Public Assessment Report for paediatric studies submitted in accordance with Article 45 of Regulation (EC) No1901/2006, as amended

EPOETIN ALFA

UK/WS/026/pd/WS/001

Rapporteur:	UK
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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	See section VII
INN (or common name) of the active substance(s):	Epoetin alfa
MAHs:	See section VII
Pharmaco-therapeutic group (ATC Code):	Drugs used in anaemia
Pharmaceutical form(s) and strength(s):	2000 IU/ml, 4000 IU/ml, 10,000 IU/ml, 40,000 IU/ml solution for injection in pre-filled syringe. 2000 IU/ml, 4000 IU/ml, 10,000 IU/ml, solution for injection

EXECUTIVE SUMMARY

Erythropoietin (EPO) is a glycoprotein that stimulates, as a mitosis-stimulating factor and differentiating hormone, the formation of erythrocytes from precursors of the stem cell compartment. Epoetin alfa obtained by gene technology is glycosylated and is identical in its amino acid and carbohydrate composition to endogenous human erythropoietin that has been isolated from the urine of anaemic patients.

Epoetin alfa has been approved in several dose strengths (2000 IU/ml, 4000 IU/ml, 10,000 IU/ml, 40,000 IU/ml solution for injection in pre-filled syringe, 2000 IU/ml, 4000 IU/ml, 10,000 IU/ml, solution for injection).

Epoetin alfa is approved in the EU for the following indications:

- Treatment of symptomatic anaemia associated with CRF in adult and paediatric patients:
  - Treatment of anaemia associated with CRF in paediatric and adult 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.
- To increase the yield of autologous blood from patients in a predonation programme.
- To reduce exposure to allogeneic blood transfusions in adult non-iron deficient patients prior to major elective orthopaedic surgery, having a high perceived risk for transfusion complications.

It is noted that for the paediatric population, Epoetin alfa is only licensed when administered intravenously for anaemia in children on haemodialysis. Children on peritoneal dialysis as well as children in pre-dialysis status of renal failure are excluded from the current wording in section 4.1 of the SmPC. The SmPC section 4.2 contains dosing information for the correction and maintenance of paediatric haemodialysis patients through the IV route as these patients commonly have central line catheters in place to utilize for the treatment.

In September 2010, one MAH submitted data regarding the paediatric use of Epoetin alfa, in accordance with Article 45 of the Regulation (EC)No 1901/2006, as amended, on medicinal products for paediatric use for the following conditions:

- Anaemia of chronic renal failure
- Chemotherapy-Induced Anaemia of Cancer
- Anaemia of prematurity

Based on the information provided, the MAH does not propose any changes in the licensed indications (section 4.1) or the dosing regime of Epoetin in the paediatric population (section 4.2). However the inclusion of data from the submitted studies is proposed for sections 5.1 and 5.2 of all SmPCs for Epoetin alfa containing products.

RECOMMENDATION

Based on the review of the presented paediatric data on efficacy and safety submitted by the MAH, the rapporteur considers the following:

<u>Anaemia in chronic renal failure</u>

Epoetin alfa is only licensed when administered intravenously for anaemia in children on haemodialysis. The MAH submitted studies that included primarily pre-dialysis paediatric

patients and patients on peritoneal dialysis and drug administration via the subcutaneous route, and proposed SmPC changes in section 5.1 in order to include the results of these studies. The addition of information from these studies is acceptable, however the information to be included has to be balanced and has to state uncertainties concluding on lack of efficacy or safety as appropriate. In addition, the rapporteur considers that a cross reference in section 4.2 should be included to clarify that the drug is not indicated in paediatric patients on peritoneal dialysis or pre-dialysis.

Anaemia of prematurity

Epoetin alfa is not licensed for the prevention and/or treatment of anaemia of prematurity. The MAH proposed to include data from one placebo controlled study which demonstrated a positive effect of recombinant human erythropoietin (r-HuEPO) treatment in premature infants.

There have been many studies in the population of premature anaemic infants with the use of erythropoietins, many of them included in 2 large Cochrane reviews (Ohlsson A, Aher SM., 2014 and Aher SM, Ohlsson A., 2014). In these reviews, it is acknowledged that EPO administration results in reduced transfusions in premature babies but the clinical significance of these changes is still questioned. In addition, a possible association of EPO administration with retinopathy of prematurity (ROP) is noted by the Cochrane reviews. Recently the potential association of epoetin beta administration (licensed for anaemia of prematurity) and ROP was the focus of a European review (PRAC, 2014). The PRAC agreed that the current evidence does not allow excluding a possible increase in the risk of retinopathy of prematurity with early treatment initiation of epoetins in preterm infants. The rapporteur considers that although this review is focused on EPO beta, the risk of ROP with erythropoietin alfa cannot be excluded due to the similar mechanism of action of all r-HuEPO.

The rapporteur concludes that the efficacy and safety of Epoetin alfa use for the prevention and/or treatment of anaemia of prematurity has not been established and the inclusion of information in section 5.1 concerning the single study proposed by the MAH is not supported.

Chemotherapy-induced anaemia of cancer

Based on the data from the studies submitted in the paediatric work-sharing procedure and the evidence available in the literature, the rapporteur is of the view that Epoetin alfa should not be recommended for use in paediatric cancer patients. Although the drug is not licensed for this indication, the MAH proposed wording for section 5.1 of the SmPC in order to include the results of 2 controlled studies in paediatric cancer patients. The wording proposed focused on positive secondary observations, placing into the background the negative main results. This is not considered acceptable and therefore the rapporteur proposes alternative wording presenting the main results of these 2 studies.

PIL changes: The MAH proposed PIL changes in order to provide clarity as to which indication concerns the paediatric population and which the adult population solely. The rapporteur agrees with these changes.

Summary of outcome

☐ No change

☒ Change

☒ New study data: section 5.1

☐ New safety information

☐ Paediatric information clarified: section 4.2

☐ New indication

SmPC changes proposed by the rapporteur:

Section 4.2 Posology and method of administration
Paediatric population
The safety and efficacy of <Epoetin alfa brand name> in chronic renal failure patients with anaemia before initiation of dialysis or on peritoneal dialysis have not been established. Currently available data for the subcutaneous use of <Epoetin alfa brand name> in these populations are described in section 5.1 but no recommendation on posology can be made.

Section 5.1 Pharmacodynamic properties
Paediatric population

Chronic renal failure
Clinical data with subcutaneous administration in children are limited. In 5 small, open label, uncontrolled studies (number of patients ranged from 9-22, total N=72), Epoetin alfa has been administered subcutaneously in children at starting doses of 100 IU/kg/week to 150 IU/kg/week with the possibility to increase up to 300 IU/kg/week. In these studies, most were predialysis patients (N=44), 27 patients were on peritoneal dialysis and 2 were on haemodialysis with age ranging from 4 months to 17 years. Overall, these studies have methodological limitations but treatment was associated with positive trends towards higher haemoglobin levels. No unexpected adverse events were reported (see section 4.2).

Chemotherapy-induced anaemia
Epoetin alfa 600 IU/kg (administered intravenously or subcutaneously once weekly) has been evaluated in a randomised, double-blind, placebo-controlled, 16-week study and in a randomised, controlled, open-label, 20-week study in anaemic paediatric patients receiving myelosuppressive chemotherapy for the treatment of various childhood non-myeloid malignancies.
In the 16-week study (n=222), in the epoetin alfa-treated patients there was no statistically significant effect on patient-reported or parent-reported Paediatric Quality of Life Inventory or Cancer Module scores compared with placebo (primary efficacy endpoint). In addition, there was no statistical difference between the proportion of patients requiring pRBC transfusions between the Epoetin alfa group and placebo.

In the 20-week study (n=225), no significant difference was observed in the primary efficacy endpoint, i.e. the proportion of patients who required a RBC transfusion after Day 28 (62% of epoetin alfa patients versus 69% of standard therapy patients).

PIL changes proposed by the rapporteur (changes to the existing text are shown in bold):

1. WHAT <Epoetin alfa brand name> IS AND WHAT IT IS USED FOR

<Epoetin alfa brand name> contains epoetin alfa - a protein that stimulates the bone marrow to produce more red blood cells which carry haemoglobin (a substance that transports oxygen). Epoetin alfa is a copy of the human protein erythropoietin (ee-rith-roe-po-eh-tin) and acts in the same way.

- <Epoetin alfa brand name> is used to treat symptomatic anaemia caused by kidney disease
  - in children on haemodialysis
  - in adults on haemodialysis or peritoneal dialysis
  - in severely anaemic adults not yet undergoing dialysis.

If you have kidney disease, you may be short of red blood cells if your kidney does not produce enough erythropoietin (necessary for red cell production). <Epoetin alfa brand name> is prescribed to stimulate your bone marrow to produce more red blood cells.

- <Epoetin alfa brand name> is used to treat anaemia ~~if you are~~ **in adults** receiving chemotherapy for solid tumours, malignant lymphoma or multiple myeloma (bone marrow cancer) ~~and your doctor decides you~~**, who** may have a high need for a blood transfusion. <Epoetin alfa brand name> can reduce the need for a blood transfusion **in these patients**.

- <Epoetin alfa brand name> is used in moderately anaemic ~~people~~ **adults** who donate some of their blood before surgery, so that it can be given back to them during or after the operation. Because <Epoetin alfa brand name> stimulates the production of red blood cells, doctors can take more blood from these people.

- <Epoetin alfa brand name> is used in moderately anaemic adults about to have major orthopaedic surgery (for example hip or knee replacement operations), to reduce the need for potential blood transfusions.

I. INTRODUCTION

On 17 September 2010, the MAH submitted the following documents for Epoetin alfa , in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use:

- Cover letter of the submission
- The MAH's overview of submitted clinical data and recommendations for the SmPC of all Epoetin alfa containing products.
- The currently approved Summary of Product Characteristics (SmPC) for all dosage strengths of the licensed Epoetin alfa products.
- 15 completed paediatric clinical trials either published in the literature or sponsored by the MAH, investigating the use of Epoetin alfa in paediatric patients with anaemia due to chronic renal failure, with chemotherapy-induced anaemia of cancer or with anaemia of prematurity.

Based on the information provided and as per the revised SmPC guidance published in September 2009, the MAH concludes that data from the efficacy and safety studies conducted in paediatric patients with these anaemia conditions should be presented in section 5.1 and 5.2 of the SmPC of all Epoetin alfa containing products. The proposed amendments of the SmPC are discussed as part of the overall assessment of the submitted paediatric studies in the relevant sections of this report.

II. SCIENTIFIC DISCUSSION

II.1 Information on the pharmaceutical formulation used in the clinical studies

Erythropoietin (EPO) is a glycoprotein that stimulates, as a mitosis-stimulating factor and differentiating hormone, the formation of erythrocytes from precursors of the stem cell compartment. Epoetin alfa obtained by gene technology is glycosylated and is identical in its amino acid and carbohydrate composition to endogenous human erythropoietin that has been isolated from the urine of anaemic patients.
Epoetin alfa has been approved in several dose strengths (2000 IU/ml, 4000 IU/ml, 10,000 IU/ml, 40,000 IU/ml solution for injection in pre-filled syringe, 2000 IU/ml, 4000 IU/ml, 10,000 IU/ml, solution for injection). It was first approved in the EU (France) in 1988. France is the reference member state for the mutual recognition procedure (MRP) for epoetin alfa, which includes Austria, Belgium, Denmark, Finland, Germany, Greece, Ireland, Italy, Luxembourg, The Netherlands, Portugal, Spain, Sweden, and the United Kingdom. Epoetin alfa is approved in the remaining member states of the EU through national procedures (Bulgaria, Cyprus, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Malta, Poland, Romania, Slovakia, Slovenia, Iceland, and Norway).
Epoetin alfa is approved in the EU for the following indications:

- Treatment of symptomatic anaemia associated with CRF in adult and paediatric patients:
    - Treatment of anaemia associated with CRF in paediatric and adult 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.
- To increase the yield of autologous blood from patients in a predonation programme.
- To reduce exposure to allogeneic blood transfusions in adult non-iron deficient patients prior to major elective orthopaedic surgery, having a high perceived risk for transfusion complications.

The paediatric haemodialysis indication for Epoetin alfa administered intravenously was approved across all EU member states following the positive opinion of the Committee for Proprietary Medicinal Products (CPMP) on 17 March 1993. No other application for additional indications in the paediatric population for Epoetin alfa has been submitted in the EU.

Rapporteur's Comment

The currently approved SmPC in section 4.1 indicates that Epoetin alfa can be use in children for the treatment of anaemia due to chronic renal failure; however there is no specific cut-off age limit suggesting that it might be use in the entire paediatric population (0 to <18 years). It is noted that the British National Formulary includes prescribing information for children older than 1 month. Regarding the method of administration, for the paediatric renal population the use of Epoetin alfa is only licensed when administered intravenously. Therefore section 4.2 contains dosing information only for paediatric haemodialysis patients as follows, excluding children on peritoneal dialysis and also children with symptomatic anaemia in pre-dialysis status:

Paediatric haemodialysis patients:

The treatment is divided into two stages:

Correction phase:

50 IU/kg, 3 times per week by the intravenous route. When a dose adjustment is necessary, this should be done in steps of 25 IU/kg, 3 times per week at intervals of at least 4 weeks until the desired goal is achieved.

Maintenance phase:

Dosage adjustment in order to maintain haemoglobin values at the desired level: Hb between 9.5 and 11 g/dl (5.9 - 6.8 mmol/l).

Generally, children under 30 kg require higher maintenance doses than children over 30 kg and adults. For example, the following maintenance doses were observed in clinical trials after 6 months of treatment.

	Dose (IU/kg given 3x week)	
Weight (kg)	Median	Usual maintenance dose
< 10	100	75-150
10-30	75	60-150
> 30	33	30-100

The clinical data available suggest that those patients whose initial haemoglobin is very low (<6.8 g/dl or <4.25 mmol/l) may require higher maintenance doses than those whose initial haemoglobin is higher (>6.8 g/dl or >4.25 mmol/l).

It is noted that the route of administration of Epoetin alfa in all of the studies submitted under this work-sharing procedure was subcutaneous.

II.2 Non-clinical aspects

1. Introduction

Non-clinical studies have not been provided or summarized by the MAH on Epoetin alfa. It is noted that no literature review has been conducted by the MAH to identify preclinical studies relevant for the paediatric use of Epoetin alfa.

2. Discussion of non clinical aspects

Some preclinical information is available at the currently approved SmPC in section 5.3 but there is not paediatric specific data from preclinical juvenile animal studies. It is stated that *"In some pre-clinical toxicological studies in dogs and rats, but not in monkeys, epoetin alfa therapy was associated with subclinical bone marrow fibrosis."* However these findings do not appear to be confirmed in clinical studies of haemodialysis patients treated with Epoetin alfa over a long period of time.

Erythropoietin is the primary regulator of erythropoiesis, stimulating growth, preventing apoptosis, and promoting differentiation of red blood cell progenitors. The EPO receptor belongs to the cytokine receptor family. Although its primary role is the regulation of red blood cell production, EPO and its receptor have been localized to several non-hematopoietic tissues and cells, including the central nervous system (CNS), endothelial cells, solid tumours, the liver, and the uterus. The presence of EPO receptors and the possibility of EPO signalling in these tissues and cells have led to numerous studies of the effects of EPO at these sites. In particular, expression of EPO and the EPO receptor in cancer cells has generated much interest because of concern that administration of recombinant human erythropoietin (r-HuEPO) to patients with breast and other cancer cells expressing the EPO receptor may promote tumour growth via the induction of cell proliferation or angiogenesis. However, evidence supporting a growth-promoting effect has been inconclusive. The currently approved SmPC, in section 5.3. contains the following preclinical information:
"Long-term carcinogenicity studies have not been carried out. There are conflicting reports in the literature regarding whether erythropoietins may play a role as tumour proliferators. These reports are based on in vitro findings from human tumour samples, but are of uncertain significance in the clinical situation."

Further juvenile toxicology animal studies of EPO and the EPO receptor in non-hematopoietic tissue might be warranted to determine the signalling pathway responsible for its effect in vivo and therefore its potential therapeutic usefulness as well as the overall effect of r-HuEPO on growth and development in the paediatric population. This is particularly relevant as there is some suggestion from the published literature that r-HuEPOs could be use for the prevention and/or treatment of anaemia of prematurity. In those cases, the safety profile of Epoetin Alfa should be established beyond any doubt before used in immature and unstable low weight preterm neonates.

II.3 Clinical aspects

1. Introduction

The MAH has provided a comprehensive overview of the information available regarding the paediatric use of Epoetin alfa. This includes data from studies of Epoetin alfa, administrated subcutaneously in paediatric patients with anaemia of CRF (including patients pre-dialysis, on peritoneal dialysis or haemodialysis), paediatric patients with chemotherapy-induced anaemia of cancer, and in premature infants with anaemia.

2. Clinical studies

2.1 Paediatric studies of Epoetin alfa in anaemia of chronic renal failure (CRF)

Paediatric studies of Epoetin alfa for the treatment of anaemia associated with CRF and not previously submitted provided by the MAH are listed below.

a. **P-309** Low-dose subcutaneous recombinant erythropoietin in children with chronic renal failure.
   Burke, JR. Pediatr Nephrol. 1995 Oct;9(5):558-61.
b. **P-238** Correction of renal anemia with recombinant human erythropoietin (rhEPO) ameliorates growth in children with preterminal renal failure (PTRF)
   Müller-Weifel DE, Amon O, Daniel K, Eife R, Leitis J, Stolpe HJ.
   (In: 9th Congress of the International Pediatric Nephrology Association) Pediatr Nephrol 1992;6(5):C170. [Abstract]
c. **P-149** Treatment of renal anemia by subcutaneous erythropoietin in children with preterminal chronic renal failure.
   Schärer K, Klare B, Braun A, Dressel P, Gretz N. Acta Paediatr 1993 Nov;82(11):953-8.
d. Pharmacokinetics and pharmacodynamics of erythropoietin during therapy in an infant with renal failure
   Kling PJ, Widness JA, Guillery EN, Veng-Pedersen P, Peters C, DeAlarcon PA. J Pediatr. 1992 Nov;121(5 Pt 1):822-5.
e. **CC-2574-P157** Open dose range study of recombinant DNA-derived human type Erythropoietin in the treatment of chronic renal failure (CRF) in children on continuous peritoneal dialysis.
f. **EP88-103 CSR** The pharmacokinetics, safety and efficacy of recombinant human erythropoietin (rHuEPO) in children with chronic renal failure.

Four of these studies have been published as journal or conference papers and 2 are company sponsored trials; the paediatric experience from these studies was summarized by the MAH. In total 72 analysed paediatric patients ranging in age from 4 months to 17 years of age have been included. These studies mainly investigate the safety and efficacy of subcutaneous use of r-HuEPO in paediatric renal patients whereas the current SmPC contains information only regarding the intravenous use. It is noticeable that the majority of the patients were not on haemodialysis as the licensed indication currently is; 44 patients were predialysis, 20 patients were on chronic ambulatory peritoneal dialysis (CAPD), 7 patients were on continuous circulating peritoneal dialysis (CCPD), and only 2 patients were on haemodialysis. The route of administration of Epoetin alfa in all of the studies was subcutaneous. One study included pharmacokinetic sampling in paediatric CRF patients (2.6 to 13.2 years of age) after intravenous administration (Study EP88-103). Doses administered ranged from 100 IU/kg/week to 150 IU/kg/week with the possibility to increase the dose up to a maximum of 600 IU/kg/week. The number of patients in each study was small (range: 9 to 22 patients) and no study had a randomised, controlled design.

The MAH concluded that “all studies demonstrated the erythropoietic efficacy of Epoetin alfa and reported a low rate of adverse events with no unexpected adverse events. Hypertension was reported in approximately 30 to 50% of the patients in all but 1 of the studies”.

2.1.a ***P-309***
Low-dose subcutaneous recombinant erythropoietin in children with chronic renal failure.

Burke, JR. Pediatr Nephrol. 1995 Oct;9(5):558-61.

- **Methods**

  - Objective
    This study aimed to determine the minimal effective dose of subcutaneous (sc) recombinant human erythropoietin (r-HuEPO) required to ameliorate the anaemia of

chronic renal failure and achieve a pre-determined target haemoglobin. A secondary aim was to determine whether correction of anaemia was associated with an improved intellectual performance.

- Study design
  Open-label, multicentre prospective 12-month duration study including 22 paediatric patients.

- Study population /Sample size
  Twenty-two children aged between 4 months and 16 years (mean 9 years) entered the trial. Ten children were receiving continuous ambulatory peritoneal dialysis (CAPD), 1 continuous cycling peritoneal dialysis (CCPD), 2 haemodialysis and 10 had chronic renal impairment (serum creatinine 0.3-0.8 mmol/1) and were not on dialysis. The aetiology of renal failure was diverse.

  Entry criteria were Hb less than 8 g/dl and repleted iron, vitamin B12 and folate stores. Patients with anaemia of non-renal origin were excluded, as were children with uncontrolled hypertension and those undergoing treatment with corticosteroid or immunosuppressant therapy.

- Treatments
  Epoetin alfa was used in this study. The initial dose was 50 U/kg administered sc twice weekly until the target Hb of 9-11 g/dl was achieved. The dose was increased by 50 U/kg per week each 4 weeks if the haemoglobin did not increase by 1 g/dl per month. When the target Hb was achieved, the weekly dosage was given as a single injection for the remainder of the study. If the Hb concentration exceeded 11 g/dl or fell below 9 g/dl, the dosage was decreased or increased by 50 U/kg per week. A dose of 300 U/kg per week was not exceeded.

- Outcomes/endpoints

  Efficacy assessment
  The effect of treatment was assessed by the mean change of haematological parameters (haemoglobin, haematocrit [HCT] and reticulocyte count) during treatment and in comparison with the dose used. Non-responsiveness to treatment was defined as a Hb concentration not rising by 2 g/dl or a target concentration of 9-11 g/dl not achieved by 16 weeks.

  Intellectual assessment
  Intellectual performance was assessed by Wechsler intelligence (IQ) score (Wisc-R form) before and at the end of the study.

- Statistical Methods
  Statistical analysis using the paired t-test was used to compare the mean results of the haematological values and I.Q. scores. Spearman's non-parametric method was used to compare the mean biochemical values at each month for 12 months. $p<0.05$ was accepted as significant.

➢ **Results**

- Efficacy outcomes
  Of the 22 children, 15 completed the 12-month study; 6 received kidney transplants and 1 child was withdrawn from the study at 11 months because of poor parental compliance.

With a dosage of r-HuEPO of 50 U/kg sc twice weekly, the target Hb (9-11 g/dl) was achieved in 14/22 (66%) children by 10 weeks. The mean Hb increased from 6.7±0.7 to 9.6±1.9 g/dl ($p<0.001$) and the HCT from 19.8%±2.4% to 29.3%±6.3% ($p<0.001$). It is noted that the mean reticulocyte count was 1.6%±1.6% initially and 3.4%±3.6% at 10 weeks (p = Not statistically significant).

By 12 weeks, 17 of 22 (76%) children achieved the target Hb>9 g/dl with the initial dosage of 50 U/kg twice weekly. At 16 weeks, 20 of 22 (90%) achieved the target Hb; 19 while receiving 50 U/kg twice weekly and the other child on an increased dosage at 12 weeks of 75 U/kg twice weekly. Two children, both of whom had severe renal osteodystrophy, did not respond to r-HuEPO.

The maintenance weekly dose of r-HuEPO between 3 and 12 months in 9 children ranged from 45 U/kg to 125 U/kg weekly.

In the 12-month period before the study, 15 of 22 children required a blood transfusion. During the study period only the 2 children with severe osteodystrophy who did not respond to the r-HuEPO were transfused.

- Safety results

  None of the patients developed iron deficiency. There were no significant changes in the monthly mean values of serum iron, transferring binding capacity, ferritin, PTH, calcium, phosphate, alkaline phosphatase and creatinine. Five children were receiving supplemental iron at the beginning of the study and 7 children were commenced on an iron supplement during the study. There was no occurrence of acute symptomatic hypertension during the 12-month study period. Two children were receiving blood pressure medication at the onset of the study and 5 children commenced medication during the study.

