BRP#2 provided by the European Directorate for the Quality of Medicines, European Pharmacopoeia Commission was also tested. The assay quantifies reticulocytes by fluorescence activated cell sorting of blood drawn four days after one subcutaneous administration to female B6D2F1 mice. This method allows establishment of a dose-response relationship for each test material and includes a check of parallelism of regressions for a valid quantitative comparison. The relative potency should be between 0.80 and 1.25.

Results are presented in the table below, where REF refers to results with Erypo, test 1 refers to one batch of SB309 (0050410/10000), Test 2 refers to a different batch of SB309 (500-M2) and BRP-#2 refers to the standard provided by the European Directorate for the Quality of Medicines, European Pharmacopoeia Commission.

Table 1 Relative potency of SB309 and Erypo in the normocythaemic mouse assay

Relative potency FACS: MANUAL settings, n=896			
	BRP-#2 vs. REF	**Test1 vs. REF**	**Test2 vs. REF**
Relative Potency	**1.039**	**0.862**	**1.022**
95% Fiducial Limits	0.0886-1.220	0.729 –1.016	0.874-1.195
Relative fiducial limits	85.3 % - 117.3% (32.1%)	84.7% - 117.9 % (33.3%)	85.6% - 116.9% (31.4%)

Secondary pharmacodynamics
No studies were submitted.

Safety pharmacology programme
No studies were submitted.

Pharmacodynamic drug interactions
No studies were submitted.

Pharmacokinetics

No studies were performed. Toxicokinetic parameters were obtained within the frame of the repeated-dose toxicology studies in rats and dogs, respectively (see Repeat dose toxicity for the methods and results).

Toxicology

Single dose toxicity
No studies were submitted.

Repeat dose toxicity (with toxicokinetics)

Two studies of 3 months duration are reported: one is in the rat and used subcutaneous administration and one is in the dog and used intravenous administration. Both routes are used clinically. Two batches of each product were used in each study.

Rat 13 week study by the subcutaneous route:
In this study, rats were allocated to treatment groups as shown in the table below. Additional rats were allocated for use in additional haematology screens and for erythropoietin and anti-erythropoietin antibody determinations. Blood was drawn prior to dosing, on day 5 at 13 time points from 2.5 minutes to 24 hours after dosing, and again at the end of weeks 5, 9, 13 and 17. All rats were dosed by subcutaneous injection three times a week with SB309 at one of two dose levels, or with Erypo at one dose level, or control (saline), for 13 weeks.

Table 2: Design of the rat 13 week toxicity study

Group No.	Test / Reference item	Dose in IU/kg b.w., s.c. 3 x weekly	No. and sex of animals MS + RP + SA_1 + SA_2	Rat no.			
				MS	RP	SA_1	SA_2
1	Vehicle (0.9% NaCL solution)	0 (control)	10 + 5 + 15 + 10 m 10 + 5 + 15 + 10 f	1- 10 16- 25	11- 15 26- 30	111-125 126-140	231-240 241-250
2	Epoetin (STADA)	500 (low dose)	10 + 15 + 10 m 10 + 15 + 10 f	31- 40 41- 50	none	141-155 156-170	251-260 261-270
3	Epoetin (STADA)	2500 (high dose)	10 + 5 + 15 + 10 m 10 + 5 + 15 + 10 f	51- 60 66- 75	61- 65 76- 80	171-185 186-200	271-280 281-290
4	Erypo® (JANSSEN-CILAG)	2500 (high dose)	10 + 5 + 15 + 10 m 10 + 5 + 15 + 10 f	81- 90 96-105	91- 95 106-110	201-215 216-230	291-300 301-310

IU: International Units
MS: main study
RP: recovery period
SA_1: satellite animals for toxicokinetics and antibody determination
SA_2: satellite animals for additional haematology
m: male
f: female

There was significant mortality in this study, such that dosing at 2500 IU/kg was stopped 18 days earlier than planned in female rats. 3 of 15 male rats and 7 of 15 female rats treated with higher dose SB309 died prematurely in this study. With the same dose of Erypo, 5 out of 15 male and 7 out of 15 female rats died prematurely. There was additionally one death in a male rat treated with 500 IU/kg SB309. All these deaths were attributed to exaggerated pharmacology with cause of death being moderate to marked congestion with dilatation of vessels, haemorrhage, stasis of blood and development of thrombi. The frequency and causes of deaths are not indicative of a difference between the products. One control female rat was also found dead during the study.

There were no differences between higher dose SB309 and Erypo with regard to body weight, body weight gain, food and drinking water consumption, biochemical parameters, ophthalmological or auditory examinations.

Comparing the two products, SB309 caused a slight reduction in urinary specific gravity and a significant increase in urine volume in males at week 6, in comparison with Erypo.

Haematological parameters of haemoglobin, red blood cell count, reticulocyte count and haematocrit consistently changed in the expected manner and in comparison to controls, each product caused a statistically significant rise. Comparing values between the two products, there was, in general, no

difference. At 6 weeks, there was a statistically significant difference in values for reticulocytes and red blood cells of male rats treated with either high dose SB309 or with Erypo. Histopathological examination of organs showed an increase in the number of haematopoietic cells compared to controls in spleen and bone marrow, as would be expected. Associated lesions in the thymus, kidney, stomach, heart and adrenal glands are considered to be related effects and were of mild to marked congestion and haemorrhage with the vessels dilated and filled with erythrocytes. The number of rats per group that exhibit increased haemopoietic cells in spleen and in bone marrow, and other effects was usually greater with SB309 than with Erypo.

Toxicokinetics

Erythropoietin was analysed in serum taken from rats and dogs in the 13 week toxicology studies. A validated double sandwich ELISA method was used to quantify erythropoietin. Antibodies to erythropoietin were assessed by a radio-immune-precipitation assay. The assay uses radiolabelled ^{125}I-recombinant human erythropoietin to bind circulating antibodies against human erythropoietin in the serum of treated subjects. The bound complex is precipitated by protein G and the radioactivity in the precipitate is measured by a gamma counter to allow quantification of antibodies to erythropoietin. Suitability of the assay was shown for human serum for specificity, stability of samples stored at -20ºC for over 9 months and for three freeze-thaw cycles. The applicability of the assay for rat and dog serum was shown by a comparative test with human and rat serum samples spiked with rabbit antiserum against recombinant human erythropoietin. Neutralising potential of antibodies to erythropoietin was assessed using stimulation of an erythroleukaemic cell line by erythropoietin. The presence of antibodies that neutralise erythropoietin in tested samples is indicated by inhibition of erythropoietin-mediated cellular growth by test serum.

The exposure achieved in this study during Day 5 is presented in the two tables below, with values from 3 rats per sex per time point. In these tables, Test 1 and Test 2 refer to SB309 and Reference indicates Erypo. Mean C_{max} and AUC and serum half-life were minimally lower in the 2500 IU/kg SB309 than in the Erypo group, but there was no statistically significant difference between SB309 and Erypo at the same nominal dose of 2500 IU/kg. The difference in exposure between the lower and higher dose of SB309 was not proportionate with the dose increase.

Tables 3-4: Toxicokinetic results from rats - 13 week toxicity study

Data assessed by means of Erypo standard

TT 4 **Toxicokinetic parameters of Erythropoietin after a single subcutaneous dose (arithmetic mean ± SD)**

	Test 1 (500 IU/kg)	Test 2 (2500 IU/kg)	Reference (2500 IU/kg)
AUC0-tlast [mIU*h/ml]	20973.60 ± 1619.42	61229.69 ± 14438.82	69520.23 ± 4912.30
Cmax [mIU/ml]	1695.49 ± 729.20	4245.33 ± 465.94	4570.52 ± 784.90
tmax [h]	7.67 ± 2.66	7.33 ± 2.42	9.00 ± 2.45
AUC0-inf [mIU*h/ml]	25013.60 ± 1956.08	82446.74 ± 12811.38	88290.75 ± 7769.58
MRT [h]	10.63 ± 0.56	10.32 ± 1.66	10.93 ± 0.47
t½ [h]	7.37 ± 0.70	8.63 ± 2.78	8.76 ± 1.46

Data assessed by means of SB309 standard

TT 11 **Toxicokinetic parameters of Erythropoietin after a single subcutaneous dose (arithmetic mean ± SD)**

	Test 1 (500 IU/kg)	Test 2 (2500 IU/kg)	Reference (2500 IU/kg)
AUC0-tlast [mIU*h/ml]	17229.08 ± 1276.45	56969.79 ± 5297.49	60259.73 ± 4421.22
Cmax [mIU/ml]	1179.31 ± 233.36	3702.02 ± 422.27	4001.01 ± 706.75
tmax [h]	7.67 ± 2.66	7.33 ± 2.42	9.00 ± 2.45
AUC0-inf [mIU*h/ml]	20514.68 ± 1507.61	72078.78 ± 8477.85	75879.93 ± 6629.35
MRT [h]	10.72 ± 0.44	10.86 ± 0.38	10.90 ± 0.48
t½ [h]	7.22 ± 0.69	8.62 ± 2.53	8.57 ± 1.41

Antigenicity

4 rats treated with SB309 developed antibodies to erythropoietin, with the first positive test in week 4, and 4 treated with Erypo were antibody positive or had borderline titres (i.e. close to the limit of detection), with the first positive test in week 3.

In conclusion, this study revealed no meaningful difference in the safety profile with respect to pharmacodynamic effects, antigenicity or toxicity between SB309 and Erypo.

Dog 13 week study by the intravenous route

In this study, two male and two female dogs were allocated to groups as shown in the table below and were injected intravenously once every day for 13 weeks with SB309 at one of two dose levels, or Erypo at one dose level, or control. Half the dogs were killed for post-mortem examinations and half entered a recovery (i.e. dose free) period of 5 weeks, and were then killed for post-mortem examinations. The study thus ran for 18 weeks. After day 10, the dose administered was reduced as shown in the table: this was a planned change, and the first 10 days of dosing is described as a loading dose. Electrocardiography was performed on Day 1, and in weeks 6 and 13 before administration of drug and at 5 minutes after administration, for 1 minute. Urine was collected over a 3 hour period following a dose of 50 ml tap water, for urinalysis, before and at weeks 6, 13 and 18 of the study: ophthalmological examinations were done at the same timepoints. All dogs in Groups 1, 3 and 4 were examined histologically, with the spleens and bone marrow of dogs in Group 2 also examined. Blood samples were drawn at weekly intervals for haematology, coagulation and clinical biochemistry. Blood samples were also drawn at appropriate timepoints for toxicokinetics of erythropoietin (a full kinetic profile was planned from blood samples taken on study day 5, with individual samples taken for trough levels at intervals) and for antibody determinations, which were drawn at weekly intervals throughout the entire period of the study.

Table 5: Design of the dog 13 week toxicity study, by intravenous dose

Group	Test or reference item	Dose [IU/kg b.w.]#	No. and sex of animals MS + RP	Dog no. MS	Dog no. RP
1	Control (0.9% NaCl solution)	0	2 + 2 m 2 + 2 f	1 - 2 m 5 - 6 f	3 - 4 m 7 - 8 f
2	Epoetin (STADA)	500/100 (low dose)	2 + 2 m 2 + 2 f	9 - 10 m 13 - 14 f	11 - 12 m 15 - 16 f
3	Epoetin (STADA)	2500/500 (high dose)	2 + 2 m 2 + 2 f	17 - 18 m 21 - 22 f	19 - 20 m 23 - 24 f
4	Erypo® (JANSSEN-CILAG)	2500/500 (high dose)	2 + 2 m 2 + 2 f	25 - 26 m 29 - 30 f	27 - 28 m 31 - 32 f

\# As of test day 10 the dose levels were reduced in groups 2 to 4 following the completion of the loading dose.

IU International Units
m male
f female
MS main study
RP recovery period

For the purposes of this assessment, the primary comparison of interest is that of Group 3 versus Group 4, i.e. SB309 versus the same dose of Erypo.

There was no difference between Groups 3 and 4 with respect to local tolerance, behaviour, external appearance on clinical observation, faeces, mortality, body weight and body weight changes, food and drinking water consumption, electrocardiographic measures, blood pressure, haematological parameters, clinical biochemistry, urinalysis, ophthalmology, organ weights or macroscopic or microscopic examinations. The examinations of spleen and bone marrow tissues did not suggest any difference between the same dose of SB309 and Erypo.

In comparison with the control group, each of SB309 and Erypo produced effects characteristic of erythropoietins. Marked haematopoietic activation of bone marrow was observed with substantial, sustained increases in reticulocyte counts, red blood cells, haemoglobin and haematocrit throughout the dosing period with tendency to revert to normal during the recovery period. There were sporadic instances where one product was associated with a significant change compared to control where the other was not (e.g. reticulocyte counts at 10, 11 and 12 weeks in males and on days 10, 12 and weeks 7, 9 and 10 in females); however, such instances are not toxicologically meaningful.

Histopathologically, increase in haematopoietic cells in spleen and in bone marrow was observed.

Toxicokinetics

Data derived from blood samples drawn on Day 5 of the study are tabulated below. Group 3 and Group 4 are in the columns headed Test 2 and Reference, respectively. There was a slight tendency for increased AUC-inf and Cmax with Erypo compared to the same dose of SB309, although there was no difference in the half life and suggests these differences may be due to a higher specific protein content of the final drug product batches.

Table 6: Toxicokinetics from the dog 13 week toxicity study

TT 4 **Toxicokinetic parameters of Erythropoietin after a single intravenous dose (arithmetic mean ± SD)**

	Test 1 (500 IU/kg)	Test 2 (2500 IU/kg)	Reference (2500 IU/kg)
AUC0-tlast [mIU*h/ml]	50581.30 ± 6772.01	314050.31 ± 97370.28	387865.97 ± 83946.49
Cmax [mIU/ml]	12652.30 ± 1467.88	60740.56 ± 14253.73	67969.50 ± 9772.75
tmax [h]	0.11 ± 0.08	0.08 ± 0.04	0.08 ± 0.04
AUC0-inf [mIU*h/ml]	53474.56 ± 7024.07	407817.69 ± 158955.86	504193.97 ± 134553.80
MRT [h]	5.46 ± 0.31	6.88 ± 0.71	7.36 ± 0.62
t½ [h]	6.45 ± 0.43	13.00 ± 4.00	12.72 ± 3.56

The trough serum concentrations measured throughout the study are presented in tabular form below. As for the kinetics with the rat, analysis was done twice, once by reference to a SB309 standard and once by reference to an Erypo standard. The tabulated values for serum erythropoietin concentration indicate no change on repeated dosing, but do indicate lower concentrations in males compared to females (subset of data not shown). These data are presented to show that the very large standard deviations confound any assessment of difference. In addition, in weeks 5 and 9, values for SB309 are skewed by data from one female dog having very substantially higher exposure (i.e. approximately 10-fold the mean of the other dogs) to erythropoietin. This dog developed antibodies to erythropoietin from week 11, consistent with a decline in the measured serum concentration of erythropoietin at week 13.

Table 7: Toxicokinetics from the dog 13 week toxicity study

	Trough serum concentration (mIU/ml)	
Erypo standard	**SB309**	**Erypo**
Week 5	405.227 ± 634.545	199.096 ± 187.284
Week 9	283.797 ± 380.968	155.977 ± 125.793
Week 13	174.033 ± 174.160	113.323 ± 75.598
SB309 standard		
Week 5	432.393 ± 685.203	207.147 ± 192.833
Week 9	296.212 ± 397.026	162.570 ± 129.893
Week 13	181.696 ± 180.012	117.185 ± 77.806

Figures show mean ± standard deviation of n = 8 dogs. Same dose of erythropoietin administered.

Antigenicity

Data on the frequency of anti-erythropoietin antibody positivity are shown below. These data are the number of samples that tested positive and, as one dog will test positive on a number of occasions, this way of presenting the data may exaggerate the numbers concerned.

Table 8: Antigenicity data from the dog 13 week toxicity study

Table 2.4-11: Antigenicity in dog intravenous 13-week toxicity study (0242)

		Control 0 IU/kg	SB309 500 IU/kg	SB309 2500 IU/kg	Erypo 2500 IU/kg
Number of samples:	negative	116	115	99	123
	borderline	22	12	20	10
	weak positive (titer 20)	2	11	13	4
	strong positive (titer 100)	0	2	8	3
	total positive	2	13	21	7
Number of animals:	total positive	1	3	5	1
	strong positive (titer 100)	0	1	2	1

One dog out of eight treated with Erypo developed antibodies to erythropoietin, which were detected from the third week. In contrast, a total of eight dogs out of 16 treated with SB309 developed antibodies to erythropoietin which were detected from the fourth week: these eight comprised three given the lower dose and five given the higher dose regime. No neutralising potential was identified in the serum samples that tested positive for antibodies. In addition to these findings, borderline positive tests were found in 18 dogs, in all groups including the control and on day -2, before any dogs were dosed. The different rate of antibody formation is not considered relevant for clinical use since human epoetin is a foreign protein for dogs. The low potential of both, SB309 and Erypo, to induce neutralising antibodies is considered reassuring (see discussion below).

Genotoxicity
No studies were submitted.

Carcinogenicity
No studies were submitted.

Reproduction Toxicity
No studies were submitted.

Local tolerance
Local tolerance was tested within the frame of the repeated-dose studies insofar the injection sites were examined. Local tolerance was also assessed in the rabbit using intravenous, subcutaneous, intramuscular, paravenous and intra-arterial injection of the 40,000 IU/syringe strength product. No concerns were identified.

Other toxicity studies
Antigenicity was assessed in the general toxicity studies and is discussed above. Other toxicity studies (dependence, metabolites, impurities) were not submitted.

Ecotoxicity/environmental risk assessment

The applicant claimed that because the product does not contain any novel components, and contains a protein that is similar to the endogenous human protein and to that contained in an existing medicinal product, availability of the product will not pose any identifiable extra risk to the environment. The applicant also claimed that CHMP guidance specifically exempts proteins from such assessment, as they are unlikely to result in significant risk to the environment.

Discussion on the non-clinical aspects

Biosimilarity in terms of non-clinical pharmacodynamics could be convincingly shown in the in-vivo assays. There were some problems with the in-vitro assays, but in the light of the unequivocal outcome of the in-vivo assays this is a minor concern. Although in-vivo assays are characterised by a rather low accuracy of the results due to inter-individual differences of the animals, it could be demonstrated by using a large number (1024) of animals that mean, standard deviation and slope of the dose-response are nearly superimposable for SB309 and Erypo. This indicates that the observed statistical variation was due to inter-individual differences of the animals and not to different actions of SB309 and Erypo.

With the exception of antigenicity in the dog which is discussed further below, there were no signs of toxicity other than that which can be attributed to major erythropoietic stimulus (i.e. suprapharmacological effects) and to compensatory changes. In comparison with the control group, each of SB309 and Erypo produced effects characteristic of erythropoietins. Whereas there were no differences in type of toxicity between SB309 and Erypo in the dog, there were differences in the magnitude of erythropoietic effect in the rat. This could be consistent with a slightly more potent erythropoietic effect of SB309 compared to Erypo (the applicant suggested this could be due to a greater amount of protein per International Unit of erythropoietin in its product compared to Erypo). However, these findings could also indicate a modest difference in biological response due to natural variation. In conclusion, in terms of toxicology, the data did not indicate a meaningful difference between the two products.

Antigenicity of SB309 in direct comparison with Erypo was extensively tested. The absolute rate of antibody formation was rather high, but this does not necessarily indicate a high antigenicity in humans since human epoetin is a foreign protein for animals. There was, however, a marked difference in antigenicity between the two products, although antibodies were non-neutralising and were not associated with any deterioration in condition of the dogs. Antibodies to erythropoietin occurred more frequently in dogs treated with SB309 than dogs treated with Erypo.
To date there is no hint that SB309 will be more antigenic than Erypo, at least in respect to the clinically relevant neutralising antibodies. In dogs no neutralising antibodies were found in the antibody assay, and pharmacodynamics data (e.g. red blood cell count) also gave no hint for neutralising antibodies. Neutralising antibodies were only detected in rats, and there was a very good agreement between the rate of antibody formation in the satellite groups (antibodies determined by RIP) and the main groups (neutralising antibodies identified by a sharp decrease in RBCs), confirming the reliability of the antibody assay, at least for the (clinically more relevant) neutralising antibodies.
Local tolerance was tested within the frame of the repeated-dose studies and in a separate rabbit study. The comparator Erypo was not included in this study but this is considered acceptable because this study aimed to detect unexpected local toxicity of SB309. The results did not raise concerns.
No secondary pharmacodynamics, safety pharmacology, and pharmacodynamic drug interactions studies have been submitted, in line with CHMP guidance. In accordance with CHMP guidance, no studies on reproductive toxicology, mutagenicity or carcinogenicity were conducted. The environmental risk assessment is satisfactory.

As a conclusion for the preclinical review, the applicant's data indicate that SB309 and the reference product Erypo could be distinguished from each other in certain *in vitro* pharmacology tests, and in some aspects, but not all, in *in vivo* tests. The differences which were identified are probably not toxicologically meaningful.

4. Clinical aspects

Introduction

The pharmacokinetic properties of SB309 and the reference product Erypo were compared in two PK studies in healthy volunteers after single dose SC and IV administration. Two clinical studies were conducted to compare the therapeutic equivalence of IV administered SB309 and the reference product Erypo in patients with anaemia due to chronic renal failure. The studies included one correction phase

study to determine response dynamics and dosing during the anaemia correction phase, and one maintenance phase study. An additional maintenance treatment follow-up study was performed to obtain long-term safety data for SB309. One uncontrolled safety trial was conducted in cancer patients with chemotherapy-induced anaemia.

GCP

The clinical trials were performed in accordance with GCP as claimed by the applicant. The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Pharmacokinetics

The applicant has submitted two PK studies in healthy volunteers to demonstrate similar PK profiles for SB309 and Erypo. Study 411-54-05-05-0000 was a two-period crossover study in 24 healthy volunteers comparing the PK profiles of the test product SB309 and the reference product Erypo after a single IV dose. Study 411-54-03-09-0001 was a three-period crossover trial in 48 healthy volunteers comparing the PK profiles of SB309 and Erypo after a single SC dose as well as the PK profiles after a single dose of SC and IV administered SB309. The design and endpoints of both studies were in line with the recommendations in the *Guidance on similar medicinal products containing recombinant erythropoietins.*

Epoetin plasma concentrations were analysed using a validated modified double sandwich ELISA.

No equivalence margins were pre-defined. However, post-hoc an acceptance range of 80-125% for AUC and 70-143% for Cmax was used by the applicant who also referred to the Scientific Advice given by CHMP in April 2004 that stated that the concept of "comparability" cannot use bioequivalence but that similar PK profiles of SB309 and the reference product would strengthen the choice of reference in the clinical trials. The advice concluded that for this purpose descriptive statistics will suffice.
The primary endpoint was AUC0-tlast and the secondary endpoints were Cmax, $t_{1/2}$, Vd, CL_{tot} and MRT.

The study results (primary analysis) suggested subavailability of SB309 compared to Erypo (1 not included in the 90% CI). The 90% CIs for both AUC0-tlast and Cmax for the SC comparison were contained in the post hoc defined acceptance ranges but only the 90% CI for Cmax for the IV comparison (see Tables X and Y below). According to the certificates of analysis of the test and the reference drug, a significant difference was present between the batches of both products regarding the total protein content: 71.77 µg/ml protein for the test drug and 83.62 µg/ml protein for the reference drug in study 411-54-05-05-0000; 78.45 µg/ml protein in the test drug and 83.62 µg/ml in the reference drug in study 411-54-03-09-0001. The concentration of epoetin in the final product is not based on protein content but is adjusted by means of a bioassay which measures the biological activity. Due to this reason, a correction of epoetin serum concentrations based on the protein content of the used batches was performed in both studies. This adjustment for protein content was justified on the basis that the assay used for the determination of erythropoietin concentrations in human plasma is based on binding of a specific antibody to the erythropoietin protein backbone, and therefore corresponds to total protein content. The 90% CIs for the corrected intra-individual ratios ($test_{IV}$/$reference_{IV}$) of AUC0-tlast and Cmax were well within the post-hoc defined equivalence margins (see Tables X and Y). T1/2 values were similar being 5.8 ± 0.6 h for test and 6.1 ± 1.2 h for reference in study 411-54-05-05-0000 and 24.7 ± 8.0 h for test and 23.0 ± 6.6 h for reference in study 411-54-03-09-0001.