- IQ assessment

  The full-scale IQ assessment was available at the start and the end of the 12-month study period in 11 children. The mean IQ of the 11 children increased from 92±16.1 to 97.5±17 (P = 0.007). Nine children showed an increase in full-scale IQ, 1 had a decrease and l child was unchanged.

Rapporteur's Comment

In the rapporteur's opinion this is a very limited study in paediatric renal patients. As mentioned by the MAH, there is a discrepancy in the number of patients reported as enrolled (n=22) versus the number given for renal status (pre-dialysis or type of dialysis) (n=23). The inclusion of patients on pre-dialysis stage in the same study as dialysis patients is considered suboptimal and the effective dose of the r-HuEPO could be overestimated as some patients may have remaining renal function and EPO production. In this paper the efficacy endpoints investigated are not clearly defined. Similarly the study doesn't appear to include robust safety monitoring apart from blood pressure measurements and identification of the iron status of the children. No adverse reactions are mentioned but it is not clearly stated whether there were any reported. The sc dose for correction phase in paediatric patients is not currently defined in the Epoetin alfa SmPC but as this study includes in the analysis pre-dialysis and dialysis patients, it is very difficult to assess if 50U/Kg twice a week is efficacious for paediatric renal patients where intravenous access isn't readily available. Regarding the reported increase of IQ in 9 out of 11 children, the rapporteur agrees with the authors' conclusion that it is uncertain whether the correction of anaemia has a direct effect on cognitive function or merely acts by improving motivation and other social skills indirectly as the child feels better.

2.1.b *P-238*

Correction of renal anemia with recombinant human erythropoietin (rhEPO) ameliorates growth in children with preterminal renal failure (PTRF).

Müller-Weifel DE, Amon O, Daniel K, Eife R, Leitis J, Stolpe HJ.
9th Congress of the International Pediatric Nephrology Association, Pediatr Nephrol 1992;6(5):C170. [Abstract]

Very limited information is provided regarding a prospective multicentre open-label study of Epoetin alfa in children with preterminal renal failure as only a brief abstract by Müller-Weifel et al has been submitted. Epoetin alfa was used at dose of 150U/kg sc per week for 6 months. Treatment started in 20 patients but 4 didn't complete the study for various reasons. In the remaining 16 patients (mean age 6.3 years) body length had changed within the last 6 months before treatment from 108.3 to 110.4 cm and increased to 114.2 cm after 6 months of treatment. Growth velocity increased, with a Z-score normalization from -2.35 to + 0.08 ($p<0.001$). Bone age was not excessively accelerated. The authors concluded that the data suggest that growth of children with preterminal renal failure can significantly improve and even normalized in most cases by r-HuEPO administration and normal Hb levels.

Rapporteur's Comment
As significant information is not provided regarding the efficacy endpoints and the methodology of the statistical analysis, the association between the use of r-HuEPO and a positive direct effect on growth can not be established. It is very likely that multiple factors including the underlying chronic disease, the nutritional status and the overall renal treatment regime influence the growth in children with end stage renal disease.

2.1.c *P-149*

Treatment of renal anemia by subcutaneous erythropoietin in children with preterminal chronic renal failure.

Schärer K, Klare B, Braun A, Dressel P, Gretz N.
Acta Paediatr. 1993 Nov;82(11):953-8.

- **Methods**

  - Objective
    The aim of this study was to document the efficacy and safety of weekly sc injections of Epoetin alfa in paediatric patients with preterminal CRF and to determine if the benefits of the treatment were not outweighed by an accelerated deterioration in renal function.

  - Study design
    Open-label, single centre prospective study including 11 paediatric patients.

  - Study population /Sample size
    Initially 15 children with preterminal CRF (4.9-9.0 mg/dl) and Hb concentrations < 10 g/dl (ranging between 6.0 and 9.3 g/dl, mean 7.9 g/dl) were entered the trial. The aetiology of renal failure was diverse. Three children were excluded because dialysis was initiated and another patient was excluded because of non-compliance. The remaining 11

patients aged between 0.6 to 17 years (mean 7.8 years) were treated by r-HuEPO for at least 11 weeks. Before the start of treatment serum ferritin levels were normal and no patient had previously received blood transfusions.

- Treatments
  Epoetin alfa was administered in a single dose of 150 U/kg/week by sc injection in the thigh. If the Hb concentration exceeded 13.5 g/dl, r-HuEPO therapy was interrupted and resumed at a dose of 75 U/kg/week when the target Hb range (11.5-13.5 g/dl) was attained. If Hb concentration decreased to <11.5 g/dl, the initial dose (150 U/kg/week) was restarted and further adapted to the response. Median duration of treatment was 451 days (ranging 77 to 666 days).

- Outcomes/endpoints
  Efficacy and safety outcomes assessed in the study are not clearly defined in the methodology section of this paper. It is mentioned that during r-HuEPO treatment, Hb, HCT, creatinine, serum urea and potassium were checked weekly and in some children treated over longer periods every 2-4 weeks. Serum ferritin and iron were generally determined at monthly intervals.

- Statistical Methods
  There is no mentioning in this paper of the statistical methodology used in the study.

➢ **Results**

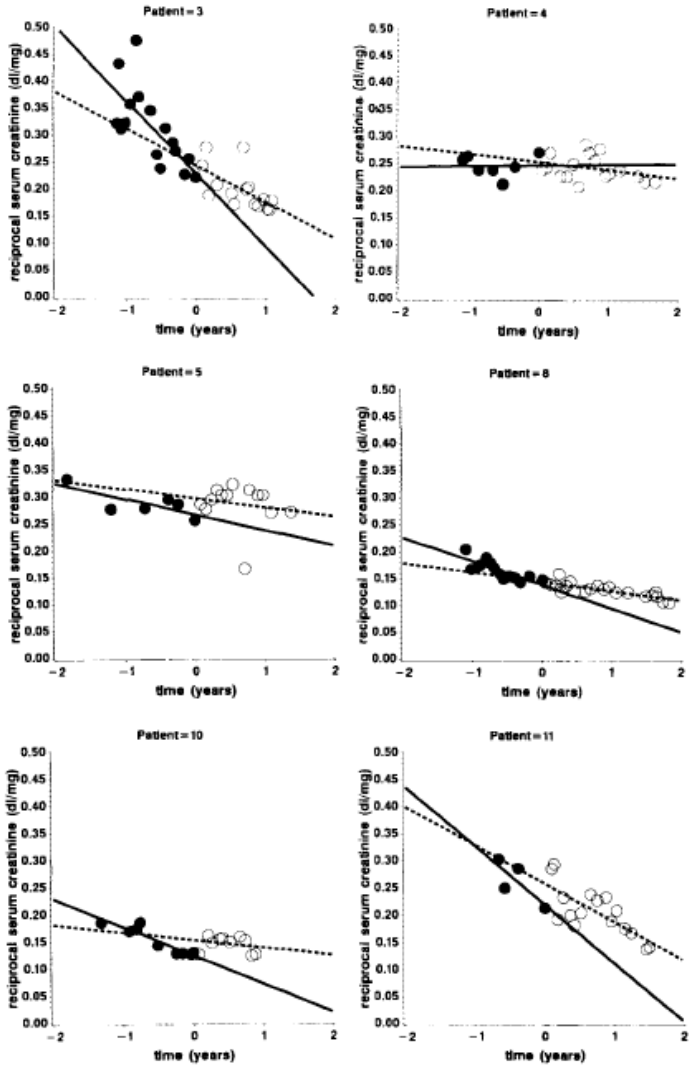
- Growth assessment
  During EPO therapy, all patients gained weight. In the two youngest (aged 0.6 and 1.4 years) out of six prepubertal patients, relative height improved during EPO therapy whilst the change was unremarkable in the older patients.

- Efficacy outcomes
  All 11 children responded to r-HuEPO therapy by an increase in Hb concentration of at least 2.0 g/dl. The mean time to attain Hb value of 2 g/dl above the average pre-treatment level was 45 days. The target Hb concentration of 11.5 g/dl was reached in 8 children within 18-203 days. The mean increase in Hb from baseline was 3.5 g/dl (0.8-4.9) within 12 weeks after the start of r-HuEPO therapy.

  The maintenance dose of r-HuEPO ranged from 75 to 205 U/kg/week (mean 135) after 20 weeks (n= 10) and from 50 to 300 U/kg/week (mean 133) at the end of the observation period.

  Mean serum creatinine increased during r-HuEPO therapy in eight patients, decreased in one infant and remained almost constant in two other patients. Sufficient data was available from six children older than 1 year to compare the slope of creatinine over periods of 232-668 (mean 432) days before and 325-666 (mean 485) days after the start of r-HuEPO therapy (Figure 1). In all except one patient, the slope was slightly flattened ($p = 0.05$).

Figure 1: Reciprocal serum creatinine levels expressed as regression lines in six patients with preterminal renal failure followed for a mean of 14 months before (■ continuous lines) and 16 months alter the start of erythropoietin treatment (○ doted lines).



- Safety results

  In most patients, serum ferritin levels decreased during r-HuEPO therapy despite constant administration of iron which was initiated in 4 patients before the start of r-HuEPO. Unequivocal iron deficiency (serum ferritin <8 pg/ml) was observed in 4 patients. Three children exhibited an increase in systolic or diastolic blood pressure of 20 mmHg or more above baseline values. In eight children, max systolic and/or diastolic values exceeded the 95th centile. In one patient aged 9.1 years r-HuEPO therapy was interrupted at a dose of 75 U/kg/week because of uncontrollable hypertension. At the end of treatment, five patients received 2-5 antihypertensive drugs and six required no antihypertensive medication. A transient burning pain at the site of the sc injection was observed in several children. Three patients developed transient hyperkalaemia but mean serum potassium levels did not change significantly.

Rapporteur's Comment

The number of paediatric renal patients included in this study is limited. The dose used was 150U/kg/week at a single dose which is an unusual correction regime compared to other

paediatric studies where the total dose is usually divided in 2 to 3 doses. It is noted that the target Hb in this study is significantly higher (11.5 to 13.5 g/dl) to what is currently recommended due to safety concerns (aim of treatment Hb 10 to 12 g/dl). Indeed the high incidence of side effects including decreased ferritin levels, hyperkalaemia and hypertension, could be due to this single administration of a high dose of Epoetin alfa. As mentioned by the authors, the maintenance dose of r-HuEPO required in the study showed great individual variation, however it was concluded that it was comparable to adult patients with preterminal CRF or on dialysis. The large variation in the ages of patients was thought to be the reason why a dose-response could not be demonstrated in this study. The authors concluded that the renal function did not deteriorate unexpectedly during prolonged r-HuEPO therapy despite increased blood pressure in some patients. In the rapporteur's opinion longer surveillance period with accurate markers of GFR for the paediatric population is needed to exclude any adverse effect of r-HuEPO on the renal function, taking in account the natural history of the underlying renal disease. Regarding the reported improvement in growth, the increase in height was only noticed in very young patients and therefore remains uncertain to whether r-HuEPO treatment has an effect on skeletal growth and maturation in the long term.

2.1.d ***Pharmacokinetics and pharmacodynamics of erythropoietin during therapy in an infant with renal failure***

Kling PJ, Widness JA, Guillery EN, Veng-Pedersen P, Peters C, DeAlarcon PA. J Pediatr. 1992 Nov;121(5 Pt 1):822-5.

This paper reports the PK and PD findings in one infant with renal failure and anaemia treated with r-HuEPO from 1 to 4 months of age. Although previous work in neonatal animals suggests that developmental PK differences exist and may be responsible for the lack of r-HuEPO efficacy in neonates, the existing PK and PD data on infants are inconclusive (Siimes et al 1992, Shannon et al 1991, Shannon et al 1992).
An infant was born at 36 weeks of gestation and was diagnosed with urethral valves, hydronephrosis, bilateral cystic kidneys, and severe bilateral vesicoureteral reflux. Because of persistent anaemia (Hb level 8.2 g/dl), r-HuEPO therapy (100 U/kg sc three times weekly) was begun at 31 days of age. Oral administration of 6 mg/kg/day elemental iron was also started. The r-HuEPO dose was increased to 175 U/kg (525 U/kg per week) at day 46. At day 52, a transfusion was given when the Hb concentration was 6.6 g/dl. After transfusion, hypertension developed which was treated with a combination of antihypertensive medicines. At day 86, r-HuEPO was withheld for 10 days; there was no change in BP, and Hb concentrations decreased to 9.0 g/dl. Administration of r-HuEPO was reinstituted at 250 U/kg (750 U/kg per week). At day 116, the Hb level was stable at 11.3 g/dl. At that time, total blood sampled had reached 162 ml (80% of the patient's estimated blood volume at birth). The r-HuEPO PK studies were performed at 31 and 103 days of age. Serum r-HuEPO was measured by radioimmunoassay. Heel-stick blood samples were obtained before and at 15 and 30 minutes and at 1, 1½, 2½, 4, 6, 7, and 44 hours after rapid IV r-HuEPO infusion. The serum r-HuEPO PK data were analyzed by using noncompartmental system analysis methods.

The PK results are summarized in table 1 below. The elimination pattern was best fit approximation with a biexponential equation. There was little difference in the t½ at 31 and 103 days. However, there were decreases in distribution volumes, t½ and mean residence time (MRT) at 103 days relative to 31 days.

Table 1: PK data at three intervals

	Before therapy; age 30 days	Dose 525 U/kg per week; age 82 days	Dose 750 U/kg per week; age 103 days
Pharmacokinetic studies†‡	100 U/kg IV		250 U/kg IV
Weight (kg)	2.618		4.100
Plasma Cl (ml/kg · hr)	12.6		14.8
Volume of distribution (ml/kg)	82.8		57.8
V_{ss} (ml/kg)	120		79.8
t½α (hr)	1.3		1.6
t½β (hr)	7.4		4.8
MRT (hr)	9.5		5.1

†Pharmacokinetic values for adults given 150 U/kg IV; data from Flaherty KK, Caro J, Erslev A, et al. (Clin Pharm Ther 1990;47:557-64). Cl = 4.98 ml/kg · hr, V_{ss} = 49.2 ml/kg, t½(β) = 6.1 hr, and MRT = 10.0 hr.
‡Pharmacokinetic values from an additional infant (29-day-old 2.861 kg boy with renal failure) given 200 U/kg intravenously: Cl = 12.4 ml/kg · hr, volume of distribution = 75.8 ml/kg, V_{ss} = 127 ml/kg, t½(α) = 0.9 hr, t½(β) = 7.8 hr, and MRT = 10.3 hr.

The authors suggest that the principal cause of the initial suboptimal response to r-HuEPO in this patient might have been an inadequate dosage. Compared with data on adults, erythropoietin PK after IV injection in this patient showed greater plasma clearance (Cl) and steady-state volume of distribution (Vss) per kilogram of body weight. However, the t½ values were similar to those in adults, so it appears that the main contribution to the differences in Cl relate predominantly to the distribution kinetics, as indicated by the difference in Vss between the infant and adults. In neonatal sheep, weight-corrected Cl and Vss values were greater. Likewise, volume of distribution was larger in neonatal rhesus monkeys than in adults. A greater Cl and larger Vss will result in a lower serum r-HuEPO concentration and therefore require a larger dosage. When expressed relative to estimated body surface area, the differences between adult and infant Cl and Vss were minimal. This may be due in part to the larger extracellular distribution volume infants. Although these findings suggest that r-HuEPO dosage may be more appropriately based on body surface area, it is more convenient and customary to determine dosage on a weight basis. In addition to the developmental differences noted in Vss, the drop in t½ between 31 and 103 days indicated that, with development, an increase in elimination kinetics (as evidenced by the lower MRT) may have played a larger role in the increased Cl observed at 103 days of age.

Rapporteur's Comment

This is a very interesting study reviewing the PK profile of r-HuEPO in neonates. During initial r-HuEPO treatment and after the increased dosing, there was no satisfactory reticulocyte or haemoglobin response. Decreased iron incorporation into erythrocytes, as suggested by the low sideroblast iron, may have contributed to the initial poor response to r-HuEPO. However the author also suggests that PK parameters unique at this age may need to be taken into account for dosage schedules in these patients. Furthermore the excessive volume of blood sampling in this neonate is an additional factor for the treatment failure as a strong correlation between the quantity of blood removed for laboratory tests and the needs for transfusion has been established from studies in anaemia of prematurity.

As only one patient was included in this study, the rapporteur agrees with the authors' suggestion that additional pharmacokinetic and pharmacodynamic studies are necessary to ensure safe and effective r-HuEPO use in infants with renal failure.

2.1.e *CC-2574-P157*

Open dose range study of recombinant DNA-derived human type Erythropoietin in the treatment of chronic renal failure (CRF) in children on continuous peritoneal dialysis.

- **Methods**

  - Objective
    The aim of this study was to review the efficacy and safety of subcutaneous administration of increasing doses of r-HuEPO in children with CRF treated with continuous ambulatory peritoneal dialysis (CAPD) and to determine the individual effective dose of r-HuEPO in increasing the haemoglobin concentration to a predefined target level. The secondary objectives of the study were to determine whether the level of anti-HLA antibodies in the blood will be reduced and to assess whether administration of r-HuEPO will improve the quality of life of children on CAPD.

  - Study design
    Open-label, multi centre titration study including 10 paediatric patients.

  - Study population /Sample size
    Ten children with CRF and on CAPD or CCPD on an outpatient basis for at least 3 months prior recruitment were included in the study. Their age ranged from 4 months to 14 years (median 7.6 years) and the aetiology of renal failure was diverse. Baseline Hb concentrations ranged from 4.6 and 10.1 g/dl (mean 6.58g/dl). The proposed study duration for each child was 9 months; 9 to 12 weeks titration phase and 6 months maintenance phase, when the target Hb with the individual effective dose was attained. The average duration of treatment was 5.1 months (range 1 to 9 months).

  - Treatments
    During the titration phase the individual effective dose to attain a target Hb concentration between 9.6-11.2 g/dl within 9 to 12 weeks. For the first 4 weeks of the study, 100 U/kg/week of r-HuEPO were given subcutaneously divided in 2 doses. Depending on the rate of the response, the dose was titrated by adding 50 U/kg/week and that dose was maintained for further 4 weeks. An increase of Hb of 1 g/dl/month was considered as a guideline for adequate response. In order to maintain correct Hb concentration, if values increased > 11.2 g/dl, the r-HuEPO administration was discontinued until the Hb level fell within the target range. Thereafter treatment was restarted at a dose reduced by 50 U/kg/week.

  - Outcomes/endpoints
    The primary determinants of efficacy in this study were the blood Hb levels together with the patients' and investigators' global evaluation. No quality of life questionnaires were used. A full screening assessment was carried out for each patient a week before the initiation of the treatment. Hematologic status was assessed weekly while iron and serum chemistry status were assessed monthly. Anti-r-HuEPO antibodies and cytotoxic antibodies were measured at the beginning and at the end of the study. All adverse events were recorded for the duration of the study and each patient was monitored for 30 mins following the r-HuEPO administration.

  - Statistical Methods
    There is no mentioning in this paper of the statistical methodology used in the study.

- **Results**
  - Efficacy outcomes

    Of the 10 patients participating in this study, only 3 completed the full 9 months of treatment, with the majority of the patients discontinuing prematurely due to renal transplant opportunities (n=5).

    All 10 children responded to r-HuEPO therapy with a dose of 50 U/kg sc twice weekly leading to an initial increase in Hb concentration of approximately 1g/dl/month. That this dose, the time elapsed until target levels of Hb (9.6-11.2 g/dl) were achieved was 5-6 months. Group mean HB levels reached 9.55±0.37 g/dl after 24 weeks. The dose required to maintain Hb levels showed marked variation from 50 U/kg/week to 175 U/kg/week and one patient was dosed with 300 U/kg/week as demonstrated a very atypical respond to treatment due to underlying problems.

    Three patients were tested for anti erythropoietin antibodies before and 2 patients after r-HuEPO treatment and were all negative.

  - Safety results

    Hypertension was reported in 3 patients of whom one was known to be hypertensive at baseline and after the initiation of the r-HuEPO treatment, adjustment of the antihypertensive medications was needed.

    Iron supplement was required in 4 patients. No significant changes were identified in blood biochemistry parameters compared to baseline.

    Thrombocytosis was reported in 2 patients. In one case, it was severe and was documented 5 weeks after commencing r-HuEPO; however the patient was receiving treatment for abnormally high platelets at baseline. The exacerbation of the condition had resolved by week 16 while r-HuEPO treatment continued at the original dose (50 U/kg sc twice weekly).

Rapporteur's Comment

The number of paediatric renal patients included in this study is limited; it is also noted that out of the 10 participants, only 7 were actually on CAPD despite the objective of the study which was to review the efficacy and safety of r-HuEPO in children treated with continuous ambulatory peritoneal dialysis. As in the previous studies, the aim was focused predominantly on achieving the Hb target levels within a predefined time period. Less attention was given in maintenance of the Hb level, possibly due the restrictions of the follow up period; also an overall assessment of the long-term benefits from the improved Hb levels and possibly the reduced need for blood transfusions would demonstrate a truly beneficial effect of the treatment with r-HuEPO. However these parameters were not reviewed in this study. The lack of validated quality of life questionnaires hinders the assessment of the effect of treatment for these paediatric CRF patients. A once a week dosing for long time maintenance of effective Hb would be preferable for these patients in order to avoid frequent injections, but this was found adequate only in 50% of the patients. Regarding the safety of the r-HuEPO treatment in these patients, hypertension was reported in 3 out of 10 patients. Furthermore 2 incidences of thrombocytosis were reported in this study. Although the authors concluded that apart for the treatment, other contributing factors were also observed in these patients to explain such findings, the rapporteur is of the view that other unusual adverse events reported in this study including recurrent peritonitis and pulmonary oedema could have been attributed in the increased blood pressure and platelet count.

2.1.f *EP88-103*
The pharmacokinetics, safety and efficacy of recombinant human erythropoietin (rHuEPO) in children with chronic renal failure

- **Methods**

  - Objective
    The primary objectives of this study were to establish the IV PK profile after multiple doses of r-HuEPO and to investigate the efficacy and safety of sc doses of r-HuEPO in children with CRF. The secondary objective of the study was to assess the effect of sustained improvement in Hb levels on cardiac function and nutritional status and growth in this population.

  - Study design
    Combined Phase1 and Phase 2 single site, open-label study.

  - Study population /Sample size
    Nine prepubertal renal patients were included in the study; those were predialysis patients with GFR<30ml/min/1.73m^2 not yet treated with dialysis (n=3) and patients treated with CAPD (n=3) or CCPD (n=3). Each patient have had an average pre-transfusion Hb >6 g/dL to <9 g/dL over previous 3 months. Their age ranged from 2.6 to 13.2 years (mean 7.8 years) and the aetiology of renal failure was diverse. The proposed study duration for each child was 26 weeks.

  - Treatments
    For the PK assessment patients received 2 IV 50 U/kg of r-HuEPO administrated two days apart followed by a third IV dose (150 U/kg) 2-3 days later.
    To evaluate efficacy of sc administration, patients received r-HuEPO at a starting dose of 50 U/kg three times per week for 25 weeks, until Hb reached a target range of 9.5-11.5 g/dl. If a rise in Hb of at least 1 g/dl was not seen after 8 weeks, the dose was increased by 25 U/kg every 4 weeks to a maximum dose of 200 U/kg three times per week.

  - Outcomes/endpoints

    PK assessment
    The primary measures for the PK phase consisted of area under the curve (AUC) and T1/2.

    Efficacy assessment
    The primary efficacy outcome was the rise of Hb after treatment with r-HuEPO. A patient was considered a responder if the Hb level rose 2-4 g/dl but not greater, into the target range of 9.5-11.5 g/dl. The patients' Hb levels were assessed at baseline and monthly from weeks 4 to 24 and again at week 26.
    The secondary outcome measures included changes in each patient's growth measurements, bone age, nutritional status, and dynamic assessments of cardiac function. Cardiac function test with resting ECG and radionuclide angiogram were carried out at baseline and at the conclusion of the study with an additional mid-study echocardiographic evaluation.

    Safety assessment
    Safety evaluations were performed periodically and included physical examination, vital signs, serum chemistry, measurements of iron store parameters and measurement of

serum, EPO levels and serum anti-EPO antibodies. All adverse events were recorded for the duration of the study.