Table X: **90% confidence intervals (ANOVA-log) for the comparison (test/reference) of primary endpoints in the PK study 411-54-05-05-0000 with and without dose correction**

Trial 411-54-05-05-0000: test i.v. vs. reference i.v.		
Without dose correction		
Variable	**point estimator**	**90% confidence limits**
AUC0-tlast	0.80	0.76 – 0.84
Cmax	0.89	0.82 – 0.97
With dose correction		
AUC0-tlast	0.93	0.89 – 0.97
Cmax	1.04	0.95 – 1.13

Table Y: **90% confidence intervals (ANOVA-log) for the comparison (test/reference) of primary endpoints in the PK study 411-54-03-09-0001 with and without dose correction**

Trial 411-54-03-09-0001: test s.c. vs. reference s.c.		
Without dose correction		
Variable	**point estimator**	**90% confidence limits**
AUC0-tlast	0.93	0.88 – 0.99
Cmax	0.82	0.75 – 0.90
With dose correction		
AUC0-tlast	1.00	0.94 – 1.05
Cmax	0.88	0.80 – 0.96

Discussion on Clinical Pharmacokinetics

The submitted PK studies were performed in accordance with the *Guidance on similar medicinal products containing recombinant erythropoietins*, although this guideline had not been in place at the time of clinical development.
Based on corrected epoetin serum concentrations similar PK profiles of SB309 and Erypo could be demonstrated for the IV route as well as the SC route of administration. For the uncorrected values, similar PK profiles could be demonstrated only for SC administration. In principle, correction for protein content is considered acceptable but, in a strict sense, only if pre-specified. However, similar PK profiles alone do not allow the conclusion of similar efficacy and safety of two biotechnology-derived medicinal products. Comparative phase III studies are required for epoetin-containing products claiming to be similar to another one already on the market.
The bioavailability of erythropoietin is known to be much lower if administered SC compared to IV and is approximately 20%. As expected, the bioavailability of SC administered epoetin was considerably lower than that of the IV administered drug in Study 411-54-03-09-0001 but the comparison IV vs. SC is not relevant for a “biosimilar” application.

Pharmacodynamics

No specific pharmacodynamic studies were conducted with SB309. The pharmacodynamics (PD) of erythropoietin is known and described in the literature.

Mechanism of action

Recombinant human erythropoietin (epoetin) promotes red blood cell production by stimulating the division and differentiation of committed progenitors in the bone marrow the same way endogenous erythropoietin does.

Primary pharmacology

After IV administration of epoetin, the typical pharmacodynamic profile shows an increase in reticulocyte count within the first 2 weeks followed by an increase in the red blood cell level as manifested by hematocrit or Hb determinations within 2 to 6 weeks. After single SC administration an increase in reticulocyte count within 3-4 days with a peak around day 8-11(13) and a return to baseline by day 22 has been described (R. Ramakrishan et al. J Clin Pharmacol, 2004; W.K. Cheung et al. Clin Pharmacol Therapeutics, 1998). A linear relationship between reticulocyte AUC and epoetin exposure has been described for single doses up to 1800 IU/kg (W.K. Cheung et al., Clin Pharmacol Therapeutics, 1998). There is high interindividual variability in the reticulocyte response to epoetin.

Discussion on Clinical Pharmacodynamics

The *Guideline on similar medicinal products containing recombinant erythropoietins* suggests that a PD study be performed investigating reticulocyte count as the most relevant pharmacodynamic marker for assessment of the activity of epoetin. As stated above, this guidance document was not available at the time the studies were performed and there was still discussion on the requirements for biosimilar applications. Although PD studies should be part of the development programme for a biosimilar epoetin, the lack of such studies is not critical since demonstration of similar efficacy and safety between the new and the reference product is required anyway.

Clinical efficacy

Two clinical studies were conducted to compare the therapeutic equivalence of IV administered SB309 and the reference product Erypo in patients with anaemia due to chronic renal failure. The studies were one correction phase study (411-54-04-05-0000 [study 04-05]) to determine response dynamics and dosing during the anaemia correction phase, and one maintenance phase study (411-54-04-04-0000 [study 04-04]). An additional maintenance treatment follow-up study (411-54-04-14-0000 [study 04-14]) was performed to obtain long-term safety data for SB309. This study is presented in the Clinical Safety section below.

Dose response studies

No studies were submitted.

Main studies

Correction Phase Study

Study 411-54-04-05-0000 [study 04-05] was performed as a randomised, double-blind, verum-controlled, multiple-dose, parallel-group, multicentre design phase III trial in haemodialysis patients with renal anaemia in patients with or without epoetin treatment to prove therapeutic equivalence of IV administered SB309 to the reference product (Erypro).

Methods

Study Participants

Male or female haemodialysis patients, aged 18-75 years with a baseline haemoglobin concentration below 9 g/dl in spite of optimal iron supplementation with or without pre-treatment with epoetin were eligible. Patients presenting (among others) any of the following criteria could not be included in the trial: contraindication for the test drug; relative or absolute iron deficiency at the end of the supplementation period; refractory anaemia with excess blasts in transformation; documented bleeding disorders; platelet count below 100x109/l; known, clinically manifested deficiency of folic acid and/or vitamin B12 (irrespective whether currently treated or not); known bone marrow fibrosis (osteitis fibrosa cystica); clinically relevant changes of dialysis regimen and/or dialyzer during the trial; clinically relevant increase of CRP (higher than 10 mg/dl) for at least 2 weeks; acute bleeding and/or

recently documented hemorrhage; known lack of response to epoetin; known hypersensitivity to epoetin (for patients who have received epoetin before); epoetin dosages > 3x200 IU/kg/week; known hypersensitivity to albumin; detectable anti-epoetin antibodies; uncontrolled hypertension; myocardial infarction, stroke, severe/unstable angina, coronary/peripheral artery bypass graft, decompensated congestive heart failure (NYHA class III – IV), cerebrovascular incident or transient ischemic attack, pulmonary embolism, deep vein thrombosis, or other thromboembolic event within the 6 months prior to double-blind study drug administration; known epilepsy; liver cirrhosis with clinical evidence of complications (portal hypertension, splenomegaly, ascites); patients with confirmed aluminum intoxication; confirmed, clinically relevant hemolysis and/or occult blood loss; presence of malignant tumors; clinically relevant malnutrition; pregnancy or lactation period in female patients.

Treatments

SB309 or Erypo, 1000 IU or 2000 IU epoetin, were administered IV, three times per week (if a dose < 3 x 1000 IU was needed the epoetin dosage could be less than three times a week).

The period of work-up of anaemia lasted up to 6 weeks. The subsequent double-blind treatment period lasted 24 weeks. Thereafter, all patients could continue treatment with the test product as a part of an open, follow-up safety trial.

Objectives

To prove the therapeutic equivalence of SB309 to the reference product (Erypo) in achieving correction of haemoglobin concentration in anaemic patients with end-stage renal failure on chronic haemodialysis.

Outcomes/endpoints

Primary efficacy endpoints were:
- Mean weekly dosage of epoetin per kg body weight during the last four weeks of treatment
- Mean haemoglobin levels during the last four weeks of treatment

Secondary efficacy endpoints included:
- Proportion of patients with treatment success (haemoglobin level ≥ 11.0 g/dl for 2 consecutive weeks without any blood transfusion within the preceding 3 months)
- Increase of haemoglobin over time
- Proportion of patients with maintenance success (maintenance of haemoglobin levels of 11 ± 1 g/dl for at least 4 consecutive weeks)
- Mean weekly dosage of epoetin per kg body weight during each interval of 4 weeks of treatment
- Mean haemoglobin levels during each interval of 4 weeks of treatment
- Mean haemocrit levels during each interval of 4 weeks of treatment
- Proportion of patients with an increase of haemoglobin of more than 1 g/dl for 4 weeks
- Percentage of haemoglobin measurements above 10 g/dl
- Percentage of haemocrit measurements above 30%
- Proportion of patients with blood transfusions

Sample size

A sample size of 204 patients per group was calculated to achieve a power of more than 80% for proof of equivalence for both primary endpoints. The total number of patients to be randomized was estimated to be 600 since a drop-out rate of approximately 30-35% was expected.

Randomisation

At the beginning of the double-blind phase of the trial, each patient was randomly assigned to one of the study drugs (1:1).

Blinding (masking)

Blinding was achieved using the double-dummy technique. Neither the investigators nor the monitors were informed about the identity of the trial medication and also had no copy of the randomization code. The investigators and patients monitors had no access to the code before the end of the trial. The investigator was allowed to unblind the individual treatment if appropriate in an emergency or on request by an authority or IEC/IRB.

Statistical methods

The 95% confidence intervals were calculated for the treatment differences between both treatment groups in the primary endpoints
The confidence interval was compared with pre-defined acceptance ranges:

- ±14 IU/kg/week for mean weekly dosage
- ±1 g/dl for haemoglobin

Statistical analysis was performed on three patient populations:

- full data set for efficacy, including all patients who started therapy and had any follow-up information regarding the primary endpoint, and did not violate major entry criteria;
- full data set for safety, including all patients who started therapy irrespective of the information regarding the primary endpoint;
- per protocol (PP) population; excluding cases of major protocol violations.
- The per protocol population was the primary analysis population.

Rationale for acceptance range for dosage and haemoglobin

For Hb, a range of ± 1g/dl has been previously used and was considered well established as an equivalence range in parallel-group trials (data from EPAR on Epoetin delta).

With respect to dosage, the lowest usual dose-adjustment used as a pre-filled syringe was 1000 IU, which roughly corresponds to 14 IU/kg/week as the lowest possible change of dosage in normal clinical practice for a person of approximately 70 kg body weight. The rationale for the choice of the acceptance range regarding the dosage was the fact that a 15 IU/kg dose had been described as being close to the no effect dosage in the EPAR on Dynepo. Accordingly, it was assumed that a difference in dose smaller than this would not matter in practice.

Results

Participant flow

The administration of study medication in the PP population was 100% for SB309 and Erypo, respectively.

Table 9 Disposition of patients in the correction phase trial

	Patients (n)		
	Total	SB309 group	Erypo group
Screened	780		
Enrolled (randomised)	609	305	304
Drop-outs after randomisation	63	31	32
Safety population	609	305	304
Full analysis set	598	300	298
PP set	541	273	268
Study completed (week 24, visit 8)	546	275	272
Premature termination of the trial	62	30	32
- Due to AEs	36	26	17

Recruitment

The study was carried out between 27th December 2004 and 24th January 2006 at multiple study centres in Bulgaria, Poland, and Serbia.

Conduct of the study

There were no protocol amendments affecting the study results.

Baseline data

The demographics of patients are summarised below.

Table 10 Demographic profile of patients in the Correction phase trial, safety population

Correction phase study [study 04-05]		
Parameters	SB309 (n=305)	Erypo (n=304)
Age (years)		
Mean±SD	52.34±11.94	53.58±12.70
Range	22-73	19-76
Groups		
12-65 years	258 (85.6)	246 (80.9)
>65 years	47 (15.4)	58 (19.1)
Sex		
Female	129 (42.3)	127 (41.8)
Male	176 (57.7)	177 (58.2)
Race		
Caucasian	305 (100.0)	304 (100.0)
Other		

Time period since suffering from ESRF (m)	357 max 24 median	307 max 26 median
Most frequent diagnosis leading to renal failure - Glomerulonephritis - Diabetic nephropathy - Hypertensive nephropathy	 89 (29.5%) 42 (13.9%) 51 (16.9%)	 82 (27.0%) 33 (10.9%) 62 (20.4%)
Baseline (week 0) haemoglobin (g/dL), mean	8.07±0.79	8.04±0.79

ESRF = end-stage renal failure, m = month(s), max = maximum

Numbers analysed

A total of 609 subjects (305 test product and 304 reference product) were randomised for treatment. A total of 609 patients were considered evaluable for safety (305 test product and 304 reference product who received study medication), 598 patients evaluable for full analysis (300 test product and 298 reference product who were treated for at least four weeks) and 541 patients evaluated as per protocol set (273 test product and 268 reference product without major protocol deviations).

Outcomes and estimation

The mean treatment duration of treatment of patients treated with SB309 was 157.79±30.05 days. For the patients treated with the reference drug the mean duration was 157.79±29.58 days. The maximally reached duration of treatment was 181 days for SB309and 178 days for Erypo.

The mean haemoglobin value over the last four weeks was 11.61 ± 1.27 g/dl for the patients treated with SB309 and 11.63 ± 1.37 g/dl for patients treated with Erypo. The 95% confidence interval of the difference (test-reference) was between - 0.245 g/dl and 0.201 g/dl and within the pre-defined equivalence range (±1.0 g/dl).

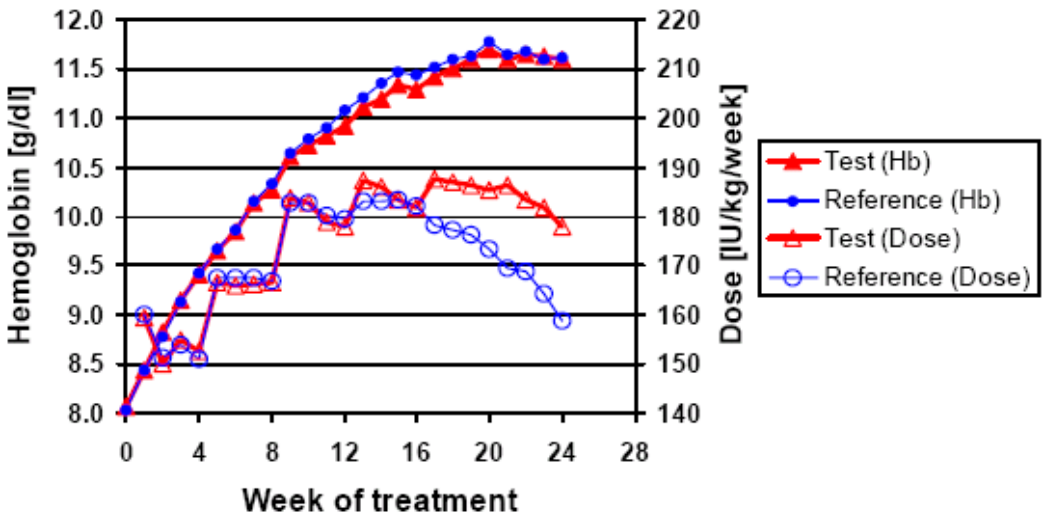
Table 11 Mean haemoglobin (g/dL) over the last four weeks (correction phase study) – PP population

Treatment	Description		
	Mean	SD	Max
SB309	11.61	1.27	14.50
Erypo	11.63	1.37	14.93

SD = standard deviation

The mean weekly epoetin dosage per kg body weight over the last four weeks was 182.20 ± 118.11 IU/kg/week (SB309) and 166.14 ± 109.85 IU/kg/week (Erypo). The 95% confidence interval of the difference (test-reference) was between –3.21 IU/kg/week and 35.34 IU/kg/ week hence equivalence of the test and reference product could not be confirmed regarding dosage using the predefined equivalence limits (see discussion below). The dosage of the test drug within the last four weeks was approximately 10% higher than the dosage of the reference product.

The mean Hb concentrations and epoetin dosages over time in both treatment groups are presented in the Figure below.



TF 8 Hemoglobin levels vs. erythropoietin dosage

Proportion of patients with treatment success

A total of 230 patients treated in each of both groups (84.2% of patients treated with test drug and 85.8% of patients treated with reference drug) registered treatment success.

Increase of haemoglobin over time

Haemoglobin increased from a mean value of 8.07 ± 0.79 g/dl at week 0 to 11.60 ± 1.37 g/dl at week 24 in the patients treated with the test drug. In the reference group, the haemoglobin level increased from a mean value of 8.04 ± 0.79 g/dl at week 0 to 11.61 ± 1.44 g/dl at week 24. In both treatment groups a plateau was observed during the last five weeks of treatment. The rate of increase of haemoglobin over time was highly similar in both treatment groups.

Proportion of patients with maintenance success

A maintenance success was achieved in 236 (86.4%) patients treated with the test product and in 227 (84.7%) patients treated with the reference drug. The 95% confidence interval for the treatment difference (test-reference) was between –4.2% and 7.7%.

Table 12 Proportion of patients with maintenance success (correction phase study) – PP population

Treatment	Maintenance success n (%)		
	Yes	No	n (%)
SB309 (n=273)	236 (86.4)	37 (13.6)	273 (100)
Erypo (n=268)	227 (84.7)	41 (15.3)	268 (100)

Source: Study 411-54-04-05-0000 [5.3.5.1 study 04-05]

Mean weekly dosage of epoetin per kg body weight during each interval of 4 weeks of treatment

A permanent and very similar increase over each interval of four weeks could be observed within the first 16 weeks in both treatment groups. Within the last eight weeks the dosage of the reference product decreased slightly but constantly and that of the test drug remained approximately constant. The treatment differences were not statistically significant for any of the 4-week periods.

Mean haemoglobin levels during each interval of 4 weeks of treatment

The course of the mean haemoglobin levels over time was practically identical for both products. No statistically significant differences were registered for any of the four week intervals between both products. The treatment difference was not statistically significant.

Mean haemocrit levels during each interval of 4 weeks of treatment

Baseline values from patients treated with SB309 increased from 24.7% at baseline to 35.6% in week 21-24. Baseline values from patients treated with Erypo increased from 24.7% (baseline) up to 35.8% in week 21-24. No statistically significant differences were registered for any of the four week intervals between both products.

Proportion of patients with an increase of haemoglobin of more than 1 g/dl for 4 weeks

All except three patients in each treatment group experienced an increase of more than 1 g/dl within a period of four weeks (SB309 n=270, Erypo n=265). The treatment difference was not statistically significant.

Percentage of haemoglobin measurements above 10 g/dl

An average of 64.3% of the haemoglobin values in patients treated with SB309 were above 10 g/dl over the total treatment time. In the Erypo group the corresponding proportion was 65.7%. There was no statistically significant treatment difference regarding this parameter. The descriptive statistics regarding the four week intervals showed a mean of 14.0% (SB309) and 15.9% (Erypo) for the period week 1-4. During week 21-24 the corresponding proportions were 86.8% and 85.5%. The treatment difference was not statistically significant.

Percentage of haemocrit measurements above 30%

On average, 68.6% of the haematocrit values from patients treated with SB309 were above 30% over the total treatment period. In the reference group the corresponding value was 69.7%. The treatment difference was not statistically significant. The descriptive statistics regarding the 4-week intervals showed an increase from a mean of 20.3% (SB309) and 19.2% (reference product) for the period week 1-4 to 89.7% in both treatment groups during week 21-24.

Proportion of patients with blood transfusions

Within the work-up period (PP population), three patients received blood transfusions. During the double-blind treatment phase, 10 patients of the SB309 group and 13 patients of the reference group required one or more blood transfusions. The treatment difference was not statistically significant.

Maintenance Phase Study

Study 411-54-04-04-0000 [study 04-04] was a randomised, double-blind, cross-over, verum-controlled, multiple-dose, multinational design phase III trial in patients with renal anaemia to prove the therapeutic equivalence of IV administered SB309 to the reference product (Erypro) for maintaining the haemoglobin concentration in these patients.

Methods

Study Participants

Patients were only eligible for enrollment if ALL of the following applied:
male or female patients, aged 18-75 years; haemodialysis patients with end-stage renal failure and renal anaemia currently on epoetin treatment for at least 3 months; patients on stable, adequate dialysis for at least three months (defined as no clinically relevant changes of dialysis regimen and/or

dialyzer); informed consent given in a written form after being provided with detailed information about the nature, risks, and scope of the clinical trial as well as the expected desirable and adverse effects of the drug. Patients were not eligible for enrollment if ANY of the following applied: contraindication for the test drug; relative or absolute iron deficiency at the end of run-in period; myelodysplastic syndrome; documented bleeding disorders; platelet count below 100x109/l; known, clinically manifested deficiency of folic acid and/or vitamin B12 (irrespective whether currently treated or not); known bone marrow fibrosis (osteitis fibrosa cystica); clinically relevant changes of dialysis regimen and/or dialyzer during the trial; clinically relevant increase of CRP (higher than 10 mg/dl) for at least 2 weeks; any blood transfusion within the last 3 months prior double-blind treatment period; acute bleeding and/or recently documented haemorrhage; hypersensitivity to epoetin; epoetin dosages > 3x200 IU/kg/week; hypersensitivity to albumin; detectable anti-epoetin antibodies; uncontrolled hypertension; any of the following within the 6 months prior to double-blind study drug administration:- myocardial infarction,- stroke,- severe/unstable angina,- coronary/peripheral artery bypass graft,- decompensated congestive heart failure (NYHA class III – IV),- cerebrovascular incident or transient ischemic attack,- pulmonary embolism,- deep vein thrombosis, or other thromboembolic event; known epilepsy; liver cirrhosis with clinical evidence of complications (portal hypertension, splenomegaly,ascites); patients with confirmed aluminium intoxication; , clinically relevant hemolysis and/or occult blood loss; presence of malignant tumors; clinically relevant malnutrition; pregnancy or lactation period in female patients; severe physical or mental concomitant diseases that might hamper the realization of thetrial according to protocol or the evaluation of efficacy or safety; anamnestic or current alcohol abuse i.e. consumption of more than 10 units of alcohol per week or a history of alcoholism or drug/chemical abuse (one unit of alcohol equals ½ l ofbeer, 200 ml wine or 50 ml of spirits); participation in another clinical trial within the last 12 weeks; legal incapacity and/or other circumstances rendering the patient unable to understand the nature, scope and possible consequences of the study; unreliability or lack of cooperation; lack of a possibility to attend the visits required by protocol.

Treatments

During the run-in period, the reference product Erypo was administered IV, 1-3 times per week. During the double-blind treatment phase, SB309 or Erypo, 1000 IU or 2000 IU epoetin, were administered IV, 1-3 times per week.

Duration of Study

Double-blind treatment of 24 weeks, preceded by an open run-in period of 12-16 weeks. In substantiated cases a prolongation of the run-in period was allowed up to max. 18 weeks. After the end of the 24 weeks double-blind treatment, all patients could continue treatment with the test product as a part of an open, follow-up safety trial.

Objectives

To prove the therapeutic equivalence of SB309 to a reference product (Erypo) for maintaining the haemoglobin concentration in anaemic patients with end-stage renal failure on chronic haemodialysis.

Outcomes/endpoints

Primary Efficacy Endpoints:

- Intra-individual change (test-reference) in mean weekly dosage per kg body weight of each product during the double-blind treatment period
- Intra-individual change (test-reference) in mean haemoglobin level during double-blind treatment with each study drug.

Secondary Efficacy Endpoints:

- Mean haemocrit levels during double-blind treatment with each study drug

- Proportion of patients with any permanent changes of haemoglobin levels of more than 1 g/dl during the double-blind period
- Proportion of patients with any transient changes of haemoglobin levels of more than 1 g/dl during the double-blind period
- Proportion of patients with any permanent dose change during the double-blind period
- Proportion of patients with any transient dose change during the double-blind period
- Proportion of patients with any haemoglobin measurement outside the target range during the double-blind treatment period
- Incidence of blood transfusions

Safety Endpoints:

- Occurrence of anti-epoetin antibodies
- Ratings of tolerability
- Evaluation of adverse events

Sample size

Sample Size Level 1: The calculated sample size of 50 patients who completed the double-blind treatment period would achieve a power of more than 80% for the two-sided proof of equivalence for the Hb targeted endpoint.

Sample size Level 2: The calculated sample size of 220 patients who complete the double-blind treatment period would achieve a power of more than 80% for the two-sided proof of equivalence regarding epoetin dosage. If approximately 35% of the randomized patients drop-out before the end of the double-blind period, a total number of 340 patients had to be randomized in the present trial. To reach this number of randomized patients, more than 340 patients had to be included in the run-in period of the study.

Randomisation

Randomisation was performed at the beginning of the double-blind period with patients randomly (1:1) assigned to the two different treatment groups

Patients were only randomised when the target Hb level was within the range of 10.5-12.5 g/dl with stable epoetin dosage and without intra-individual change in Hb of more than 0.6 g/dl over 4 weeks.

Blinding (masking)

This has been previously described in the correction phase study above.

Statistical methods

The 95% confidence intervals of the intra-individual change (test-reference) were calculated for:

- mean weekly dosage per kg body weight of each product during the double-blind treatment period
- mean haemoglobin level during double-blind treatment period

The confidence intervals were compared with pre-defined clinically relevant acceptance ranges:

- ±14 IU/kg/week for dosage
- ±0.6 g/dl for haemoglobin

The intervals were calculated by means of ANOVA.

The evaluation of the secondary and safety endpoints was performed according to the type of distribution of the respective parameter. A Chi-square test was applied for parameters with discrete distribution, a t-test or a Mann-Whitney-Wilcoxon test was applied for continuous parameters.

The statistical analysis was performed on three different patient populations:

- Full data set of efficacy, including all patients who started therapy and had any follow-up information regarding the primary endpoint after switch-over, and did not violate major entry criteria.
- Full data set for safety, including all patients who started therapy irrespective of the information regarding the primary endpoint.
- Per protocol population, excluding cases of major protocol violation and drop-outs.

Results

Participant flow

The administration of study medication was correctly performed in 96.7% of all cases for SB309 and in 97.5% of all cases for the reference medication (PP set).

Table 13 Disposition of patients in the maintenance phase trial

	Patients (n)			Comments
Screened	407			Without 15 patients from centres 1, 6, and 7
Enrolled	402			Started open run-in treatment period
Safety population (randomised)	313	Period 1: 155 Period 2: 145	Period 1: 158 Period 2: 146	Patients eligible for randomisation into the double-blind study phase
Full analysis set	282	143	139	Without patients treated less than 1 month in the second study period
PP set	239	121	118	Without patients with major protocol deviations
Study completed (week 24, visit 10)	269	135	134	-
Premature termination	44	20	24	26 due to adverse events 9 met exclusion criteria 7 on own request 1 non-compliance 1 contact to patient lost

Recruitment

The study was carried out between 3rd May 2004 and 15th December 2005 at multiple study centres in Germany and Poland.