- Statistical Methods
  Due to the small number of patients enrolled, data analysis only included descriptive summaries at baseline and other time points where sufficient data were available. Bone age assessments by 2 reading methods were compared using the Wilcoxin sign rank test.

➢ **Results**

- Efficacy outcomes
  Of the 9 patients participating in this study, only 3 fully meet the eligibility requirements and therefore were fully evaluated. Table 2 summarizes all the participants in the study and the reasons of exclusion. It is noted that only 6 patients completed that 26 weeks of the study but one was excluded due to protocol violation.

Table 2

EP 88-103
PATIENT STATUS SUMMARY

		ENROLLED n=9				
	Not evaluable protocol violation transfusion prior to dosing			Partially Evaluable n=3		Evaluable n=3
n=2 withdrawn Wk5 Transplant Wk 20 ADE		n=1 completed 26 weeks	n=1 withdrawn Wk 22 blood loss due to surgery		n=2 completed 26 wks. 1 st 6 Wk Fe Def 2 mos some Fe def	
CCPD CAPD		CAPD	pre-dialysis		CAPD pre-dial (to HD)	2 CCPD 1 pre-dial

The 3 patients who were fully evaluated had an overall mean Epoetin alfa dose of 47U/kg (range 28.62 to 60.07 U/kg). Taking in account all patients it is noted that the weekly starting dose of 142.22 U/kg dropped almost steadily at week 20 (28.87U/kg, n=7) and rose continually to 47.13U/kg at week 26 (n=6).

Regarding the haematological response, the mean Hb at baseline was 7.478 g/dl (range 6 to 9.9 h/dl); at week 6 (n=8) the average Hb was 11.625g/dl (range 8.1 to 13.8 g/dl) and at week 26 (n=6) the average Hb was 9.45 g/dl (range 7.8 to 10.1 g/dl). The authors stated that *"no efficacy conclusions could be drawn from the trial due to multiple factors, especially the fact that such a small number of patients were evaluable for efficacy."*

- PK results
  Pharmacokinetic profile was considered similar to that of adults with rapid decay from the initial peak and similarly the T1/2 was also comparable.

- Safety results
  All patients reported to have at least 1 adverse event, with a total of 82 reports documented. 14.6% of the reports were considered to be relevant to the study drug. The majority of adverse events were due to pain at the sc injection site. There was one episode of shock and blindness due to retinal artery thrombosis described. For this child the possibility of hypercoagulable state was investigated but several other confounding factors were also identified. The authors noted that the child was continued on r-HuEPO

treatment off study “at the insistence of the parents” but no further information is available. There were no incidents of increased blood pressure reported in this study.
The serum ferritin results were considered “questionable” due to an administrative error in the case record form. The serum iron levels fluctuated considerably throughout the study and interpretation of the overall patients’ iron status is difficult to establish.

- Secondary outcome measures
  Although the study was aiming to evaluate the impact of sustained improvement in Hb over 6 months of Epoetin alfa therapy on growth factors, nutritional status and cardiac parameters, the small number of enrolled patients and the even smaller of evaluable children severely limits the assessment of the data. The limited follow-up period did not allow full evaluation of the effect on growth velocity or pubertal maturation. The authors conclude that interpretation of any cardiac data in impossible although the results observed were most likely reflected change from the raised Hb levels.

Rapporteur’s Comment
The rapporteur is of the view that this study failed to address the original objectives both in terms of the effect of r-HuEPO treatment on Hb levels in renal paediatric patients as well as the effect treatment had in growth and cardiac parameters. The authors acknowledged the fact that they underestimated the difficulties recruiting and maintaining the paediatric patients in single-centre prospective study. It is therefore accepted that due to the limitations of this study, no useful conclusions can be dawn either on the efficacy/safety or on PK and dosing parameters of the r-HuEPO treatment in paediatric renal patients.

Discussion of paediatric clinical information on anaemia of CRF

Based on the data from the submitted paediatric clinical studies in patients with anaemia due to renal failure, the MAH concludes that although subcutaneous treatment with Epoetin alfa was associated with increased haemoglobin levels and no unexpected adverse events, no study had a randomised, controlled design and the number of patients in the studies was small (the largest study had 22 patients). Therefore the MAH does not propose any changes regarding the extension of the use of Epoetin Alfa in pre-dialysis or peritoneal dialysis paediatric patients with additional wording for sections 4.1 and 4.2.
However the MAH proposes the addition of further information in section 5.1 relating to the experience of treating paediatric renal patients with anaemia with Epoetin Alfa through subcutaneous administration. The proposed wording is:
Proposed Additions to Section 5.1, Pharmacodynamic properties:
Epoetin alfa was evaluated in an open-label, non-randomised, 52-week clinical study in 116 paediatric CRF patients undergoing haemodialysis. The median age of patients enrolled in the study was 11.6 years (range 0.5 – 20.1 years).
Epoetin alfa was initiated at 75 IU/kg/week i.v. in 2 or 3 divided doses post-dialysis, titrated by 75 IU/kg/week at intervals of 4 weeks (up to a maximum of 300 IU/kg/week), to achieve a 1 g/dL/month increase in haemoglobin. The target haemoglobin level was 9.6 – 11.2 g/dL. 81% of patients achieved the target haemoglobin level. The median time to target was 11 weeks and the median dose at target was 150 IU/kg/week. Of the patients who achieved the target, 90% did so on a t.i.w. dosing regimen. After 52 weeks, 57% of patients remained in the study, receiving a median dose of 200 IU/kg/week.
Subcutaneous administration of epoetin alfa at starting doses of 100 IU//kg/week to 150 IU//kg/week with the possibility to increase up to 300 IU/kg/week has also been studied in 72 paediatric CRF patients (including dialysis and patients not yet on dialysis).

Epoetin alfa treatment was associated with increases in haemoglobin levels in all the studies. Clinical data with subcutaneous administration in this population are limited. No unexpected adverse events were reported. Most of the adverse events reported (hypertension, pyrexia, and headache) were either recognized complications of CRF and/or dialysis, or were associated with common concurrent illnesses.

Rapporteur's Comment

The rapporteur agrees with the MAH that data on the safety and efficacy of subcutaneous dosing is rather limited and should be assessed with caution. In the current approved SmPC, there is information only regarding the intravenous use in paediatric patients on haemodialysis. This limits the availability of Epoetin alfa treatment to paediatric renal patients who have central venous access, excluding a large number of paediatric renal patients who use peritoneal dialysis methods or are in predialysis stages. However based on the studies presented here the subcutaneous of Epoetin alfa in non-haemodialysis paediatric patients and in paediatric patients on peritoneal dialysis is not supported. In the rapporteur's view the inclusion of data from the presented studies of subcutaneous administration of Epoetin alfa in paediatric chronic renal patients in section 5.1 of the SmPC can not be acceptable as such. As the proposed wording conflicts with the current licensed indication of the intravenous use in haemodialysis paediatric patients, the rapporteur is of the view that the inclusion of data from these studies will confuse prescribers further to whether the subcutaneous use of Epoetin alfa is beneficial or not.

It is also noted that the first paragraph of the proposed wording is not in reference with the studies submitted in this work-sharing procedure. Therefore data from this study has not been assessed here to be included in any changes in the SmPC. As this appears to be useful paediatric information, the MAH will be asked to provided further information and possible the study report for review by the rapporteur.

2.2 Paediatric Studies of Epoetin Alfa in Chemotherapy-Induced Anaemia of Cancer

Epoetin alfa is not currently indicated in the EU for the treatment of anaemia associated with myelosuppressive chemotherapy in paediatric cancer patients. The efficacy and safety of epoetin alfa for the treatment of chemotherapy-induced anaemia in paediatric patients was evaluated in 3 large Company-sponsored multicenter, randomised, controlled studies (PR99-11-034/044, EPO-INT-51 and EPO-INT-79). The data from Study PR99-11-034/044 have not previously been submitted. The MAH notes that the results from Study EPO-INT-51 and Study EPO-INT-79 were previously submitted in 2003 to support safety in a variation application to introduce an additional dosing regimen for Epoetin alfa for the treatment of anaemia in adult patients receiving chemotherapy. However the results from these studies are included again in this submission for reference.

2.2.a ***PR99-11-034/044***
A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Effect of Weekly Epoetin Alfa on Anaemia and Quality of Life in Children With Cancer Undergoing Myelosuppressive Chemotherapy

- **Methods**

  - Objective

The aim of this study was to evaluate the efficacy and safety of once weekly dosing of Epoetin Alfa on anaemia and quality of life (QoL) in children with malignant solid tumours, Hodgkin's disease, acute lymphocytic leukemia (ALL), or non-Hodgkin's lymphoma (NHL).

- Study design

  Phase 3b study. The study was originally designed as 2 separate randomized, multi-centre, double-blind, placebo-controlled studies (PR99-11-034 and PR99-11-044) in anaemic children with cancer and were later combined into one study due to slow accrual. Study PR99-11-034 planned the enrolment of anaemic children with newly diagnosed malignant solid tumour or Hodgkin's disease and Study PR99-11-0344 planned to include anaemic children with ALL or NHL. After the 2 original protocols were combined, randomization was stratified by cancer type (1 stratum for children diagnosed with solid tumours or Hodgkin's disease and 1 stratum for children diagnosed with ALL or NHL). At the end of the 16-week study treatment period or upon early withdrawal from the study, all patients who were randomly assigned to treatment and who received chemotherapy over a minimum period of 8 weeks were eligible to receive Epoetin alfa therapy off study free of charge for up to an additional 16 weeks, if deemed clinically appropriate by the treating physician.

- Study population /Sample size

  Paediatric patients (aged 5-18 years) with anaemia who were newly diagnosed with malignant solid tumour, Hodgkin's disease, ALL, or NHL were randomly assigned in a 1:1 ratio to receive either Epoetin alfa or an equivalent volume of placebo administered intravenously once per week for 16 weeks during their chemotherapy treatment. Anaemia was defined as the following values:

  - <10.5 g/dL for boys and girls ≥5 to ≤12 years of age;
  - <11.0 g/dL for girls >12 years of age; or
  - <12.0 g/dL for boys >12 years of age;

  Patients with elevated serum creatinine at study entry (Cr>0.8mg/dl for children <10 years, >1.1mg/dl for children 10-15 years and >1.4mg/dl for children >15 years) were excluded from the study.

  Two-hundred twenty-four patients were enrolled. The modified intent-to-treat (mITT) group comprised 111 patients in both treatment groups. The safety population contained 112 Epoetin alfa patients and 110 placebo patients. Two patients did not receive any study drug and of the remaining 222 patients, 184 (82.1%) completed the study, while 40 (17.9%) patients withdrew from the study early (19 [16.8%] patients in the Epoetin alfa group; 21 [18.9%] patients in the placebo group). The 2 treatment groups were statistically significantly different with respect to age, age category, weight, height, and systolic blood pressure.

- Treatments

  Patients were scheduled to receive their first myelosuppressive chemotherapy within 7 days of baseline or may have received up to their second myelosuppressive chemotherapy within 60 days prior to study enrolment. The initial dose of Epoetin Alfa was 600 U/kg for a maximum dose of 40,000 U administered IV once per week. Haemoglobin was checked just before the start of the chemotherapy dose at Study Week 4 for the "3-week group" or Study Week 5 for the "4-week group" (these groups are further explained below). If Hb had not increased by at least 1g/dL from the baseline, then the dose was increased to 900 U/kg for a maximum dose of 60,000 U administered IV each week. If Hb increased to ≥15 g/dl for patients >12 yrs, or increased to ≥14 g/dl for

patients ≤12 yrs, Epoetin alfa was withheld. If Hb decreased to ≤13 g/dl for patients of any age, Epoetin alfa was resumed at 75% of previous dose.

- Outcomes/endpoints

  Patients were evaluated based on their scheduled chemotherapy regimen. For patients who were receiving chemotherapy every 3 weeks, scheduled study visits occurred every 3 weeks. This group was labelled as the "**3-week group.**" For patients receiving chemotherapy weekly, every 2 weeks, or every 4 weeks, scheduled study visits occurred every 4 weeks. This group was labelled as the "**4-week group**".

  Efficacy

  Efficacy was assessed by patient-reported outcome assessments completed by the patients and by the patients' parents or caregivers. The same parent or caregiver was to complete the assessments throughout the study which were to be performed before the start of the next dose of chemotherapy and within 24 hours of the clinical laboratory tests. The primary endpoint was the last value total score of the patient-reported Paediatric Quality of Life Inventory (PedsQL Inventory). The primary efficacy analysis was the comparison of Epoetin alfa versus placebo on the difference between the last value minus the baseline value. The time course of PedsQL evaluations over the course of the study were also explored. The secondary endpoints included parent-reported assessments on the PedsQL Inventory, patient-and parent-reported assessments on the PedsQL Cancer Module, Hb levels, and transfusion requirements. Analysis of the secondary endpoints was similar to that of the primary endpoint.

  Safety

  Safety was assessed by comparing the incidence and severity of adverse events in the Epoetin alfa group versus the placebo group. Clinical laboratory tests (haematology, iron profile, and serum chemistry), physical examinations, and vital sign measurements were also assessed.

- Statistical Methods

  The efficacy and safety analyses were to be based on the modified intent-to-treat (mITT) population. The mITT population included all patients who entered the study and were randomly assigned to either the Epoetin alfa or placebo group, received at least 1 dose of study drug, and had at least 1 post-randomization QOL evaluation. The safety population included all patients entered into the study who received at least 1 dose of study drug.

  The primary analysis was to utilize an analysis of covariance (ANCOVA) model to estimate the treatment effect on the primary and secondary QoL endpoints. Additionally, multivariate longitudinal analysis methods were to be used to evaluate the reported QoL Inventory and Cancer module over the 16-week study treatment period. An ANCOVA analysis was used to evaluate the treatment effect on the change from Baseline to Week 16 and to Last Value Hb values, with the baseline Hb value as a covariate. Longitudinal analysis was also used to examine change in Hb over time.

➢ **Results**

- Efficacy outcomes

  QoL

  There were no statistically significant differences between study groups with regard to patient-reported PedsQL Inventory scores. When the data were analyzed by age, patients 5 to 7 years of age who received epoetin alfa treatment experienced a significant improvement (p=0.0431) in PedsQL Inventory adjusted mean score at Last Value

(adjusted mean score=87.98) compared with patients 5 to 7 years of age in the placebo group (adjusted mean score=78.09). This difference in the total score may be attributed to a significant improvement (p=0.0074) in the physical functioning (walking, running, chores, etc.) of patients in that age category.
When parent-reported PedsQL Inventory scores were evaluated by patient age categories, there were no statistically significant differences among children 5 to 7, 8 to 12, and 13 to 18 years of age with regard to study drug treatment. When the parent-reported PedsQL Inventory data were explored after exclusion of any value taken within 28 days after a transfusion, or when transfusions were treated as a covariate, no statistical differences or trends emerged.
No statistically significant difference was noted between study treatment groups for patient-reported and parent-reported Cancer Module scores.

Haemoglobin
In the analysis of mean Hb increases from Baseline to Last Value for all cancer types combined, there was a statistically significant difference favouring Epoetin alfa (p=0.0308).
Patients in both study treatment groups experienced increases in Hb levels from Baseline to Week 16, excluding Hb values collected within 28 days after packed red cell (pRBC) transfusion, but the increases were not statistically significant between the study treatment groups.
In the analysis by type of cancer, excluding Hb values collected within 28 days after pRBC transfusion, Epoetin alfa was more effective at Week 16 in patients diagnosed with ALL than placebo. The mean (SD) increase in Hb levels at Week 16 for patients diagnosed with ALL was 2.62 (2.539) g/dl with Epoetin alfa (n=27) compared with 2.00 (1.999) g/dl with placebo (n=26) (p=0.0313).

Transfusions
Overall, there was no statistically significant treatment group difference in the numbers of patients receiving at least 1 pRBC transfusion before receipt of study drug. There was a strong trend indicating that fewer Epoetin alfa patients than placebo patients received pRBC transfusions after receipt of study drug (72/111 [64.9%] vs. 86/111 [77.5%]); however, this was not statistically significant. Transfusion requirements in the Epoetin alfa group compared with the placebo group were statistically significantly reduced during Weeks 9 to 12 (p=0.0021, Fisher exact test) and Weeks 13 to 16 (p=0.0363, Fisher exact test). There was a trend favouring the Epoetin alfa study treatment group compared with the placebo group in patients who completed the study and were pRBC transfusion-free through Week 16 (p=0.0512, Fisher exact test).

A posthoc analysis of transfusions after Day 28 post-randomisation showed significantly fewer patients in the Epoetin alfa group received at least 1 pRBC transfusion after Day 28 compared with patients in the placebo group (57/111 [51%] vs. 77/111 [69%]; p=0.009). The median time to first pRBC transfusion after Day 28 was significantly delayed in the Epoetin alfa group (71 days) compared with the placebo group (53 days; p=0.03).

- Safety results
  The safety group was composed of 112 patients who received at least 1 dose of Epoetin alfa and 110 patients who received placebo. Patients in both treatment groups were exposed to a similar number of days of treatment.
  Although no patients were withdrawn due to the development of an intercurrent illness or were lost to follow-up, a total of 40 patients were withdrawn from the study including 1

from an SAE (Epoetin alfa Patient; implantation complication [clot in the intravenous line]), and 1 from an SAE that resulted in death (Epoetin alfa Patient; cardiac/respiratory arrest, probable sepsis). Two additional patients were withdrawn at the request of the Sponsor due to the development of an SAE: one Epoetin alfa Patient (sagittal thrombosis) and one placebo Patient (cerebral infarction). Two patients, one from each group were withdrawn due to disease progression, and 1 Epoetin alfa patient was withdrawn due to discontinuation of chemotherapy prior to an 8-week period during the study. Eleven patients withdrew consent to participate. Fourteen patients withdrew due to other reasons that would have made them noncompliant with inclusion/exclusion criteria.

The number of patients who reported at least 1 study drug treatment-emergent AE (TEAE) or reported at least 1 SAE was similar between the 2 groups (20.5% and 68.8% respectively, in the Epoetin alfa group and 20.0% and 71.8% respectively, in the placebo group). Gastrointestinal Disorders, such as abdominal pain, mucositis, diarrhoea, and vomiting were reported by the greatest number of patients regardless of treatment group. Serious adverse events were reported by 77 (68.8%) patients in the Epoetin alfa group and 82 (74.5%) patients in the placebo group. Platelet, bleeding, and clotting disorders (thrombocytopenia, purpura, and epistaxis) were reported by a greater number of Epoetin alfa patients (61, 54.5%) compared with placebo patients (56, 50.90%). Six patients in the Epoetin alfa group and 2 patients in the placebo group experienced a clinically relevant thrombotic vascular event. Blood pressure variations did not appear related to study drug administration and mean values were within normal limits in both treatment groups. Only 8 patients (4 in each treatment group) reported serious adverse events that were considered related to study drug administration. The number of deaths occurred in each treatment groups was same (Epoetin alfa: one patient with advanced malignancy and one patient with agranulocytosis and sepsis – Placebo: one patient with respiratory insufficiency and one patient with agranulocytosis and haemorrhage). The investigators concluded that none of the deaths was considered study drug related.

Rapporteur's Comment
This is a very interesting study trying to investigate the benefits of the Epoetin treatment in paediatric cancer patients. Despite the expected benefit of the Hb improvement, the overall well-being of the patients as evaluated by themselves or their carers was unchanged compared to placebo. This confirms findings from other studies in children with cancer (Marec-Berard et al, 2009) in which no quality-of-life and no survival benefit has been demonstrated. Furthermore although fewer Epoetin alfa patients were transfused during Weeks 9 to 12 and Weeks 13 to 16, in this study there was no significant difference between Epoetin alfa and placebo patients who received at least 1 pRBC transfusion overall. These results raise reasonable doubts to whether the use of Epoetin alfa for the management of anaemia in children with cancer should be recommended due to lack of obvious benefits for the paediatric oncology patients.

2.2.b ***PRI/EPO-INT-51/EPO-CA-484***
An open-label, randomized study evaluating the effect of Epoetin Alfa on the reduction of blood transfusions in newly diagnosed paediatric subjects receiving myelosuppressive chemotherapy for malignancy.

- **Methods**
  - Objective
    The aim of this study was to evaluate the haematological response to Epoetin alfa treatment in newly diagnosed paediatric subjects with solid tumours or non-myeloid

hematologic malignancies receiving myelosuppressive chemotherapy, with or without radiotherapy or surgery, and to assess the safety of the dosage regimen.

- Study design
  Multicenter (conducted in the EU), open-label, randomised, controlled study of Epoetin alfa versus standard therapy in newly diagnosed paediatric cancer patients. The study consisted of a 1-week pre-study screening phase followed by a 20-week open-label treatment phase.

- Study population /Sample size
  Paediatric patients (aged <18 years) with anaemia (Hb >7.0 g/dl and <12.0 g/dl) who were newly diagnosed with solid tumour or non-myeloid hematologic malignancy and who were expected to receive myelosuppressive chemotherapy for at least 20 weeks (treatment phase of 20 weeks) were enrolled in the study. Treatment with Epoetin alfa was discontinued and the patient was withdrawn from the study if chemotherapy was stopped.

  Two hundred thirty-two patients were randomised with 116 patients each in each of the groups. Randomisation was stratified by cancer type, with 1 stratum for patients with ALL and the other for patients with non-ALL malignancies. A majority of the subjects (147/232, 63%) were stratified to the non-ALL tumour group; only 37% of the paediatric patients participating in this study were diagnosed with ALL. In the intent-to-treat population, demographic characteristics were generally well balanced between the 2 treatment groups.
  The mean baseline haemoglobin (all patients) was 10.3 g/dl (range 5.7-15.9 g/dl). The mean haemoglobin at baseline in the ALL stratum was 9.4 g/dl (range 6.6-12.3 g/dl) in the Epoetin alfa group and 9.1 g/dl (range 6.0-12.1 g/dl) in the standard therapy group. At baseline, 35% of all patients were transfusion dependent while 74% of patients in the ALL stratum were transfusion dependent.

- Treatments
  Eligible subjects were randomized to 1 of 2 groups: the Epoetin alfa group receiving 600 IU/kg/week sc or IV (increased to 900 IU/kg/week based on haemoglobin levels: Hb >7.0g/dl and ≤10.0g/dl after the first 4 weeks) or the control group receiving no Epoetin alfa (standard of care). The first dose of study drug was to be administered as soon as possible after randomization. The route of administration (sc or IV) was allowed to change during the study; investigators were encouraged to use the most convenient route of administration.

- Outcomes/endpoints

  Efficacy
  The primary efficacy evaluation was the proportion of subjects transfused after Day 28. Secondary efficacy evaluations were days to first transfusion after Day 28, volume of transfusion after Day 28, number of blood units transfused after Day 28, number of transfusion episodes, and haemoglobin levels.

  Safety
  The safety evaluations consisted of adverse events, clinical laboratory tests (haematology, chemistry, and iron parameters), tumour response, vital signs measurements, and body weight.

The associated evaluations and procedures are presented by visit in table 4:

Table 4 : Scheduled evaluations

		On-Study Visits							
	Prestudy[a]	Random-ization							Study Completion/ Withdrawal[b]
Visit	1	2	3	4	5	6	7	8	9
Procedure / Week	-1	1	2	4	8	12	16	20	21
Informed consent	X								
Demographics (date of birth, gender and ethnic origin)	X								
Vital signs [c]	X		X	X	X	X	X	X	X
Medical history	X								
Current medication	X								
Staging of malignancy	X								
Tumor response									X
Chemotherapy, radiotherapy, surgery	X		X	X	X	X	X	X	X
Local laboratory tests:									
- hemoglobin [d]	X	X	X	X	X	X	X	X	X
Central laboratory tests:									
Hematology [e]	X								X
- hematocrit									
- RBC									
- WBC, including differential									
- platelet count									
- reticulocyte count									
Serum Chemistry	X								X
Iron Parameters	X				X				X
- serum iron									
- ferritin									
- transferrin saturation									
Serum folate, vitamin B_{12}	X								
Pregnancy test [f]	X								
Transfusion data (volume, number of units, date, type)	X		X	X	X	X	X	X	X
Epoetin alfa administration [g]		X	X	X	X	X	X	X	
Record of adverse events		X	X	X	X	X	X	X	X

[a] All procedures were to be performed within 7 days prior to randomization. Note: Informed consent was to be obtained as soon as the subject was considered for study.
[b] Visit to be scheduled at Week 21 or 1 week after last dose of epoetin alfa.
[c] Vital signs were to be performed prior to study drug administration and other assessments. They included weight, height, and resting systolic and diastolic blood pressures.
[d] Hemoglobin was assessed every week by the local laboratory.
[e] Hematology tests, except hemoglobin, were performed by the central laboratory.
[f] Pregnancy tests were to be performed in female subjects of childbearing potential and were to be negative for the subject to be eligible to participate in the study.
[g] In subjects receiving epoetin alfa, the injections were to be done once a week, on the same day +/- 24 hours.

- Statistical Methods

  The primary efficacy evaluation, the proportion of subjects transfused after Day 28, was analyzed using a logistic regression model with terms for the treatment group and prognostic factors. For the secondary evaluations, the time to first transfusion after Day 28 was depicted using Kaplan-Meier curves and compared using the log-rank test stratified by tumour type and Cox's proportional hazard model. Haemoglobin levels were analyzed using a linear model for repeated measurements, and changes in haemoglobin levels from baseline were compared using an analysis of covariance.

  The efficacy and intent-to-treat populations were used for the primary evaluation, but only the efficacy population was used for the secondary evaluations, with 1 exception; haemoglobin levels were summarized for the intent-to-treat population.

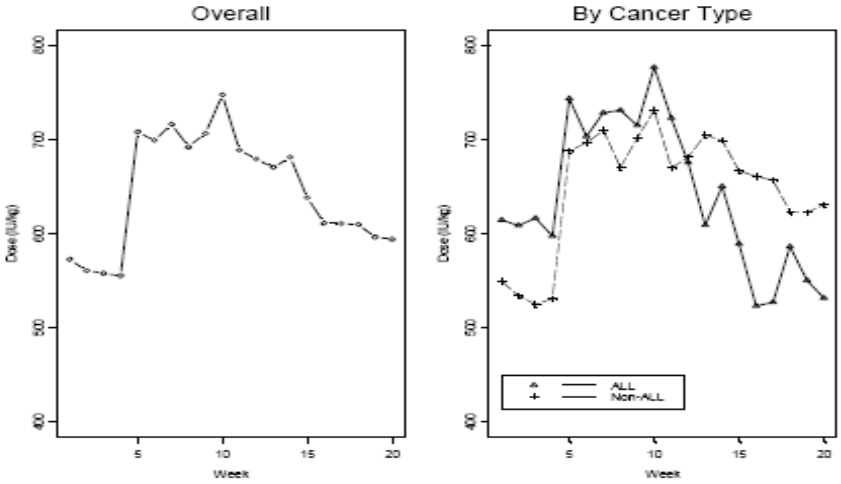
➢ Results

- Efficacy outcomes

  Epoetin alfa dosage

  Overall, the mean weekly dosage for Epoetin alfa subjects in the intent-to-treat population ranged from 555.1 to 946.7 IU/kg/week.

Figure 3: Mean Weekly Dosage of Study Drug (IU/kg/week)



Overall, 27% of subjects were administered a combination of IV. and SC dosing; 37 (32%) of subjects were administered Epoetin alfa solely by the sc route and 49 (42%) of subjects were administered Epoetin alfa solely by the IV route. An examination of the weekly Epoetin alfa dosage by route of administration revealed that the mean IV dosage was slightly higher than the mean sc dosage at all time points through Week 12. In the remaining weeks, (Weeks 13 through 20), the mean sc dosage was slightly higher than the mean IV dosage. The mean mixed dosage was generally between the mean IV and sc dosages throughout the course of the study.

Transfusions

No significant difference was observed in the proportion of patients who required a RBC transfusion after Day 28 (Epoetin alfa 70/113 [62%] patients versus standard therapy 77/112 [69%] patients) (p=0.3181; odds ratio=0.75 [95% CI: 0.43, 1.32]). Secondary endpoints also followed the same trend. However in the subgroup of patients with ALL, an unplanned exploratory analysis showed a significant difference in the proportion of patients transfused after Day 28 between the standard therapy (39/44 [89%]) and Epoetin alfa group (27/41 [66%]) (p=0.016; odds ratio=0.25 [95% CI: 0.08, 0.77]). No significant effect was observed in the non-ALL stratum. The investigators suggested that the lack of significance in the non-ALL stratum could have been due to the heterogeneity within the stratum or to the large number of patients who underwent surgery.

Haemoglobin

Mean haemoglobin levels in both treatment groups declined about 1 g/dl during the first 9 weeks, followed by a gradual increase through Week 16. A statistically significant difference of 0.03 g/dl/week (Epoetin alfa minus standard care) in the rate of haemoglobin rise over time was observed (p=0.0140). Unplanned exploratory modelling by cancer stratification suggested that there was a significantly higher rate of rise in the Epoetin alfa treatment group (p=0.0117) within the ALL cancer stratification. There was no significant treatment effect seen in the non-ALL cancer stratification (Figure 5).

Figure 4: Haemoglobin Levels (g/dl) Over Time

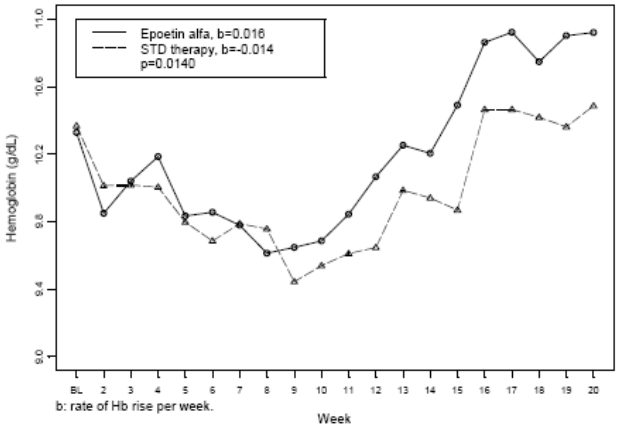
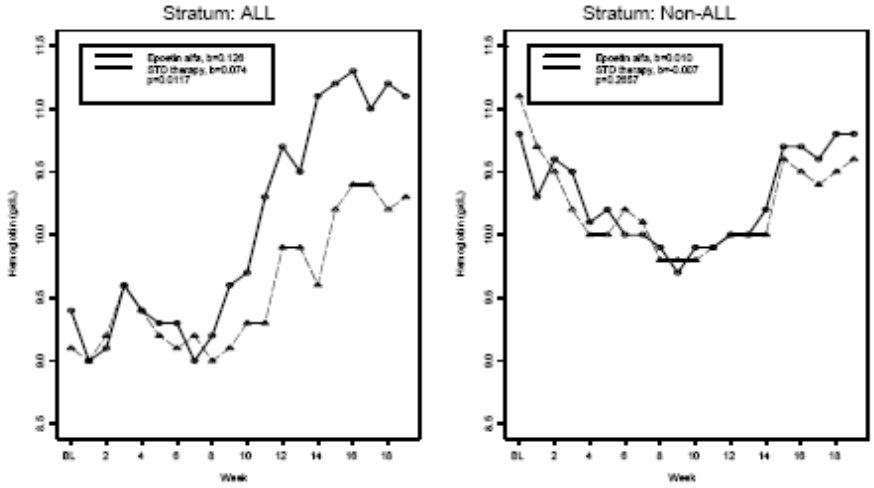


Figure 5 : Haemoglobin Levels Over Time by Cancer Stratification



- Safety results

  The incidence of adverse events was generally similar between the 2 treatment groups; the most commonly reported treatment-emergent adverse events included fever (43% standard therapy, 38% Epoetin alfa), granulocytopenia (39% standard therapy, 42% Epoetin alfa), and vomiting (34% standard therapy, 31% Epoetin alfa). These events are not unexpected in an oncology population undergoing chemotherapy. There was a slightly higher incidence of leucopenia in the Epoetin alfa treatment group (12%) compared with the standard therapy group (4%). Hypertension was reported as an adverse event in 4 (3%) of subjects in the standard therapy group and 2 (2%) of subjects in the Epoetin alfa treatment group. Treatment-emergent adverse events were reported in 84% of standard therapy subjects and 92% of subjects treated with Epoetin alfa.

  Six subjects died during the study; 2 subjects in the standard therapy group (1 ALL cancer stratification and 1 non-ALL cancer stratification) and 4 subjects in the Epoetin alfa group (1 ALL cancer stratification and 3 non-ALL cancer stratification). All of the deaths were attributable to the underlying disease, and none of the events were considered by the investigator to be related to study drug administration.

  A total of 13 thrombotic/vascular events were reported in 9 subjects (8 Epoetin alfa subjects and 1 standard therapy subject). In 5 of the 13 events, the thrombosis was related to the subject's catheter; in the subject who experienced cardiac arrest, the event was attributed to an improper infusion of potassium chloride. The subject who

experienced the cerebral haemorrhage had received asparaginase prior to the occurrence of the event. One event in the Epoetin alfa group was assessed as probably related by the investigator and Epoetin treatment was discontinued; another event was assessed as doubtfully related to Epoetin alfa treatment.
Sixty-four percent of subjects in both treatment groups showed a complete response to chemotherapy. There were no real differences between treatment groups with respect to the response to chemotherapy. In the ALL cancer stratification, subjects in both treatment groups showed a substantially better response to chemotherapy; a complete response was seen in 89% of ALL standard therapy subjects and 93% of ALL Epoetin alfa subjects. In non-ALL subjects, 49% of standard therapy subjects and 48% of Epoetin alfa subjects showed a complete response to chemotherapy.
Nine subjects withdrew from the study due to adverse events, including 7 subjects administered Epoetin alfa and 2 standard therapy subjects. All the events leading to withdrawal were serious.

Rapporteur's Comment
The lack of an overall significant treatment effect has been attributed by the investigators in the heterogeneity of the non-ALL cancer population and the larger percentage of patients undergoing major surgery/procedures. It is noted however that the number of patients in each tumour groups is very limited to allow further stratification of the results.
The open label design of this study limits the validity of the safety information presented here. However it is accepted that it is very difficult to assess the safety profile of the Epoetin treatment in a cancer population undergoing the initial phases of aggressive chemotherapy. The increased number of thrombotic episodes in the Epoetin group has to be taken into consideration as the evidence for role of r-HuEPO treatment in such events is still inconclusive. The biological background underlying the thrombotic effects of r-HuEPO is multifaceted (polycythemia +/- hyperviscosity syndrome, hypertension, thrombocytosis, platelet hyperactivity, activation of blood coagulation) and it most likely requires the presence of additional prothrombotic factors. However as many studies highlighted the problem of an increased trend of thrombotic complications, especially venous thromboembolism, in patients undergoing therapy with r-HuEPO, therapy with Epoetin Alfa might not be ultimately beneficial or advantageous in patients with chemotherapy induced anaemia.

2.2.c ***PRI/EPO-INT-79/EPO-CA-490***
An open-label, follow-up study evaluating the safety of epoetin alfa (RWJ-22512) in recently diagnosed pediatric subjects receiving myelosuppressive chemotherapy for malignancy.

- **Methods**

  - Objective
    The aim of this study was to evaluate the safety of long-term (up to 1 year, including the treatment period of Study PRI/EPO-INT-51) Epoetin alfa treatment in paediatric subjects who completed Study PRI/EPO-INT-51 and who were continuing to receive myelosuppressive chemotherapy with or without radiotherapy or surgery.

  - Study design
    Phase 3 open-label, multicenter, follow-up safety study (up to 1 year duration).

- Study population /Sample size

  Subjects were recruited from those previously randomized to either Epoetin alfa or standard therapy in Study PRI/EPO-INT-51.

  A total of 89 subjects from Study PRI/EPO-INT-51 were enrolled in the study, including 36 subjects who received standard therapy in Study PRI/EPO-INT-51 and 53 subjects who received Epoetin alfa in Study PRI/EPO-INT-51. A majority of the subjects (57 subjects, 64%) had a diagnosis of non-ALL; 32 (36%) had a diagnosis of ALL. When the proportion of subjects in the ALL population of Study EPO-INT-51 who continued into the current study was compared with that of the non-ALL population, the percentages were found to be similar. Thirty-eight percent (32 subjects) of the 85 subjects in the ALL population of Study EPO-INT-51 continued into the current study, compared with 39% (57 subjects) of the 147 subjects in the non-ALL population of Study EPO-INT-51 who continued into the current study.

- Treatments

  Subjects who were receiving Epoetin alfa in Study PRI/EPO-INT-51 continued at their most recent dosage (600 or 900 IU/kg once a week) of Epoetin alfa. Subjects who were not receiving Epoetin alfa in Study PRI/EPO-INT-51 were started on a dosage of 600 IU/kg once a week of Epoetin alfa, which was maintained for the first 4 weeks of this study. After 4 weeks of Epoetin alfa administration for subjects previously randomized to the standard therapy group in Study PRI/EPO-INT-51, a dosage adjustment could be made based on the subject's haemoglobin concentration. For all subjects, if the haemoglobin concentration increased to 13 g/dl or higher, administration of Epoetin alfa was to be interrupted until the haemoglobin concentration returned to 12 g/dl or lower; Epoetin alfa treatment was then to be resumed at a dosage of 600 IU/kg once a week. If the haemoglobin concentration decreased to 10 g/dl or lower, subjects who were receiving 600 IU/kg once a week of Epoetin alfa were to be increased to 900 IU/kg once a week of Epoetin alfa; subjects who were receiving 900 IU/kg once a week of Epoetin alfa were to remain at that dosage. If the haemoglobin concentration decreased to 7 g/dl or lower, the subject could be transfused, if clinically indicated. If a transfusion was necessary, the dosage of Epoetin alfa was not to be adjusted for 1 week following the transfusion.

- Outcomes/endpoints

  No efficacy evaluations were performed in this study. Safety evaluations were based on the incidence and severity of adverse events and the findings from clinical laboratory tests and vital sign measurements.

  An overview of key study procedures performed during this study is summarized in table 5.

Table 5: Scheduled evaluations

Procedure	Visit Number / Week	1 / 0	2 / 2	3 / 4	4 / 8	5 / 12	6 / 16	7 / 20	8 / 24	9 / 28	Study Completion/ Withdrawal[a] 12 / 31
Informed consent[b]		X									
Vital signs[c]		X[d]	X	X	X	X	X	X	X	X	X
Weight and height[c,e]		X[d]	X	X	X	X	X	X	X	X	X
Chemotherapy		X[d]	X	X	X	X	X	X	X	X	
Local laboratory tests											
Hemoglobin[f]		X[d]	X	X	X	X	X	X	X	X	X
Central laboratory tests[g]											
Hematology		X[d]									X
• Hematocrit											
• RBC											
• WBC, including differential											
• Platelet count											
• Reticulocyte count											
Serum chemistry		X[d]									X
Iron parameters		X[d]				X					X
• Serum iron											
• Ferritin											
• Transferrin saturation											
Serum folate, vitamin B_{12}		X[d]									
Pregnancy test[h]		X									
Epoetin alfa administration[i]		X	X	X	X	X	X	X	X	X	X
Adverse events collected			X	X	X	X	X	X	X	X	X

Abbreviations: RBC=red blood cell; WBC=white blood cell.

[a] The last visit was scheduled at Week 31 or 1 week after administration of the last dose of epoetin alfa. This visit could occur up to 1 year after the start of Study PRI/EPO-INT-51.

[b] Informed consent was obtained as soon as the subject was considered for the study.

[c] Measured before administration of study drug and other study assessments were performed.

[d] These results were recorded from those obtained at the completion visit (Week 21) of Study PRI/EPO-INT-51 (unless the first dose of study drug was not administered within 7 days of obtaining the results).

[e] Height was measured only at Visits 1 and 12.

[f] Hemoglobin was measured once a week by the local laboratory.

[g] All laboratory tests except hemoglobin were performed at the central laboratory.

[h] Pregnancy tests were performed in female subjects of childbearing potential who were sexually active. The test results had to be negative for the subject to be eligible to participate in the study.

[i] Epoetin alfa injections were administered once a week on the same day of each week ± 24 hours; the duration of treatment was up to 31 weeks.

- Statistical Methods

  All summaries and analyses were based on data from the safety ITT population, which included all subjects enrolled in the study and for whom assessments of safety parameters were available. The safety parameters to be evaluated were the incidence and severity of adverse events and changes from baseline in clinical laboratory tests, vital sign measurements, and weight. No statistical comparisons were performed.

➢ **Results**

Mean baseline haemoglobin levels were higher in the formerly Epoetin alfa group (10.7 g/dL) compared with the formerly standard therapy group (9.9 g/dl). Mean platelet values were also higher in the formerly Epoetin alfa group (253.9 x 109/L) compared with the formerly standard therapy group (184.7 x 109/L). Mean baseline ferritin was higher in the formerly standard therapy group than in the formerly Epoetin alfa group, as expected; the lower mean baseline ferritin level in the formerly Epoetin alfa group reflected the utilization of iron stores during erythropoiesis following administration of Epoetin alfa during Study PRI/EPO-INT-51. A higher proportion of subjects in the formerly Epoetin alfa group (15 [28%]) was considered clinically iron deficient at baseline (defined as transferring saturation less than 20%) compared with the formerly standard therapy group (3 [8%]).

The mean weekly dosage during the first 30 weeks of the study for subjects in the formerly standard therapy group ranged from 442.4 to 667.6 IU/kg/week. For subjects in

the formerly Epoetin alfa group, the mean weekly dosage ranged from 455.9 to 707.1 IU/kg/week.

- Safety results

  Thirty-one (86%) subjects in the formerly standard therapy group and 47 (89%) subjects in the formerly Epoetin alfa group reported adverse events. The most frequently reported adverse events were fever (25% formerly standard therapy, 28% formerly Epoetin alfa) and vomiting (19% formerly standard therapy, 25% formerly Epoetin alfa). Other commonly reported adverse events included upper respiratory tract infections and granulocytopenia. The majority of adverse events were mild in severity and transitory in nature, and most were determined by the investigator to be unrelated to study drug. Overall, 29 (91%) of subjects with ALL reported adverse events, including 16 (94%) subjects in the formerly standard therapy group and 13 (87%) subjects in the formerly Epoetin alfa group. Overall, 49 (86%) of subjects with non-ALL reported adverse events, including 15 (79%) subjects in the formerly standard therapy group and 34 (89%) subjects in the formerly Epoetin alfa group.

  Although there were approximately 3 times as many subjects in the Epoetin alfa Study PRI/EPO-INT-51 group as in the Epoetin alfa Study PRI/EPO-INT-79 group, the overall incidence of adverse events reported in the 2 groups was similar. One hundred six (91%) Epoetin alfa-treated subjects in Study PRI/EPO-INT-51 and 31 (86%) subjects in the formerly Epoetin alfa group in Study PRI/EPO-INT-79 reported adverse events. Overall, the most frequently reported adverse events were granulocytopenia (55 [36%]), fever (52 [34%]), and vomiting (43 [28%]). The proportion of subjects reporting each of these adverse events, however, was higher in the Epoetin alfa group in Study PRI/EPO-INT-51 than the formerly standard therapy group in Study PRI/EPO-INT-79 (granulocytopenia, 42% versus 17%; fever, 38% versus 22%; vomiting, 31% versus 19%). These differences are likely a result of less aggressive anti-tumour therapy in Study PRI/EPO-INT-79 as compared to Study PRI/EPO-INT-51, thereby resulting in fewer adverse events reported.

  A total of 5 adverse events, reported in 5 subjects (2 formerly standard therapy subjects and 3 formerly Epoetin alfa subjects), were classified as thrombotic/vascular events. All of the events were assessed by the investigator as unrelated to study drug administration, with the exception of thrombosis in one case, which was assessed as doubtfully related. None of the thrombotic/vascular events resulted in the termination of Epoetin alfa administration. When the incidence of thrombotic/vascular events occurring in the first 21 weeks of Study PRI/EPO-INT-79 in subjects who had previously received standard therapy in Study PRI/EPO-INT-51 was compared with the incidence in Epoetin alfa-treated subjects in Study PRI/EPO-INT-51, the 2 groups were found to be similar.

  Five subjects withdrew from the study due to adverse events, including 4 subjects in the formerly standard therapy group and 1 subject in the formerly Epoetin alfa group. All of the events leading to the withdrawals were serious; however, all of the events were assessed by the investigator as unrelated to study drug.

  <u>Haemoglobin</u>

  Both treatment groups exhibited mean increases in haemoglobin from baseline to the last visit. As expected, these mean increases were greater for subjects in the formerly standard therapy group at the last visit (1.6 g/dl) compared with those for subjects in the formerly Epoetin alfa group (0.5 g/dl). When changes in haemoglobin levels over time were evaluated by cancer stratification, a notable overall difference between the 2 groups was seen. On most weeks throughout the study, overall haemoglobin levels in the ALL stratification were higher than those in the non-ALL stratification. These differences were particularly evident from Week 20 through the final week of the study. The higher

haemoglobin levels seen for the ALL group supported observations noted with regard to Epoetin alfa administration; the mean weekly dosages of the non-ALL group were higher than those of the ALL group for most weeks of the study, indicating the need for higher doses of Epoetin alfa to increase haemoglobin levels. A comparison of weekly mean haemoglobin levels across Study PRI/EPO-INT-51 and Study PRI/EPO-INT-79 revealed distinct differences with respect to Epoetin alfa administration. For subjects in the formerly standard therapy group, mean haemoglobin levels were below 10.0 g/dL on most weeks during Study PRI/EPO-INT-51. In contrast, after beginning Epoetin alfa treatment during Study PRI/EPO-INT-79, mean haemoglobin levels for the formerly standard therapy group ranged from 10.2 to 11.9 g/dL. For subjects in the formerly Epoetin alfa group, all mean haemoglobin levels were above 10 g/dL during Study PRI/EPO-INT-51 as well as during Study PRI/EPO-INT-79. Epoetin alfa treatment appeared to be associated with an initial rise in haemoglobin level over several weeks, which gradually levelled out over time but remained elevated.

Rapporteur's Comment
The design of this study does not allow any efficacy evaluation. Similarly due to the open-label design it is very difficult to assess the evidence on the safety profile of the treatment with r-HuEPO. The thrombotic episodes reported raise concerns as it is noted that they are not associated with an increase of the Hb above the levels defined as safe (<12g/dl).

Discussion of paediatric clinical information on Chemotherapy-Induced Anaemia of Cancer

Three large Company-sponsored studies in paediatric patients with chemotherapy-induced anaemia were conducted. These studies did not demonstrate statistically significant differences between the Epoetin alfa group versus placebo or standard of care groups for the primary endpoints of the 2 studies. In Study PR99-11-034/044, a statistically significant difference between the Epoetin alfa group and placebo group was noted in an ad hoc analysis of the proportion of patients receiving a RBC transfusion after Day 28. While there was not a statistically significant difference in this endpoint for the overall population in Study EPO-INT-51, in the subgroup of patients with ALL, a statistically significant difference was shown. The lack of significance in the non-ALL subgroup was attributed to the heterogeneity in that stratum and the large number of patients who had surgeries.
Based on the evidence submitted during this work-sharing procedure, the MAH proposes the addition of further information in section 5.1 relating to the experience of treating paediatric patients with Chemotherapy-Induced Anaemia with Epoetin Alfa. The proposed wording is:

Proposed Additions to Section 5.1, Pharmacodynamic properties:
The safety and efficacy of epoetin alfa 600 IU/kg i.v or s.c. once weekly has been evaluated in a randomised, double-blind, placebo-controlled, 16-week study and in a randomised, controlled, open-label, 20-week study in anaemic paediatric patients receiving myelosuppressive chemotherapy for the treatment of various childhood non-myeloid malignancies. In both studies, a dose increase up to 900 IU/kg was permitted if haemoglobin had not increased after the first 4 or 5 weeks of therapy.
In the 16-week study, a significant reduction (p=0.009) was observed in the proportion of patients requiring a RBC transfusion after Day 28 (epoetin alfa 57/111 [51%] patients versus placebo 77/111 [69%] patients).
In the 20-week study, no significant difference was observed in the proportion of patients who required a RBC transfusion after Day 28 (epoetin alfa 70/113 [62%] patients versus standard therapy 77/112 [69%] patients). However in the subgroup of paediatric patients with acute

lymphoblastic leukaemia (ALL), a significant difference (p=0.016) was observed (epoetin alfa 27/41 [66%] patients versus standard therapy 39/44 [89%] patients).