Conduct of the study

There were no protocol amendments affecting the study results.

Baseline data

The overall average age of patients enrolled was 55.19 ±13.28 years. All patients were Caucasian. The treatment groups were well balanced with regard to demographic, anthopometric and disease-specific baseline characteristics.

The demographics of patients are summarised in the table below.

Table 14 Demographic profile of patients in the Maintenance phase trial, safety population

Maintenance phase study [study 04-04]	
Parameters	SB309/Erypo (n=313)
Age (years)	
Mean±SD	55.19±13.28
Range	20-77
Groups	
12-65 years	232 (74.1%)
>65 years	81 (25.9%)
Sex	
Female	125 (39.9%)
Male	188 (60.1%)
Race	
Caucasian	313 (100)
Other	0 (0)
Time period since suffering from ESRF (m)	3-347, median 37
Most frequent diagnosis leading to renal failure	
-Glomerulonephritis	106 (34.6%)
-Diabeticnephropathy	51 (16.7%)
- Hypertensive nephropathy	23 (7.5%)

ESRF = end-stage renal failure, m = month(s)

Numbers analysed

A total of 313 patients were randomised for treatment and considered evaluable for safety, 282 patients were evaluable for full analysis and 239 patients evaluated as per protocol set.

Outcomes and estimation

The mean treatment duration in the PP population was 82.31±4.75 days for SB309 and 82.79±7.69 days for the reference product.

Primary Endpoints

The mean haemoglobin values measured during run-in phase and double-blind treatment with SB309 and the reference product are shown in the table below. The 95% CI interval of the intra-individual difference (test - reference) of the mean haemoglobin level during double-blind treatment with each study drug was between 0.09 g/dL and 0.28 g/dL and thus entirely within the pre-defined equivalence range (±0.6 g/dL).

Table 15 Mean haemoglobin (g/dL) over treatment period (maintenance phase study) – PP population

Treatment	Description		
	Mean	SD	Max
Run-in	11.56	0.69	13.42
SB309	11.35	0.76	14.22
Erypo	11.54	0.65	13.84

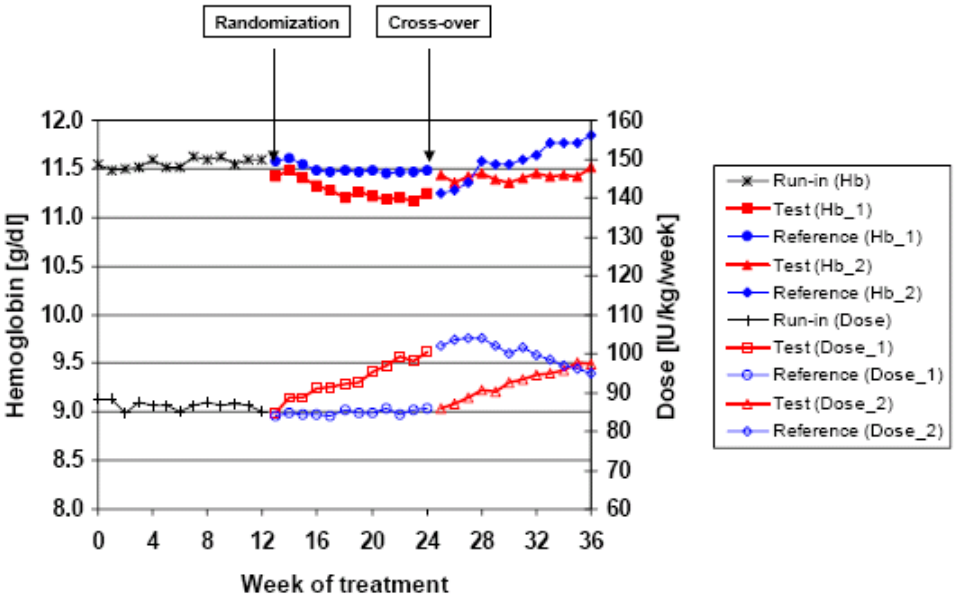
SD = standard deviation

The mean epoetin dosage administered during double-blind treatment with SB309 and the reference product was 92.68±62.60 IU/kg/week and 92.58±64.31IU/kg/week, respectively. The maximum weekly dosage was 437.25 IU/kg/week in the run-in phase and 398.41 IU/kg/week with SB309 compared to 393.07 kg/IU/week with Erypo.

The 95% CI interval of the intra-individual difference (test - reference) of the mean weekly dosage per kg bodyweight of each product during double-blind treatment was between -4.67 IU/kg/week and 4.29 IU/kg/week and within the pre-defined equivalence range.

Results of the primary efficacy parameters are summarised below. Following a switch from the reference to the test drug the dose increased by approximately 10-15% and the haemoglobin level decreased transiently by approximately 5%. After a switch from test to reference product the dose decreased by approximately 10% and simultaneously an increase of approximately 10% was observed in haemoglobin levels. This difference could possibly be explained by the difference in mean bioactivity between the SB309 and Erypo batches used in the study as measured by the Ph.Eur. normocythaemic mouse assay, although all batches remained within the Ph. Eur. limits, namely 80%-125% (with error limits of 64 to 156%). The inter-batch difference in bioactivity spanned a range of 23%. After correction for bioactivity, the results of the 95% CI: intervals for the difference in dosage between the two products were 3.806-13.917 IU/kg/week (for details on correction for bioactivity see below).

Figure 2 Haemoglobin levels vs nominal-based epoetin dosage



Secondary Endpoints

Mean haematocrit levels during double-blind treatment period

Mean haematocrit levels during the double-blind treatment period with each study drug appeared similar: 34.30 ± 2.52% for test treatment and 34.87 ± 2.15% for reference treatment, although the difference was statistically significant ($p<0.0001$); the 95% confidence interval for the mean difference (test-reference) was between 0.28% and 0.85%.

Proportion of patients with any permanent changes of haemoglobin levels of more than 1 g/dl during the double-blind period

A permanent change in Hb was observed in 10.5% of the patients under test treatment and in 11.3% of the patients under reference treatment. The treatment difference was not statistically significant

Proportion of patients with any permanent or transient dose change during the double-blind period

During treatment with test product 94 patients (39.3%) had a permanent dose change and 141 patients (59.0%) had a transient dose change. A permanent dosage change during treatment with the reference product was necessary in 98 patients (41.0%), whilst transient dosage changes occurred in 155 patients (64.9%). The treatment difference was not statistically significant.

Proportion of patients with any haemoglobin measurement outside the target range

In the course of the treatment with SB309 and with the reference product, 32.6% of patients on test and and 36.4% of patients on reference drug experienced Hb values outside the target Hb range (10.5-12.5 g/dL). The treatment difference was not statistically significant

Incidence of blood transfusions

During the run-in phase only one patient needed a blood transfusion. In the course of the double-blind treatment phase three patients on test drug and two patients on reference drug received blood transfusions.

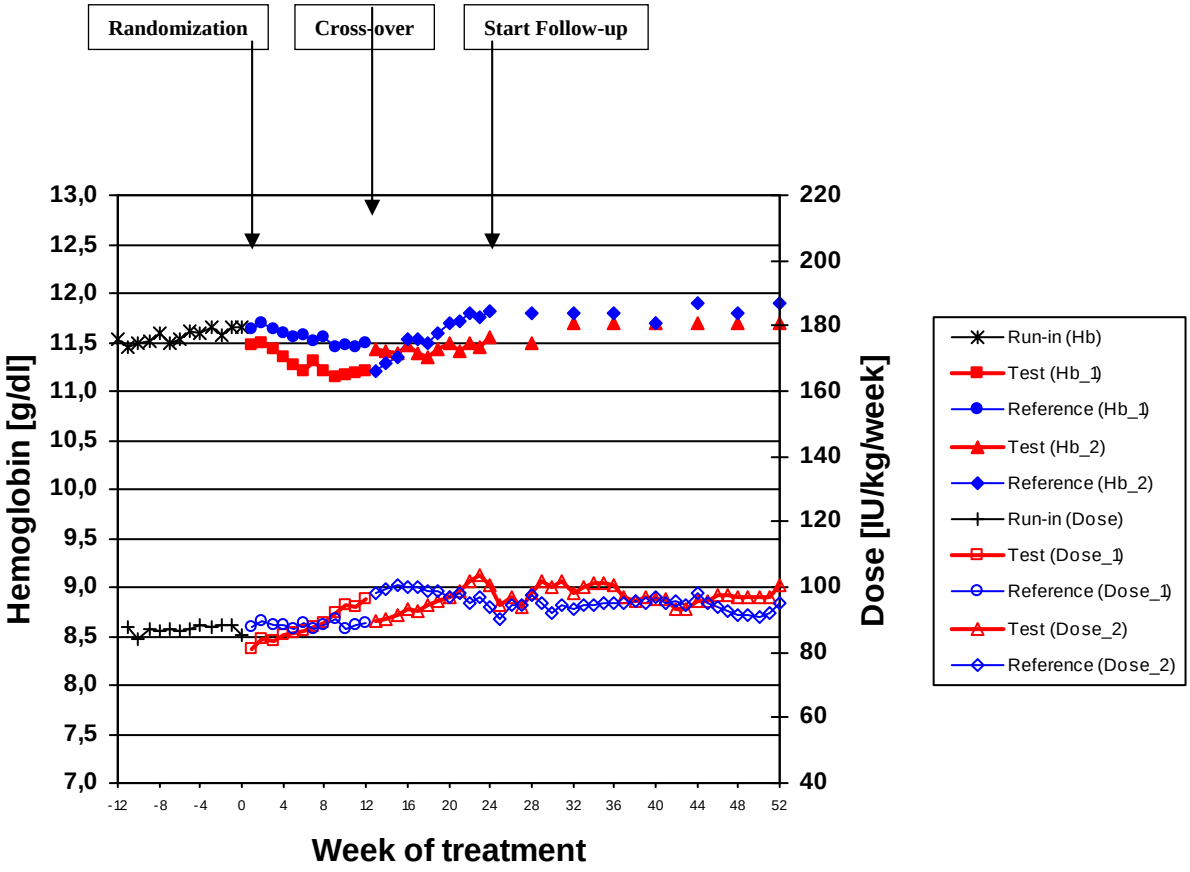
Ancillary analyses

Due to concerns of carry-over effects from the first to the second treatment phase and that the study duration may have been too short to fully assess treatment differences, the applicant provided additional analyses, including a comparison of Hb values and epoetin doses over the last 4 weeks of of each treatment period (and therefore excluding the first 8 weeks), as an attempt to minimise carry over effects from previous epoetin treatment. The equivalence margins were also met with this new post-hoc analysis.

In addition, the applicant presented the mean Hb levels and epoetin dosages over the complete 52-week treatment period (see Figure below). A stable Hb had already been achieved at the 12-week time point of the second treatment phase and the epoetin dose did not further increase in the test/test group (in fact it declined thereafter and got closer to the reference dose). Of note, a similar percentage of patients in both treatment groups, i.e. 87% and 85% enrolled in the test-reference group and reference-test group, respectively, completed the 24-week comparative phase. In addition, a similar percentage of these completers, i.e. 86% and 87% of the test-reference and reference-test group, respectively, entered the follow-up phase during which all patients were treated with the test product.

To avoid possible bias due to drop-outs, the epoetin doses only for those patients that completed the parent study and enrolled in the follow-up study are depicted in Figure below. The mean treatment difference in epoetin dosage at the end of the parent study was higher in this group compared to the overall completer group indicating that the decline in dosage observed after the 24-week time point of the comparative phase was not due to drop-out of patients on high doses of the test drug.

Figure 3:



Adjustment for bioactivity

Although there were differences in bioactivity in the batches, Erypo batches were found on average to have 8% higher bioactivity than SB309 batches, although all batches remained within the Ph. Eur. limits, namely 80%-125% (with error limits of 64 to 156%). The difference in bioactivity was shown to be associated with a correspondingly higher protein content in the Erypo batches which contained on average 9% over the labelled amount of protein, compared with on average 1% over the labelled amount with SB309. On the other hand, the average specific activities for both products were remarkably similar (130.80 for test vs. 130.75 units/µg for reference).

The applicant therefore provided an additional analysis adjusting epoetin dosage for inter-batch variability in bioactivity. For this purpose, the applicant utilised a correction factor in the reanalysis of the data with respect to dosage. However, even with the application of a correction factor, the correction phase study failed to meet its pre-specified criteria for equivalence since the 95% confidence interval fell between (-23.5, 17.48) IU/kg/week. In addition, introduction of a correction factor into the maintenance phase study led to a widening of the revised 95% CI for dosage of 3.086-13.917 IU/kg/week. However, both 95% CIs were included in the modified acceptance range of ± 45 IU/kg/week (for details of the widening of the equivalence margins see below).

A comparison of results for uncorrected and corrected data is given in the Table below.

Table 16: Comparison of effects of SB309 and Erypo in the correction and maintenance treatment of anaemic haemodialysis patients (double-blind period)

Primary endpoints	Correction phase study		Maintenance phase study	
	SB309	**Erypo**	**SB309**	**Erypo**
Haemoglobin values, g/dL				
	Over the last 4 weeks		Over the treatment period (12 weeks)	
- Mean	11.61±1.27	11.63±1.37	11.35±0.76	11.54±0.65
- Maximum	14.50	14.93	14.22	13.84
95% CI of the difference (test - reference), g/dL	-0.245-0.201		0.09-0.28	
Pre-defined equivalence range, g/dL	±1.0		±0.6	
Epoetin dosage, IU/kg/week				
	Over the last 4 weeks		Over the treatment period (12 weeks)	
Nominal/labelled dosage				
-Mean	182.20±118.11	166.14±109.85	92.68±62.60	92.58±64.31
Maximum	571.43	585.37	437.25	393.07
95% CI of the difference (test - reference), IU/kg/week	-3.21-35.34		-4.67-4.29	
Pre-defined equivalence range, IU/kg/week	±14.0		±11.11	
Bioactivity corrected dosage				
Mean	186.12±120.26	183.09±122.59	93.47±62.77	102.50±72.42
Maximum	560.71	660.73	424.66	441.08
95% CI of the difference (test – reference), IU/kg/week	-23.543-17.48		3.806-13.917	
Equivalence range, IU/kg/week	±36.6		±20.5	

The applicant clarified that dose correction for bioactivity was performed based on the exact bioactivity of every single syringe administered throughout the trial to every patient.

Widening of acceptance range

The correction phase study did not meet the co-primary end-point of mean weekly dosage of epoetin per kg bodyweight during the last 4 weeks of treatment since this showed a mean difference of 16 IU/kg/week (corresponding to 9.6% of reference dose) with a 95% CI of -3.21 to 35.34 IU/kg/week (corresponding to 1.9-21% of reference dose), which was outside the pre-specified equivalence range (+/-14 IU/kg/week [corresponding to 8.4% of the reference dose]).

The applicant initially argued that the difference in epoetin dose observed between test and comparator products was considered to be attributable to the batches of reference product having up to 15% higher activity and that this deviation from the labelled content was within the Ph. Eur. approved limits for bioactivity of 80-125%. The applicant therefore suggested a widening of the equivalence margins to at least the release specification of 80 to 125% and showed in a post-hoc analysis that a change in bioactivity of up to 25%, on average, did not relevantly influence Hb levels in the study population.
During the scientific assessment, the applicant clarified that the pre-defined equivalence margin of 14 IU/kg/week was wrong and should be corrected to 45 IU/kg /week because of a misreading of the EPAR of Dynepo were it is stated that the no-effect dosage for Dynepo is 15 IU/kg given three times weekly (TIW) and not only once weekly. This newly proposed acceptance range was also supported by literature. The applicant provided evidence that a difference of 35.3 IU/kg/week in epoetin dose (worst case scenario in the correction phase trial) was clinically not relevant in the investigated study population, whether this difference was calculated as absolute value or as percentage of the reference

dose (21%). The applicant also provided further reassurance that such a difference does not result in a different safety profile.

Study 441-54-04-46-0000

This uncontrolled safety trial was conducted in cancer patients with chemotherapy-induced anaemia. A 12 week interim report was provided. A comprehensive historical comparison was presented as supportive information (data not shown).

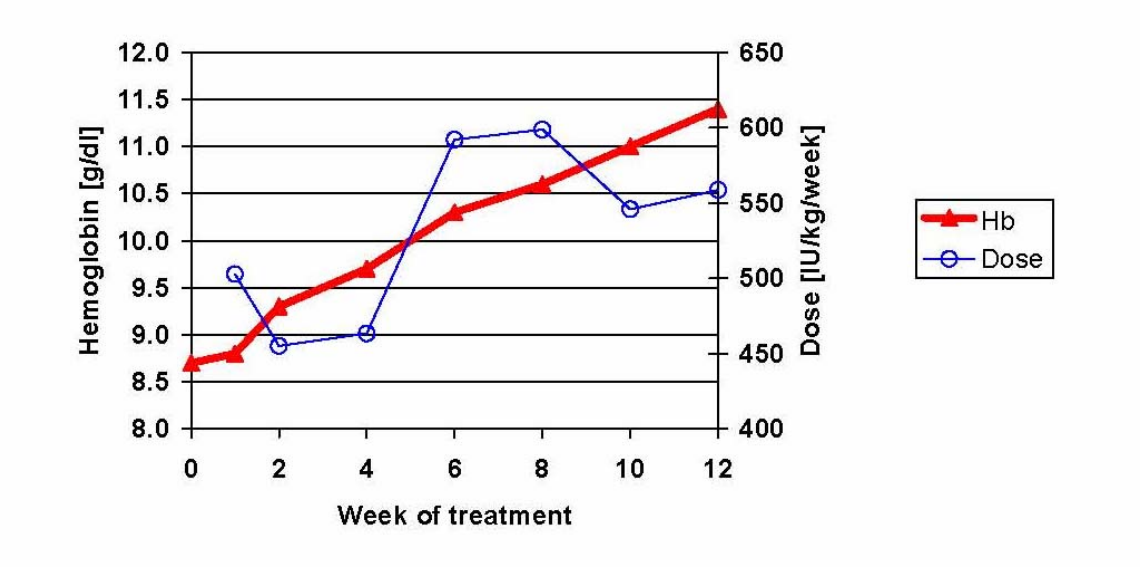
Study objective
The primary objective of this trial was to provide information on the incidence of clinically significant thrombotic events (deep vein thrombosis requiring anticoagulant therapy, embolic events including pulmonary embolism, myocardial infarction, cerebral ischemia, left ventricular failure and thrombotic microangiopathy) within the first 12 weeks of treatment with SB309.

Disposition of patients
A total number of 261 male and female anaemic (Hb <10 g/dL) patients with cancer (solid tumors, malignant lymphoma or multiple myeloma) gave their informed consent, of which 216 patients were enrolled after fulfilling of inclusion and exclusion criteria. The information for efficacy and safety was based on data from 208 patients. The evaluation of serious adverse events (SAEs) was based on data from 216 patients due to the fact that SAEs were reported on a regular basis for all patients enrolled. A total of 97 patients dropped out, 90 patients during the first 12-week treatment period.

Haemoglobin
The baseline mean Hb value was 8.7 ± 0.92 g/dl (n=207). Treatment with SC SB309 led to a continuous increase in Hb by on average 2.7 g/dl to a mean of 11.4 ± 1.98 g/dl within 12 weeks. This Hb increase was statistically significant compared to baseline values ($p<0.0001$) demonstrating a strong evidence for the efficacy of SB309 in the target population.
Published data on epoetin alfa show similar mean haemoglobin values after treatment periods of 12-28 weeks of 11.3-12.0 g/dl and a mean Hb increases in the range of 1.8-3.3 g/dl (Littlewood et al. 2001: 2.2-3.3 g/dL within 12-24 weeks, Cortesi et al. 2005: 1.8 g/dL within 10 weeks, Gabrilove et al. 2001: 1.8 g/dL within 16 weeks, Sasha et al. 2003: 1.9 g/dL within 16 weeks, Quirt et al. 2001: 2.8 g/dL within 16 weeks). The results obtained from the current trial are thus in line with literature data.

Epoetin dose
The range of the mean weekly epoetin doses applied was 502.7 ± 151.08 IU/kg to 598.7 ± 265.04 IU/kg (n=207). Between weeks 4 and 8 an apparent increase of the mean dosage was observed followed by a decrease from week 8 onwards until the end of first treatment period. This corresponds to the dosage recommendations given in the protocol.
The graphical presentation (Figure 4) demonstrates that SB309 is effective regarding the recommended initial dose and its ability to reach the target haemoglobin concentration of approximately 12 g/dl. This aligns with published results from similar trials with Epoetin alfa in cancer patients.

Figure 4: Haemoglobin levels vs. erythropoietin dosage (mean values for data available at respective visits)



Analysis performed across trials (pooled analyses and meta-analysis)

None submitted.

Clinical studies in special populations

None submitted.

Supportive studies

Study 441-54-04-14-0000

Patients with renal anaemia completing either of the above efficacy studies were eligible to receive SB309 in this open-label, uncontrolled safety trial with particular focus on the formation of anti-epoetin antibodies. A total of 745 patients were included. An interim report covering data from 23-May 2005 until 27-April-2006 was presented for serious adverse events (SAEs) with the initial submission. The applicant provided further interim data on the follow-up study covering the first 28 weeks. These data suggested that adequate Hb levels could be well maintained with the use of SB309 (data not shown). No case of lack/loss of efficacy was reported.

Discussion on clinical efficacy

Dose response studies are not considered necessary for a medicinal product claimed to be similar to one already licensed since posology will be the same as for the reference product.

The titration trial was conducted broadly in accordance with CHMP guidance. It was noted that a comparative trial in renal anaemia patients using the SC route of administration was not possible at the time of clinical development due to the temporary contraindication of Erypo.

The study results indicate that both products can control Hb levels to the same extent, but higher doses of SB309 were required for control to be achieved. The applicant claimed that this difference in epoetin dosage was due to differences in syringe content (with regard to bioactivity and protein content) of SB309 and Erypo despite the same nominal dose and all syringes remaining within the release specifications of 80-125%. This is supported by the almost identical specific bioactivity of both products. Although these arguments were considered plausible, correction of epoetin dosage for bioactivity was not endorsed because it is doubtful that a true correction can be achieved due to the high intrinsic variability of the bioassay used to determine bioactivity (an indicator may be that correction led to contrasting effects in the correction phase and maintenance phase study). In addition, adjusting every single administered syringe for bioactivity is not practical and difficult if not impossible to verify. Moreover, the applicant could show that changes in bioactivity of up to 25% did,

on average, not relevantly affect Hb levels. Also in the light of these data, a bioactivity correction for a mean difference of 8% in bioactivity does not appear to be justified.

The applicant also argued for wider equivalence margins than those pre-specified. The CHMP considered the acceptability of the post-hoc correction of the equivalence margin to ±45 IU/kg/week. The worst case scenario for the treatment difference in epoetin dose was a difference of 35.1 IU/kg per week (upper limit of the 95% CI) in the correction phase study. This value is clearly below the assumed no-effect level of 45 IU/kg/week. The applicant provided an analysis from the correction study showing that, on average, a dose increase of approximately 40 IU/kg/week was required to achieve a borderline relevant increase in Hb of 1 g/dL in patients on haemodialysis. Since the background variability in Hb is high in this patient population, even in "stable" patients on stable epoetin doses, the chosen limit of 1 g/dL for definition of clinical relevance appeared acceptable. In an additional analysis the applicant could provide evidence that the clinical effect of batch changes (measured as frequency of subsequent dose adjustments) of SB309 or due to product changes (from Erypo to SB309 or vice versa), was not increased compared to batch changes of the reference product Erypo and therefore unlikely to elicit a safety concern. In addition, the applicant could show that Hb levels and epoetin doses were very similar in a subgroup of patients receiving test and reference product of similar bioactivity further supporting the assumption that SB309 and Erypo have similar efficacy. Moreover, data from the follow-up study in patients with renal anaemia demonstrate that Hb levels can be well maintained with the use of different batches of SB309. In conclusion, the applicant could reasonably justify the modified equivalence margin of ± 45 IU/kg/week and, more importantly, could demonstrate that a difference of 35.1 IU/kg/week in epoetin dose (worst case scenario) was clinically not relevant in the studied population. The CHMP requested further reassurance that differences in dose up to 45 IU/kg/week (modified equivalence margin) will not result in a different safety profile (see safety section below).

Taken together, the study results and additional analyses requested by CHMP provided convincing evidence that SB309 and Erypo have similar efficacy when used IV. The following considerations led to the conclusion that similar efficacy can also be assumed for the SC route of administration: The demonstration of similar efficacy for the IV route, together with the similarity of PK profiles, especially bioavailability, for both the IV and SC route of administration suggests similar efficacy also for SC use. The comparison of the efficacy data from the oncology trial with published data are in line with this conclusion.