Rapporteur's Comment

The issue of the use of r-HuEPOs for the treatment of cancer patients (adults or children) remains still highly controversial. In a recent update from American Society of Clinical Oncology/American Society of Hematology (2010), clinicians are urged to discuss potential harms (e.g. thromboembolism, shorter survival) and benefits (e.g. decreased transfusions) of ESAs and compare these with potential harms (e.g. serious infections, immune-mediated adverse reactions) and benefits (e.g. rapid Hb improvement) of RBC transfusions. Similar guidance is not available in paediatric patients; however in 2009 Marec-Berard et al published the "The Standards, Options, and Recommendations (SOR) from the project undertaken by the French National Federation of Cancer Centres (FNCLCC) related to the use of ESAs in anaemic children with cancer. Those were based on a review of the most reliable scientific data available and this review confirmed four points: treatment increases haemoglobin levels so it might decrease the need for blood transfusions; no quality-of-life and no survival benefit has been demonstrated; treatment does not seem associated with significantly more side effects; impact on thromboembolic events and patient quality of life remains unclear. Based on these findings "*Systematic administration of ESA is not recommended for the prevention or treatment of anemia in pediatric cancer patients. However, treatment decision must be made on a case-by-case basis and, when treatment is considered, the intravenous route must be preferred*".

Based on the data from the studies submitted in the paediatric work-sharing procedure and the evidence available in the literature, the rapporteur is of the view that Epoetin alfa should not be recommended for the use in paediatric cancer patients. Although the clinicians should be able to assess the individual patient needs, the inclusion of wording regarding the use of Epoetin in cancer anaemia in section 5.1 could lead to an underestimation of the safety risk, in light of a non proven benefit. The rapporteur is of the view that the following wording should be included in section 4.2 of the SmPC with supporting information in section 5.1:

4.2 Posology and method of administration

The efficacy and safety of Epoetin alfa in paediatric cancer patients have not been established (also see section 5.1)

5.1 Pharmacological properties

The safety and efficacy of Epoetin alfa has been evaluated in a randomised, double-blind, placebo-controlled, 16-week study (n=222) and in a randomised, controlled, open-label, 20-week study (n=232) in anaemic paediatric patients receiving myelosuppressive chemotherapy for the treatment of various childhood non-myeloid malignancies. In both studies there was no statistical difference between the proportion of patients required RBC transfusion between the Epoetin alfa treatment group and placebo or standard care. Furthermore in the placebo-controlled study, administration of Epoetin alfa in paediatric patients with cancer did not have a statistically significant effect on patient-reported or parent-reported Paediatric Quality of life Inventory or Cancer Module scores compared with placebo.

2.3 Paediatric studies of Epoetin alfa in anaemia of prematurity

Haemoglobin concentrations typically decrease during the first few months after birth and this decrease is termed the physiological anaemia of infancy. The decrease in haemoglobin is greater and more rapid in preterm infants, reaching a nadir around 5 to 6 weeks. Low serum concentrations of erythropoietin also occur during this period and in vitro studies show that erythroid progenitors from the marrow and blood of preterm infants respond normally to

erythropoietin (Stockman 1977; Shannon 1995). Epoetin alfa is not currently indicated in the EU for the treatment of anaemia of prematurity. Several published randomised, controlled studies have evaluated the safety and efficacy of epoetin alfa in the treatment of anaemia of prematurity. As part of this paediatric work-sharing procedure under Article 45, the MAH submitted the following 6 studies investigating the prevention and/or treatment of anaemia in low-birthweight preterm neonates with r-Hu EPO.

Erythropoietin, protein, and iron supplementation and the prevention of anaemia of prematurity	P-243 Bechensteen et al., Arch Disease of Childhood 1993;69:19-23
Recombinant human erythropoietin stimulates erythropoiesis and reduces erythrocyte transfusions in very low birth weight preterm infants	L91-028 Shannon et al: Pediatrics 1995;95:1-8
Comparison of high dose therapy of r-HuEPO, given two or three times a week in premature infants	CC 2574 P-415 Bock et al. J Perinat Med 1995;23:133-138
Enhancement of erythropoiesis by recombinant human erythropoietin in low birth weight infants: a pilot study	K90-033 Shannon et al. J Pediatr 1992;120:586-592
Recombinant human erythropoietin in the anemia of prematurity: results of a placebo-controlled study.	H87-077 Shannon et al. J Pediatr 1991;118:949-955
Placebo-controlled, double-blind, dose-ranging study of the safety and efficacy of recombinant human erythropoietin (r-HuEPO) in the prophylaxis and treatment of the anaemia of prematurity	CC 2574 P-129 Clinical Report

2.3.a *P-243*

Erythropoietin, Protein, and Iron Supplementation and the Prevention of Anaemia of Prematurity.

Bechensteen AG, Håga P et al.
Arch Dis Child. 1993 Jul;69(1 Spec No):19-23.

- **Methods**

  - Objective
    The objective of this study was to determine whether very low birth weight infants respond to exogenous erythropoietin with increased erythropoiesis. In order to ensure non-restrictive erythropoiesis they were richly supplemented with protein and iron.

  - Study design
    Open-label, multicentre randomised controlled study, including premature infants enrolled in the study at 3 weeks of age. The study period was from 3 to 8 weeks of age with an additional assessment at 16 weeks.

  - Study population /Sample size
    Twenty nine premature babies were enrolled in the trial at 3 weeks of age. Inclusion criteria were: (1) birth weight 900-1400 g and (2) birth weight above the 3rd centile for gestational age (GA).
    Exclusion criteria were: (1) ongoing ventilator treatment, (2) fractional inspired oxygen (FiO_2) >40%, (3) previous or present steroid medication, (4) blood transfusion less than 96 hours before start of study, (5) ongoing infection with antibiotic treatment started less

than 96 hours before start of study, (6) obvious signs/symptoms of neurological impairment, (7) ABO/Rh incompatibility or other haematological disease, (8) other disease or illness (renal disease, heart disease, syndromes, etc), and (9) parenteral nutrition. The objective was to enrol 'healthy' infants only. The babies were withdrawn from the study if serious infection (defined as antibiotic treatment for more than 72 hours) or increased oxygen demands (defined as FiO_2 >40% for more than 24 hours) occurred.

- Treatments
  The r-HuEPO was given subcutaneously in a dose of 100 U/kg three times a week from 3 to 7 weeks of age. Indication for blood transfusion was haemoglobin concentration below 8.0 g/dl. All infants received breast milk supplemented with 9 g/l human breast milk protein from 3 to 8 weeks of age. Eighteen mg iron was given daily from week 3 and was doubled if serum iron concentration fell below 16.0µmol/l. At the end of the study period (8 weeks) the dose was reduced to 18 mg/day, which is the routine supplement for preterm infants in Norway.

- Outcomes/endpoints
  The effect of treatment was assessed by the change of haematological parameters (haemoglobin, haematocrit and reticulocyte count) during treatment. A blood sample was collected once a week by heel prick. Blood pressure was recorded daily and weight was measured daily, length and head circumference weekly.

- Statistical Methods
  Tests of treatment effects were based on conventional regression techniques. Initial values (at age 3 weeks) were used as covariates to compensate for differences in initial values and to increase the power of the tests.

➢ **Results**

- Efficacy outcomes
  Reticulocytes, both in percentage of red cells and in absolute numbers, increased rapidly and significantly (p<0.0001) after one week of r-HuEPO treatment. Significant treatment effects on reticulocyte values were found after one, two, and three weeks of treatment. In the control group the reticulocyte counts showed the normal rise and were significantly higher at 4 to 8 weeks of life compared with initial values (p<0.01). During the last week of r-HuEPO treatment (6 to 7 weeks of age) there was a small decline in reticulocyte count (p<0.05), but a highly significant fall was observed after the cessation of r-HuEPO treatment at 7 weeks of age (p-<0.0001).

Figure 6 : Absolute reticulocyte concentration

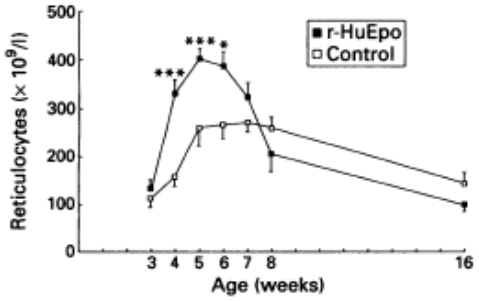


*Figure 1 Absolute reticulocyte concentration in the r-HuEpo and control groups. Mean values; bars represent SE. Significant difference between treatment group and controls: *p<0·05, ***p<0·001.*

The treatment effect was already significant on the haemoglobin and packed cell volume values after one week (age 4 weeks), and this effect was sustained throughout the treatment period. The lowest mean haemoglobin concentration in the r-HuEPO group was 11.2 g/dl at 5 weeks of age while that of the controls was 9.8 g/dl (week 7). The red cell indices were similar in both groups throughout the study.

Figure 7 :Haemoglobin and packed cell volume

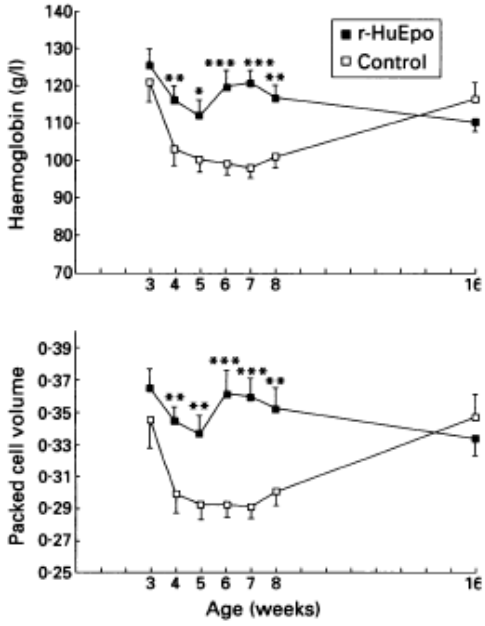


*Figure 2 Haemoglobin and packed cell volume in the r-HuEpo and control groups. Mean values; bars represent SE. Significant difference between treatment groups and controls: *p<0·05, **p<0·01, ***p<0·001.*

All but three infants (two r-HuEPO treated, one control) required an increase in iron dosage due to serum iron concentration less than 16.0µmol/l. Serum iron fell initially in the r-HuEPO treated group. After one week of treatment they had significantly lower values than the controls but after that the concentrations were equivalent.
Serum ferritin concentrations displayed the expected fall in both groups and there were no significant differences between them. No case of neutropenia (neutrophils $<10^9$/l) was observed during the r-HuEPO treatment. Platelet counts increased slightly during the study period in both groups with no significant differences between them.
During the study period four infants in the control group were transfused with red blood cells, none in the r-HuEPO group.

- Safety results
  Growth (weight, length, and head circumference) was similar in the two groups with a weight gain of about 200 g/week, nearly corresponding to the in utero increments.
  No adverse effects were observed during the study. In particular, no hypertension or differences in blood pressure between the groups were encountered. There were no reactions to the injections, the oral iron, or the protein supplementation. One patient in the control group was withdrawn from the study due to suspected, but at no time verified, septicaemia.

Rapporteur's Comment
From this randomised trial in premature low birthweight babies, some evidence suggest that these children are able to respond to exogenous r-HuEPO treatment and therefore could avoid

the observed anaemia of prematurity at 5 to 8 weeks of life. It is noted that there are published studies (Obladen et al 1991, Shannon et al 1991) in which such a clear cut response with moderate doses has not been observed. An interesting observation is that the infants included in this study were otherwise healthy. Furthermore the authors of the study suggest that the supplementation with iron and protein could further facilitate that increased erythropoiesis. A point of interest is the drop observed in reticulocyte counts during the last week of r-HuEPO treatment and the first week after cessation of treatment at 7 weeks of age. The authors of the study suggest that the cause of this possible decline in erythropoiesis might be that the endogenous erythropoietin production ceases when haemoglobin increases.
No adverse effects of r-HuEPO were observed, neither hypertension nor local or systemic reactions to the injections. It is noted that growth rate was similar between the 2 groups with no clear advantage for the group with better Hb levels. However this is a rather small study to answer whether all preterm babes would benefit from r-HuEPO treatment by prevention of anaemia of prematurity.

2.3.b ***CC-2574-P415***
Comparison of high dose therapy of r-HuEPO given 2 or 3 times a week in premature infants.
Bock W et al 1995

- **Methods**

  - Objective
    The objective of this study was to investigate the difference in response to high dose of r-HuEPO given twice or three times weekly in premature infants.

  - Study design
    Randomised, open-label dose comparative study of Epoetin alfa given in premature infants.

  - Study population /Sample size
    Forty eight (n=48) preterm infants (≤ 34 weeks GA) were enrolled in the trial. Inclusion criteria were birth weight >900g, age >7 days and HCT≤40%. .
    Exclusion criteria were: (1) ongoing ventilator treatment, (2) fractional inspired oxygen (FIO2) >40%/o, (3) previous or present steroid medication, (4) blood transfusion less than 96 hours before start of study, (5) ongoing infection with antibiotic treatment started less than 96 hours before start of study, (6) obvious signs/symptoms of neurological impairment, (7) ABO/Rh incompatibility or other haematological disease, (8) other disease or illness (renal disease, heart disease, syndromes, etc), and (9) parenteral nutrition. The objective was to enrol 'healthy' infants only. The babies were withdrawn from the study if serious infection (defined as antibiotic treatment for more than 72 hours) or increased oxygen demands (defined as FiO2 >40% for more than 24 hours) occurred.

  - Treatments
    The infants in Group A (n=23) were treated with sc Epoetin alfa 300 IU/kg 3 times weekly and those in Group B (n=25) with 450 IU/kg 2 times weekly, for not less than 4 weeks. Oral iron supplementation adjusted to 10 mg/kg/day as closely as possible.

  - Outcomes/endpoints
    The main response criterion was defined as time elapsed until HCT≥ 35% was achieved. As some infants didn't achieved this level within 6 weeks respective times were censored. For those infants who exceeded the target level within the period, the time

required to reach 35% HCT was estimated by interpolation between respective HCT measurements. The completed or censored times were then compared for both treatment regimes.

- Statistical Methods
  Comparison of changes to HCT above 35% was based on Cox's model.

➢ **Results**

- Efficacy outcomes
  There were no significant treatment effect on the main response criterion and no significant differences between the 2 groups in the effect on reticulocytes, haematocrit, and ferritin levels. Ferritin depletion could not be compensated as the dose was restricted due to gastrointestinal problems. Premature infants starting with a baseline HCT lower than 32% showed a major increase in HCT during the first week of treatment without any initial drop in the recorded values.

Figure 8

Erythrocytes volume ml, median,

(kg body weight x 80ml x HCT%)

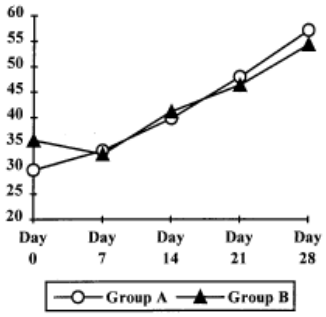
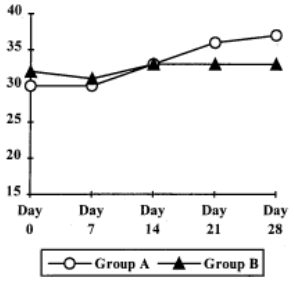


Figure 9

Hematocrit %, median

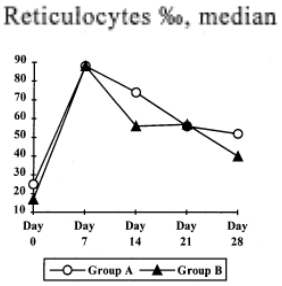


Four patients needed blood transfusions during the treatment period, 2 due to major surgical operations and 2 due to persistent anaemia during the first week of treatment (day 3 and 4).

- Safety results
  There were no local reactions to the injections. No other adverse reactions were recorded in both groups.

Rapporteur's Comment

Based on the results of this study the authors suggest that in preterm infants with anaemia, Epoetin alfa can safely used in doses of 300U/kg three times weekly. The reasoning for the selection of the 2 tested doses is not clearly explained. The use of HCT as an efficacy end-point is not considered optimal as reticulocyte counts better reflect the effect of treatment in erythropoiesis. When assess the effect of Epoetin alfa on median reticulocytes count (‰), a significant drop is noted after the 2nd week of treatment in both groups but more obvious in the twice weekly group. It is not therefore robustly proven that the proposing dosing regime of sc Epoetin alfa (300U/kg x 3 week) should be used in all premature infants for the treatment of anaemia.



2.3.c ***H87-077***

Recombinant human erythropoietin in the anemia of prematurity: results of a placebo-controlled pilot study.

Shannon KM, Mentzer WC, et al
J Pediatr. 1991 Jun;118(6):949-55.

- **Methods**

  - Objective
    The objective of this study was to investigate the use of r-HuEPO in small premature infants who were highly likely to require transfusion for anaemia of prematurity.
  - Study design
    Randomised, double-blind, placebo-controlled study of r-HuEPO in premature infants (1250 g or less at birth).

  - Study population /Sample size
    Twenty premature babies were enrolled in the trial. To ensure an even distribution of very immature infants in the treatment and control arms, patients were stratified at entry into groups of "large" (birth weight 901 to 1250 gm), and "small" (birth weight ≤900 gm) infants. Ten small and ten large babies were entered into the trial. Within these two subgroups, five infants each were randomly assigned to receive either r-HuEPO or placebo.

    Inclusion criteria were: (1) GA at birth ≤33 weeks; (2) birth weight ≤1250 g; (3) age 10 to 35 days; (4) clinical stability as judged by the ability to tolerate enteral feedings, absence of infections, minimal requirements for respiratory support (a fraction of inspired oxygen <0.3, ventilator rate <20 breaths per minute, and ventilator pressures of 20/4 mm Hg or less) and absence of seizures; (5) phlebotomy requirements of <7.5 ml/wk; (6) absence of intraventricular haemorrhage above grade I; (7) HCT at the first dose of study medication of ≤35%; and (8) no history of significant haemolytic disease caused by ABO or Rh incompatibility.
  - Treatments

Intravenous injections of r-HuEPO at a dose of 100 units per kilogram, or of an identical volume of the placebo suspension, were given twice each week for 6 weeks. A supplemental oral dose of iron, 3 mg/kg per day, was given to all infants at the discretion of the attending neonatologist.

- Outcomes/endpoints
  The effect of treatment was assessed by the change of haematological parameters (haemoglobin, haematocrit and reticulocyte count) during treatment. At entry and after 6 weeks, blood was obtained by venipuncture for determination of antibodies against EPO. Studies performed at regular intervals after treatment included complete blood cell counts (CBCs) with reticulocyte counts and for erythropoietin levels (at 1, 2, 4, 8, 12, and 24 weeks), haemoglobin electrophoresis (at 12 and 24 weeks), and determination of anti-EPO antibodies (at 12 and 24 weeks).

- Statistical Methods
  All statistical comparisons between treatment and control groups were performed with a two-tailed unpaired t test.

➢ **Results**

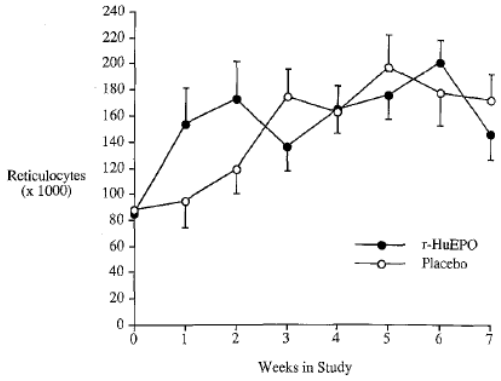
- Efficacy outcomes

Hematologic measurements

Infants assigned to treatment with r-HuEPO had mean HCT values of 33.4% at entry and of 28.1% at the end of the treatment phase. HCT values were similar in control infants: 34.3% at entry and 28.2% at the end of treatment. Moreover, there were no significant differences in HCT values between EPO and control babies at any time during the study.

Mean absolute reticulocyte counts increased during treatment to 163,700 cells/mm^3 in r-HuEPO treated infants, and to 157,500 cells/mm^3 in the control group. As shown in Figure 10, reticulocyte counts rose promptly in the EPO group, reached a mean of 172,000 cells/mm^3 by 2 weeks, and ranged between 135,000 and 200,000 cells/mm^3 thereafter. In control infants, reticulocyte counts rose more gradually and stabilized in a similar range. Reticulocyte counts in the EPO infants versus those in the control infants after 1 week and 2 weeks were not significantly different. The rate of increase in reticulocyte count was significantly greater in the EPO group at 1 week but not at 2 weeks. There were no differences in reticulocyte counts between EPO and control infants during weeks 3 through 7.

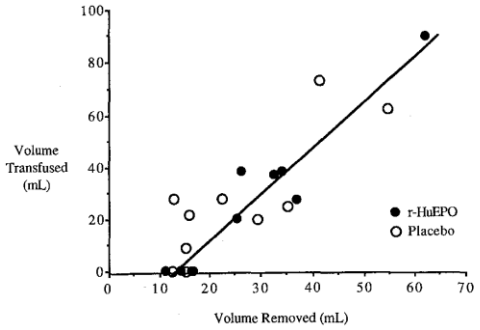
Figure 10 : Absolute reticulocyte counts (mean ±SEM) in r-HuEPO and control infants during treatment phase of trial.



Transfusions and blood sampling.

Six infants assigned to treatment with r-HuEPO, and eight control subjects, received one or more erythrocyte transfusions during the treatment phase of the trial (p = not significant). Larger infants were less likely to receive transfusions than those with birth weights≤900 gm (5/10 vs. 9/10 small babies; p = 0.07 by Fisher Exact Test). Large and small infants who were transfused received similar total volumes of packed erythrocytes. Figure 11 shows that there was a highly significant correlation between the amount of blood withdrawn for these studies and the volume of packed cells transfused (r= 0.89;p = 0.0001). Grouping the study population according to the amount of blood sampled for laboratory tests revealed a bimodal distribution: a group of nine infants had <20 ml (range 11.2 to 16.9 ml) removed; 10 others had losses >25 ml (range 25.4 to 90 ml). All six babies with no transfusions had <20 ml sampled.

Figure 11 : Linear regression plot of volume of blood transfused during treatment phase as function of total blood sampled.



- Safety results

  Two major adverse events were observed in this study. A baby assigned to the EPO group died of fulminant necrotizing enterocolitis in week 5 of treatment, and an infant in the control group acquired meningitis complicated by parenchymal brain abscesses 1 week after entry. The latter survived but has significant neurologic damage. Both patients weighed <900 gm at birth.

  There were no significant differences between EPO and control patients with respect to total leukocyte counts or to any subpopulation of leukocytes. There were no differences in the mean platelet counts of EPO and control patients. No hypertension developed, and seizures were observed only in the placebo- treated baby who had meningitis. The 19 surviving patients had normal age-adjusted hematologic values and generally excellent growth and development 6 months after completing treatment. None of the babies developed antibodies against r-HuEPO.

Rapporteur's Comment

This randomised double blind study demonstrated a lack of any significant differences between r-HuEPO-treated and control babies with respect to rates of growth, haematocrit values, mean absolute reticulocyte counts, and overall transfusion requirements. It is therefore suggested that a weekly r-HuEPO dose of 200 U/kg is largely ineffective in small premature babies. The authors attempted to give possible explanations for this finding. The selection of the dose was based mainly on data from adult renal patients. However this extrapolation does not take into account the special demands and the difference in PD and PK parameters during treatment of preterm sick babies. As this was a pilot study, a dose escalating design could have helped identify whether a higher dose would have been more efficacious but also safe. The lack of adequate iron supplementation could also be an additional reason for the treatment failure as the iron stores of premature infants are already very low at birth. A very interesting finding of the study is

that there is a strong correlation between the quantity of blood removed for laboratory tests and the volume of packed erythrocyte transfusions, which could be a contributing factor to the anaemia but also the lack of adequate increase of HCT despite treatment.