In conclusion, based on the argumentation and additional data provided by the applicant, comparable clinical efficacy between SB309 and Erypo has been demonstrated not only with regard to the Hb-targeted endpoint but also with regard to epoetin dose for both routes of administration. The observed difference in epoetin dose appears to be due to a difference in the syringe content (in terms of bioactivity and protein content) of the test and reference product batches despite the same nominal dose but is not considered clinically relevant. The difference in syringe content may be explained by the use of different bioassays for determination of bioactivity for the test product (normocythaemic mouse bioassay used in the EU) and the reference product (exhypoxic polycythaemic mouse bioassay used in the USA).

Clinical safety

Patient exposure

Safety data were derived from 922 adult haemodialysis patients (correction phase study: n=609 patients, thereof 206 without epoetin pre-treatment; maintenance phase study: n=313 patients) have been provided. Of these, 618 patients were treated with SB309 and 617 patients with Erypo for 12-24 weeks in the double-blind phases of the respective studies. A total of 745 patients who completed the correction phase study (n=513) and the maintenance phase study (n=232) are further treated for at least 52 weeks with SB309 in the ongoing follow-up study 411-54-04-14-0000.
The clinical safety data were also derived from 208 patients with chemotherapy-induced anaemia and treated with SB309 in Study 441-54-04-46-0000.

Adverse events

The most frequently observed AEs were hypertension, AV-fistula thrombosis/complications, infections and cardiovascular events. The observed spectrum of AEs was that expected for patients on haemodialysis. Cardiovascular events are the most common cause of death in this population.

Although, overall there did not appear to be significant differences in the safety profiles of the test and reference drugs, there were nevertheless, differences seen in the correction phase trial which showed more common AEs considered at least possibly drug-related for SB309. Particularly, an increased incidence of drug-related cases of hypertension and SAEs involving hypertensive crisis, haemorrhagic stroke, cerebrovascular events and TIA were seen with SB309 in the correction phase trial. In this trial, the rate of hypertensive events was 9.2% (8.2% related) (which occurred in 6.6% of patients) with SB309 compared to 5.9% (5.5% related) (which occurred in 4.3% of patients) with reference. On the other hand, AV fistula thromboses occurred more often in Erypo treated compared to SB309 treated patients (incidence 4.6% vs. 2.3%, respectively). A total of 16 patients (11 SB309 versus 5 Erypo) had SAEs belonging to the SOC "nervous system disorders". Following an assessment of the systolic and diastolic blood pressure measurements, it was assumed that these patients were at a higher risk due to their significantly higher blood pressure values (147.77 mmHg±18.33) compared to all other patients (139.93 mmHg±19.55). Although, in the correction phase study overall SAEs were reported at a similar rate, i.e. in 94 and in 96 cases of test and reference treatment, respectively, SAEs relating to cerebrovascular events were more frequent in the SB309 group (10 vs. 3), whereas SAEs relating to AV fistula thromboses were more frequent in the Erypo group (9 vs.4). Hypertension/hypertensive crisis occurred in 2.1% of patients during test treatment and in 2.0% of patients during reference treatment.

In the maintenance phase trial, hypertension occurred in 1.9% of SB309 treated and in 2.2% of Erypo treated patients. There were 3 cases of hypertensive crisis with SB309 compared with only one in the reference group. On the other hand, peripheral occlusive disease and coronary artery disease was more frequent in the reference than in the test group (1.6% vs. 0.3% and 1.3% vs. 0%, respectively). Again, the absolute numbers were small. Overall, 43 SB309 treated patients experienced 71 SAEs and 52 Erypo treated patients experienced 75 SAEs. With respect to SAEs the numbers for hypertension and hypertensive crisis were 2.8 % in the test vs. 0% in the reference group. However, none were apparently drug related.
In patients with chemotherapy-induced anaemia, eighty-four patients experienced a total of 163 AEs during the 12-week treatment period. Ninty-one of these events were assessed as serious and 65 AEs as severe by the investigators. Twenty-one patients dropped-out due to 58 AEs within the first 12 weeks. The AEs experienced during the trial were typical for patients with cancer receiving chemotherapy. The incidences of adverse events observed in the present trial are comparable with literature data in this population (Cortesi et al., 2005, Littlewood et al., 2001, Prescribing Information Procrit 2007). The causal relationship of these AEs and the study medication was judged as not related in 87.1% (n=142), unlikely in 8.0% (n=13), probable in 2.5% (n=4, deep vein thrombosis, thrombophlebitis, GI disorder, rash), possible in 1.2% (n=2, deep vein thrombosis, atrial fibrillation) and not assessable in 0.6% (n=1, infection) of cases. The two patients for which the event was judged as possibly related to study medication dropped-out. The mean systolic blood pressure remained more or less constant from visit 0 (123.07 ± 15.31 mmHg) to visit 5 (122.97 ± 14.23 mmHg). The same applies for the mean diastolic blood pressure: visit 0 (76.18 ± 10.41 mmHg) and visit 5 (76.98 ± 9.06 mmHg). Local tolerability as assessed by the investigators after each administration of study drug was either excellent (83.2%-92.1%) or good (7.9%-16.8%).

Incidence of clinically significant thrombotic events in patients with chemotherapy-induced anaemia
At the date of the interim report 9 cases (AE or SAEs) were identified to belong to the events defined as primary endpoint: 1 superior vena cava occlusion (AE), 2 cardiac failures, 1 acute cardiac failure, 2 cardiopulmonary failures, 2 deep vein thromboses, and 1 thrombophlebitis. The cardiac failure, the acute cardiac failure and the cardiopulmonary failure were associated with a fatal outcome. One of the 9 events occurred within the second treatment period. The incidence rate of clinically significant thrombotic events in the safety population of patients (n=208) within the 12 weeks of treatment was thus 3.9% (8 of 208). This incidence rate is similar or lower than the published incidence rates for

thrombotic events in epoetin treated cancer patients being between 5-6% (Vansteenkiste et al., 2002; Prescribing Information Epogen, 2004) and approx. 30% (Rosenzweig 2004). For patients with metastasic breast cancer and receiving a five drug chemotherapeutic regimen but not treated with epoetin an incidence of 17.5% of such events was published by Goodnough (1984). The definition of thrombotic events in the present trial was as broad as possible in order to avoid any positive bias in favour of the test drug. Three cases (one of which was uncertain) of death in the oncology trial were associated with the development of a thrombotic event.

Immunogenicity

In both comparative trials in patients with **renal anaemia**, serum samples for determination of anti-epoetin antibodies were drawn at start and during the study. The samples were frozen at -20º C and kept until analysis in a central laboratory. In all patients, the last available blood sample was analysed first. Only if anti-epoetin antibodies were detected all previous blood samples for the respective patient analysed in order to detect the time point of first occurrence. In suspicious cases with respective clinical symptoms, blood samples could be analysed at an earlier time point. Usually, antibody testing should be performed from the beginning and on an ongoing basis to detect possible problems with immunogenicity early on. For determination of anti-erythropoietin antibodies in human serum samples a validated radio-immuno-precipitation assay (RIP-assay) was employed. This assay has been previously described and published by Casadevall et al. In the **correction phase study**, eleven patients were positive for anti-epoetin antibodies (7 patients in the SB309 group and 4 in the reference group, see Table below). However, in all these 11 patients anti-erythropoietin antibodies were already present at the screening visit. Although positive at the final visit, one patient was finally regarded as negative in all available samples. In the **maintenance study**, three (approx 1%) of the randomised patients had positive results for anti-epoetin antibodies which were already present at the screening visit (see Table 17). No indication of PRCA was present in any of the patients with a positive result in the screening test for anti-erythropoietin antibodies.

Table 17: Patients with occurrence of anti-erythropoietin antibodies

Study	Patient	Treatment / sequence	Visit	Finding
411-54-04-05-0000 [5.3.5.1 study 04-05] Correction phase study	1017	SB309	1, 3, 5, Final	Positive
	1064	SB309	1, 3, 5, Final	Positive
	1077	Erypo	1, 3, 5, Final	Positive
	1203[a)]	Erypo	1, 3, Final	Positive
	1269	Erypo	1, 3, 5, Final	Positive
	1345	SB309	1, 3, 5, Final	Positive
	1382	SB309	1, 3, 5, Final	Positive
	1418	Erypo	1, 3, 5, Final	Positive
	1567	SB309	1, 3, 5, Final	Positive
	1583	SB309	1, 3, 5	Positive
	1671[b)]	SB309	1, Final	Positive
411-54-04-04-0000 [5.3.5.1 study 04-04] Maintenance phase study	132[c)]	Test - Reference	1, 5, 8, Final	Positive
	217	Test - Reference	1, 4, 5, 7, 8, Final	Positive
	227	Reference - Test	1, 4, 5, 7, 8, Final	Positive
	5035 (drop-out)	Run-in phase	1, 4	Positive

Serum samples for determination of antibodies were collected at visit 1 (screening), visit 3, visit 5, and visit 8 (final) in the correction phase study and at visit 1 (screening), visit 4, visit 5, visit 7, visit 8, and visit 10 (final).
[a)] No data available for Visit 5; [b)] no data available for Visit 3 and 5; [c)] no data available for Visit 4 and 7.

In the oncology study samples from 189 patients with **chemotherapy-related anaemia** were evaluated in view of occurrence of anti-epoetin antibodies. All samples tested showed a negative result.

Serious adverse event/deaths/other significant events

There was no significant treatment difference in mortality between treatment groups in haemodialysis patients. During the correction phase trial, 26 vs 17 patients of the test and reference group, respectively, were withdrawn due to an AE, those withdrawn due to SAEs were 22 vs 14, with withdrawal figures involving the nervous system SOC showing 10 vs 2 for SB309 and reference, respectively. During the maintenance phase trial, 20 patients of each treatment group were withdrawn due to an AE. In the uncontrolled follow up study, 41 patients had study medication withdrawn. For SAEs see above.
In patients with chemotherapy-induced anaemia, a total number of 19 patients died in the course of the trial until 26-Jul-2007 (14 within the first 12-week treatment period). One patient died before start of treatment. Fourteen cases of death were judged as not related and five cases as unlikely related to the study medication. A total of 93 SAEs were observed in 41 patients. In 19 patients (8.8 % of the study population) the SAE had a fatal outcome. The majority of SAEs reported so far belong to the SOCs blood and lymphatic system disorders (22.6%, n=21) and infections and infestations (17.2%, n=16), and renal and urinary disorders (10.8%, n=10). Among the first two groups pancytopenia was reported for 8.6% (n=8) of SAEs, followed by anaemia, febrile neutropenia and leukopenia (each 3.2%, n=3). Within the group of infections and infestations 5.4% (n=5) belong to sepsis, and 4.3% (n=4) belong to bronchopneumonia. Only eight SAEs could currently be identified to belong to the events defined as primary endpoint (2x cardiac failure, acute cardiac failure, 2x cardiopulmonary failure, 2x deep vein thrombosis, and thrombophlebitis). The majority of SAEs were assessed as severe (79.6%, n=74). Only 19.4% (n=18) of all reported events were assessed as moderate and 1.1% (n= 1) as mild. Most of the reported SAEs were judged as not related to study medication (82.8%, n=77). An unlikely relationship to study drug was reported for 14.0% of SAEs (n=13). Three events were judged as possibly related and concerned atrial fibrillation and deep vein thrombosis. The study medication was withdrawn in 20 of 208 patients (9.6%) due to an adverse event.

Laboratory findings and vital signs

Laboratory parameters were generally unremarkable and not significantly different between treatment groups. Vital signs: In the correction phase study, 4 out of a total of 53 SB309-treated patients with normotensive blood pressure at baseline developed hypertension. The majority of patients showed hypertension at the beginning (n=226) and at the end (n=225) of the trial. Within the reference group, one out of a total of 60 patients with normal blood pressure at entry experienced hypotension and 4 patients developed hypertension at final visit. Blood pressure indicating hypertension was measured in 217 patients at entry visit.

Safety in special populations
Not applicable

Safety related to drug-drug interactions and other interactions
Not applicable

Discontinuation due to adverse events
Not applicable

Post marketing experience
Not applicable

Discussion on clinical safety

Patients with renal anaemia

The observed spectrum of AEs is that expected for patients on haemodialysis. Concerning the adverse event profile of SB309 observed in the correction phase trial, increase in blood pressure and propensity to thrombosis during epoetin therapy could at least be partly explained by an increase in blood volume and the change in viscosity and rheologic properties of the blood with increasing Hb/haematocrit. However, there is no evidence from the study data that SB309 would lead to overshooting Hb response. In fact, mean Hb values were very similar during the correction phase study and, if anything, somewhat lower in the maintenance phase study. Thus the most likely explanation for the observed small differences appears to be variability in this high-risk population.

The applicant conducted a number of analyses to address the concern of increased hypertensive events with SB309 observed in the anaemia correction study. High systolic BP has been identified as the only relevant risk factor for SAEs in the SOC Nervous System Disorder and this finding re-emphasizes the already known critical need for effective BP control in this high-risk population. Overall the data do not conclusively suggest that patients are at increased risk for hypertension and related events when using SB309 compared to Erypo. In the same line, no such increased risk has been identified for SB309 in the maintenance phase study (or in the oncology trial). The MAA has committed to an undertaking to monitor blood pressure in both naïve and pre-treated patients and provide a proposal within a timeframe to be agreed by CHMP. Concerning the SOCs of specific interest (blood and lymphatic system, cardiac disorder, vascular disorders) and SAEs in the SOC Nervous System Disorder, the applicant committed to keep these events under review. The Applicant will further monitor hypertensive encephalopathy and will also include other CNS SOC events as part of the RMP.

Patients with chemotherapy-related anaemia

The Applicant provided an interim report on the oncology trial 441-54-04-46-0000 and a final 12-week safety report. The observed AE profile in this study was in line with that expected in this very ill population but due to the non-comparative nature of the study, direct comparison with the reference product was not possible. The incidence of thrombotic events was low, despite a very broad definition of this term. Based on the current safety information and published series, there is no concern regarding the treatment of cancer patients with chemotherapy-induced anaemia with SB309.

Immunogenicity

Concerning immunogenicity, the applicant presented an interim report including 12-month data on 227 patients with renal anaemia and a later update on 585 patients. The size of this database is considered sufficient. No new anti-epoetin antibodies developed during IV treatment with SB309 , which is reassuring. All samples tested from the oncology trial (N=189 patients) were negative for anti-epoetin antibodies.

Immunogenicity of epoetin is considered greater for SC use than IV use and in immunocompetent (particular renal anaemia) patients than immunocompromised patients. Immunogenicity of SC use of SB309 has not been evaluated in patients with renal anaemia and, therefore, a respective warning and restriction to IV use in this population has been included into the SPC.

The screening assay is considered sufficiently validated and sensitive.

The applicant did not perform a neutralisation assay to examine whether the detected antibodies have neutralising properties because no new antibodies developed during the study and in all antibody-positive cases, titres decreased or remained stable during the study period indicating a lack of a boost effect of SB309. The applicant could show that a qualified and sufficiently validated neutralisation assay is available for the post-marketing phase. However, to support all aspects of the validation some additional tests should be performed as a follow up measure.

Contraindications and warnings for epoetin zeta are in line with Reference Product, Eprex/Erypo.

Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan, which included a risk minimisation plan.

The description of the applicant's pharmacovigilance system contains comprehensive information on all relevant aspects and is considered acceptable.

The applicant identified potential risks which were not detected in the studies but which are known class effects for epoetins. Therefore the applicant plans special pharmacovigilance activities to evaluate the potential risk of thromboembolic reactions in oncological patients as well as immunogenicity in patients with renal anaemia in association with the use of SB309.

The RMP relating to the immunogenicity aspect (close monitoring using specific questionnaires) is generally acceptable. The applicant was asked to design their post-marketing investigations to take this into account in addition to the investigation of the risk of neutralising antibody formation, and thromboembolism in cancer patients.

The overall safety profile of SB309 and the reference product Erypo appear to be similar. However, since pre-marketing data are limited, the applicant was asked to present an appropriate pharmacovigilance plan in order to further study the safety profile of SB309, particularly rare SAEs such as immune mediated PRCA.

In conclusion, the Risk Management Plan is considered acceptable for the current application provided the Applicant will also include other CNS events in addition to hypertensive encephalopathy for further monitoring and provides a proposal on how to monitor blood pressure in both naïve and pre-treated patients in the post-marketing phase.

The applicant has committed to perform a SC study in accordance with the Guideline on similar medicinal products containing recombinant erythropoietins (CHMP/94526/05) using the reference product Erypo as comparator. In addition, the applicant has committed to submitting a protocol for market survey to monitor potential off-label use.

Summary of the risk management plan

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Pure Red Cell Aplasia (PRCA)	• Routine pharmacovigilance including targeted questionnaires • Study to evaluate safety and tolerability of epoetin zeta administered iv for the maintenance treatment of renal anaemia (CT-830-04-004) • Post-authorisation cohort study of epoetin zeta for the treatment of renal anaemia (PMS-830-07-	• Contraindication in section 4.3 of the SPC for use in patients who have previously experience PRCA following treatment with erythropoetins ▪ Warning in section 4.4 of the SPC regarding PRCA ▪ Mention in section 4.8 of the SPC

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
	0043) • Prospective open non-controlled multi-centre study to evaluate safety and tolerability of epoetin zeta administered sc for the treatment of anaemia in cancer patients (CT-830-05-0009)	
Increased risk of PRCA with off-label subcutaneous administration in renal failure patients	• Routine pharmacovigilance including targeted questionnaires • Study to evaluate safety and tolerability of epoetin zeta administered iv for the maintenance treatment of renal anaemia (CT-830-04-004) • Post-authorisation cohort study of epoetin zeta for the treatment of renal anaemia (PMS-830-07-0043) • Prospective open non-controlled multi-centre study to evaluate safety and tolerability of epoetin zeta administered sc for the treatment of anaemia in cancer patients (CT-830-05-0009 • Drug utilisation study on use of epoetin zeta	▪ Advice to use i.v. route only in treatment of renal anaemia, in Section 4.2 of the SPC. ▪ Warning in section 4,4 of the SPC that iv route only should be used in chronic renal anaemia patients due to lack of immunogenicity data ▪ Educational leaflet
Thrombotic vascular events (TVE)	• Routine pharmacovigilance including targeted questionnaires • Study to evaluate safety and tolerability of epoetin zeta administered iv for the maintenance treatment of renal anaemia (CT-830-04-004) • Post-authorisation cohort study of epoetin zeta for the treatment of renal anaemia (PMS-830-07-0043) • Prospective open non-controlled multi-centre study to evaluate safety and tolerability of epoetin zeta administered sc for the treatment of anaemia in cancer patients (CT-830-05-0009	• Risk of thrombotic vascular events (TVE) including serious and life threatening cardio-vascular complications including the dose recommendation that the target haemoglobin not exceed 12 g/dl are mentioned in Sections 4.1, 4.2, 4.3, 4.4 and 4.8 of the SPC.
Tumour Growth		

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Potential	• Routine pharmacovigilance • Study to evaluate safety and tolerability of epoetin zeta administered iv for the maintenance treatment of renal anaemia (CT-830-04-004) • Post-authorisation cohort study of epoetin zeta for the treatment of renal anaemia (PMS-830-07-0043) • Prospective open non-controlled multi-centre study to evaluate safety and tolerability of epoetin zeta administered sc for the treatment of anaemia in cancer patients (CT-830-05-0009	• Risk of tumour growth potential are mentioned in Sections 4.4 and 5.1 of the SPC.
General safety and long term use	• Routine pharmacovigilance • Study to evaluate safety and tolerability of epoetin zeta administered iv for the maintenance treatment of renal anaemia (CT-830-04-004) • Post-authorisation cohort study of epoetin zeta for the treatment of renal anaemia (PMS-830-07-0043)	

The CHMP, having considered the data submitted in the MA application is of the opinion that the above mentioned risk minimisation activities are necessary for the safe and effective use of the medicinal product.

Overall conclusions, risk/benefit assessment and recommendation

Quality

Extensive, high quality studies were performed to compare SB309 to the reference product Erypo/Eprex at both the drug substance and the drug product level. The characterisation of the drug substance and the comparability studies to compare drug substance from different scale manufacturing process is also considered high quality applying state-of-the-art analytical methods with a high level of detail.

Manufacturing Processes and analytical methods have been appropriately validated and safety with regard to adventitious agents demonstrated. Satisfactory controls have been applied.

Two major objections at the time of D121 List of Questions have been resolved and a number of remaining minor points remaining were proposed as commitments to be concluded in the post-authorisation period.

Non-clinical pharmacology and toxicology

The comparability of SB309 and Erypo was extensively tested preclinically at several levels (receptor binding, growth stimulation of cultured bone marrow cells, haematopoesis in mice, rats and dogs, immunogenicity in rats and dogs) so that the claim of biosimilarity relies on a robust and broad preclinical data base. Therefore, since all aspects of epoetin action were covered by the preclinical development programme (as far as technically feasible), and no unexpected effects were detected the use of SB309 in patients appears safe from a pharmaco-toxicological point of view.

Efficacy

From a clinical point of view the applicant has provided sufficient evidence that SB309 and the reference product Erypo are similarly effective in correcting and maintaining haemoglobin concentrations and in this respect qualify as biosimilar products.

Both pivotal efficacy trials met their primary endpoint with respect to mean haemoglobin levels. Although, in the correction phase trial, the 95% CI of the treatment difference in epoetin dosage was outside the pre-specified equivalence margins, the applicant clarified that these pre-set margins were due to a misreading of the EPAR on Dynepo and therefore should be corrected to 45 IU/kg /week. This newly proposed acceptance range was further supported by literature.

In addition, the applicant provided evidence that a difference of 35.3 IU/kg/week in epoetin dose (worst case scenario) was clinically not relevant in the investigated study population, whether this difference was calculated as absolute value or as percentage of the reference dose (21%).

Moreover, the applicant could provide evidence that the clinical effect of batch changes (measured as frequency of subsequent dose adjustments) of SB309 or due to product changes (from Erypo to SB309 or vice versa) was not increased compared to batch changes of the reference product Erypo and therefore unlikely to elicit a safety concern if test is used instead of reference. A sub-group analysis of patients who received batches of test and reference of similar bioactivity showed very similar and stable Hb values and therefore provided additional reassurance of biosimilarity.
Although the oncology study, by design, could not prove similar efficacy of SB309 and Erypo, the observed increases in Hb over time are in good agreement with published data on epoetin alfa and therefore further support the conclusion of biosimilarity..

Safety

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics
SB309 is a biological medicinal product. Data from clinical studies with SB309 are in line with the safety profile of other authorized epoetin-containing medicinal products and did not reveal unanticipated or unusual safety findings.
The overall safety profile of SB309 and the reference product Erypo appear to be similar. However, since pre-marketing data are limited, the applicant was asked to present an appropriate pharmacovigilance plan in order to further study the safety profile of SB309, particularly rare SAEs such as immune mediated PRCA. Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 5 adequately addressed these.

User consultation

A satisfactory user consultation for readability of the patient leaflet has been undertaken

Risk-benefit assessment

Based on the data on quality, efficacy and safety, the risk-benefit ratio is considered positive for the IV indications. Biosimilarity between SB309 and Erypo has been sufficiently established. The applicant has applied for both the intravenous and the subcutaneous route of administration for their epoetin-containing medicinal product SB309. However, no comparative efficacy and safety data on subcutaneous use have been provided. Despite this short-coming, the benefit-risk ratio is also considered positive for the SC use of SB309 in the chemotherapy-associated anaemia indication based on the following considerations. In terms of efficacy, IV administered SB309 and Erypo have been shown to have similar PK profiles as well as similar efficacy in correcting anaemia and maintaining Hb levels in patients with renal anaemia. Based on this similarity for the IV route, the demonstration of similar PK profiles, particularly bioavailability, for the SC route of administration suggests similar efficacy also for SC use. The comparison of the efficacy data from the chemotherapy-associated anaemia trial with published data are in line with this conclusion. The safety profiles of IV administered SB309 and Erypo have been shown to be generally similar. In addition, no new safety concern (including immunogenicity) emerged from the chemotherapy-associated anaemia study. In fact, the AE incidences in the chemotherapy-associated anaemia trial, particularly the incidence of clinically significant thrombotic events, were similar or lower than those published for epoetin alfa. Based on these considerations the chemotherapy-associated anaemia indication applied for is considered approvable.
The benefit-risk ratio is not considered positive for the major orthopaedic surgery indication because immunogenicity of SC administered SB309 has not been assessed in immunocompetent individuals. Antibody data cannot be extrapolated from IV to SC use or from immunocompromised to immunocompetent individuals. The applicant has withdrawn this indication.
Although there are no remaining major issues there are still some safety concerns with respect to increased SAEs in the Central Nervous System SOC with SB309 both in the correction study as well as the follow up study.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns

the following additional risk minimisation activities were required: see details in Annex II of the Product Information

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of SB309 in the treatment of:

anaemia associated with chronic renal failure in adult and paediatric patients on haemodialysis and adult patients on peritoneal dialysis (IV use)

severe anaemia of renal origin accompanied by clinical symptoms in adult patients with renal insufficiency not yet undergoing dialysis (IV use)

anaemia and reduction of transfusion requirements in adult patients receiving chemotherapy for solid tumours, malignant lymphoma or multiple myeloma, and at risk of transfusion as assessed by the patient's general status

Increasing the yield of autologous blood from patients in a pre-donation programme

was favourable and therefore recommended the granting of the marketing authorisation.