2.3.d *K90-033*

Enhancement of erythropoiesis by recombinant human erythropoietin in low birth weight infants: a pilot study.

Shannon KM, Mentzer WC et al
J Pediatr. 1992 Apr;120(4 Pt 1):586-92.

- **Methods**

  - Objective
    The objective of this study was to investigate the use of r-HuEPO in small premature infants who were highly likely to require transfusion for anaemia of prematurity.

  - Study design
    Randomised, double-blind, placebo-controlled study of r-HuEPO in premature infants (1250 g or less at birth). The duration of the study was 6 weeks.

  - Study population /Sample size
    Eight premature babies were enrolled in the trial.
    Inclusion criteria were: (1) GA at birth ≤33 weeks; (2) birth weight ≤1250 g; (3) age 4 to 28 days; (4) clinical stability as judged by the ability to tolerate enteral feedings, absence of infections, minimal requirements for respiratory support [a fraction of inspired oxygen <0.3, ventilator rate <20 breaths per minute, and ventilator pressures of 20/4 mm Hg or less] and absence of seizures; (5) phlebotomy requirements of <7.5 ml/wk; (6) absence of intraventricular haemorrhage above grade I; (7) HCT at the first dose of study medication of ≤37%; and (8) no history of significant haemolytic disease caused by ABO or Rh incompatibility.

  - Treatments
    Subcutaneous injections of r-HuEPO at a dose of 100U/kg, or an identical volume of placebo, were given from Monday through Friday. If the reticulocyte count was not greater than 200,000 cells/mm^3 when measured at the end of 2 weeks or more than 300,000 cells/mm^3 after 3 weeks, the daily dose of r-HuEPO was doubled to 200U/kg. Supplemental oral iron therapy was ordered for all infants at a starting dosage of 3 mg/kg/day, divided in three doses and given between feedings. The iron dosage was increased to 6 mg/kg/day for infants who were tolerating full caloric feedings. Infants also received 1 ml/day of multivitamins (including 50µg of folic acid) and vitamin E (15U/day).

  - Outcomes/endpoints
    The effect of treatment was assessed by the change of haematological parameters during treatment. Blood was obtained by venipuncture for a complete blood cell count, with differential and reticulocyte counts, haemoglobin electrophoresis, and iron studies (serum iron, ferritin, and transferrin levels and transferrin saturation), and for determination of antibodies to erythropoietin at entry and after 6 weeks.

  - Statistical Methods
    Data analyses were performed by means of standard descriptive and inferential statistics. Inferential statistics included two-tailed, unpaired Student t tests or repeated measures analysis of variance, as appropriate, for continuous data, and the chi-square

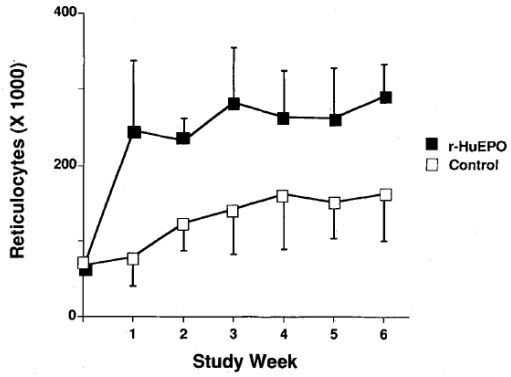
test or Fisher Exact Test, as appropriate, for nominal data. The comparison-wise alpha for the study was set as p = 0.05.

- **Results**
  - Efficacy outcomes

    Hematologic measurements

    Reticulocyte counts were higher after 1 week of treatment in r-HuEPO-treated infants. The mean reticulocyte count during treatment was 262.600± 60.153 cells/mm^3 in infants assigned to the r-HuEPO group, and 136,400±57,300 cells/mm^3 in the control infants. When tested by repeated-measures analysis of variance, reticulocyte counts during treatment were significantly higher in the r-HuEPO group (p = 0.009).

    Figure 12 : Absolute reticulocyte counts (mean±SEM) in r-HuEPO and control infants during treatment phase of trial.

    Overall, infants assigned to treatment with r-HuEPO received 100U/kg/d for a total of 15 weeks, and 200U/kg/d for 9 weeks. The mean reticulocyte count was 251.200±27.700 cells/mm^3 at the end of weeks in which 100U/kg/d was given, and 269,500±73,300 cells/mm^3 after 200 units/kg per day (p=not significant).

    Pre-treatment HCT were 33.4% ±2.6% in r-HuEPO- treated babies and 33.5%± 3.7% in the control infants. The corresponding values after 6 weeks of treatment were 31.4%±0.9% and 25.2%±1.7%, respectively (p = 0.0007).

    Iron intake during treatment was 4.0±1.1 mg/kg per day in babies who received r-HuEPO and 3.8±0.6 mg/kg per day in the control infants. There were no significant differences between r-HuEPO-treated and placebo infants with respect to transferrin, feritin, or transferrin saturation values. Infants assigned to the r-HuEPO group had significantly lower serum iron concentrations during treatment than did the control infants (p = 0.04 by repeated measures analysis of variance).

    Treatment with r-HuEPO was not associated with neutropenia or leukocytosis.

    Transfusions and blood sampling.

    One of four infants assigned to treatment with r-HuEPO, and three of four control subjects, received one or more erythrocyte transfusions. The only r-HuEPO treated infant who received a transfusion became unstable soon after entering the trial and had the largest phlebotomy requirement of any baby in our study (44.5 ml).

  - Safety results

    There were no major adverse events. Babies assigned to the placebo group gained more weight overall than the r-HuEPO infants (1182±211g vs. 611±225g; p=0.01) and had a higher percentage increase above entry weight (116%±12% vs. 75%±28%; p = 0.04). However, when the weekly weight change of each infant was plotted against standard graphs for low birth weight babies, we found that the slower weight gains in r-HuEPO-

treated infants were consistent with their lower entry weights (data not shown). Caloric intakes were similar in the two groups.
The authors concluded that all babies did well and none acquired antibodies against r-HuEPO.

Rapporteur's Comment
The authors conclude that compared to the previous study (H87-077), reticulocyte counts during treatment and HCT values at the end of therapy were higher in infants who were randomly assigned to receive r-HuEPO than in the placebo group. Furthermore although this trial was not designed to demonstrate a significant reduction in erythrocyte transfusions, our data provide evidence that the enhanced rate of erythropoiesis seen in r-HuEPO-treated infants resulted in fewer transfusions. This is a rather small study including only 8 preterm infants and only 4 of them received r-HuEPO; therefore the evidence proving a positive effect of the treatment isn't robust. The fact that increasing the weekly dosage of r-HuEPO from 500 to 1000 U/wk had no effect on reticulocyte counts raises further questions on the effectiveness of the treatment. The investigators do not offer any explanation why the subcutaneous route was chosen in this trial compared to the IV administration in study H87-077. Regarding the safety profile of the r-HuEPO treatment, the authors haven't provided detailed information. Interestingly weight gain in the r-HuEPO treated infants was less rapid than in the control infant. There was not adequate explanation for this finding in these otherwise "healthy" premature neonates; however if more unstable low birthweigth neonates were to be treated with r-HuEPO, such a reduced growth rate could have serious implications.

2.3.e *L91-028*
Recombinant human erythropoietin stimulates erythropoiesis and reduces erythrocyte transfusions in very low birth weight preterm infants.
Shannon KM, Keith JF 3rd et al.
Pediatrics. 1995 Jan;95(1):1-8.

- **Methods**

  - Objective
    The objective of this study was to investigate whether treatment with r-HuEPO would stimulate erythropoiesis and would thereby reduce the need for erythrocyte transfusions in preterm infants.

  - Study design
    Multicentre randomised (stratified by centre), double-blind, placebo-controlled study of r-HuEPO in premature infants.

  - Study population /Sample size
    157 preterm infants were enrolled in the trial.
    Inclusion criteria were: (1) GA at birth <31weeks; (2) birth weight ≤1250 g; (3) age 7 to 42 days (depending on weeks of gestation); (4)stable clinical status (5) phlebotomy requirements of <7.5 ml/wk; (6) HCT at the first dose of study medication of <40%; and (7) platelet count greater than 50 000/mm^3. Infants were excluded if they had diastolic blood pressure greater than 60 mm Hg or a documented history of iron deficiency.
    Of the 157 infants studied, 115 completed 6 weeks of treatment and 29 were discharged home before 6 weeks. One infant in the placebo group died from necrotizing enterocolitis during treatment. These 145 infants (92% of the study population) completed the study as designed.

- Treatments
  Subcutaneous injections of r-HuEPO at a dose of 100 U/kg, or an identical volume of the placebo suspension, were given from Monday through Friday for 6 weeks or until the infants were ready to be discharged home. Doses of r-HuEPO (or placebo) were adjusted weekly according to changes in body weight. Patients received oral iron supplements at study entry to achieve a total enteral intake of 3 mg/kg/d of elemental iron. Total iron intake was increased to 6 mg/kg/d when the infants tolerated full caloric feedings enterally. Infants also received 15 units of supplemental vitamin E and an additional 1mL/d of an enteral multivitamin preparation.

- Outcomes/endpoints
  The study's primary endpoint was identified a priori as erythrocyte transfusion. Blood was obtained by venipuncture for a complete blood count with differential and reticulocyte count, serum iron, and ferritin at entry and at the end of treatment. Complete blood counts with reticulocyte counts were measured weekly, and the iron studies were repeated after 3 weeks of treatment. The total amount of blood sampled for studies prescribed in the protocol was approximately 10 mL.

- Statistical Methods
  The study was designed to enrol 200 subjects without planned interim analysis. Sample size determination was based on a predicted transfusion rate of 75% in the placebo group. The target was set to be a 25% reduction in the baseline transfusion group to an r-HuEPO group transfusion rate of 56%. It was believed that the targeted therapeutic effect was of sufficient magnitude to be clinically important. Statistical power of 80% or greater was computed for the planned sample size based on the difference above and a two-tailed alpha of .05 for both the χ^2 test (contingency table analysis) and the log-rank test (survival analysis). However slower than expected enrolment prompted a decision in April 1993 to conduct an unplanned interim analysis of a 143 of 146 cases (enrolled during the 20 months between October 1991 and June 1993). The interim analysis used group sequential clinical trials methodology, employing statistically conservative boundaries for early stopping. In October 1993, due to persisting problems with enrolment the study was closed.
  Intention-to-treat was used to analyze all data from 157 patients at the final analysis. Univanate statistical methods used χ^2 (with continuity correction for 2 x 2 tables) for categoric data and unpaired Student's t-tests for parametric data. The Mann-Whitney U test was used when distributional assumptions of parametric statistics were not met, particularly for data on phlebotomy losses and the number and volume of transfusions. Repeated-measures analysis of variance was used to compare weekly observations between the treatment groups (e.g. hematologic indices, growth, and nutrition). Cases with missing values were not eliminated from the analyses of variance. Correlation analysis and analysis of covariance (equality-of-slopes test) were used to study the relation between phlebotomy losses and transfused volumes. Survival(time-to-event) analysis supplemented the Mann-Whitney U test in analyses of transfusion experiences adjusted for the actual duration of treatment, which was important in relation to the potential for unequal exposure in subjects not completing the planned 6-week treatment period. Multivanate analysis was performed using logistic regression, stratified by study center, to refine the univanate estimate of the therapeutic effect of r-HuEPO on transfusion.

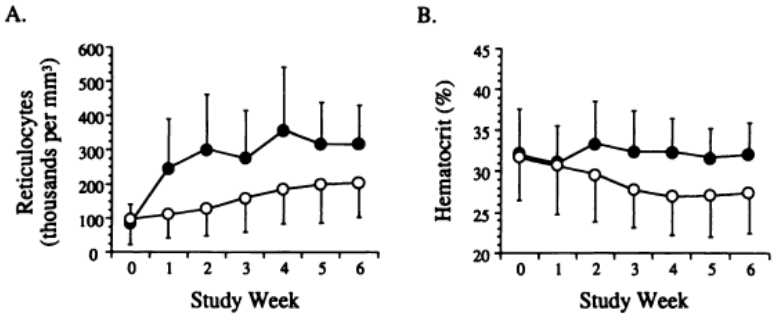
➢ **Results**

- Efficacy outcomes

Hematologic measurements

Figure 13 compares weekly reticulocyte counts and HCT in the two groups. As expected there was a steady rise in the mean absolute reticulocyte count in the placebo group after 6 weeks (Fig 13A). In contrast to the gradual rise seen in the placebo group, the mean reticulocyte count increased abruptly in r-HuEPO treated infants from 84,720/μL at entry to 246,670/μL after 1 week of treatment, and averaged between 270,000/μL and 360,000/μL thereafter. The difference in reticulocyte counts between the r-HuEPO and placebo groups was highly significant (P = 0.0001). Figure 13B compares HCT values in r-HuEPO and placebo-treated infants.

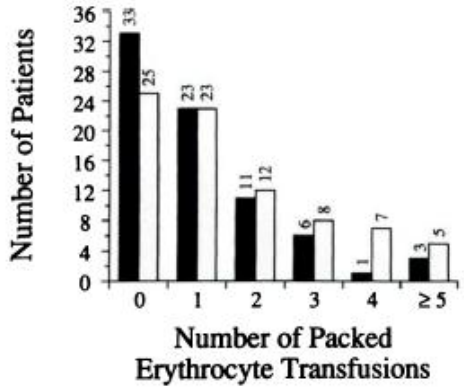
Figure 13 : **(A) Weekly reticulocyte counts in r-HuEPO(solid circles) and placebo infants (open circles) at study entry and during treatment. (B) Weekly HCTs in the two groups at study entry and during treatment.**



Erythrocyte Transfusions.

Overall, infants assigned to treatment with r-HuEPO received a total of 85 transfusions and 1271 mL of packed erythrocytes, whereas the infants in the placebo group received 128 transfusions and 1912 mL of packed erythrocytes. Thirty-three of 77 infants assigned to treatment with r-HuEPO and 25 of 80 infants in the placebo group received no transfusions during the study (43% versus 31%; P = 0.18 by χ^2test and P =0 .17 by log-rank test).

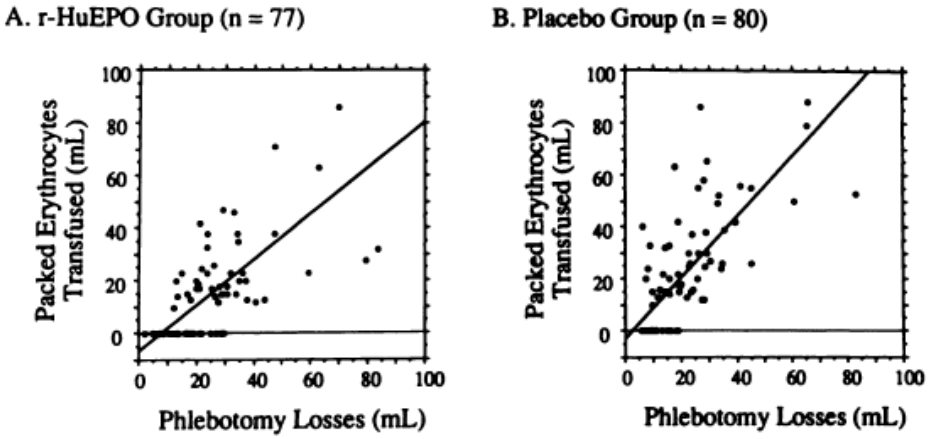
Figure 14: **The number of infants in each group who received zero, one, two, three, four, and five or more transfusions of packed erythrocytes during the study.**



* Infants assigned to receive r-HuEPO are shown in solid bars, and placebo-treated infants are shown in open bars.

Figure 15 shows a strong correlation between phlebotomies and transfusions in both groups. However, the slopes of the regression lines were significantly different between the r-HuEPO and placebo groups (0.87 versus 1.16; P<0.0001), with r-HuEPO treated infants receiving less packed erythrocytes at any given level of phlebotomy loss than the infants in the placebo group.

Figure 15: Relation between the volume of blood removed for laboratory tests and the volume of packed erythrocyte transfusions in recombinant human erythropoietin (r-HuEPO) (A) and placebo (B) recipients.



Serum iron levels fell in r-HuEPO treated infants but increased in the placebo group during the first 3 weeks of treatment. This pattern reversed after 3 weeks, with serum iron values increasing in the r-HuEPO group and declining in the placebo group.

There were no differences between infants in the r-HuEPO and placebo groups with respect to platelet counts, total white blood cell counts, or neutrophil counts.

- Safety results

  Three r-HuEPO and four placebo treated infants developed necrotizing enterocolitis, including the placebo-treated infant who was the only death during the study. There were no differences in the rates of documented or suspected infections between r-HuEPO-treated and placebo infants. Two r-HuEPO-treated infants developed systemic hypertension, one during week 3 and the other during week 6 of treatment. The infants in the r-HuEPO and placebo groups had similar rates of growth.

  All participating centres maintained follow-up clinics for very low birth weight infants. The authors surveyed these clinics and have confirmed four post-discharge infant deaths among 125 infants followed until they were at least 6 months old. Three placebo-treated infants died; two of probable sudden infant death syndrome and one neurologically compromised baby from aspiration pneumonia. The only late death in an r-HuEPO treated infant occurred at 11 months of age from late gastrointestinal complications due to necrotizing enterocolitis. The authors concluded that this suggests that the risk of late death was not increased in infants previously treated with r-HuEPO.

Rapporteur's Comment

Based on the findings of this study, the authors concluded that treatment with r-HuEPO safely reduces transfusions in premature infants who are clinically stable. They view reductions in blood loss from phlebotomy, using clear-cut criteria for transfusion, and administering r-HuEPO as complementary strategies to reduce the frequency and volume of transfusions. Changes in practice over the past few years have resulted in an overall decrease in the numbers of transfusions in infants. However, considerable variation remains. The small differences in frequency and volume of transfusion obtained in this study are disappointing, particularly if the goal is to avoid transfusions entirely in small, sick infants. It is unlikely that phlebotomy losses can be decreased sufficiently to achieve this goal, given that withdrawing 1 mL of blood from a 1000 g infant is equivalent to taking 70mL of blood from an adult (Blanchette and Zipursky 1984). The rapporteur is of the view that significant questions remain with respect to both the optimal doses of r-HuEPO and iron as well as the best time to initiate treatment. Selection of patients remain crucial as the overall risk:benefit ratio of the r-HuEPO treatment in very low birthweight unstable premature neonates has not yet been established.

2.3.f *CC-2574-P129*

Placebo-Controlled, Double-Blind, Dose-ranging Study of the Safety and Efficacy of recombinant human Erythropoietin (R-HUEPO) in the Prophylaxis and Treatment of the Anemia of Prematurity.

- **Methods**

  - Objective
    The objective of this study was to investigate the efficacy and safety of subcutaneous r-HuEPO in the prophylaxis and treatment of anaemia in premature infants.

  - Study design
    Randomised (2:1 randomization), single centre, double-blind placebo-controlled dose-ranging study.

  - Study population /Sample size
    24 preterm infants were enrolled in the trial. Recruitment to the study was limited to premature infants who were between 27 and 32 weeks and 6 days GA at birth and be at least 7 days or older (range 8.3 and 10 days).
    This study was scheduled to involve 36 infants. However there were 3 deaths in the r-HuEPO group, two of whom died from sudden infant death syndrome a month after ceasing therapy with r-HuEPO. The hospital's ethics committee decided the early discontinuation of the trial. The data were analysed to determine whether there was any association between the deaths of the infants with the treatment with r-HuEPO. The study was therefore terminated after 24 infants were recruited.

  - Treatments
    Of the infants randomized to the treatment, the first group (Group 1) received 50U/kg sc r-HuEPO twice a week, Group 2 received 100U/kg sc twice a week, Group 3 received 150U/kg sc twice a week and the Group 4 was given 200U/kg sc twice a week.
    Treatment continued until infants were discharged from the hospital or at a gestational age of 40 wks.

  - Outcomes/endpoints
    The effect of treatment was assessed by the change of haematological parameters during treatment. Blood was obtained weekly or biweekly for haematological and biochemical evaluation, with particular reference to changes in the Hb, HCT, reticulocyte count and the transfusion requirement. Specific transfusion guidelines were included in the study protocol. Infant should be considered for blood transfusion if they were symptomatic (with Hb<10.5g/dl) or had Hb< 8g/dl.
    The safety was assessed by clinical observations throughout the treatment phase. Follow up for up to 1 year after the termination of the treatment was also undertaken. However, only data from the first 3 months were available at the time of the writing of the study report assessed here.

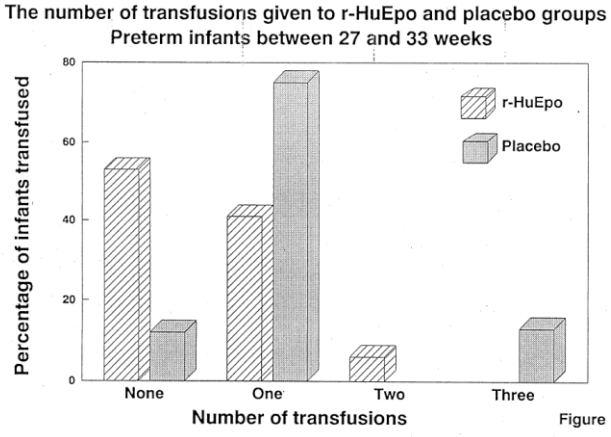
  - Statistical Methods
    Statistical analysis of the data was by analysis of variance and the Student's t-test form normally distributed data and by the Mann-Whitney U test for the non parametric data. The data were analysed in each of the dosing groups but in addition a further grouping of all the r-HuEPO treated infants was also made; the majority of the statistical comparisons

have been made using this combined group because of the relatively small number of patients in each of the individual groups.

- **Results**
  - Efficacy outcomes

Erythrocyte Transfusions.
The number of transfusions required showed an inverse relationship to the dose of r-HuEPO given, with only 1 of 8 infants (12.5%) in the placebo group not requiring a transfusion, while 8 of 15 (53%) in the r-HuEPO group did not require any transfusions. This demonstrated a trend to a reduction in the need for transfusion, though this didn't quite reach significance (p<0.08).

Figure 16



Figure

The mean volume transfuse per kg body weight in the r-HuEPO treated group showed a trend to a lower value re3quired being 10.2mis (53%) of the mean volume given to the placebo group (19.2mls).

Hematologic measurements
There were no significant differences between infants in the r-HuEPO and placebo groups with respect to Hb levels and HCT.
There was a sustained and significant increase in the mean reticulocyte count in the r-HuEPO group from week 2 onwards (<0.05). The reticulocyte count value at termination was significantly higher in the r-HuEPO group compared to placebo (p<0.01).
There were no differences between infants in the r-HuEPO and placebo groups with respect to platelet counts, total white blood cell counts, or neutrophil counts.
As in previous studies, corresponding significant decrease in serum ferritin and increase in RBC folate was recorded in the r-HuEPO group compared with the placebo group.

- Safety results

The infants in the r-HuEPO and placebo groups had similar rates of growth.
The systolic blood pressure rose during the study, consistent with the known physiological changes in neonates. There was a smaller mean rise of 14.9mmHg in the r-HuEPO group compared with placebo (22.3mmHg) at week 4. This difference was not present at the study termination.
There were no differences in the rates of adverse events between r-HuEPO-treated and placebo infants. Adverse events included episodes of apnoeas and bradycardias (n=3 in r-HuEPO group, n=1 in placebo group).

Three infants died after cessation of therapy, all of whom were in the actively treated arm of the study. One patient in the r-HuEPO group died 2 days after cessation of treatment with cause being volvulus of gut. Two more infants in the r-HuEPO group died 1 month after cessation of treatment with cause being sudden infant death syndrome. Both infants had apnoeas and bradycardias in the early course of the treatment but those were resolved by the time of discharge. The authors of the study report concluded that these adverse events could not be reasonably attributed to the study medication.

Rapporteur's Comment
The fact that the study was not able to be completed has limited the statistical significance of the study overall. Although it was set up to identify optimal dosing regime, almost all of the results presented are from comparison of the r-HuEPO group as a whole to placebo. Once again there is no clear benefit of r-HuEPO treatment in reduction of the need for transfusion in preterm neonates. Haemoglobin and HCT values remained unaffected but there was significant rise in reticulocyte counts after 2 weeks of treatment in the r-HuEPO groups as a total compared with the placebo group. The 2 cases of sudden infant death syndrome associated with the r-HuEPO treatment group raises significant concerns but it is accepted it is difficult to establish a causative relationship.

Discussion of paediatric clinical information on anaemia of prematurity

The reduced life span of neonatal erythrocytes, a steady expansion in blood volume due to rapid growth, and large phlebotomy losses for laboratory tests impose enormous erythropoietic demands on growing preterm infants. Erythropoiesis is quantitatively insufficient in this setting, leading to a progressive anaemia of prematurity. This condition is characterized by low reticulocyte counts, a low percentage of erythroid precursors in the bone marrow, and serum EPO levels that are within or below the normal range for non-anaemic adults. Affected infants have large numbers of erythroid progenitors in their blood and bone marrow that respond normally to EPO in vitro. Taken together, these data implicate inadequate EPO production as the primary pathophysiologic abnormality in anaemia of prematurity and suggest that treatment with r-HuEPO might reduce the use of red-cell transfusions.
The MAH proposes additions to Sections 5.1 and 5.2 of the SmPC to reflect the available data of epoetin alfa in anaemia of prematurity. Furthermore, the MAH requested the rapporteur's assessment of the available efficacy and safety data regarding the need for an update of other sections of the SmPC (Sections 4.1, 4.2, and 4.4) as an outcome of this procedure.

Proposed Additions to Section 5.1, Pharmacodynamic properties
The safety and efficacy of epoetin alfa, 100 IU/kg/5x week s.c. has been evaluated in a randomised, double-blind, placebo-controlled study in anaemic preterm infants (hematoocrit <40%), with a birth weight of 1250 g or less, a gestational age at birth less than 31 weeks, and at high risk for RBC transfusions; infants with grade III or greater intracranial haemorrhage were excluded. Infants received iron supplementation (elemental iron 3-6 mg/day orally). Treatment with epoetin alfa was associated with a higher reticulocyte count and haematocrit, and a reduction in erythrocyte transfusions. The safety profiles and rates of growth were comparable between the 2 treatment groups.

In support of the proposed additions to section 5.1, the MAH feels it is appropriate to also propose the inclusion of pharmacokinetic information for this patient population.
Proposed Additions to Section 5.2, Pharmacokinetic properties
Pharmacokinetic data in neonates is limited. A study of 7 preterm very low birth weight neonates and 10 healthy adults given i.v. erythropoietin suggested that distribution volume was

approximately 1.5 to 2 times higher in the preterm neonates than in the healthy adults, and clearance was approximately 3 times higher in the preterm neonates than in healthy adults.

Rapporteur's Comment

Premature infants experience a lower nadir of HCT than normally seen in full term infants which is inversely related to gestational age; this results in a normocytic, normochromic anaemia coincident with a low reticulocyte count and low EPO levels. Some premature infants tolerate anaemia of prematurity well. Others, especially the smallest, sickest infants, develop signs and symptoms such as tachycardia, tachypnea, apnea and bradycardia, poor weight gain, oxygen requirement, diminished activity, pallor, and elevated serum lactate. Since the late 1980s r-HuEPO has been studied as an alternative to RBC transfusion in the treatment of anaemia of prematurity. Two decades later haematologists and neonatologists have not reached consensus on when r-HuEPO should be used in very low birth weight (VLBW, <1500 grams) infants. Initial trials and reports focused on r-huEPO to prevent or treat AoP with the goal of eliminating RBC transfusion. Later studies found response to r-HuEPO was influenced by: 1) significant volumes of blood loss, especially in the smallest, sickest infants, 2) the physiology of r-HuEPO which requires days to weeks to increase HCT, and 3) need for supplementation of protein, iron, folate, and vitamin E. In addition, recent reports have raised the red flag of undesirable side-effects, including a possible increase in retinopathy of prematurity with early administration of r-HuEPO. On the other hand there is some evidence suggesting a role of erythropoietin during the development of the CNS and therefore a potential role as a neuroprotective agent both for the term infant with hypoxia-ischemia as well as for the extremely preterm infant (Chatagner et al 2010).

Despite the volume of evidence and if r-HuEPO reduces RBC transfusion in VLBW infants, why, then, is its administration not routine yet? One answer lies in the magnitude of the drug's effect. Although r-HuEPO administration did reduce RBC transfusion in some of the trials assessed here, questions persist about whether the absolute reduction in transfusion volume (ml per kilogram per patient) achieved is of clinical significance in this era of single-donor and safer RBC transfusion protocols.

The submitted r-HuEPO studies don't shed light on optimal dosing. The very first r-HuEPO studies used doses roughly equivalent to adult dosing protocols. These doses were found to be insufficient for premature infants who require larger doses of the hormone per kilogram of bodyweight compared to adults due to higher volume of distribution and faster elimination. Although infants require relatively high doses of r-HuEPO, a therapeutic threshold does seem to exist above which no further erythropoiesis response is obtained. Head-to-head comparison of "high dose" (1500 units/kg/week) versus "low dose" (750 units/kg/week) of r- HuEPO did not reduce RBC transfusion in ELBW infants (Maier et al 1998). Similar lack of significant effect difference between 2 high doses was found in study CC-2574-P415. Finally, it is well documented that infants receiving r- HuEPO have increased nutritional needs. These infants have lower ferritin levels and hypochromic red cells necessitating supplementation with iron to achieve full benefit of r- HuEPO treatment. Both intravenous and oral iron supplementation have been shown to cause additional complications from these already unstable neonates.

Regarding the studies submitted in this work-sharing procedure, the MAH wishes to include data from one placebo controlled study (K90-033) which demonstrated a positive effect of r-HuEPO treatment in premature infants. However other studies (H87-077 and CC-2574-P129) fail to demonstrate a significant reduction of the neonates' needs for transfusion. Some safety concerns have also been identified including 2 cases of sudden infant death syndrome which led to the early termination of study CC-2574-P129.

The rapporteur is of the view that the efficacy and safety of r-HuEPO use for the prevention and/or treatment of anaemia of prematurity has not been established. Therefore the evidence from the studies submitted is inconclusive and therefore should not be included in section 5.1 of the SmPC.

The inclusion of PK information in section 5.2 would be helpful as Epoetin alfa is licensed for use in very young children with anaemia due to CRF which is the approved indication. The rapporteur is of the view that inclusion of PK data as proposed by the MAH could be confusing for the prescribers as it might be considered only applicable to premature neonates. The MAH is requested to review the data available and propose wording which would reflect any available information regarding the pharmacokinetic properties in term neonates and other relevant paediatric subsets with anaemia of CRF.

III. RAPPORTEUR'S CONCLUSION AT DAY 70 AND RECOMMENDATION

Based on the review of the presented paediatric data on efficacy and safety the rapporteur considers the following:

Anaemia in chronic renal failure

The inclusion of data from the presented studies in paediatric chronic renal patients in section 5.1 of the SmPC is not accepted as proposed by the MAH. As the proposed wording conflicts with the current licensed indication of the intravenous use in haemodialysis paediatric patients, the rapporteur is of the view that the inclusion of data from these studies will confuse prescribers further to whether the subcutaneous use of Epoetin alfa is beneficial or not. Based on the studies presented here the subcutaneous of Epoetin alfa in non-haemodialysis paediatric patients and in paediatric patients on peritoneal dialysis is not supported.

Chemotherapy-Induced Anaemia of Cancer

Based on the data from the studies submitted in the paediatric work-sharing procedure and the evidence available in the literature, the rapporteur is of the view that Epoetin alfa should not be recommended for the use in paediatric cancer patients. Although the clinicians should be able to assess the individual patient needs, the inclusion of wording regarding the use of Epoetin in cancer anaemia in section 5.1 could lead to an underestimation of the safety risk, in light of a non proven benefit. The rapporteur is of the view that the following wording should be included in section 4.2 of the SmPC with supporting information in section 5.1:

4.2 Posology and method of administration

The efficacy and safety of Epoetin alfa in paediatric cancer patients have not been established (also see section 5.1)

5.1 Pharmacological properties

Paediatric population

The safety and efficacy of Epoetin alfa has been evaluated in a randomised, double-blind, placebo-controlled, 16-week study (n=222) and in a randomised, controlled, open-label, 20-week study (n=232) in anaemic paediatric patients receiving myelosuppressive chemotherapy for the treatment of various childhood non-myeloid malignancies. In both studies there was no statistical difference between the proportion of patients required RBC transfusion between the Epoetin alfa treatment group and placebo or standard care. Furthermore in the placebo-controlled study, administration of Epoetin alfa in paediatric patients with cancer did not have a statistically significant effect on patient-reported or parent-reported Paediatric Quality of life Inventory or Cancer Module scores compared with placebo.

Anaemia of prematurity

Regarding the studies submitted in this work-sharing procedure on anaemia of prematurity, the MAH wishes to include data from one placebo controlled study (K90-033) which demonstrated a

positive effect of r-HuEPO treatment in premature infants. However other studies (H87-077 and CC-2574-P129) fail to demonstrate a significant reduction of the neonates' needs for transfusions. Some safety concerns have also been identified including 2 cases of sudden infant death syndrome which led to the early termination of study CC-2574-P129. Similarly the submitted studies don't shed light on optimal dosing in neonates. The very first r-HuEPO studies used doses roughly equivalent to adult dosing protocols. These doses were found to be insufficient for premature infants who require larger doses of the hormone per kilogram of bodyweight compared to adults due to higher volume of distribution and faster elimination. Despite this, a therapeutic threshold does seem to exist above which no further erythropoiesis response is obtained.
The rapporteur is of the view that the efficacy and safety of r-HuEPO use for the prevention and/or treatment of anaemia of prematurity has not been established. The evidence from the studies submitted is inconclusive and therefore should not be included in sections 5.1 and 5.2 of the SmPC.

IV. ADDITIONAL CLARIFICATIONS REQUESTED

- It is noted that the first paragraph of the proposed wording for section 5.1 regarding the renal anaemia indication is not in reference with the studies submitted in this work-sharing procedure.

  Proposed wording

  "Epoetin alfa was evaluated in an open-label, non-randomised, 52-week clinical study in 116 paediatric CRF patients undergoing haemodialysis. The median age of patients enrolled in the study was 11.6 years (range 0.5 – 20.1 years). Epoetin alfa was initiated at 75 IU/kg/week i.v. in 2 or 3 divided doses post-dialysis, titrated by 75 IU/kg/week at intervals of 4 weeks (up to a maximum of 300 IU/kg/week), to achieve a 1 g/dL/month increase in haemoglobin. The target haemoglobin level was 9.6 – 11.2 g/dL. 81% of patients achieved the target haemoglobin level. The median time to target was 11 weeks and the median dose at target was 150 IU/kg/week. Of the patients who achieved the target, 90% did so on a t.i.w. dosing regimen. After 52 weeks, 57% of patients remained in the study, receiving a median dose of 200 IU/kg/week"

  Therefore data from this study has not been assessed here to be included in any changes in the SmPC. As this appears to be useful paediatric information, the MAH will be asked to clarify the proposed data by provided further information and if previously not assessed the study report for review by the rapporteur.

- The applicant is requested to respond in the proposals for the SmPC text with reference to the paediatric use of Epoetin alfa in paediatric cancer patients in sections 4.2 and 5.1.

- The MAH is requested to review the data available and propose wording which would reflect any available information regarding the pharmacokinetic properties in term neonates and other relevant paediatric subsets with anaemia of CRF.

- The MAH is requested to propose the paediatric wording which should be included in the PIL of all Epoetin alfa containing preparations reflecting the available paediatric information.

Following the circulation of the Day 70 PdAR, the rapporteur received comments from HU and SE who fully supported the rapporteur's conclusion and request for additional information.

V. MAH RESPONSES TO THE PRELIMINARY PDAR DAY 89

As an introduction to the response document, the MAH stated that their proposed labelling text was intended to bring the SmPCs for epoetin alfa in line with The European Commission Guideline on Summary of Product Characteristics (SmPC; Volume 2C Notice to Applicants, 2009, Revision 2). Moreover, the MAH cited relevant extracts of the revised SmPC guideline to illustrate the rationale for the proposed paediatric text.

The MAH stated that, at the time their responses were submitted, there was an ongoing Type II Variation for epoetin alfa in the Mutual Recognition Procedure. This variation aimed to update section 4.8 of the SmPC. At the same time the MAH suggested that additions should be made to sections 5.1 and 5.2 of the SmPCs for Epoetin alfa, including changes relating to use in the paediatric population.
It is noted that this variation procedure has been finalised and changes have been implemented in the SmPCs. Changes to the SmPC relating to the type II variation and affecting the paediatric population are discussed separately under the individual responses to the questions/requests for supplementary information included in the Day 89 PdAR.

The MAH commented on the rapporteur's conclusions regarding use of Epoetin alfa in anaemia of chronic renal failure and anaemia of prematurity (part A) and responded to the additional clarifications requested (part B):

Part A

1. Anaemia in chronic renal failure

Rapporteur's comments Day 89: The inclusion of data from the presented studies in paediatric chronic renal patients in section 5.1 of the SmPC is not accepted as proposed by the MAH. As the proposed wording conflicts with the current licensed indication of the intravenous use in haemodialysis paediatric patients, the rapporteur is of the view that the inclusion of data from these studies will confuse prescribers further to whether the subcutaneous use of Epoetin alfa is beneficial or not. Based on the studies presented here the subcutaneous use of Epoetin alfa in non-haemodialysis paediatric patients and in paediatric patients on peritoneal dialysis is not supported.

MAH response:

The MAH agreed that based on the studies submitted, use in non-haemodialysis (non-HD) and peritoneal dialysis (PD) paediatric patients is not supported since epoetin alfa is only indicated in paediatric patients receiving HD and no extension to this indication is sought. The subcutaneous administration studies include paediatric patients on HD, an approved indication for epoetin alfa. The MAH continues to support SmPC changes in section 5.1 regarding the subcutaneous use of Epoetin alfa in dialysis and non-dialysis patients. The MAH's rationale for proposing this study summary in section 5.1 is to fulfil the guidelines for the SmPC which state that data on paediatric patients should be included regardless of whether or not it is related to an indication.
The MAH proposed the following wording in section 5.1, under the heading "Paediatric population" and subheading "Chronic Renal Failure":

Subcutaneous administration of epoetin alfa at starting doses of 100 IU/kg/week to 150 IU/kg/week with the possibility to increase up to 300 IU/kg/week has also been studied in 72

paediatric CRF patients (including dialysis and patients not yet on dialysis). Epoetin alfa treatment was associated with increases in haemoglobin levels in all the studies. Clinical data with subcutaneous administration in this population are limited.

No unexpected adverse events were reported. Most of the adverse events reported (hypertension, pyrexia, and headache) were either recognized complications of CRF and/or dialysis, or were associated with common concurrent illnesses.

Rapporteur's comments:

The MAH is proposing wording for inclusion in section 5.1 (the same text as initially proposed by the MAH in the original Art. 45 submission) related to subcutaneous use of epoetin alfa in paediatric CRF patients.

The rapporteur at Day 89, considering that the proposed wording for section 5.1 could potentially confuse prescribers as to the licensed indications in children and/or the appropriate route of administration.
The SmPC guideline states that results of all pharmacodynamic (clinically relevant) or efficacy studies conducted in children should be presented in section 5.1, even if there is no authorised indication in any subset of the population. The rapporteur agrees to include the results of the available studies. However, the information to be included has to be balanced and has to state uncertainties and conclude on lack of efficacy or safety as appropriate.

The rapporteur considers that the text proposed by the MAH for section 5.1 does not accurately reflect the available data:
- The proposed wording does not reflect that the cumulative number of patients derives from a number of small studies. It is not ideal to pool the results of these studies as the included populations and the study design differed significantly, such as age, chronic renal failure stage (i.e. some patients on dialysis and some pre-dialysis), type of dialysis, duration of follow-up, efficacy outcomes, etc.
- There are a number of methodological limitations of the study design that are not captured in the proposed wording. This is important for the prescriber in order to understand the strength of the scientific evidence provided. Methodological limitations in these studies are: open label uncontrolled design, small number of patients recruited, efficacy endpoints not clearly defined, dialysis and pre-dialysis patients studied together, lack of long term follow-up and evaluation of long term effect, lack of validated quality of life questionnaires.

In the current SmPC of Epoetin alfa, posology in children is only given for its intravenous use in paediatric patients with CRF on haemodialysis. The studies discussed here include primarily pre-dialysis paediatric patients and patients on peritoneal dialysis (only 2 on HD) and drug administration via the subcutaneous route. Therefore, the rapporteur considers that in addition to changes in section 5.1, a cross reference in section 4.2 should be included to clarify that the drug is not indicated in paediatric patients on peritoneal dialysis or pre-dialysis.
Based on the above considerations, the rapporteur proposes the following wording:

Section 4.2:
Paediatric population
The safety and efficacy of <Epoetin alfa brand name> in chronic renal failure patients with anaemia before initiation of dialysis or on peritoneal dialysis have not been established. Currently available data for the subcutaneous use of <Epoetin alfa brand name> in these populations are described in section 5.1 but no recommendation on posology can be made.

Section 5.1:
Paediatric population
Chronic renal failure
Clinical data with subcutaneous administration in children are limited. In 5 small, open label, uncontrolled studies (number of patients ranged from 9-22, total N=72), Epoetin alfa has been administered subcutaneously in children at starting doses of 100 IU/kg/week to 150 IU/kg/week with the possibility to increase up to 300 IU/kg/week. In these studies, most were predialysis patients (N=44), 27 patients were on peritoneal dialysis and 2 were on haemodialysis with age ranging from 4 months to 17 years. Overall, these studies have methodological limitations but treatment was associated with positive trends towards higher haemoglobin levels. No unexpected adverse events were reported (see section 4.2).

2. Anaemia of prematurity

Rapporteur's comments Day 89: Regarding the studies submitted in this work-sharing procedure on anaemia of prematurity, the MAH wishes to include data from one placebo controlled study (K90-033) which demonstrated a positive effect of r-HuEPO treatment in premature infants. However other studies (H87-077 and CC-2574-P129) fail to demonstrate a significant reduction of the neonates' needs for transfusions. Some safety concerns have also been identified including 2 cases of sudden infant death syndrome which led to the early termination of study CC-2574-P129. Similarly the submitted studies don't shed light on optimal dosing in neonates. The very first r-HuEPO studies used doses roughly equivalent to adult dosing protocols. These doses were found to be insufficient for premature infants who require larger doses of the hormone per kilogram of bodyweight compared to adults due to higher volume of distribution and faster elimination. Despite this, a therapeutic threshold does seem to exist above which no further erythropoiesis response is obtained.
The rapporteur is of the view that the efficacy and safety of r-HuEPO use for the prevention and/or treatment of anaemia of prematurity has not been established. The evidence from the studies submitted is inconclusive and therefore should not be included in sections 5.1 and 5.2 of the SmPC.

MAH response:
The MAH considers the data from the larger placebo-controlled double-blind study (L91-028) to be robust with 157 paediatric patients (77 patients in the epoetin alfa group and 80 in the placebo group). The dose used in this study was 500 IU/kg/week.
Study CC2574-P415 included 48 patients; however there was no placebo control. In the other studies the number of patients per treatment group ranged from 4 to 25. Study H87-077 enrolled only 20 patients including very small infants (~27 weeks and ~900 g). The investigators commented the dose was probably too low; also investigators felt that more studies using a controlled double-blind design were warranted. Study L91-028 addressed these limitations and, as mentioned above, was proposed in the original Article 45 Work-sharing to be summarized in section 5.1. Study CC2574-P129 only included 24 patients and examined 4 doses of epoetin alfa with a small number of patients per dosing group (≤9 patients). For the analysis, the data were pooled from 3 dosing groups (100 to 300 IU/kg/week). While there was not a significant decrease in number of transfusions and increase in the reticulocyte counts, there was a trend. The 2 sudden infant deaths were not assessed by the investigator as being related to epoetin alfa treatment and occurred 1 month after the cessation of epoetin alfa treatment. Data from the other smaller studies described in the Article 45 Work-sharing were not summarized in section 5.1 of the SmPC because the small number of patients per treatment group did not provide any additional efficacy or safety data.

The MAH continues to believe that the available data from Study L91-028 concerning the treatment of anaemia of prematurity should be included in the SmPC, in accordance with the SmPC guidance. However, the MAH acknowledges that the SmPC must clarify that the safety and efficacy of epoetin alfa in this patient population have not been established. To address this point, and in line with the Rapporteur's conclusion on the study findings, the MAH recommends that this be clearly stated in the study summary. The overall proposed revisions to the MAH's original wording for section 5.1 of the SmPC are shown below.

Anaemia of prematurity
The safety and efficacy of <Epoetin alfa brand name>**for treatment of anaemia of prematurity have not been established**. ~~e~~**E**poetin alfa, ~~(~~100 IU/kg/5x week ~~s.c.~~**administered subcutaneously**) has been evaluated in a randomised, double-blind, placebo-controlled study in anaemic preterm infants (~~hematoocrit~~**haematocrit** <40%), with a birth weight of 1250 g or less, a gestational age at birth less than 31 weeks, and at high risk for RBC transfusions; infants with grade III or greater intracranial haemorrhage were excluded. Infants received iron supplementation (elemental iron 3-6 mg/day orally). Treatment with epoetin alfa was associated with a higher reticulocyte count and haematocrit, and a reduction in erythrocyte transfusions. The safety profiles and rates of growth were comparable between the 2 treatment groups.

Rapporteur's comments:

The MAH continues to support the inclusion of results from the study L91-028 (Shannon KM et al, 1995) in section 5.1 of the SmPC. At the same time the MAH offered justification why data from the other smaller studies are not summarized in section 5.1 of the SmPC (either small number of patients or suboptimal study design).
The rapporteur agrees that, compared to the other studies submitted by the MAH in this patient population, study L91-028 appears to be the most scientifically robust. On the other hand there have been many studies in the population of premature anaemic infants with the use of erythropoietins. These have been well described in 2 large reviews: Early erythropoietin for preventing red blood cell transfusion in preterm and/or low birth weight infants (Ohlsson A, Aher SM., Cochrane Database of Systematic Reviews 2014, Issue 4.) and Late erythropoietin for preventing red blood cell transfusion in preterm and/or low birth weight infants (Aher SM, Ohlsson A., Cochrane Database of Systematic Reviews 2014, Issue 4.). The study by Shannon et al was included in the 30 studies of the Aher and Ohlsson Cohrane review. The authors' conclusions in this review were:

"Late EPO administration results in a reduction in the use of one or more red blood cell transfusions following initiation of therapy. It minimally reduces the number of red blood cell transfusions per infant. It is not associated with reductions in mortality or other neonatal morbidities. The use of late EPO is not associated with any short-term serious side effects except for a possible association with retinopathy of prematurity (ROP) stage 3 or higher. A large proportion of extremely low birth weight/preterm neonates require red blood cell transfusions during the first few days of life, when neither early nor late EPO administration could possibly have an impact. The decision to use late EPO will depend on the baseline rate of red blood cell transfusions in this population in a specific neonatal intensive care unit, the costs, the associated pain, and the values assigned to the clinical outcomes. Other means of reducing the need for red blood cell transfusions should be considered, including reduced blood sampling and the use of 'satellite packs' from directed or universal donors." It is therefore acknowledged that EPO administration results in reduced transfusions in premature babies but the clinical significance of these changes is questioned.

Furthermore a recent European review by the Pharmacovigilance Risk Assessment Committee

(PRAC) has considered the current evidence for retinopathy associated with epoetin beta treatment of anaemia of prematurity. Epoetin beta is licensed for the prevention of anaemia of prematurity in infants with a birth weight of 0.75 to 1.5 kg and a gestational age of less than 34 weeks. This review has considered the 2 systematic Cochrane reviews (mentioned above) which suggest that epoetin beta may increase the underlying risk of retinopathy in premature infants. In January 2014, the PRAC agreed that the current evidence does not allow excluding a possible increase in the risk of retinopathy of prematurity with early treatment initiation of epoetins in preterm infants. The summary of product characteristics of Epoetin beta will be amended to include this possible risk of retinopathy.

To conclude on the potential risk for ROP stage 3 or higher, the authors of the 2 Cochrane reviews analysed studies that reported on ROP >/= 3 regardless of at what age the EPO treatment was initiated. They included seven studies in the early EPO review and three studies in the late EPO review. It is noted that in these 2 reviews efficacy and safety results are reported in general for EPO treatment without differentiation between the different EPO preparations, e.g. EPO alfa or beta. Out of the 10 studies reviewed for the ROP outcome, at least 2 (Al Kharfy, 1996 and Haiden 2005) used EPO alfa whereas for 5 of them the product used is unnamed in the publications.
The rapporteur considers that although the PRAC review is focused on EPO beta (licensed for anaemia of prematurity), the risk of ROP with erythropoietin alfa can also not be excluded based on the similarities between the two EPOs.

The MAH proposed to include in the SmPC the results of an isolated study; however large reviews have not concluded on the clinical benefit of EPO administration in neonates with anaemia of prematurity. In addition, there is a potential increased risk of ROP with EPO treatment in premature infants. Therefore including the results of this single study would not inform prescribers accurately on the overall benefits and risks of this treatment in this vulnerable population. Furthermore EPO alfa is not routinely used for anaemia of prematurity in neonatal intensive care units, as it is not currently licensed for this indication.

Based on the above considerations, the rapporteur does not support the inclusion of information in section 5.1 of the SmPC concerning the single study proposed by the MAH.

B. Responses to additional clarifications requested

Question 1

It is noted that the first paragraph of the proposed wording for section 5.1 regarding the renal anaemia indication is not in reference with the studies submitted in this work-sharing procedure.

Proposed wording
“Epoetin alfa was evaluated in an open-label, non-randomised, 52-week clinical study in 116 paediatric CRF patients undergoing haemodialysis. The median age of patients enrolled in the study was 11.6 years (range 0.5 – 20.1 years). Epoetin alfa was initiated at 75 IU/kg/week i.v. in 2 or 3 divided doses post-dialysis, titrated by 75 IU/kg/week at intervals of 4 weeks (up to a maximum of 300 IU/kg/week), to achieve a 1 g/dL/month increase in haemoglobin. The target haemoglobin level was 9.6 – 11.2 g/dL. 81% of patients achieved the target haemoglobin level. The median time to target was 11 weeks and the median dose at target was 150 IU/kg/week. Of the patients who achieved the target, 90% did so on a t.i.w. dosing regimen. After 52 weeks, 57% of patients remained in the study, receiving a median dose of 200 IU/kg/week”

Therefore data from this study has not been assessed here to be included in any changes in the SmPC. As this appears to be useful paediatric information, the MAH will be asked to clarify the proposed data by provided further information and if previously not assessed the study report for review by the rapporteur.

MAH response:

The MAH stated these data have been submitted and reviewed at the time the indication was approved. However, these data were not presented in section 5.1 of the SmPC and therefore the MAH proposed text which was submitted for review as part of the Type II Variation. The same text was included in the Article 45 submission for completeness and transparency but was not intended to be reviewed under this procedure.

Rapporteur's comment:

It is noted that following the type II variation procedure, the SmPC has already been updated with the following in section 5.1, under the heading "paediatric population" and the subheading "chronic renal failure":

Epoetin alfa was evaluated in an open-label, non-randomised, open dose-range, 52-week clinical study in paediatric CRF patients undergoing haemodialysis. The median age of patients enrolled in the study was 11.6 years (range 0.5 to – 20.1 years).

Epoetin alfa was administered at 75 IU/kg/week intravenously in 2 or 3 divided doses post-dialysis, titrated by 75 IU/kg/week at intervals of 4 weeks (up to a maximum of 300 IU/kg/week), to achieve a 1 g/dl/month increase in haemoglobin. The target haemoglobin level was 9.6 to– 11.2 g/dl. Eighty-one percent of patients achieved the target haemoglobin level. The median time to target was 11 weeks and the median dose at target was 150 IU/kg/week. Of the patients who achieved the target, 90% did so on a 3 times-per-week dosing regimen.

After 52 weeks, 57% of patients remained in the study, receiving a median dose of 200 IU/kg/week.

As the study report has already been assessed and changes already implemented in the SmPC, the issue is resolved.

Question 2

The applicant is requested to respond in the proposals for the SmPC text with reference to the paediatric use of Epoetin alfa in paediatric cancer patients in sections 4.2 and 5.1.

MAH response:

The MAH agrees that wording should be included in section 4.2 to provide clarity and prevent confusion concerning use of epoetin alfa in paediatric cancer patients. Wording to this effect was proposed under the Type II Variation. The Company has reviewed its original proposal, and taking into account the standard statements provided in the SmPC Guideline, recommends the following minor changes to the original wording for section 4.2:

Treatment of paediatric patients with chemotherapy induced anaemia

The safety and efficacy of <Epoetin alfa brand name>in paediatrics patients receiving chemotherapy ~~has~~ **have** not been established **(see section 5.1).**

In response to the rapporteur's proposal for section 5.1, the MAH stated:
The MAH reiterated that the rationale for inclusion of information from these studies is what is directed by the SmPC guidance, which requires the inclusion of paediatric study data regardless of the indication status. Furthermore, the inclusion of wording in section 4.2, describing that safety and efficacy of epoetin alfa in paediatric patients receiving chemotherapy have not been established, clarifies that the treatment with epoetin alfa in chemotherapy induced anaemia is not an approved indication in paediatric patients. Study PR99-11-034/044 was a large (224 enrolled patients), placebo-controlled, MAH-sponsored study. The transfusion endpoint of this study, unlike the studies in the adult oncology indication, was defined as proportion of subjects not transfused during the study. There was no statistically significant difference between the 2 treatment groups on the proportion of subjects not transfused. However, the MAH considers that the inclusion of the ad hoc analysis of the proportion of patients receiving a RBC transfusion after Day 28 is relevant because this is the definition of the primary endpoint of transfusion avoidance in the approved adult population. Transfusions occurring during the first month of the study are not included because an observed treatment effect would not be expected until after this period. The MAH also acknowledges the view of the Rapporteur regarding the inclusion of the quality of life data showing no evidence of improvement with epoetin alfa treatment and agrees this information should be added to section 5.1.
The MAH considers the inclusion of the data in patients with ALL from the Company sponsored EPO-INT-51 study is warranted. The ALL subgroup was a prospectively stratified subgroup. There was a statistically significant improvement in the proportion of patients transfused, other transfusion-related and hematologic variables for the epoetin alfa treated ALL patients compared with the ALL patients treated with standard of care. The lack of a statistically significant difference in the overall population is most likely due to heterogeneity in the non-ALL group with only small numbers of patients having a particular tumor type as well as an imbalance in tumor types between the 2 treatment arms.
The MAH concluded that it is appropriate to summarise the 2 studies separately within section 5.1, in order that the results can be clearly described. Additionally, it is considered important to describe the safety profile established across the studies to ensure transparency of the data. However, to simplify the text, it is proposed that the total efficacy population be described, to allow deletion of the relative incidences of required transfusions (the results being described by percentage change only). This proposed change applies to each study, and the ALL subset.
The overall proposed revisions to the MAH's original proposal for section 5.1 are provided below (additions in bold, deletions with strikethrough).

Chemotherapy induced anaemia
~~The safety and efficacy of~~ ~~e~~Epoetin alfa 600 IU/kg **(administered** ~~i.v or s.c.~~**intravenously or subcutaneously** once weekly**)** has been evaluated in a randomised, double-blind, placebo-controlled, 16-week study and in a randomised, controlled, open-label, 20-week study in anaemic paediatric patients receiving myelosuppressive chemotherapy for the treatment of various childhood non-myeloid malignancies. In both studies, a dose increase up to 900 IU/kg was permitted if haemoglobin had not increased after the first 4 or 5 weeks of therapy.

In the 16-week study **(n=222)**, a significant reduction (p=0.009) was observed in the proportion of **epoetin alfa-treated** patients requiring a RBC transfusion after Day 28 (~~epoetin alfa 57/111 [51%]) patients versus~~ **compared with placebo** ~~77/111 [(69%] patients).~~ **However, in the epoetin alfa-treated patients there was no statistically significant effect on patient-reported or parent-reported Paediatric Quality of Life Inventory or Cancer Module scores compared with placebo.**

In the 20-week study **(n=225)**, no significant difference was observed in the proportion of patients who required a RBC transfusion after Day 28 (**62% of** epoetin alfa ~~70/113 [62%]~~ patients versus **69% of** standard therapy ~~77/112 [69%]~~ patients). ~~However i~~In the **prospectively stratified** subgroup of paediatric patients with acute lymphoblastic leukaemia (ALL**; n=85**), a significant difference (p=0.016) was observed (**66% of** epoetin alfa ~~27/41 [66%]~~ patients versus **89% of** standard therapy ~~39/44 [89%]~~ patients).

The safety profile was similar to studies conducted in adults, and as expected for a paediatric cancer population on myelosuppressive chemotherapy.

Rapporteur's comments:

The MAH has agreed (with minor modifications) with the changes proposed for section 4.2 by the Rapporteur and, as the type II variation is finalised, the wording is already implemented in the SmPC. Issue resolved.

Regarding the changes in section 5.1, the MAH does not agree with the wording proposed by the rapporteur and has re-introduced the text proposed in the initial submission with a few modifications.

The rapporteur does not agree with the text proposed for the following reasons:
- In the 16-week double blind placebo controlled study (PR99-11-034/044), the primary efficacy endpoint compared the score of the patient reported paediatric quality of life inventory in the two groups. However, the MAH in the proposed text primarily mentions results from a post-hoc analysis of one of the secondary efficacy outcomes, i.e. transfusion requirements after day 28 post-randomisation and subsequently refers to the primary efficacy endpoint. The rapporteur considers that this way of reporting the study results is unbalanced as it gives the same gravity to the primary efficacy endpoint and other results from post-hoc analysis.
- In the 20 week open label controlled study (PRI/EPO-INT-51/EPO-CA-484), the subgroup (ALL) hypothesis is not prespecified, i.e. it is not discussed in the study report that different results were expected in the ALL sub-population nor that the trial has been powered for the proposed subgroup analysis. Therefore, the positive effects in this population are considered to be exploratory findings.

It is noted that the SmPC guideline states regarding information to be included in section 5.1:

"It may be appropriate to provide limited information, relevant to the prescriber, such as the main results (statistically compelling and clinically relevant) regarding pre-specified endpoints or clinical outcomes in the major trials, and giving the main characteristics of the patient population. Such information on clinical trials should be concise, clear, relevant and balanced, and should summarise evidence from relevant studies supporting the indication. The magnitude of effects should be described using absolute figures. (Relative risks or odd ratio should not be presented without absolute figures).
In the exceptional cases when clinically relevant information from subgroup or post-hoc analyses is presented, it should be identified as such in a balanced manner reflecting the limited robustness of both positive and negative secondary observations."

It appears that for both trials the MAH underlines positive secondary observations placing into the background the negative main results. This is not considered acceptable. It seems paradoxical to include the results of post hoc analysis when not all the main results of the planned analysis of primary and secondary endpoints have been presented. This is even more

true in trials that overall have negative results in the main planned analysis.
The rapporteur concludes that the text in section 5.1 should only include the main results from the 2 studies.

The Rapporteur proposes the following wording:

5.1 Pharmacological properties
Epoetin alfa 600 IU/kg (administered intravenously or subcutaneously once weekly) has been evaluated in a randomised, double-blind, placebo-controlled, 16-week study and in a randomised, controlled, open-label, 20-week study in anaemic paediatric patients receiving myelosuppressive chemotherapy for the treatment of various childhood non-myeloid malignancies.
In the 16-week study (n=222), in the epoetin alfa-treated patients there was no statistically significant effect on patient-reported or parent-reported Paediatric Quality of Life Inventory or Cancer Module scores compared with placebo (primary efficacy endpoint). In addition, there was no statistical difference between the proportion of patients requiring pRBC transfusions between the Epoetin alfa group and placebo.
In the 20-week study (n=225), no significant difference was observed in the primary efficacy endpoint, i.e. the proportion of patients who required a RBC transfusion after Day 28 (62% of epoetin alfa patients versus 69% of standard therapy patients).

Question 3
The MAH is requested to review the data available and propose wording which would reflect any available information regarding the pharmacokinetic properties in term neonates and other relevant paediatric subsets with anaemia of CRF.

MAH response:

Labelling statements concerning the half-life and PK profile in paediatrics have been proposed under the Type II Variation. This reflects the available data in paediatric CRF patients. In addition, the MAH proposes to retain the wording for PK data in neonates, as submitted in the original Article 45 Work-sharing proposal. The Rapporteur has requested wording to reflect any available information on PK in term neonates. There are no additional data in this population, hence no wording can be proposed.

The MAH's overall proposal for section 5.2 of the SmPCs related to the paediatric PK information for all presentations is shown below (paragraph 1 was proposed as part of the ongoing Type II Variation; paragraphs 2 and 3 are those for review under this Article 45 Work-sharing). This reflects the totality of the PK data in the paediatric population.

Paediatric population

A half-life of approximately 6.2 to 8.7 hours has been reported in paediatric subjects with chronic renal failure following multiple dose intravenous administration of epoetin alfa. The pharmacokinetic profile of epoetin alfa in children and adolescents appears to be similar to that of adults.

Pharmacokinetic data in neonates is limited.

A study of 7 preterm very low birth weight neonates and 10 healthy adults given i.v. erythropoietin suggested that distribution volume was approximately 1.5 to 2 times higher in the

preterm neonates than in the healthy adults, and clearance was approximately 3 times higher in the preterm neonates than in healthy adults.

Rapporteur's comments:

The PK information in section 5.2 regarding the paediatric population in general have already been implemented as the type II variation has been finalised. Therefore, the rapporteur has no further comments regarding the first paragraph of the text proposed.

The MAH has not identified any additional paediatric PK data apart from the ones presented in the original submission regarding preterm neonates.
The proposed wording is considered acceptable. Issue resolved.

Question 4
The MAH is requested to propose the paediatric wording which should be included in the PIL of all Epoetin alfa containing preparations reflecting the available paediatric information.

MAH response:
The most meaningful way to describe the available paediatric information to patients is by defining the populations in which epoetin alfa can be used. The Company acknowledges that the Package Leaflet should be clear in this regard, and the leaflets have been reviewed to determine if clarification is required.

Section 3 *How to Use <Epoetin alfa brand name>* already uses a format that defines the populations by indication (for example, "People with kidney disease", "Adults on chemotherapy"). This explains to the patient those indications that are restricted to use in adults only. It is recommended that the same approach is adopted in leaflet section 1 *What <Epoetin alfa brand name> is and What it is Used For*. The indication in CRF is already defined by use in children or adults (based on dialysis requirements), but the restriction to use in adults is not consistently defined for the other indications. To address this point, changes are proposed to the Package Leaflet wording, as shown below (the text below is taken from the leaflet for all strengths excluding the 40,000 IU/ml formulations, but the changes are applicable to both Package Leaflets).

1. WHAT <Epoetin alfa brand name> IS AND WHAT IT IS USED FOR

<Epoetin alfa brand name> contains epoetin alfa - a protein that stimulates the bone marrow to produce more red blood cells which carry haemoglobin (a substance that transports oxygen). Epoetin alfa is a copy of the human protein erythropoietin (ee-rith-roe-po-eh-tin) and acts in the same way.

- <Epoetin alfa brand name> is used to treat symptomatic anaemia caused by kidney disease
  - in children on haemodialysis
  - in adults on haemodialysis or peritoneal dialysis
  - in severely anaemic adults not yet undergoing dialysis.

If you have kidney disease, you may be short of red blood cells if your kidney does not produce enough erythropoietin (necessary for red cell production). <Epoetin alfa brand name> is prescribed to stimulate your bone marrow to produce more red blood cells.

- <Epoetin alfa brand name> is used to treat anaemia ~~if you are~~ **in adults** receiving chemotherapy for solid tumours, malignant lymphoma or multiple myeloma (bone marrow cancer) ~~and your doctor decides you~~**, who** may have a high need for a blood transfusion. <Epoetin alfa brand name> can reduce the need for a blood transfusion **in these patients**.

- <Epoetin alfa brand name> is used in moderately anaemic ~~people~~ **adults** who donate some of their blood before surgery, so that it can be given back to them during or after the operation. Because <Epoetin alfa brand name> stimulates the production of red blood cells, doctors can take more blood from these people.

- <Epoetin alfa brand name> is used in moderately anaemic adults about to have major orthopaedic surgery (for example hip or knee replacement operations), to reduce the need for potential blood transfusions.

Rapporteur's comments:

The proposed changes provide clarity as to which indication concerns the paediatric population and which the adult population solely and are considered acceptable.

VI. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

Based on the review of the presented paediatric data on efficacy and safety the rapporteur considers the following:

Anaemia in chronic renal failure

During this work-sharing procedure, the MAH submitted studies in paediatric chronic renal patients and proposed to include data from these studies in section 5.1 of the SmPC. In the current SmPC of Epoetin alfa , posology in children is only given for its intravenous use in paediatric patients with CRF on haemodialysis. However, the studies submitted by the MAH included primarily pre-dialysis paediatric patients and patients on peritoneal dialysis (only 2 on HD) and drug administration via the subcutaneous route.

The rapporteur agrees to include the results of these studies in section 5.1 of the SmPC. However, the information to be included has to be balanced and has to state uncertainties or conclude on lack of efficacy or safety as appropriate. In addition, the rapporteur considers that a cross reference in section 4.2 should be included to clarify that the drug is not indicated in paediatric patients on peritoneal dialysis or pre-dialysis.

SmPC changes

Section 4.2:

Paediatric population

The safety and efficacy of <Epoetin alfa brand name> in chronic renal failure patients with anaemia before initiation of dialysis or on peritoneal dialysis have not been established. Currently available data for the subcutaneous use of <Epoetin alfa brand name> in these populations are described in section 5.1 but no recommendation on posology can be made.

Section 5.1:

Paediatric population

Chronic renal failure

Clinical data with subcutaneous administration in children are limited. In 5 small, open label, uncontrolled studies (number of patients ranged from 9-22, total N=72), Epoetin alfa has been administered subcutaneously in children at starting doses of 100 IU/kg/week to 150 IU/kg/week with the possibility to increase up to 300 IU/kg/week. In these studies, most were predialysis patients (N=44), 27 patients were on peritoneal dialysis and 2 were on haemodialysis with age ranging from 4 months to 17 years. Overall, these studies have methodological limitations but treatment was associated with positive trends towards higher haemoglobin levels. No unexpected adverse events were reported (see section 4.2).

Anaemia of prematurity

The MAH submitted paediatric studies with the use of r-HuEPO for the treatment of anaemia of prematurity. Among the studies submitted, the MAH proposed to include data from one placebo controlled study (K90-033, Shannon et al, 1995) which demonstrated a positive effect of r-HuEPO treatment in premature infants, as the MAH considered this study to be the most scientifically robust compared to the others.

There have been many studies in the population of premature anaemic infants with the use of erythropoietins. These have been well described in 2 large Cochrane reviews (Ohlsson A, Aher SM., 2014 and Aher SM, Ohlsson A., 2014). In these reviews, it is acknowledged that EPO administration results in reduced transfusions in premature babies but the clinical significance of these changes is still questioned.

In addition, a possible association of EPO administration with retinopathy of prematurity (ROP) is noted by the Cochrane reviews. In particular, the potential association of epoetin beta administration and ROP was the focus of a European review (PRAC, 2014). Epoetin beta is licensed for the prevention of anaemia of prematurity in infants with a birth weight of 0.75 to 1.5 kg and a gestational age of less than 34 weeks. The PRAC agreed that the current evidence does not allow excluding a possible increase in the risk of retinopathy of prematurity with early treatment initiation of epoetins in preterm infants. The summary of product characteristics of Epoetin beta will be amended to include this possible risk of retinopathy.

The rapporteur considers that although this review is focused on EPO beta, the risk of ROP with erythropoietin alfa can also not be excluded based on the similarities between the two EPOs.

The rapporteur is of the view that the efficacy and safety of epoetin alfa use for the prevention and/or treatment of anaemia of prematurity has not been established. Furthermore EPO alfa is not routinely used for anaemia of prematurity in neonatal intensive care units as it is not currently licensed in this indication. In addition, there is a potential increased risk of ROP with EPO treatment in premature infants. Based on these considerations, the rapporteur does not support the inclusion of information in section 5.1 of the SmPC concerning the single study proposed by the MAH.

Chemotherapy-Induced Anaemia of Cancer

Based on the data from the studies submitted in the paediatric work-sharing procedure and the evidence available in the literature, the rapporteur is of the view that Epoetin alfa should not be recommended for the use in paediatric cancer patients. Although the drug is not licensed for this indication, the MAH proposed wording for section 5.1 of the SmPC in order to include the results of 2 controlled studies in paediatric cancer patients. The wording proposed focused on positive secondary observations placing into the background the negative main results. This is not considered acceptable and therefore the rapporteur proposes alternative wording presenting the main results of these 2 studies.

SmPC changes

Section 5.1
Paediatric population
Chemotherapy-induced anaemia
Epoetin alfa 600 IU/kg (administered intravenously or subcutaneously once weekly) has been evaluated in a randomised, double-blind, placebo-controlled, 16-week study and in a randomised, controlled, open-label, 20-week study in anaemic paediatric patients receiving myelosuppressive chemotherapy for the treatment of various childhood non-myeloid malignancies.
In the 16-week study (n=222), in the epoetin alfa-treated patients there was no statistically significant effect on patient-reported or parent-reported Paediatric Quality of Life Inventory or Cancer Module scores compared with placebo (primary efficacy endpoint). In addition, there was no statistical difference between the proportion of patients requiring pRBC transfusions between the Epoetin alfa group and placebo.
In the 20-week study (n=225), no significant difference was observed in the primary efficacy endpoint, i.e. the proportion of patients who required a RBC transfusion after Day 28 (62% of epoetin alfa patients versus 69% of standard therapy patients).

PIL changes
The MAH proposed PIL changes in order to provide clarity as to which indication concerns the paediatric population and which the adult population solely. The rapporteur agrees with these changes.

PIL changes (shown in bold):

1. WHAT <Epoetin alfa brand name> IS AND WHAT IT IS USED FOR

<Epoetin alfa brand name> contains epoetin alfa - a protein that stimulates the bone marrow to produce more red blood cells which carry haemoglobin (a substance that transports oxygen). Epoetin alfa is a copy of the human protein erythropoietin (ee-rith-roe-po-eh-tin) and acts in the same way.

- <Epoetin alfa brand name> is used to treat symptomatic anaemia caused by kidney disease
  - in children on haemodialysis
  - in adults on haemodialysis or peritoneal dialysis
  - in severely anaemic adults not yet undergoing dialysis.

If you have kidney disease, you may be short of red blood cells if your kidney does not produce enough erythropoietin (necessary for red cell production). <Epoetin alfa brand name> is prescribed to stimulate your bone marrow to produce more red blood cells.

- <Epoetin alfa brand name> is used to treat anaemia ~~if you are~~ **in adults** receiving chemotherapy for solid tumours, malignant lymphoma or multiple myeloma (bone marrow cancer) ~~and your doctor decides you~~**, who** may have a high need for a blood transfusion. <Epoetin alfa brand name> can reduce the need for a blood transfusion **in these patients**.

- <Epoetin alfa brand name> is used in moderately anaemic ~~people~~ **adults** who donate some of their blood before surgery, so that it can be given back to them during or after

the operation. Because EPREX stimulates the production of red blood cells, doctors can take more blood from these people.

- <Epoetin alfa brand name> is used in moderately anaemic adults about to have major orthopaedic surgery (for example hip or knee replacement operations), to reduce the need for potential blood transfusions.

VII. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

Johnson & Johnson / Janssen-Cilag:

Eprex 2000 iu/ml solution for injection in pre-filled syringe	2000 iu/ml	Solution for injection	Epoetin alfa
Eprex 4,000 iu/ml solution for injection in pre-filled syringe	4,000 iu/ml	Solution for injection	Epoetin alfa
Eprex 10,000 iu/ml, solution for injection in pre-filled syringe	10,000 iu/ml	Solution for injection	Epoetin alfa
Eprex 40,000 iu per ml, solution for injection in pre-filled syringe	40,000 iu/ml	Solution for injection	Epoetin alfa